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Article

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Real-Time Monitoring of Bodily Fluids Using a Novel Electromagnetic Wave Sensor

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Abstract—**The use of a novel low power electromagnetic sensor for real-time detection of lactate in cerebrospinal fluid (CSF) is investigated. CSF holds key indicators relating to a patient's future health. A multipurpose sensor platform is currently being developed with the capability to detect the concentration of materials in volumes ≤1 ml. This paper presents results from a microwave cavity resonator designed and created for this purpose, using varying concentrations of lactate in water. The work demonstrates the feasibility of monitoring bodily fluids in real-time. Such advancements are essential for improved and cost-effective delivery of healthcare services to patients.**

Keywords— **Electromagnetic waves, real-time sensing, lactate, cerebrospinal fluid, hospital setting.**

I. INTRODUCTION

Cerebrospinal fluid (CSF) is a clear, colourless bodily fluid produced in the brain which occupies the subarachnoid space and the ventricular system around and inside the brain and spinal cord. CSF is produced at a rate of 0.2-0.7 ml/min, or approximately 600-700 ml/day, and provides buoyancy for the brain, protecting it from injury in the event of jolting. In addition it plays an important role in the homeostasis and metabolism of the central nervous system (CNS) since it rinses metabolic waste through the blood brain barrier and back into the bloodstream.

Patients who are undergoing surgical or endovascular aneurysm repair (EVAR) of acute and chronic thoraco-abdominal aortic disease [1, 2] have an inherent risk of paraplegia. This is caused by restriction of the spinal cord blood flow and lack of oxygen during the procedures, typically referred to as spinal cord ischemia [3]. Despite the use of various strategies for the prevention of spinal cord ischemia, paraplegia and paraparesis continue to occur after thoracoabdominal aortic aneurysm repair. CSF drainage is often used as an adjunct for spinal cord protection [4]. This procedure reduces the pressure upon the spinal cord and thus the risk of paraplegia is decreased. At the moment any CSF collected would normally be discarded as biological waste.

CSF analysis currently comprises a group of laboratory tests that measure antibodies and DNA of common viruses, bacteria, cell count, chloride, cryptococcal antigen, glucose, glutamine, lactate dehydrogenase, oligoclonal banding to look for specific proteins, total protein and whether there are cancerous cells present [5]. Analysis of CSF biomarkers is an integral part of neurology and the aforementioned techniques have been used to diagnose inflammatory and infectious CNS disorders in adults and children for decades. During recent years, however, numerous biomarkers for neuronal and astroglial injury, as well as disease-specific protein inclusions, have been developed for neurodegenerative disorders in adults [6].

With the development of CSF biomarkers that reflect pathological events within CNS, important clinical diagnostic tools are becoming available [7]. Biomarkers for specific pathogenetic processes would also be valuable tools both to study disease pathogenesis directly in patients and to identify and monitor the effect of novel treatment strategies.

Advancing from the current laboratory based analysis techniques to online methods could provide the basis for improved patients' treatment regimes, better quality of care, and enhanced resource efficiency within hospitals.

Therefore, researchers at Liverpool Heart and Chest Hospital (LHCH) and Liverpool John Moores

University (LJMU) in the UK believe that real-time CSF analysis could harbour important information which may indicate sub-clinical cord ischemia and compromise. This is supported by work conducted by Drenger *et al* [8], who observed that lactate concentration in CSF increased with the onset of patient paraplegia. Three cerebral biochemical markers, adenylate kinase (AK), neuron-specific enolase (NSE) and protein S-100 can be determined in the CSF after coronary artery bypass grafting [1]. Moreover, protein S-100B, neuron-specific enolase, myelin basic protein and glial fibrillary acidic protein in CSF and blood of patients with an acute or chronic progressive neurological disorder with brain damage are important indicators for medical practitioners. Particularly in disorders with acute brain damage, determination of the aforementioned proteins in CSF and blood can be helpful to establish structural and/or functional brain damage to determine severity and prognosis of the disease process and to monitor treatment effects [9].

The normal physiological level of lactate in blood or CSF is approximately 1 mmol; in pathology it may rise to around 10-15 mmol, or in exercise even higher [10]. CSF analysis would be most practical immediately after it has been drained from a patient, allowing a surgeon to take immediate actions. In many cases this could remove the need for subsequent surgical procedures, thus improving the efficiency of hospital resources and arguably improving patient care.

Notably, biomarkers of α-synuclein pathology and other pathologies associated with Parkinson's disease (PD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) are currently under intense investigation [7].

Moreover, transmeningeal pharmacotherapy for cerebral cortical disorders requires drug delivery through the subdural/subarachnoid space, ideally with a feedback controlled mechanism. A device suitable for this function has been recently developed [11], which is equipped with fluid-exchange ports for both drug delivery and local CSF removal.

Through the use of electromagnetic sensing, in particular microwave techniques, it is proposed that the key requirement of CSF analysis, namely timeliness and precision, could be met. Microwave sensors provide a rapid non-invasive method of material analysis, which is robust and has huge potential for a wide range of biomedical applications. In addition, microwave analysis promises the potential for inexpensive equipment, therefore increasing the attractiveness of any device placed into operating theatres, particularly considering the strained nature of many hospital budgets. Microwave spectroscopy has seen use for a variety of purposes, including monitoring of water quality [12], filter monitoring [13] and also for use monitoring oil, gas and water concentrations [14]. It is thought that the use of microwave spectroscopy, as in the previously mentioned applications, will provide affordable and rapid diagnostics for the healthcare scenario described in this work. Notably, the technique is also non-ionising, utilising (at most) one-tenth the power required for transmission by a typical modern day mobile phone; it is therefore thought safe for use during surgical procedures. Medical professionals would find the prospect of online detection of such analytes exciting, as current practice is time consuming and leads to multiple invasive procedures.

This work is being carried out as part of a collaborative venture between LJMU and LHCH. As a precursor to testing on human samples this work considers the microwave response of a bespoke sensor system when varying the level of lactate in water.

II. THEORY OF OPERATION

A. *Electromagnetic Waves*

Electromagnetic (EM) waves are waves of energy that travel through a vacuum at the speed of light, approximately c=3×10^8 m/s. EM waves consist of two primary components: an electric (E) field and a magnetic (H) field [15]. The electric field and magnetic field oscillate in phase perpendicular to each other and perpendicular to the direction of energy propagation. EM waves can be visualised as a sinusoidal wave.

EM waves can be used to analyse lactate due to their material specific interaction properties. This technique has a number of advantages, making it suitable for biomedical applications. Analysis using microwaves is non-ionising with a low power output of approximately 1mW (0 dBm). They have a good penetration depth and associated equipment can be portable for use at the bedside. The multi-parameter nature of wide band microwave analysis can provide unique signal spectrum signatures. Typically these would be in the form of a reflected signal S_{11} or/and a transmitted signal $|S_{21}|$, which are influenced by parameters such as conductivity and permittivity [16]. Conductivity is a measure of a material's ability to conduct an electric current. Permittivity relates to a material's ability to transmit an electric field and is a complex value which varies with frequency, and accounts for the energy stored by a material (ε') as well as any losses of energy (ε'') which might occur.

B. *Microwave Cavity*

Microwave cavities are widely used for characterising the properties of materials [17-19] including characterisation of stimulation-mediated cell signaling responses [20]. A cavity is usually made by shorting the two ends of a waveguide segment. The electrical power is transported through the waveguide by means of electromagnetic waves, which can take several different forms (modes), depending on the frequency, the dimensions and the material properties inside.

The different configurations of electric and magnetic field which can exist in a waveguide are known as transverse electromagnetic (TEM) modes. The transverse electric (TE) and transverse magnetic (TM) are the two types of modes which usually exist in the waveguide.

A cavity will resonate when it is excited at an appropriate frequency. In the case of this work, the cavity is excited by a circular patch antenna placed inside it. The resonant modes occur when the electric and magnetic fields form standing waves, which depend on the internal dimensions of the cavity and the dielectric properties of the lactate in water used for this work. Therefore, its relative permittivity (ε_r) will change. The resonant frequency for TE_{nml} and TM_{nml} modes [21] in a circular waveguide can be calculated using (1):

$$f_{nml} = \frac{c}{2\pi\sqrt{\mu_r \varepsilon_r}} \sqrt{\left[\left(\frac{p_{nm}}{a} \right)^2 + \left(\frac{l\pi}{d} \right)^2 \right]} \qquad (1)$$

where: c is the speed of light

μ_r is of the relative permeability

ε_r is the relative permittivity

p_{nm} is the value of the Bessel function for the TE or TM modes of a circular waveguide

a is the radius of the cavity

d is the height of the cavity.

Therefore, all TE and TM modes are dependent on $\sqrt{\varepsilon_r}$, so when the waveguide is excited by a range of frequencies, the magnitude signal spectrum is captured and resonant peaks corresponding to these particular modes will shift to lower frequencies as the permittivity is increased.

C. *High Frequency Structure Simulator (HFSS)*

Ansys High Frequency Structure Simulator (HFSS) is a 3D full wave EM field simulation package which can be used to design microwave structures [22]. HFSS allows complex geometries to be created, which is particularly useful in these sorts of applications. The outputs of HFSS include S-parameters, Full-Wave SPICE extraction and 3D electromagnetic field simulation [23].

The TE and TM modes for the circular cavity used for this work have been simulated using HFSS. Fig. 1 shows some of the configurations for the TM modes in a cylindrical waveguide, with the red colour representing the maximum field intensity and the blue colour representing the minimum.

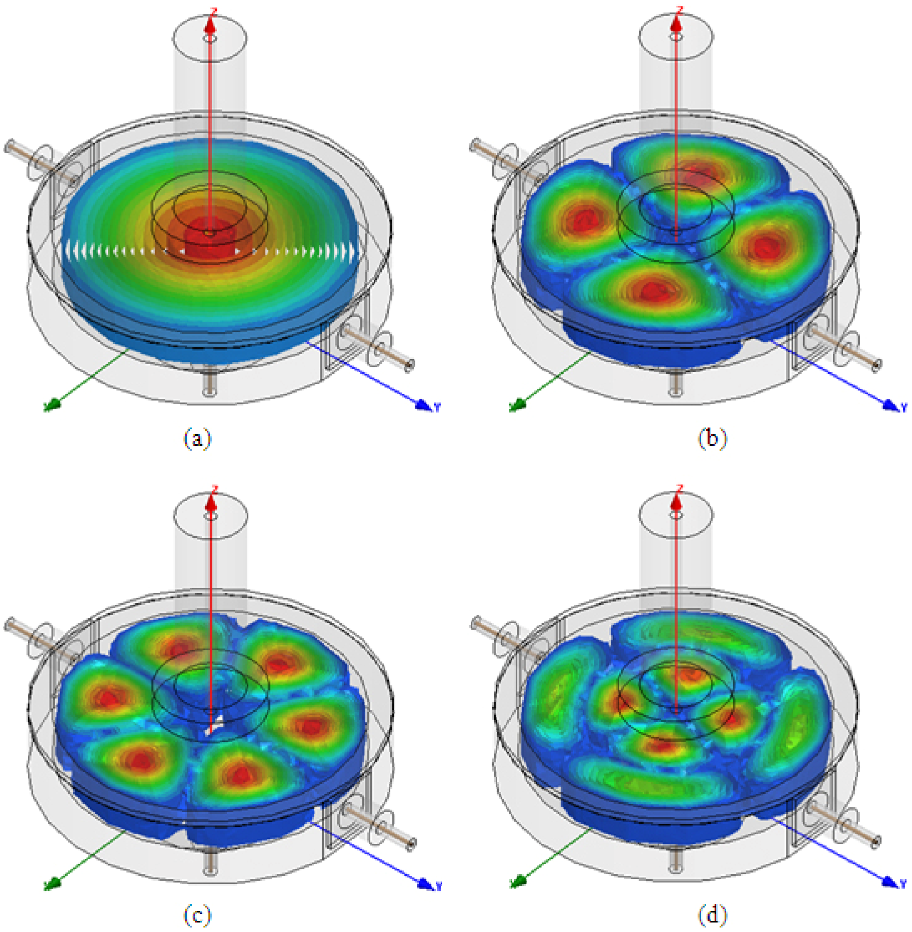

Fig. 1 Modes in a cylindrical cavity: (a) TM_{010}, (b) TM_{210}, (c) TM_{310}, (d) TM_{220}.

III. RESEARCH METHOD

A. *Preparation of Lactic Acid*

Serial dilutions of L(+)-lactic acid were prepared to cover a range from low, physiological to supraphysiological levels (0-64 mmol/l) in distilled water. Sample concentrations were as follows: 0 mmol (water), 0.5 mmol, 2 mmol, 4 mmol, 8 mmol, 16 mmol, 32 mmol and 64 mmol. All of the samples were stored in a refrigerated unit at temperatures in the region of 5 °C. Samples were removed only to be exposed to the cavity for a short period of time, after which they were returned to the refrigerator.

The evaluation of the proposed novel microwave technology for real-time bodily fluid analysis was performed on a lactate, since it is a marker of ischemia in CSF. There are two reasons for this: (1) lactate is relatively inexpensive and (2) CSF provides a relatively simple background which can be synthesised in-vitro. A small sample volume of 0.5 ml, which is enough to saturate the internal cavity volume, is placed in a glass tube (0.5 mm diameter and 180 mm in length).

B. *Acquisition Measurement*

Measurement was performed using a ZVL-6 Rohde and Schwarz Vector Network Analyser (VNA). The instrument can generate frequencies up to 6 GHz. Measurement was made via the cavity discussed in Section II. Fig. 2 shows the patch antenna placed in the bottom of the cavity. The bottom port, which was soldered inside the cavity to the patch antenna, was attached to the VNA output port. This means that it was only possible to measure the S_{11} parameter. Temperature variations were minimised through the use of an environmental chamber. The results have been found to be repeatable through numerous spectra acquisitions for each sample over the course of a week.

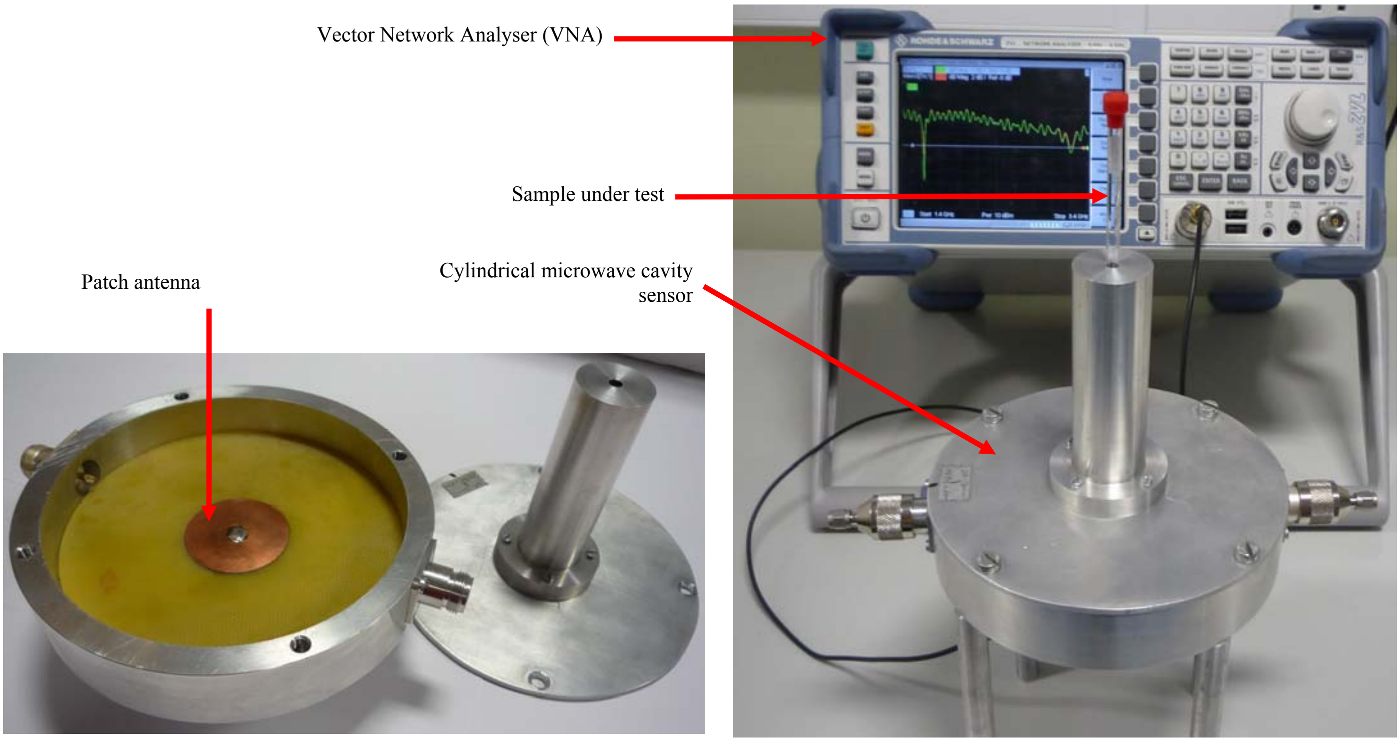

Fig. 2 Experimental setup for lactate measurement, with cavity shown (left) dismantled and (right) in use for analysis.

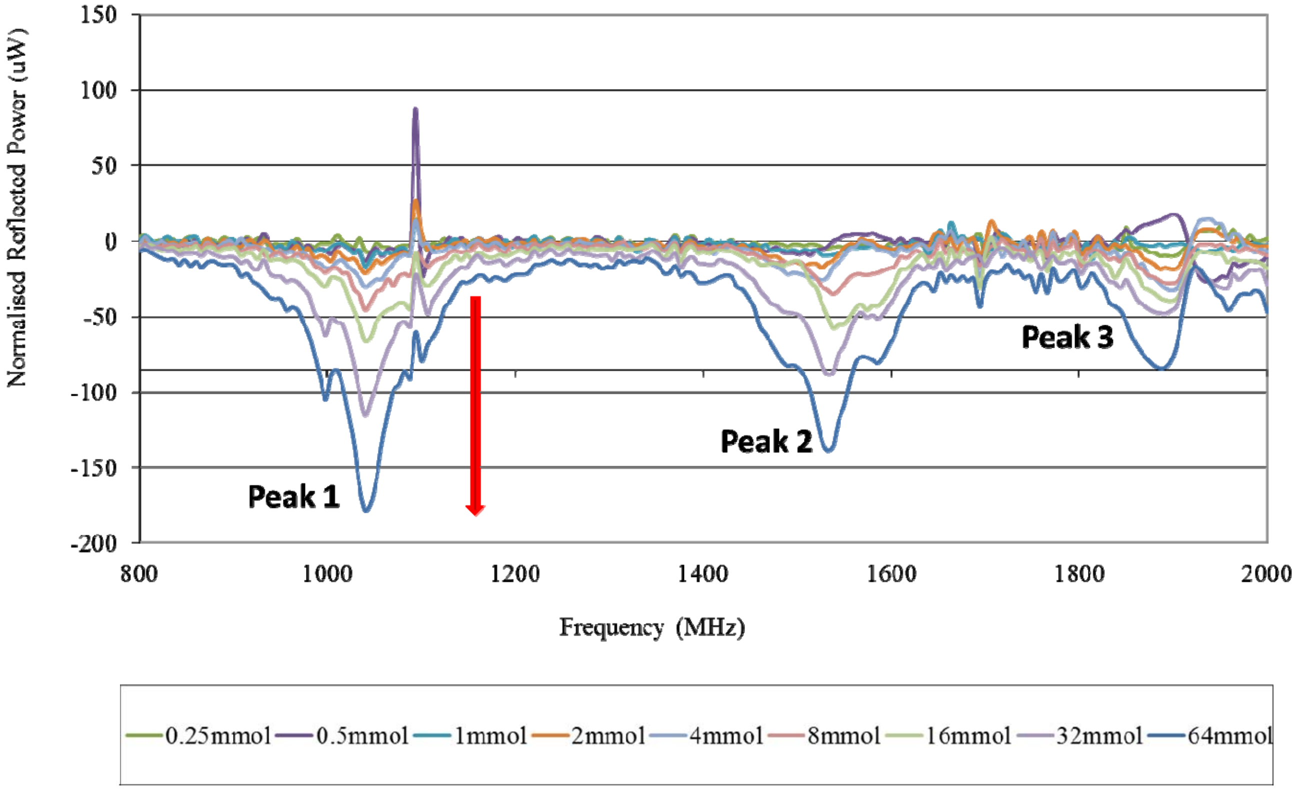

Fig. 3 Experimental spectra from 800-2000 MHz, shown as a normalised reflected power (µW). The direction of the arrow indicates the increasing peak amplitudes with the increasing lactate acid concentration.

To perform the analysis, samples were removed from the refrigerator, then placed into the cavity and the spectrum S_{11} was captured directly. As it takes less than 2 seconds for the full spectra capture, depending on the desired number of points, the analysis is truly real-time, which is vital for both patients and medical practitioners. The cavity was designed to accept sample containers within 0.5 mm diameter glass tubes, which must contain identical fluid volumes above the internal height of cavity. This system facilitates empirical analysis of small volume of materials presented to the cavity and is useful for determining specific areas of interest in the microwave spectrum.

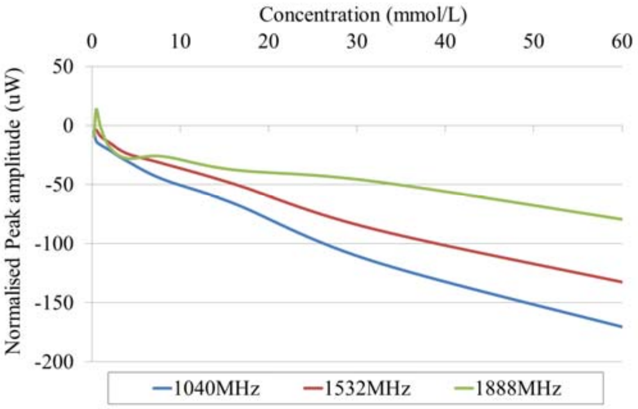

Fig. 4 Linear representation of peak amplitudes from the resonant cavity in the range of 800-2000 MHz.

IV. RESULTS

The spectrum for each lactate sample has been normalised against a 0 mmol (water) sample for ease of viewing and analysis. The results shown in Fig. 3 have been converted from the logarithm (dBm) scale to a linear (µW) scale. There are three peaks of interest at approximately (1) 1040 MHz, (2) 1532 MHz, and (3) 1888 MHz. The main interest at these peaks is the shift in signal amplitude.

It is clear to the eye that the sensor response is reasonably linear, particularly at higher lactate concentrations. For lower concentrations, Fig. 4 has been produced to confirm linearity for these peaks, in addition to the third peak shown in Fig. 3. This later peak however suffers from a loss of precision at lower concentrations.

Assuming the near linear relationship discovered between peak amplitude and concentration, the results in Fig. 4 suggest that at 1040 MHz, the sensor response is 2.5 µW/mmol/l, while at 1532 MHz it is reduced to 2.1 µW/mmol/l. At 1888 MHz, the relationship can be said to be 0.86 µW/mmol/l provided the concentration of lactate is > 10 mmol/l. The results are repeatable and reproducible.

Thus, online monitoring of bodily fluids is shown to be possible, which could lead to significant clinical improvements realised via real-time information provided during surgical procedures. Such information gives the opportunity for rapid analysis of material in order to determine a, potentially immediate, course of remedial action for a patient.

Future elements of the work will consider the ability to rapidly scan biological fluids and tissues ex-vivo at the bedside. In addition, rapid detection of cancer cells or tumour architecture, which can also be applied to samples of sputum, lung nodules, and biopsies of oesopageal, lung and lymph tissue is possible and is being considered by the authors [24]. Ultimately however, the ability to gain useful information from microwave scans of tissues in-vivo could serve to avoid a range of invasive diagnostic procedures.

V. CONCLUSIONS

A novel resonant cavity sensor reported in this paper has shown promising results for lactate in water, with a linear response being apparent at 1040 MHz (2.5 µW/mmol/l) and at 1532 MHz (2.1 µW/mmol/l). Importantly, it was proven that differing concentrations of lactate can be determined based on the changing dielectric properties of the resulting material, which leads us to believe that this technique could also be applied to human CSF.

Further work is ongoing in order to determine the effect of other more complex background media, as one might find in the human body. Provided the method can operate within the context of more complex media, this work shows significant promise toward developing a rapid testing mechanism for use during surgery. This will inevitably lead to fewer subsequent surgical procedures which will be beneficial to patients and healthcare organisations alike.

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