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Next-Generation Technologies for Early Disease Detection and Treatment: Harnessing Intelligent Systems and Genetic Innovations for Improved Patient Outcomes

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Abstract

There are significant challenges to developing improved technologies for the early detection and treatment of emerging diseases. Early detection requires reducing the time it takes to identify and test potential reasons for emerging human diseases. New technological advancements in next-generation sequencing and the annotations of human genomes provide an opportunity to leverage such information to design new ways of testing individuals for the presence and progression of diseases. Deep-sequencing approaches toward the construction of human DNA, RNA, and protein annotations present new opportunities for understanding the pathophysiology underlying differences in individual responses to pathogens and other environmental factors.

This paper discusses a vision of next-generation technologies and how the challenge of early disease detection motivates research aimed at developing a set of new sensor platforms. Such technologies may revolutionize early detection diagnostic tests and dramatically improve response times. Our goal is to support the development of advanced sensor technologies required to inform treatment decisions, to manage maladies ranging from day-to-day ailments to the horrors of newly emerging infectious diseases. Our approach—developing advanced sensors and associating rapidly with annotations of genomes to inform treatment decisions—will use a virus as a case study because it is a challenge for biomarker discovery that can be used in drug design and diagnostics development. As such, our approach provides proof of concept validation and advanced next-generation sequencing methods that will enable diagnostics development for other new diseases.

Keywords: Early Detection, Emerging Diseases, Next-Generation Sequencing, Human Genomes, Deep Sequencing, DNA Annotations, RNA Annotations, Protein Annotations, Pathophysiology, Sensor Platforms, Diagnostic Tests, Response Times, Advanced Sensors, Biomarker Discovery, Drug Design, Treatment Decisions, Infectious Diseases, Genomic Data, Proof of Concept, Diagnostics Development.

1. Introduction

Health is one of the most fundamental concerns of humanity. Early detection of diseases remains the ultimate goal in curing various illnesses. Early treatment typically results in a lesser impact on employing drugs, thus increasing the likelihood of better patient outcomes. Biomarker discovery, which could be in the form of gene expression analysis, RNA detection, or protein identification, is a popular first step toward early disease detection using large-scale biomolecular profiling of patients. Advances in biomedical technologies have enabled researchers to interrogate biomolecular information from patient samples at an unprecedented level of scale and resolution. Modern sequencing machines are capable of reading and analyzing hundreds of millions of DNA molecules concurrently with a sample preparation time of a few hours, thus making them exceptionally suitable for large-scale studies that involve a large number of samples. With this advance in sequencing speed, miniaturized chips have been developed for single molecular analysis purposes and have laid the foundation for the forthcoming sequencing application in the clinical industry.

Genome-wide association studies have identified hundreds of genetic variants that could be associated with a higher disease infection rate, but typically on the scale of common diseases in complex genetic architecture, genetic causes remain incompletely understood, cryptic, or both. Furthermore, it has also been revealed that many complex human traits, such as telomere malfunctions, somatic point mutations, and chromosome number aberrations, spark off diseases by eliciting DNA damage and eventually weakening protective chromatin structures. These discoveries illuminate the fact that disease susceptibility is not simply the result of a few malfunctioning genes. Instead, it should stem from flawed molecular characteristics, such as gene expression levels and distribution of functional proteins in patients. The relevance of gene expression to disease phenotype is supported by clinical studies that have identified important regulatory genes

in the gene regulatory network through the application of anti-cancer drugs. Collectively, all these findings highlight the significance of devising targeted detection and prognostic agents for some of the molecular traits of cells in any possible disease stage.

In this review, we will introduce and summarize advanced single molecular and cellular technologies, discuss their potentials and limitations in advancing our ability for early disease diagnosis and treatment, and provide a perspective on where we believe clinical single-cell and single-molecular biology will make a large, positive impact shortly.

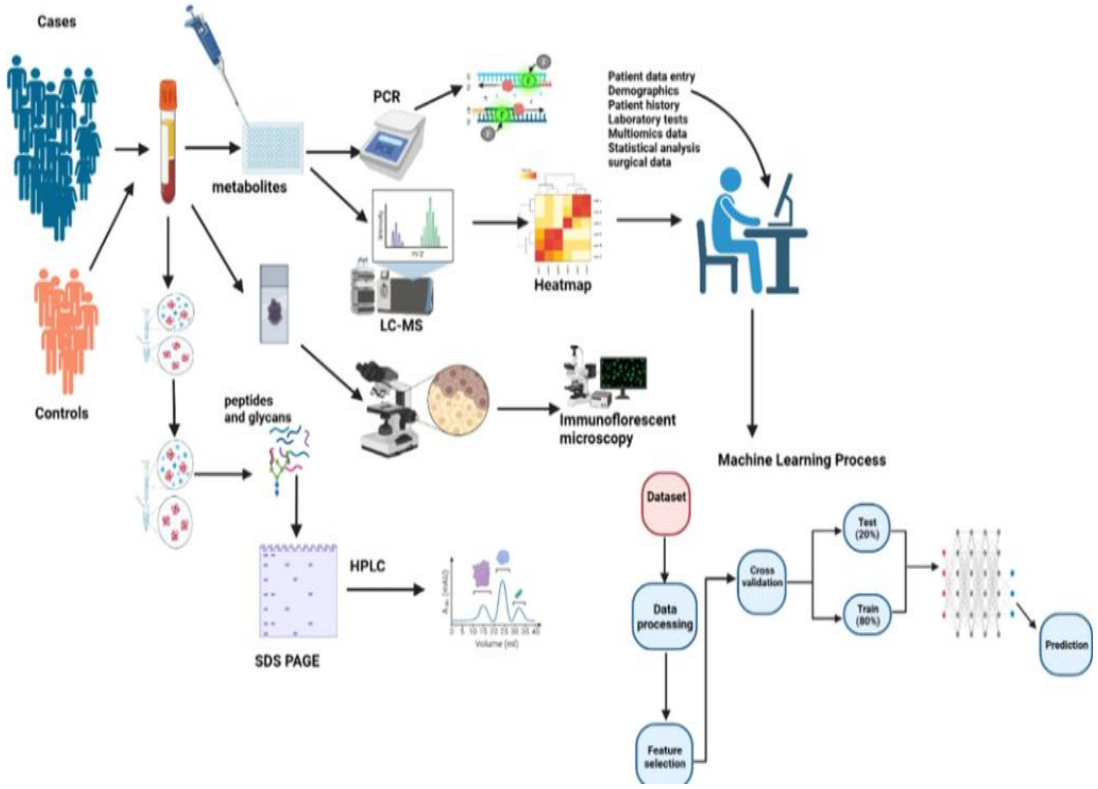

Fig 1 : Pathways to chronic disease detection and prediction

2. Overview of Disease Detection Technologies

Early diagnosis of both acute and chronic diseases is critical in providing clinical intervention, thereby enhancing patient prognosis. As we acquire more detailed molecular profiles of individuals through high-throughput genomics methods, it opens up possibilities of using sophisticated computational models to predict disease onset, progression, and development. In this chapter, we provide an overview of current and future technologies that are used for early disease detection and treatment: (1) Chemical Imaging and Targeted Sensing Technologies, (2) Microfluidics and Lab-on-a-Chip Platforms, (3) Wearable and Implantable Bioanalytical Devices, (4) Nanoscale Material Based Bioanalytical Methods, and (5) Computation and Information Technologies. A new trend toward preventive care using a combination of compact technology, including portable diagnostic instruments and advanced artificial intelligence diagnosis tools, has started. The combination of ubiquitous sensing technology, advanced diagnostics, and leading computational methodology will create a paradigm shift in addressing emerging healthcare needs.

Early diagnosis of both acute and chronic diseases is critical in providing clinical intervention, thereby enhancing patient prognosis. Over the past several years, the focus of disease diagnosis has shifted from late-stage reactive medicine in intensive care units to early-stage sustainable diagnostic paradigms. This critical shift has been achieved by the improvement and innovation of bioanalytical techniques that can detect molecular and cellular targets at earlier stages of disease initiation. Many advances have been accomplished in these disease detection tools recently so many comprehensive diagnostic solutions are now available for both clinicians and researchers. As we acquire more detailed molecular profiles of individuals through high-throughput genomics methods, it opens up possibilities of using sophisticated computational models to predict disease onset, progression, and development; this field of research is commonly termed predictive healthcare. In addition to diagnostic and prognostic implications, the use of these modern bioanalytical techniques advances our basic understanding of disease pathology and can facilitate the development of therapeutic options tailored to an individual’s profile.

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Equation 1 : AI-Driven Disease Risk Prediction Model

where

P_d = Probability of disease presence,

X_i = Biomarker or genetic feature i,

α_0, α_i = Model coefficients from AI training,

n = Number of features analyzed.

$$P_d = \frac{1}{1 + e^{-(\alpha_0 + \sum_{i=1}^{n} \alpha_i X_i)}}$$

2.1. Traditional Methods

Here we highlight some fundamental constraints to traditional methods before discussing recent technological advances that have created new opportunities. Detection of cancer has traditionally been dependent on the anatomy-modifying effects of cancerous tissue growth. Vitrification has been one of the earliest biological techniques applied to diagnosis, dating back to the late nineteenth century. The definitive diagnosis of cancer, however, usually involves histologic examination, which demands biopsy, a tissue removal process that is quite invasive. From the examination of morphology and histological features, three-stage models have been developed for tumorigenesis of selected cancer types, representing a progression toward neoplasia. The staging systems are based on the extent to which the original tumor has spread to surrounding or distant organs and requires a resection. Such data are used to determine a cancer patient's treatment approach.

Defining the outcome of cancer treatment frequently depends upon surgical pathological interim information. A biopsy followed by histology gets specific diagnoses of benign and malignant neoplasms, and distinguishes organ and tissue origin, respectively. Surgery that removes the "bulk" of the neoplasm is frequently the first step in therapy but is often followed by radiation and/or chemotherapy. For non-solid thyroid tumors, surgery is often followed by radioactive iodine therapy. Ductal carcinomas in situ in the mammary gland have caused much debate; they have been considered a type of cancer but also a precursor to invasive carcinoma. The ignorance about the biology of such diseases and a lack of applicable therapy usually leads to the removal of aberrant tissues by surgical dissection.

2.2. Emerging Technologies

The growing interest in health and wellness is leading to a new wave of technological developments dedicated to detecting diseases at very early onset. This interest is backed by a slow critical cultural change due also to the increasing demographic index. Health signs, temperature, heart rate, and others are parameters that we have always used to diagnose common diseases. With humanity's interests that we can now define as historical, the know-how and the imagination of mankind are giving us technologies that will help people better monitor their health conditions, detecting pathologies at very early onset.

The most meaningful of these technologies is related to a new wave of nanomedicine research and applications toward a new generation of diagnostics. New products will be able to monitor only the illnesses we feel, for example, avoiding taking antibiotics even if no pathogens are present in our throat, with the inevitable resistance building up to antibiotics that have negative effects on our health. New nanosensors can replace invasive diagnostic methods with important social and health benefits for the patient. Nanotechnology will also increase the effectiveness of established diagnostic procedures. Health systems have to aim to work better and to obtain meaningful results, meaning to repair people, not treat patients diversely. The health, prevention, and care of people are the principal values of mankind, enforcing an admirable contract between humanity and science.

3. The Role of Intelligent Systems in Healthcare

The cost of healthcare continues to rise, and the challenges we face only continue to grow in scale. These challenges are not only limited to health and disease management but also include the cost of delivery and management of clinical ecosystems. Healthcare has slowly seen the emergence of next-generation intelligent systems, and the pace is starting to pick up. The use of advanced analytical models on big data repositories has opened up avenues to statistical and computational modeling of complex patient responses. In turn, this may reveal patient-specific trends and signal alterations in physiological responses that are indicative of future adverse events leading to hospital readmissions. Emerging regulatory interest in digital endpoints for drug trials and precision medicine has one foot in artificial intelligence and commerce.

At every doorstep, in proportion to advances in our ability to measure biological systems and responses, the complexity of these datasets expands in two dimensions: samples and variables. Substantial redundancy exists across these variables, both within and across these biological samples for many disease phenotypes detected from measured data. As such, it is possible to engender complex structured ensemble models using diverse machine learning methods. These expand upon biological knowledge to build systems models for practical implementation designed for future clinical scenarios. With the emergence of precise patient-specific structure- and learn-based predictive models, we expect the next generation of

artificial intelligence algorithms to shift the paradigm squarely to precision medicine. Such patient-specific trends and phenotypic shifts will be particularly helpful in patient-onset population acute/chronic disease models, possibly sidestepping the noticeable future high costs of healthcare management. Such red alarms would also clearly inform patients of the future onset of pathological events and enhance patient adherence to management lifestyle advice.

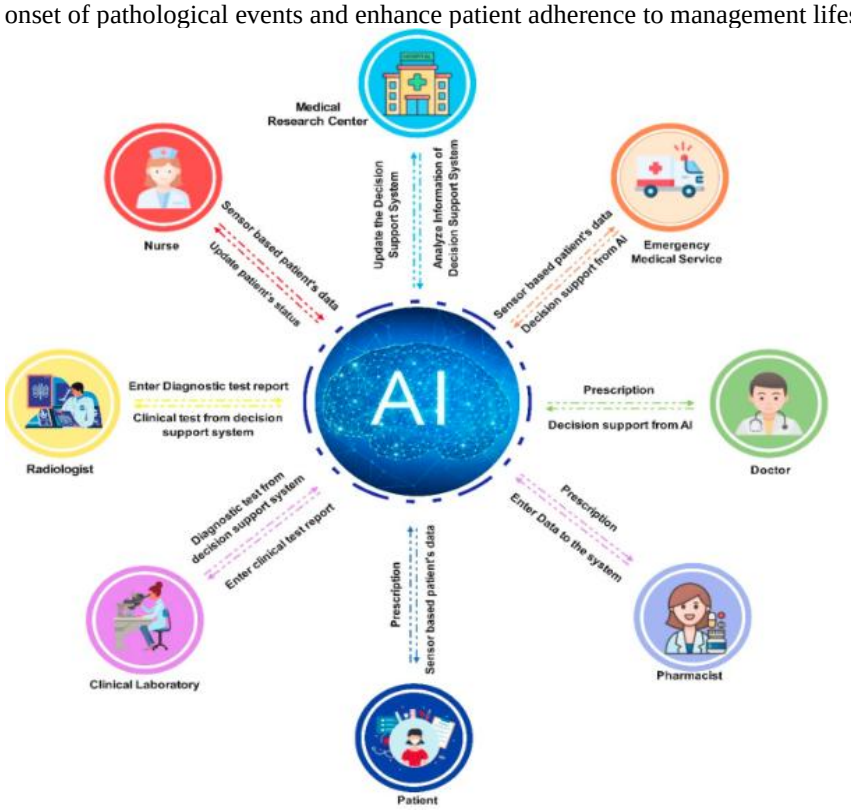

Fig 2 : Intelligent Healthcare

The crux of such predictive data modeling involves rigorous development and testing of non-biased and non-overfitting patient-specific prediction models that rely on diverse, high-dimensional, and multiscale omics datasets. Such models should ideally be guided by general principles of complex network modeling and should rely minimally on prior information and knowledge for exploratory learning. The models need to be vetted against held-out data to reduce overfitting errors and ensure transferability and generalization to other similar populations for practical application in predictive medicine. By design, such low-parameter models should exhibit broad patient applicability, should not alter the performance in subgroup analysis, and should ideally incorporate interpreted accurate structural biological characteristics. With minimal training and testing modalities, these predicted models should not compromise data privacy and should ideally be housed in cloud-based intelligent systems to aid patient lifestyle modification. As the complexity and volume of such predictive models broaden, care should be taken to ensure these models are ethically developed and honestly represent predictive patterns in medical datasets to avoid regulatory pitfalls that we previously encountered with other intelligent system implementations of artificial intelligence.

3.1. Artificial Intelligence in Diagnostics

The fundamental pillars of successful healthcare interventions exist in early disease detection, accurate information on the evolution of the disease stages, and effective treatment stages. Technologies designed to cover all three of these areas will positively affect disease outcomes, healthcare expenses, and quality of life. The worsening healthcare issues introduced by growing elderly communities worldwide, accompanied by a decrease in medical staff, also create demand for technological growth in these areas. Next-generation advanced technologies such as artificial intelligence, machine learning, big data analytics, cloud computing, and the Internet of Medical Things are increasingly being developed and embedded in healthcare devices. In diagnostics, doctors make use of these advancing technologies, tools, and software to handle patient data, results, and images when determining treatment stages, surgery, or medication.

Artificial intelligence, such as machine learning, deep learning, and natural language processing, enables large-scale data analytics and generates a new perspective for personalized medicine and detecting the early symptoms of expected diseases. Currently, image-based or icon-based smartphones are being used to connect patients with artificial intelligence, such as sophisticated chatbots, when doctors are not available. With the basic knowledge, capability, and workload of artificial intelligence growing at rapid rates, most of the low and medium-complexity work done in hospitals will currently

be offloaded to artificial intelligence. The result will be a dramatic decrease in disease reporting errors and costs due to limitations associated with human inattention and exhaustion. Software and applications developed for artificial intelligence systems will have a strong effect on clinical workflows. The evolution and use of self-service and direct-to-consumer solutions will force regulatory changes that are necessary to resolve the current regulatory limitations on the remote incorporation of artificial intelligence systems into healthcare.

3.2. Machine Learning Applications

This method uses large datasets to reconstruct an analytical pipeline able to study new biochemical characteristics in senescence, based solely on known features. The capacity of machine learning to perform in such a new space would be difficult to predict for other methods. Given data artifacts, spurious crown interactions, batch effects, and multiple testing, machine learning approaches need to develop techniques and tools to translate data into meaning. Tools of statistical inference from low-throughput data must be completely reformulated to handle the entirely new scale and structure of data that arise in high-throughput settings. Expansion of chemistry and biology tempers the overfitting inherent in many feature selections in prediction and classification problems. Automatically aggregating across hundreds of potentially correlated features by selecting predictors from surveys to biological context is recommended. Systems biology research tries to develop modeling computational tools for understanding and linking the huge quantities of data in the biochemistry literature. While shapes are dominated by movement, the interaction among people or other scenes is not directly utilized; however, eye gaze contains useful information about interactions between individuals in different social settings. Biology and other life sciences are quite broad in scope and are fundamentally different from more focused disciplines. Systems biology work aims to create strategies using computational tools to more fully understand heterogeneous biochemical data. The products of cells in diverse organisms can be represented using computational and machine learning methods as highly interconnected biological networks. Biomolecules, which include nucleic acids and proteins, regulate and react. Efforts driven by researchers in fields such as bioinformatics, statistics, computer science, organic chemistry, applied mathematics, and a host of related areas have greatly expanded the focus on developing tools for describing and studying biology's huge internal structures. Biologically relevant materials are thus complex and poorly understood, due partially to data gathering's general inefficiency and very noisy estimates of chemically meaningful small effect sizes. Machine learning is a tool for automatically searching for patterns in large datasets, but requires careful application and implicit feature extraction.

4. Genetic Innovations in Disease Treatment

By understanding genetic factors in disease development, we are also learning to develop DNA-based diagnostics and prognostic tests, as well as gene-selective drugs to cure illnesses for which there is no cure. The biggest breakthrough work here has been in genetic-based cancer treatments. Most cancers are caused by only a few particular genetic mutations, typically two or three mutations per cancer, all within a much larger set of known mutations. Unlocking a genetic cure for cancer is a complex and fascinating challenge. When it is complete, it will likely inspire a whole arsenal of potential genetic therapies. But this is just one step in a significantly broader campaign for DNA-based cancer tests and cures.

The next genetic frontier in which we are likely to see significant progress is in finding genes responsible for rare, inherited genetic diseases, conditions caused by mutations in one or perhaps two genes. Unlike cancers, these causes of diseases usually have relatively little genetic variation among patients. As a result, the genetic roots of most inherited diseases can be discovered with comparative speed through a search for similar gene variations among affected members of families with the condition. In many cases, the discovery of these roots paves the way for DNA-based diagnostic tests, prenatal tests, and gene-based treatments. A few such cures are already available. For example, bone marrow transplantation is a treatment for several genetic diseases caused by a deficiency in an enzyme, and certain treatments can be processed in a test tube to correct a genetic defect in patients with hypercholesterolemia.

4.1. Gene Editing Technologies

Breaking the information on DNA using restriction enzymes or linking DNA using DNA ligase were the early forms of gene editing in the pre-DNA sequencing era. These methods have led to the development of molecular biology and enabled the study of genes and their function. The sequencing of the DNA of mice using gene editing technologies in mouse embryonic stem cells has allowed for more complex modification of the gene after obtaining the sequence information.

Gene editing mechanisms use the recombination process and damage the DNA. Homologous recombination mechanisms that are active in the cells can be harnessed for this purpose under some conditions. One of them, and the most important, is that the cells are dividing. Because stem cells have a relatively high division rate when a gene is damaged and DNA containing the correct gene is added, the gene is repaired through the existing homologous recombination mechanism. Genes may be microdeleted during this mechanism to suppress gene expression. In addition to this, this technique can sometimes result in the insertion of a gene into the DNA. This technique is significantly limited in cell types other than a

very few species-specific embryonic cell types. The zinc finger nuclease, TALEN, and the CRISPR / Cas9 gene editing technologies are targeted methods resulting in higher rates and can be used in most cell types.

Equation 2 : Genetic Mutation Impact on Disease Progression

$$D_s = \sum_{i=1}^{n} \gamma_i M_i$$

where

D_s = Disease severity score,

M_i = Expression level of mutation i,

γ_i = Weight assigned to mutation i,

n = Number of mutations considered.

4.2. Personalized Medicine

Personalized medical treatments require sensitive and specific diagnostic tests. They are essential to personalize protocols for patients by determining disease progression, assigning phenotypes, monitoring disease onset and treatment, and developing personalized medicine. A method based on unique proteomic signatures can pre-symptomatically determine the basal levels of biomarkers with high specificity and sensitivity. Sequencing customized medications for cancer to match the genetic makeup of patients, as well as for polypharmacological efficacies, is well on its way. Bypassing sensitivity and specificity problems from early diagnostic tests is essential for personalized medicine to be practiced on a large scale to enable regular people to greatly benefit.

Despite extensive sequencing, the identification of genetic activities in each person encoded by the newest complete human genome is still substantially incomplete. Genetic activities are induced by proteomes, other molecular species, and environmental influences. As an actual human cell proteome remains to be experimentally determined and proteins are the functional machinery of cells, they offer the stumbling blocks for personalized medicine. Proteomes, first their malformations by diseases, can and must be experimentally detected. Early-stage cancer states, including premalignant states, and other systemic and tissue-specific diseases are primary candidates. To Ultimately fulfill the promise of early diagnostic tests to greatly benefit regular people requires that easy sampling, non-invasive from systemic or highly selective tissues, such as blood or stool, pancreatic juice, or urine, can be routinely accomplished.

5. Integration of Intelligent Systems and Genetic Innovations

Intelligent systems include several systems, the design of which closely mirrors the way humans approach abstract problem-solving operations. In essence, the systems are information-processing machines, designed to handle vast amounts of data by pointing to meaningful groupings of information and by storing those patterns for further reference and pattern recognition. They are employed in a learning mode, capable of amassing enormous amounts of data and information. As they become more confident in their ability to recognize meaningful patterns in the data they are ingesting, they become more adept at making pertinent distinctions quickly in rapidly changing environments. It is precisely this ability for rapid, often intuitive, learning based upon a rich and meticulous analysis of information that makes intelligent systems so attractive for the next generation of neither early nor preemptive disease detection nor targeted disease treatment.

Whether the use of intelligent systems is being ascribed to a variety of activities—from business decision-making to optimization of resource use to national security concerns—the industry is beginning more and more to utilize a variety of artificial intelligence approaches to both support and solve several existing problems and to create innovative opportunities. Very shortly, it is expected that two very important applications will be developed in the area of preemptive health care: the rapid detection of early biological threats, both to the physical plant and to the workers employed within the plant, and the recognition and exposition of particular susceptibility to a variety of diseases. Now including the genetic component of human population structure, these intelligent systems await the discovery and understanding of various elements within the human DNA structure that impact the emergence of specific diseases. The particular markers might be revealed through the judicious joining of biology and artificial intelligence methods.

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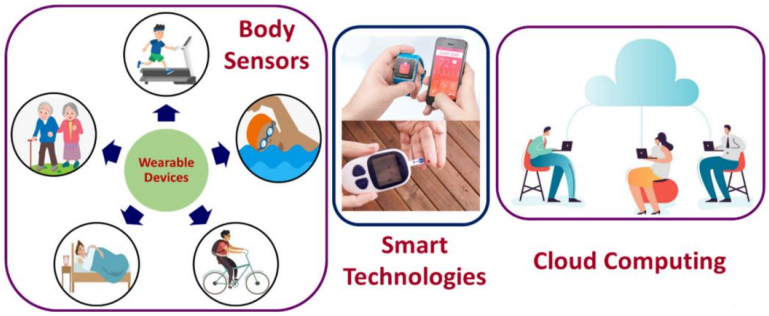

Fig 3 : Artificial Intelligence (AI) and Internet of Medical Things (IoMT) Assisted Biomedical Systems

5.1. Synergistic Approaches

In the search for biomarkers and innovative technologies to achieve earlier diagnoses and more effective treatments, researchers are often endeavoring to reach the same goal from different perspectives. In particular, collaboration between basic researchers working on molecular routes and clinical researchers on potential applications is essential. Both basic and applied researchers can derive inspiration from entirely different disciplines. They also happen to face some common challenges. Indeed, while clinical researchers search for markers of diagnostic and therapeutic relevance, basic researchers are looking for modifiable factors. Information on biomarkers is an indirect and essential part of the information collection. The challenges faced with the collection of biomarker datasets are similar in that they all require a certain level of rigor and follow-up: pool and platform validation and reference range publication.

Because advanced disease emergence is preceded by the aging of interconnected molecular factors of different natures, these factors can be integrated using advanced bioinformatics approaches. Conducting a multidisciplinary analysis of blood samples and combining data across studies not only will lead to the emergence of robust biomarkers but also reveal molecular determinants and appropriate targets for intervention. Data integration is becoming such an essential issue that numerous new institutions and programs are being set up to handle the large volume of information and the complexity of the questions to be addressed. Increases in available computing capacity and the emergence of new tools used to analyze raw data are revolutionizing life science. Complex data from large cohorts for predictive model construction and validation analysis are becoming realizable as well, and on a routine basis in some cases. As a result, additional, potentially accurate biological and non-biological markers that could be used in disease diagnosis and prediction are emerging. That is, in part, what the fourth paradigm of science refers to. Bioinformatics tools can be applied to disease diagnosis and model construction analysis as early as blood sampling and have become realizable at an unprecedented pace.

5.2. Case Studies

When considering potential applications of bio-integrated technologies in clinical medicine, it is important to realize that the vast amount of information provided by these systems has the potential to transform the detection of disease. As an example, we consider simple chemical tests for diseases such as diabetes that have been developed through sensor technologies that extract information from a handful of important chemical targets, generally single species in small volumes of biofluids such as blood or urine. In many situations, the complications, discomfort, and expense to the patient associated with the physical hallmarks of these tests limit the frequency with which they can be used. This poses obvious challenges for conditions such as type 1 diabetes, where frequent monitoring is especially important for the prevention of long-term complications. Taking advantage of the richness of information now available from bio-integrated devices, it has recently been shown that dozens of molecular species in microliter volumes of biofluids can be monitored in real-time, without pain or discomfort to the patient, through a small, minimally invasive pore in the skin. The resulting data can provide early warning to the patient, enabling them to take action that can prevent or delay the onset of the hallmark physical manifestations of several diseases. This type of medical insight represents an important step toward a new digital metabolic record that could improve outcomes not just for patients with diabetes but also for those with a host of other health conditions. Biointegrated devices could monitor numerous targets in the circulatory system that drive the development of the leading worldwide non-communicable killers, such as chronic hypertension, chronic kidney disease, or heart failure. The capacity for continuous, multiplexed, minimally invasive monitoring of important biological molecules to improve patient outcomes can only grow, as the technologies underlying these capabilities mature.

6. Challenges in Implementation

In the relatively near future, we may have technical capacities available that will support disease prevention proactively, generally for prior detection and relatively minor intervention. Certainly, research has already shown that different diseases often have early-stage indicators in common; thus, a platform technology to detect these indicators at preclinical levels would provide a powerful, proactive tool for human health care. There is already a strong knowledge of major diseases, including the development of early-stage diagnostics and therapeutic solutions that could be modulated with

appropriate technologies. Furthermore, there are a growing number of enabling technologies today, and there are new high-impact unmet needs in bioengineering and instrumentation to detect target noxious molecules at the early stage for previously unaddressed millions of patients. The challenge is to integrate bioanalytical sciences and process applied research in close collaboration with medical diagnostic and therapeutic professional end users. This requires fundamental advances in which individual molecules are detected under extremely complex backgrounds, which have influenced the development of hierarchical sensing from top-down to cell and molecular structures as opposed to the conventional homogeneous solution-based in vitro models. The hierarchical sensing strategies employ a combination of physical mechanisms with absolute single-molecule specificity to achieve a precision of roughly 30 minutes for select molecule count levels from 1 femto milliliter that can ultimately lead to measuring over the low attomolar range of a single toxic molecule.

6.1. Ethical Considerations

To address these issues, a period of extensive conversations and agreements will be required. It is mandatory that decisions made during this time maintain respect for moral values, privacy, and freedom that societies, cultures, and religions have forged and published through centuries. Such dialogue should occur primarily in the public sector and take into account, when requested, relevant expert views from the private sector. Discussions will need to involve ethicists, regulators, and legislative authorities. Their role is to weave the guidelines and regulations that each territory will require individually, respecting the constitutional provisions of every country and the quality of political and legal guarantees that each citizen has a right to expect.

Privacy risks in biomedicine can only be partially mitigated through regulatory safeguards, as the most serious risks arise from complex social behaviors that are difficult to anticipate and almost impossible to regulate using prescriptive rules. Predicting people’s reactions to information about their health risks and diseases is delicate and uncertain. Still, general privacy-protecting rules are attainable. The public is well aware that while personal data should be protected, the yield of information disclosure on diseases can be crucial in preventing outbreak dangers and health risks. In exchange for providing access to personal health data, biobanks and other providers of personal health information can offer aggregate statistical diagnostic information about groups based on a valuable resource that they are willing to make socially available. This way, it should be possible to maintain the confidentiality of all the data.

6.2. Regulatory Hurdles

Medical and diagnostic devices are regulated by the Food and Drug Administration in the United States. They fall into two categories: (1) 510(k) devices, which require demonstration that the proposed device is substantially equivalent to a "predicate device" that was approved or marketed before 1976, and (2) premarket approval devices, which are considered to have greater risk and require clinical data to prove safety and efficacy. A PMA device often requires multiple clinical trials to demonstrate safety and efficacy, and thereafter regulatory approval, which is a time-consuming and expensive process. Each clinical trial often takes years and costs millions of dollars. The additional problem is whether traditional PMA validation paradigms, which often require large patient samples collected over months and years, are appropriate for the ML algorithms that may use complex mathematical features that may be difficult to represent biologically.

The ability of traditional validation paradigms to accurately reflect the performance of ML in a clinical setting has been questioned because complex statistical and computational analyses are difficult to replicate in validation models. Moreover, we must consider that, although ML may be especially useful in tasks where significant amounts of data can be analyzed, they can also easily overfit the validation datasets, and especially small training data may increase the risk of high false-negative rates. Last but not least, at present, companies are often unwilling to invest in technologies for which they cannot expect to recoup their investments, and in addition, there is a reticence on the part of the FDA to approve technologies that are not able to demonstrate that they are safe and effective for the intended use.

6.3. Technical Limitations

Although the potential of early disease detection and treatment is immense, today's technology is unable to fully realize this potential. Generally, diseases are best treated at the beginning stages, when the course of the disease is still alterable with a minimum of therapeutic intervention. However, today's diagnostic tools are only able to detect the presence of a disease after it has significantly progressed and has caused substantial destruction or dysfunction of tissue when the cost of treating the disease is much higher and the likelihood of curing the disease is much lower. Even when diseases are detected early or only suspected to be present, patients may suffer the risk of unnecessary biopsies or surgeries to determine the presence and stage of the disease, or to eradicate the suspected disease. Oncologists commonly rely on patients returning for follow-up examinations at regular intervals through several years to determine whether patients are expected to relapse with the disease while monitoring for potential side effects of anti-cancer therapies.

The modern approach for diagnosing most medical conditions is significant and based on visual scanning and visual imaging. In general, imaging is a single snapshot in time, offers limited information, and has significant limitations in terms of analysis and image content. Modern tools are simply unable to predict either the development or the course of a disease. Furthermore, diagnosis is further complicated by the fact that patients can present with a very wide range of

symptoms; many of these symptoms may apply to myriad diseases. As such, physicians must search for some method of guessing the disease and gather data from which a diagnosis can be generated. In this approach, both false positives and false negatives are recognized as equally dangerous. False negatives fail to alert the physician to a real disease, and false positives carry an expense in terms of patient suffering and patient risk, whether that risk is the result of the corrective action or some other factor. By aiming for inclusive and high-specificity screens, patient risk from surgery and therapy might still be reduced, but patient expense has been significantly increased.

7. Future Directions in Disease Detection and Treatment

Future Directions in Early Disease Detection and Treatment There is widespread awareness of the potential for systems biology to impact the treatment of human diseases through the development of novel diagnostic tests and therapeutic approaches. Tissue-specific transcriptomics, proteomics, and metabolomics will contribute to the identification and validation of blood protein, RNA, and metabolite markers for disease processes. However, several additional technologies and capabilities must be in place before these new types of markers take their place in the arsenal of tools employed for disease diagnosis and monitoring. Furthermore, comparing disease and normal states in model organisms or after the knockdown of candidate genes allows the characterization of more global and dynamic aspects of biomarker gene function that can often provide valuable insights for biomarker improvement. Data on positional candidates and models of disease stratification can be used to help narrow the list of serum biomarker successes for the development of confirmation assays. The relationships between the targets or target processes and the disease need to be better established, and various validation activities are needed to develop the clinical tests. Validation activities accumulate data on the relationship between serum marker levels and disease, determine the biological significance of the level of the marker and variations in its level, and establish the relationship of the serologic marker to alternative diagnostic tests. There are many clinical study settings used in biomarker validation to select the requirements, design, and statistical requirements that are needed to move serum marker candidates through the validation pipeline.

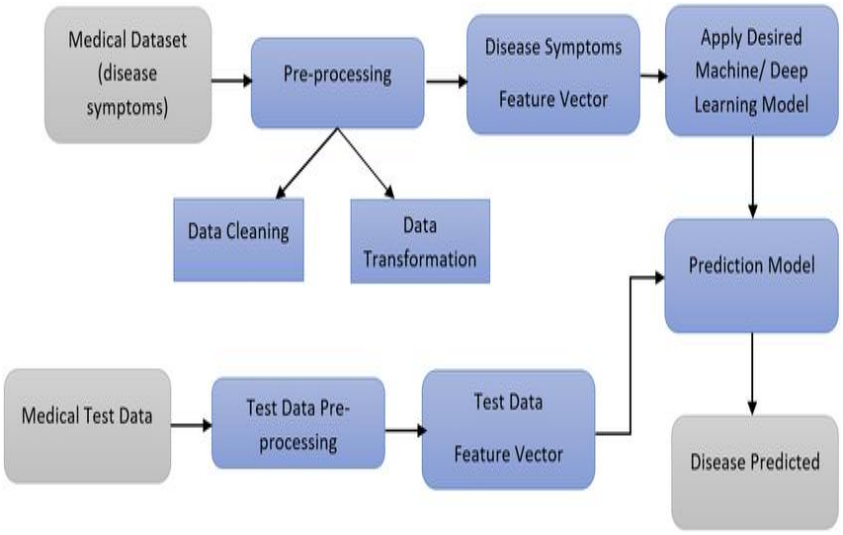

Fig 4 : Framework for disease detection system

7.1. Innovative Research Areas

Much hope has been placed in recent decades into the Human Genome Project and its notion of personalized medicine, where the patient's biology guides the medical care process. The project highlighted the importance of personal variations within the DNA blueprint that could explain in part why not all of the human population responds the same way to a particular drug, leading to differences in treatment efficacy and adverse reactions. Personalized medicine may provide the answer to why one in four asthma patients fails to respond to corticosteroid treatment, as well as being steered to more effective pharmacological inhibitors and anti-thrombotic agents with less access to unwanted side effects. In recent years, a wide range of innovative research areas has emerged that are implementing new-generation technologies for dealing with these complex, disease-associated individual characteristics. Precision screening of dysregulated pathways within cancer patients may become a potent engine for matching drugs to their pathology. Diverse screening for rare transcripts and the transcriptomes specific to stem cells provide a chemical harbinger of the subsequent cellular responses. The results from N-of-1 trials using monitoring techniques such as genomics or transcriptome profiling can lead to a predicted therapeutic outcome and the confidence to assess the value of a treatment.

7.2. Potential Collaborations

One route to success in improving the health of the global community will be through increased collaboration among the presenters at the workshop and others within their organizations with expertise in such disparate fields as software development, sensors, diagnostics, social science, behavioral science, interactions with and between physicians and their patients, environmental science, and pharmaceutical and molecular biology methods for treatment. In addition, workshops that would bring together providers of funds with those who could seek and implement solutions are needed. Areas of collaboration might include, for example, the development of a regulatory and business environment that encourages and expedites innovation combined with empirical studies on incentivizing the provision of new types of clinical services.
Donors could collaborate with those practicing primary health care in creating scalable, evidence-based approaches to early disease detection and treatment at a much lower cost to society than today's standard of care. There is a need to explore different strategies and ecological approaches to early case detection in various situations, possibly using low-cost real-time sensors. By addressing early case detection, it is possible to prevent hospitalizations, avoid consuming excess clinical resources surrounding hospitalization, reduce morbidity by earlier treatment of diseases and conditions, and possibly prevent some deaths. The biggest challenge will be how to do so in a sustainable way.

8. Patient Outcomes and Quality of Life

Patient outcomes and quality of life. The increasing supply of health information has given rise not only to patient empowerment but also to the focus on patient-centered outcomes in addressing chronic diseases. Conceptual frameworks have been proposed that document the potential range of health information that could be collected along the disease management pathway, with corresponding patient outcomes. Health system performance frameworks have been constructed to assess health surveillance, health indicators, and health disparities, not only in ways that were traditionally focused on extensive clinical measures but also using a multitude of generalized measures and stages of care, including the pre-diagnostic period. Consequently, patient outcomes in the diagnostic period could include absolute patient burden, misclassification costs, and the impact of safety and/or efficacy profiles of drugs as direct positive or negative outcomes on a patient’s utility score. Not only patient morbidity but patient function may likewise be incorporated as a key patient-centered outcome, which may include parity or equivalence of treatment between and among patients, with health disparities avoided.
As more diagnostic tests are deployed and available to a growing number of patients on a real-time basis, expanded analysis has surfaced of their value, particularly concerning desired patient outcomes and quality of life. A variety of innovative diagnostic tests that might go beyond the conventional binary test outcomes of 'normal' or 'abnormal' have been suggested, such as those that take into account cancer and heart disease susceptibility, the etiologies of chronic diseases, lifestyles, preventive treatment decisions, and other care management needs. Such innovative tests have been claimed to be 'clinically meaningful' in that they have the potential to enrich diagnostic care by providing end users with personalized information and guidance for care decisions, a compelling rationale that motivates their deployment and commercialization. However, the nature of the benefit of 'meaningful' tests has been based on their ability to provide better sensitivity and specificity values, which are necessary but not sufficient to classify the complexity of both population and individual outcomes. A more comprehensive understanding of outcomes is essential to inform and determine the optimal use of diagnostic tests from a clinical vantage point. The benefits of greater numbers of diagnostic testing options are, nevertheless, likely to play a critical role in the growth of interventional tests that can provide treatment guidance.

8.1. Measuring Impact

Numerous estimates of the economic impact of early disease detection have been performed. We summarize here three examples as an illustration of the potential economic impact. First, 125 million people are living with chronic HBsAg infection. Early detection through the utilization of new tests could allow such people to take antiviral medications that could reduce the risk of death, liver damage, cancer, and adverse effects on others due to the spread of the virus. Thus, the disease burden among patients would be reduced, which could lead to a substantial reduction in health-related costs, both for patients and for society. Second, in response to the new recommended guidelines on lipid test measurements by the age of 9-11 years, an economic evaluation that included newly identified children with familial hypercholesterolemia who might benefit from early treatment showed that active case-finding from universal screening was less costly than waiting for cases to present through clinical care.
Finally, there is the potential for integrating early detection of thyroid disease, celiac disease, and diabetes, where diagnosis might lead to changes in diet and medication that would enable savings on lost productivity as well as reductions in the utilization of health resources due to surgery. A further example is the potential positive economic impact of enabling early detection and management of sexually transmitted infections to reduce their spread and the impacts of drug resistance. The positive economic impact of new technologies for early detection would be large for the diagnostic tests that are being developed.

8.2. Improving Patient Engagement

One of the big promises of new digital health technologies is that they can greatly improve patient engagement. If this works out, there are many potential benefits. Patients who are better informed about the trajectory of their diseases and therapies may be more likely to make necessary lifestyle and behavior changes, from increased exercise to compliance with personalized medicine decisions. Patients who are more engaged may get diagnosed earlier, follow treatment regimens more closely, suffer fewer emergency events, and ultimately lose fewer healthy person-years. Here are some ways that digital health technologies are starting to improve patient engagement. These technologies are transforming patient education and adding some real glamour to the Internet of Things. The proliferation of different health and fitness apps provides an enormous variety for patients to learn about activity options, track their diseases, and link easily to electronic health records. Many apps and wearables provide real-time feedback, which is a powerful driver of behavior change. Patients are increasingly looking to digital health technologies to provide support and patient communities.

9. Economic Implications of Next-Generation Technologies

The adoption of next-generation technologies for early disease detection and intervention has the potential to substantially reduce health spending. By catching potentially costly diseases like cancer in their earliest stages before they have progressed, technologies have the potential to reduce use and spending on costly diagnostic and treatment procedures. With good evidence that catching diseases in their earliest stages can improve health, the widespread use of these methods could improve health outcomes. When technologies are available that can cut healthcare costs and have been shown to improve health, why don't payers adopt them more widely? One possible answer is that many payers do not capture the full benefits of investing in next-generation technologies because they are short-term payers. In the case of the Medicare program, beneficiaries receive coverage regardless of whether innovative methods are used, and they are subject to premiums and other cost-sharing and premium increases that will vary little based on the program's overall spending requirements. Faced with this cost-sharing structure, cost-conscious beneficiaries should demand more than traditional treatments, but this heightened consumer demand is missing from the private insurance sector. Lastly, next-generation technologies are used less because they tend to have an upfront cost that is significantly higher than traditional testing and diagnostic examination. Overall, the positive health gains that are associated with them and are estimated to be large are relevant in the context of cost control efforts.

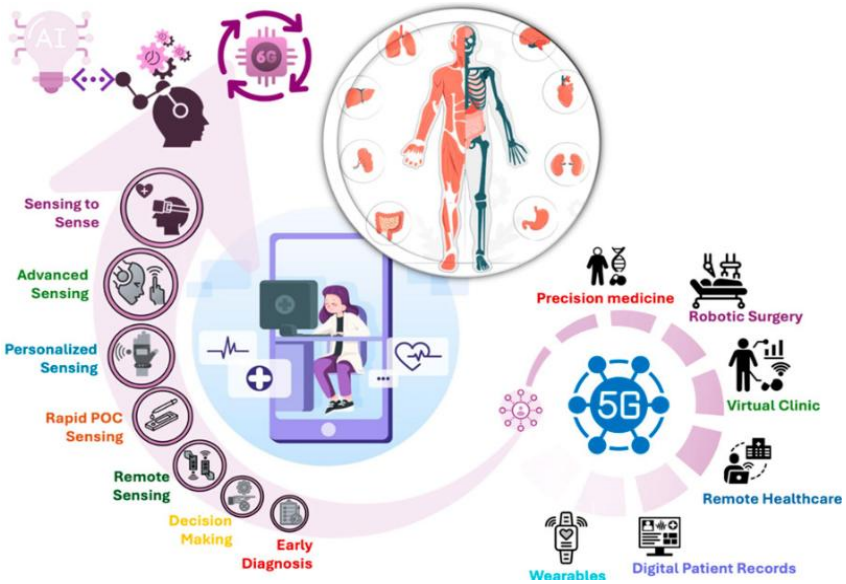

Fig 5 : Aspects of 6th generation sensing technology

9.1. Cost-Benefit Analysis

The emergence of newer medical technologies raises concerns about cost. It comes as a surprise to many people that the conventional tests most often used for early disease detection are not subject to formal scientific methods of choice in technology assessment. This chapter has used these methods to test the quality of these conventional tests and allows the reader to observe why conventional tests are used rather infrequently in practice. The new information that comes from this study is that conventional tests seem to add little to the accuracy of diagnosis from the findings of the history and physical examination and that their increase in direct costs to the healthcare system is truly substantial.

However, it would seem to be possible that conventional tests are in use because they increase the degree of certainty that exists in the recommendations made to patients with symptoms or diseases. These recommendations derive from the detection process that, in turn, follows from the decision analysis that occurs when a physician sees a patient with

symptoms or with a disease for which there is some attribute of the existing symptoms that suggests changes in currently recommended treatments. If patients and families are willing to pay for the extra information about the probability of disease or for the extra recommendations that come from the conventional tests, then the use of these tests is justified. The frequency with which these tests are requested by physicians and permitted by patients suggests that the implicit degree of certainty that is being purchased is in the eyes of the beholder.

Equation 3 : AI-Optimized Personalized Treatment Efficacy

$$E_t = \frac{\sum_{i=1}^{n} \delta_i R_i}{n}$$

where

E_t = Expected treatment efficacy score,

R_i = Patient response to treatment i,

δ_i = AI-determined weight of treatment i,

n = Number of treatment options evaluated.

9.2. Healthcare System Impact

Genomic advances may improve patient outcomes and alleviate healthcare system strains. Over the coming decades, technology will enable more accurate disease prediction and provide for immediate clinical intervention. For example, a simple yearly blood test may identify patients at elevated risk for cancer, thereby allowing for early intervention and successful treatment. With personalized, preventative medicine, patients would suffer less from chronic disease. With these interventions, the need for future treatments may be reduced. In the United States currently, late-stage cancer treatment accounts for significant healthcare system costs. With decreasing costs of next-generation sequencing, such treatments may become possible or even socially expected. Such improvements in treatment and quality of life are worthwhile and may serve to improve the healthcare system's financial health.

10. Global Perspectives on Disease Detection and Treatment

Disease is a major cause of poverty. The costs of major infectious diseases are huge, whether appraised in terms of human lives lost as a direct result of these infections or in terms of the associated damage to economies and people's livelihoods. Receiving attention are new diseases such as SARS and bird flu, but today tuberculosis is the single leading infectious killer of adults, and AIDS is the leading cause of death between the ages of 15 and 59 years. More people in the world live in fear of infectious diseases than sometimes progressive, gut-wrenching cancer or heart complaints. The segments from this summit set emerged from a Break-Out Group and encapsulated global perspectives on disease detection and treatment.

Every year, human disease causes suffering and claims lives in all regions of the globe, regardless of the level of economic development of nation-states. Threats to human and animal health come from an evolving mix of factors, including those originating from regional, national, and global efforts. Earlier in 2006, it was reported that drug-resistant TB has been steadily increasing over the last decade in the six countries containing more than half the world's cases and that nearly 50% of new cases occur in India, China, Indonesia, Nigeria, Bangladesh, the United Republic of Tanzania, South Africa, Ethiopia, the Russian Federation, and Pakistan. The annual incidence of new TB cases, accounting for a large and high-quality component of the global surveillance data, has changed only by a small percentage, and this can be described as a consistent level of improvement. Additionally, TB accounts for a third of all deaths among people with functioning immune systems, and it is the leading cause of death for people already infected with HIV. In 2004, 17.4 million people were living with the AIDS virus.

10.1. Comparative Analysis of Healthcare Systems

Healthcare is at a crossroads. Rising costs now each close to 20% of gross domestic product in the wealthiest countries, and up to 13% in some emerging countries. Given rapidly aging populations and the rising costs of treating chronic diseases and cancer, costs are projected to double by 2050. How can we reduce the burden of tomorrow's healthcare without compromising the quality of services? Digital technologies could be part of the answer, by contributing to early detection of disease and to less expensive treatments scientifically proven to be effective. However, for this potential to be realized, contributing technologies, healthcare services, regulatory frameworks, and reimbursement systems need to be radically transformed.

We provide a comparative analysis of healthcare and show that many countries are not ready for more cost-effective care, using the most compelling arguments to develop these technologies. Most healthcare systems are characterized by siloed approaches, high-acuity interventions that occur after disease development, which is impractical, and many types of knowledge that are suboptimally aggregated and applied. Moreover, nations do not use the same technologies and are not willing to pay for them. Improving the governance of healthcare represents major challenges on both sides of the Atlantic. We advocate that embedding these next-generation technologies for early detection of disease in future healthcare systems should become a core objective, which should be implemented well before 2030. More efficient healthcare systems are

part of the pursuit of high-quality jobs, income growth, and GDP growth, enhancing social welfare and societal well-being, enabling us to experience longer, healthier lives with a lower burden of disease, and creating trust in governments.

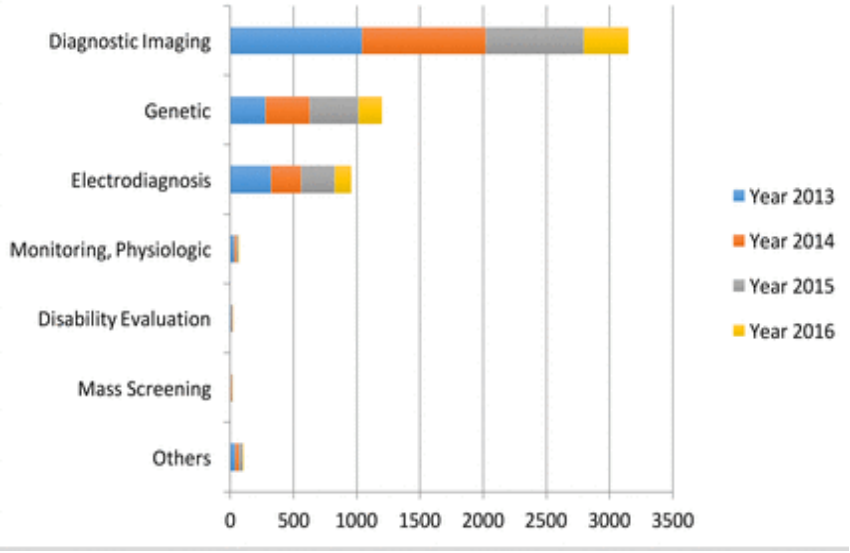

Fig 6 : Artificial intelligence in healthcare: past, present and future

10.2. International Collaborations

Scientific research at the interface of the life sciences and physical sciences is becoming an international enterprise, driven, in large part, by the internationalization of research, development, and commercialization. Important drivers of these phenomena include the reduction of trade barriers, the international demand for advanced technologies and innovation, and the widespread belief that collaborative research and the free exchange of scientific knowledge are a win-win proposition for all countries. As a result, there has been a significant increase in cross-border scientific and technical collaboration among researchers worldwide in areas ranging from basic to applied research in academic, government, and corporate sectors, driving the globalization of science. This trend suggests vast opportunities for international collaborations in various aspects of focused technology development, through a genuine partnership that leverages the complementary strengths, capabilities, and investment of each partner.

The virtues of international collaboration are clear. Key resources are required for successful research activities, including people, including internationally acclaimed scientists, postdoctoral researchers, and graduate and undergraduate students; research infrastructures and facilities; knowledge, know-how, scales-indifferent problem-solving skills, and algorithm development; new conceptual frameworks; and organizational skills in building productive international partnerships. In particular, the generation of critical mass when researchers work together can accelerate the exchange of advanced technology and provide more fertile conditions for innovation and scientific breakthroughs, leading to the acceleration of focused technology that addresses critical national needs. This result arises when international collaborations in research and technology development focus on problems of international interest, with a research process oriented towards design, testing, and performance under conditions of use, and when their outcomes are widely publicized. One area where such purposeful international collaborative research and technology development can be particularly effective is in focused technology leading to more rapid, earlier detection of life-threatening diseases and improved treatment outcomes. The world's population is aging rapidly, and with this demographic pendulum shift comes a greater occurrence of chronic and/or age-related diseases. Consequently, one of the primary aims of this new research model is earlier detection and treatment of disease to postpone the time of onset, diminish duration, or slow the progression of life-threatening diseases, thereby improving the quality and prognosis of life in the aging population. In turn, the benefit to humanity is a more productive and fulfilled life.

11. Conclusion

The early and sensitive detection of specific diseases relies on the distinct biomolecules that signal the presence of the disease in patient specimens. These biomarkers are represented by a variety of classes of analytes, including proteins; hormones, cholesterol, and metabolites monitored by a variety of assays; and a broad range of cancer and nucleic acid markers detected using PCR. However, traditional methods widely used for measuring these analytes are typically run in centralized facilities that restrict availability to patients living in remote areas or areas in lower-income countries, and they have lengthy durations for generating clinical results. Taking advantage of the powerful next-generation DNA sequencing technology, ultrasensitive nucleic acid detection for EBV has been achieved by briefly amplifying the target DNA sequences, and labeling the process with practices that eliminate the competition for hybridization space on DNA

probes used for detection. Strand displacement bypass of competition from contaminating nucleic acid sequences facilitates direct detection in patient samples without additional purification, and it provides molecular control that is expected to be widely applicable for achieving this level of detection sensitivity for other DNA sequences.
These modular and robust technologies further demonstrate how next-generation technologies for early disease detection can be developed by employing strategies that exploit, and overcome, known molecular control issues. Through these advances, we have created next-generation technologies for early detection of nucleic acid signatures in air and patient samples. These sample-to-gene technologies harness automated liquid handling and polymerase chain reactions that can be readily implemented by public health agencies for biothreat detection and emergency response to public health threats. We have also used modular and information-rich systems for RNA detection that, when combined with deep learning, can be easily designed for the detection of other threats, infections, or cancers. These early disease detection systems are equally useful for detecting pathogens responsible for hospital-acquired and opportunistic infections. Subclinical infections, if identified through routine testing, could be treated immediately, mitigating the risk of serious complications and limiting potential outbreaks. The early disease detection systems are also designed to meet the needs of lower-income countries, as the software will be open source and implemented on platforms with minimal IT requirements. However, more importantly, these shared sample-to-gene technologies will provide a cost-effective means for monitoring newly emerging viruses that pose serious global health threats. The full spectrum of these next-generation early disease detection systems will play a central role in the ongoing wildlife surveillance that is required for predicting novel viruses that can threaten us all.

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