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TECHNOLOGICAL TRENDS IN PATIENT-CENTRIC HEALTHCARE: A REVIEW

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ABSTRACT

The traditional healthcare system adheres to a fixed set of guidelines in treating patients. It follows a 'One Size Fits All' approach in clinical trials, drug development, dose implementation to treat a genetically diverse population who show varied drug responses. So, this traditional setup is not enough to support individualized treatment plans. Hence, the healthcare system has evolved into a patient-centric nature which considers individual variability to design an optimal treatment regimen. Two forms of patient-centric healthcare are precision and personalized medicine. Precision medicine involves the tailoring of treatments to an individual based on large population-level data derived from many areas including genomics, bioinformatics, proteomics, pharmacogenomics etc. In contrast, personalized medicine is heavily dependent on genomics and do not rely on large populational-level data. It is an approach where treatment is tailored based on the individual data collected through digital devices such as wearables, AI platforms etc. Both these forms require latest technologies to establish a formidable patient-centric healthcare system. Technological trends in personalized and precision medicine are discussed in this review. The scientific breakthroughs and technological innovations in personalized and precision medicine has led to more accurate, specific and robust health care that is customized for individual patient.

Keywords: Patient-Centric Healthcare, Personalized Medicine, Precision Medicine, Technological Trends.

I. INTRODUCTION

The healthcare system in the world has undergone significant changes over the years. The traditional healthcare system is a disease-oriented care system where only the physician's perspective complies excluding that of the patient's. The physicians adhere to a fixed set of guidelines when treating a patient for a particular disease (Sacristan.,2013). In traditional clinical trials, the drugs and dosages are implemented following a 'one size fits all' strategy. This strategy does not consider genetic variability, ethnicity, epigenetic factors and disease stage at the individual level which are main factors that influences the variability in response to drugs among individuals with the same disease. As a result, most of the commercially available drugs nowadays work only for about one-third of the patients. The rest are subjected to various inconveniences, side-effects and sometimes to mortality instead of any clinical benefit.

In order to overcome these constraints and drawbacks of the traditional healthcare system, the healthcare professionals, scientists and engineers have now paved their way towards a healthcare system that is patient-centric. Patient-centric healthcare is developed around the patient. Unlike traditional healthcare, patient-centric healthcare follows flexible guidelines by allowing the patient to voice their concerns, requirements and make informed decisions. It allows the patient to understand their health condition and to choose their preferred treatment option. Furthermore, it considers the opinions and requirements of the patient's family members as well. The patient-centric healthcare approach employs many data-driven strategies, tools, equipment and various biometric devices. Several studies have reported that patient-centric healthcare has increased overall patient satisfaction. Two forms in which patient-centric healthcare can be established are through precision medicine and personalized medicine.

Precision medicine involves customizing treatment to an individual based on the individual's characteristics. It doesn't emphasize the idea that unique treatments are designed for each individual. Instead, in precision medicine, large amounts of population-level data are taken into consideration to ascertain the ideal treatment for an individual. In precision medicine, to determine treatment for particular disease individuals are classified into subpopulations based on genetics, responsiveness to treatment, demographics, prognosis etc. Accordingly, the most appropriate treatment for a patient is determined based on the subpopulation to which the individual falls into. Therefore, precision medicine deviates from the traditional 'one size fits all' strategy, by giving the most appropriate drug only to the individual who benefits rather than prescribing the same drug to all who have the particular disease. Thus, the side-effects, inefficiencies and inconveniences caused following a 'one size fits all' strategy is eliminated. Precision medicine integrates lifestyle data with data from many areas such as

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genomics, bioinformatics, proteomics, epigenomics and pharmacogenomics (Ginsburg and Philips.,2018). Personalized medicine is based on genomics and incorporates an individual's genetic make-up and preferences in determining treatments (Ginsburg and Philips.,2018). Unlike precision medicine, the personalized medicine approach is not based on large population data and analytics. Instead in personalized medicine own data of an individual is collected through various technological devices to ascertain the treatment for an individual (Ho et al.,2020).

Both these forms are transformational tools in healthcare that is gaining momentum. Both these forms employ the newest technologies to realize an effective patient-centric healthcare. This review aims to discuss the latest technological trends in precision and personalized medicine.

II. LATEST TECHNOLOGICAL TRENDS IN PRECISION MEDICINE

Some latest technological trends in precision medicine are discussed below.

Droplet digital PCR (ddPCR)

Droplet digital PCR is a type of digital PCR which is an alternative approach to the traditional qPCR. Figure 1 illustrates the workflow of ddPCR. Initially, the PCR master mix consisting of primers, dNTPs and probes are prepared (Fig 1 A). Next, the master-mix is sent through an oil flow which results in the generation of droplets (Fig 1B). The droplets formed will be collected into PCR tubes (Fig 1C) and placed in a thermocycler for amplification (Fig 1D). Upon amplification, a droplet reader analyses the results (Fig 1E). The droplets containing only the target sequence emits a fluorescent signal. By counting such positive emissions (Fig 1F) the absolute copy number of the sequence of interest in the original sample is calculated (Tan et al.,2021).

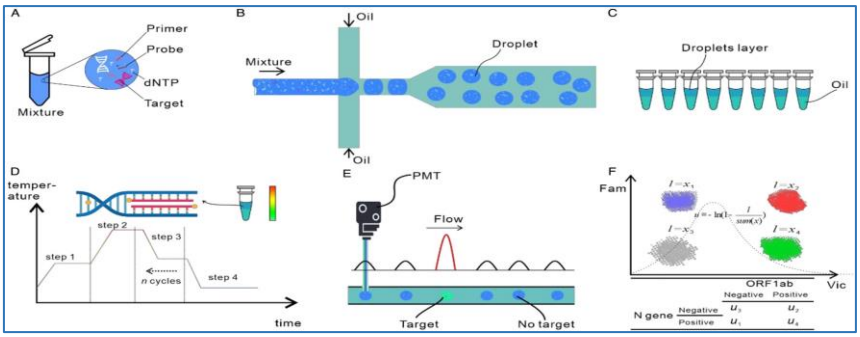

Figure 1: Workflow of ddPCR (Tan et al., 2021)

Compared to conventional qPCR, ddPCR is advantageous due to its higher precision, sensitivity, stability and absolute quantification (Tan et al.,2021). Recently several studies have been conducted to compare the diagnostic accuracy of qPCR and ddPCR in COVID 19 testing. One such study had tested 103 individuals showing SARS COV 2 suspected symptoms and 75 close contact individuals using both conventional qPCR and ddPCR. Fig 2 illustrates the study results. Accordingly, among the 103 suspects, 49% have been recorded positive using qPCR (Fig 2A) while 87% have been reported as positive using ddPCR (Fig 2B). Moreover, among the 75 close contacts, 14% have been reported as positive following qPCR while 35% have been reported positive using ddPCR (Dong et al.,2021). These results emphasize the increased accuracy and reduced false-positive result generation of ddPCR compared to qPCR.

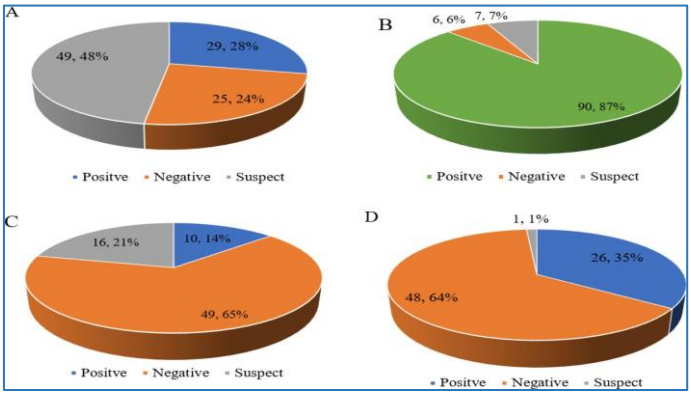

Figure 2: qPCR and ddPCR results of 103 symptomatic patients and 75 close contacts (Dong et al.,2021)

Another similar study has been conducted by Suo et al.,2020 using 57 pharyngeal swab samples collected from 57 individuals who were initially tested negative for COVID 19 using real-time PCR (RT-PCR) but later developed COVID 19 symptoms. The samples were tested again using digital PCR (dPCR). The study results showed that dPCR has a lower limit of detection 500 times lower than that of RT-PCR. Moreover, the study concludes that ddPCR has a superior ability to reduce false negatives compared to RT-PCR. Therefore, these studies validate the superiority of ddPCR compared to qPCR and RT-PCR and its suitability to be used in the clinical diagnosis of SARS COV 2.

Digital Biomarkers

Biomarkers are a fundamental part of clinical practice and medical research. Biomarkers are biological molecules that indicate an underlying disease condition. With the advent of digital devices in healthcare, digital biomarkers have been proposed as a new diagnostic tool. Digital biomarkers are objective, behavioral, physiological and quantifiable data that can be collected through various digital devices. Digital biomarkers have replaced the limitations of traditional biomarkers. Digital biomarkers are less invasive compared to traditional biomarkers. They provide both quantitative and qualitative measurements continuously for a low cost. Moreover, contrary to traditional biomarkers which are only confined to biological specimens, in digital biomarkers the behavioral data are also collected. Behavioral data hold a diagnostic value as well (Babrak et al.,2019).

Presently, digital biomarkers are used across many medical arenas. In neurogenerative diseases like Parkinson's and Alzheimer's disease, digital biomarkers are used to access the treatment outcome in the early stages of the disease (Babrak et al.,2019). They are also used to monitor diseases associated with the Central Nervous System (CNS). The capability of these markers to measure symptoms that have been untraceable with traditional markers facilitate monitoring such CNS related diseases. One of the most commonly used applications of digital markers is in the treatment of T2DM. Various apps and devices integrated with digital markers have now been introduced to monitor the dose of Insulin used for the treatment in T2DM (Seyhan and Carini.,2019).

CRISPR Cas 9

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. Cas 9 is the protein associated with CRISPR. CRISPR Cas 9 is a powerful gene-editing tool utilized in precision medicine. The three main components of this gene-editing tool are the Guide RNA, Cas 9 protein and the desired DNA piece. Guide RNA is engineered in the lab to match the mutant DNA sequence. Cas 9 protein acts like a scissor to cut the double-stranded DNA at the mutant position. The desired DNA is the healthy DNA which replaces the cleaved region of the mutant DNA.

Figure 3 illustrates the mechanism of CRISPR Cas 9. Initially, the guide RNA and the Cas 9 protein are administrated into the patient via injection. Next, the guide RNA will identify the mutant DNA. Subsequently, the Cas 9 protein will cleave the double-stranded DNA at the point of mutation. Next, the desired DNA molecule will be inserted to replace the cleaved mutant DNA region.

Applications of CRISPR Cas 9 spans across many industries. In precision medicine, CRISPR holds enormous therapeutic potential. One disease treated using CRISPR Cas 9 is Sickle Cell Anemia which is caused by a single gene mutation in the Beta globulin gene. In this approach blood cells from sickle cell anemia patient are removed and edited using CRISPR Cas 9 to replace the mutant Beta globulin gene with a healthy gene. Studies have shown that when such edited blood cells were re-administrated into patient's body, the symptoms associated with the disease reduced notably. Most of the patients who have received successful treatments using CRISPR Cas 9 have shown significant improvements to the extent that they no longer need any blood transfusions. This genetic tool can be applied to both monogenic and polygenic diseases. Currently, clinical trials based on CRISPR Cas 9 are being conducted on a wide spectrum of diseases such as multiple myeloma, cancer and diabetes to name a few.

Two distinct gene-editing tools which existed before the introduction of CRISPR Cas 9 are Zinc Finger Nucleases (ZFNs) and Transcription Activator Like Effector Nucleases (TALENs). Studies have shown that CRISPR Cas 9 offers distinct advantages over ZFNs and TALENs. The use of ZFNs and TALENs demands extensive skills to construct and handle and are expensive. In contrast, CRISPR Cas 9 is highly efficient, flexible and is inexpensive (Bak et al.,2017).

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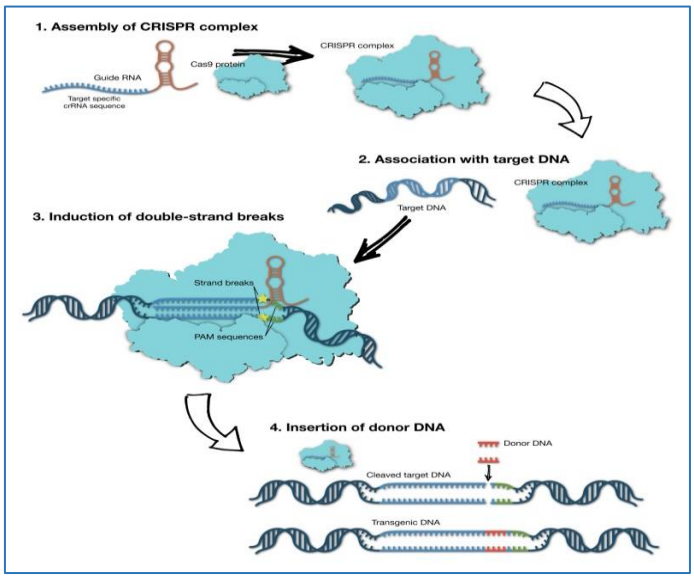

Figure 3: Mechanism of CRISPR Cas 9 (Markossian et al.,2004)

Apart from the aforementioned technological trends, few other technological trends in precision medicine are Single Molecular Array Technology (SiMoA) which is used in PSA detection in prostate cancer, Fiber microarrays, Microfluid technologies which help to detect minute levels of biomarkers in small fluid volumes and single-cell analysis approaches such as Multiplex imaging and Raman micro spectroscopy (Ho et al.,2019).

III. LATEST TECHNOLOGICAL TRENDS IN PERSONALIZED MEDICINE

Some latest technological trends in personalized medicine are discussed below.

CURATE.AI

In traditional healthcare, the drug dose is determined based on Maximum Tolerant Dose (MTD) and typically a fixed dose is administrated. But the dosing requirements change from person to person over the period of treatment. Therefore, the dose needed by a patient might be of a lesser value than the MLD. Thus, in a traditional healthcare setting the exact dosage demanded by the patient's body is not administrated. This limitation in traditional medicine has been overcome by Artificial Intelligence (AI) platforms and devices. These devices are capable of determining the exact dose that should be given to gain successful patient outcomes. These platforms work for both single drug doses as well as for combinational therapies.

CURATE.AI is the latest AI-driven platform that predicts the ideal dose of a drug or a combination of drugs that should be administrated to a patient based on a personalized profile of individual data collected from a patient (Blasiak et al.,2020). CURATE.AI technology was used in a recent study to determine the optimized dose of Enzalutamide and ZEN-3694 to administer to a prostate cancer patient. Initially, the patient was treated by the dose prescribed by the physician adhering to standard healthcare guidelines. The reduction of the Prostate Specific Antigen (PSA) until elimination is the targeted outcome of the combinational therapy. For the initial 6 months, the patient was treated with MLD for both drugs as prescribed by the physician. Accordingly, 80mg of Enzalutamide and 36mg of ZEN-3694 were administrated for the first 6 months of the treatment period. Afterwards, the CURATE.AI platform was used to predict the suitable dose for the treatment. Using the individual data collected from the initial 6 months, a personalized profile was created in CURATE.AI to determine the ideal dosage for future treatment. According to the personalized profile, CURATE.AI predicted to reduce the ZEN-3694 dose to 24mg from 36mg while 80mg of Enzalutamide was continued to be given as the physician recommended. The predicted PSA level of CURATE.AI for this dose combination was 0.65ng/ml. When the CURATE.AI predicted dose combination was administrated to the patient for 10 weeks, the PSA level reduced to 0.68ng/ml from 0.91ng/ml. Therefore, it is seen that the reduced PSA level was closer to CURATE.AI predicted PSA level. Afterwards, the patient was administrated 12 mg of ZEN-3694 and 80mg of Enzalutamide as recommended by the physician. This new dose combination resulted in an increase in PSA level to 1.60ng/ml. This value was approximately equal to the CURATE.AI predicted PSA level for the above physician recommended dose combination. Next, when the ZEN-3694 dose was again increased back to 24mg, the PSA level reduced to less than 1ng/ml. Afterwards, the patient was treated with the values predicted by CURATE.AI

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for the remaining period of treatment. Figure 4 shows the change of PSA levels at the physician recommended dose and CURATE.AI predicted dose during the course of treatment. Accordingly, it can be seen that the PSA levels reached a higher value when treated using physician recommended dose (following traditional treatment strategy). In contrast PSA level decreased significantly at CURATE.AI predicted dose (Pantuck et al.,2018). Therefore, these results emphasize the potential and power of CURATE.AI to predict the right dose for the right patient at the right time to achieve maximum therapeutic benefit. Up to date CURATE.AI has been used in single and combinational drug optimizations in treating several diseases such as Multiple Myeloma, Acute Lymphoblastic Leukemia, Immunosuppression etc.

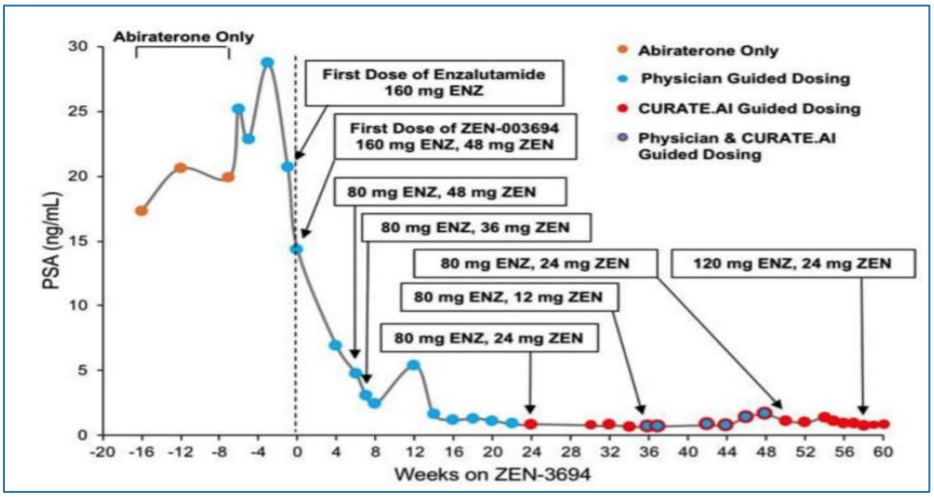

Figure 4: The PSA level at the physician recommended dose and at CURATE.AI predicted dose (Pantuck et al.,2018)

Glucose monitoring contact lenses

Diabetes is a metabolic disorder with more than 400 million affected patients worldwide. The conventional methods of blood glucose level monitoring are invasive as it requires pricking the finger to obtain blood. Even most of the wearable devices which have been introduced to monitor glucose level in the body are risky to use as they require implantation of various electronic chips and power sources which can damage the body. A recent technological invention introduced to conquer these issues is 'Glucose monitoring contact lenses made of non-enzymic Phenylboronic acid (PBA) based Hydroxyethyl Methacrylate (HEMA). This contact lens can monitor glucose level in real-time. The contact lens monitors the glucose level from tears. The lens increases its thickness linearly to the glucose level. The contact lens utilizes a smartphone that captures the light emitted from the LED installed in the lens to analyze the thickness of the lens. Next based on the thickness of the lens the glucose level of the patient will be determined (Fig 5). The key advantages of this lens are its non-invasiveness, reversible glucose-sensing ability, portability and flexibility. Additionally, the absence of any enzymes and embedded power circuits in the lens makes it a safe wearable device to monitor blood glucose level in real time (Lin et al.,2018).

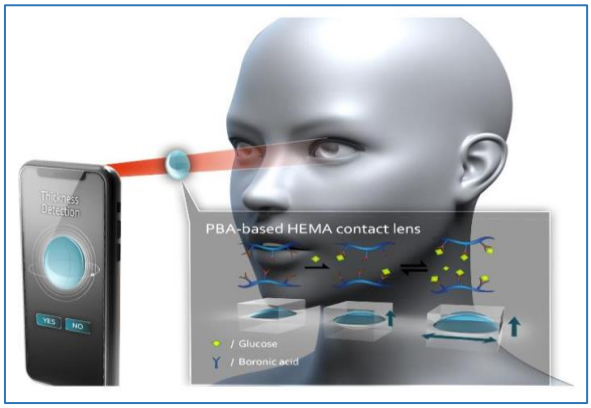

Figure 5: Capturing of the light emitted by the LED in the lens by the smartphone to determine the thickness of the lens (Lin et al.,2018)

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Textile based ECG

In conventional ECG, the electrocardiogram is obtained by mounting Ag/AgCl electrodes at multiple locations in the body. These electrodes use a gel to minimize the contact impedance between the skin and the electrodes. Hence the electrodes used in a traditional ECG setting is referred to as 'wet electrodes'. There are many issues reported regarding the use of conventional ECG such as allergic reactions and skin irritations caused due to the long-term use of Ag/AgCl electrodes. Moreover, due to the drying of the gel, the performance of the electrodes can diminish over time. To overcome these limitations observed in a conventional ECG setting, new devices consisting of dry electrodes have now been introduced. One such type of device is 'textile-based ECG'. Textiles are ideal to develop dry electrodes due to many reasons. Textiles are flexible, comfortable to wear. In addition, electronic components can be easily integrated into textiles. Since textiles are worn frequently, the use of conductive textiles allows monitoring the cardiac activity remotely. Conductive textiles used to make textile-based ECG have high durability, high electrical conductivity and are reusable (Yapici and Alkhidir.,2017).

One such textile-based ECG has been introduced recently in which graphene derived cloth embedded with ECG sensors are incorporated. Figure 6 illustrates a graphical representation of the comparison of ECG obtained from conventional Ag/AgCl electrodes and the said graphene derived textile-based electrodes. Accordingly, it can be seen that the textile-based ECG largely correlates with the conventional Ag/AgCl electrode derived ECG. Hence the use of such textile-derived ECG can replace the conventional ECG and the limitations associated with it (Yapici and Alkhidir.,2017).

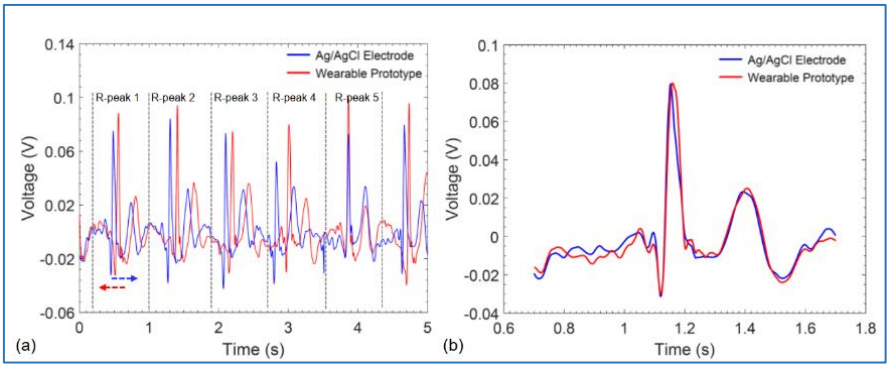

Figure 6: Comparison of the ECG from traditional Ag/AgCl electrodes and graphene derived textile-based electrodes (Yapici and Alkhidir.,2017)

Apart from the aforementioned technological trends in personalized medicine, some other technological trends in personalized medicine are various organ on chip platforms, microfluid-embedded wristbands for pulse measurements, FDA approved mobile apps for Alzheimer's diseases, personalized cell therapies such as mitochondrial replacement therapy and CART-T cell immunotherapy and use of nano diamonds in drug delivery (Ho et al.,2019).

IV. CONCLUSION

In a conventional healthcare model, drug development, clinical trials and patient care involves administration of same drug regimen to genetically diverse population. But with the technology advancements in both precision and personalized medicine there is a paradigm shift to the value-based patient-centric healthcare. This has surpassed the traditional failing strategy by efficiently delivering tailored treatments to the patients. In conjunction with its growing significance, many pharmaceutical companies and clinical research organizations (CROs) are embracing patient-centricity in every phase of drug discovery, drug development and clinical trials. This new healthcare model is all about empowering patients and to provide high-quality individualized patient experience. Overall, precision and personalized medicine fits hand in glove with patient-centric healthcare.

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