

## APPLICATIONS OF IMPLANTABLE MEDICAL SENSORS FOR HEART FAILURE: A REVIEW

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## ABSTRACT

Implantable medical devices are active medical devices which are either partially or totally introduced surgically into the human body for treatment purposes. These biosensors are basically powered by Hybrid cathode Lithium batteries. Use of practical implantable cardiac pacemaker's dates back to 1950s powered by Zn/HgO batteries. Later Lithium batteries with hybrid cathodes of Ag<sub>2</sub>V<sub>4</sub>O<sub>11</sub> and CF were developed. These hybrid batteries offer power density and energy density along with the stability and reliability required for implantable medical applications. Heart Failure (HF) is a chronic, degenerative condition which impairs the heart's ability to pump blood at normal filling pressures. The aim of this review is to highlight the applications of implantable medical sensors such as Radiofrequency based Wireless Heart Failure Sensors (HFS); Swan-Ganz catheterization; Echocardiography (ECHO) in monitoring heart failure. In comparison the new HFS has more benefits in terms of simplicity of implantation procedure, safety profile, small size and accuracy when compared to SG catheters and ECHO.

**Keywords:** Heart Failure, Biosensors, ICDs, medical devices, ECHO, Hemodynamic monitors. Heart failure.

## INTRODUCTION

A biosensor is an analytical device, used for the detection of an analyte, that combines a biological component with a physicochemical detector [1] biosensor reader device with the associated electronics or signal processors that are primarily responsible for the display of the results in a user-friendly way [2].

A biosensor consists of basically two components,

1. The sensitive biological element such as (tissues, cell receptors, micro organisms, antibodies, enzymes etc.) that interacts with the analyte under study.
2. The detector element that transforms the signal resulting from the interaction of the analyte with the biological element into another signal (i.e., transduces) that can be more easily measured and quantified.

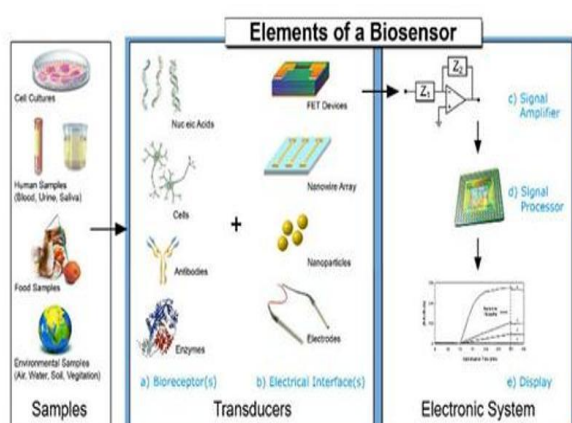


Fig 1 Biosensors: Fundamentals and Applications [1]

A biosensor typically consists of a bio-recognition component, biotransducer component, and electronic system which include a signal amplifier, processor, and display. The recognition component, often called a bioreceptor, uses biomolecules from organisms or receptors modeled after biological systems to interact with the analyte of interest. This interaction is measured by the biotransducer which outputs a measurable signal proportional to the presence of the target analyte in the sample [3]. An important part in a biosensor is to attach the biological elements (small molecules/protein/cells) to the surface of the sensor (metal, polymer or glass). The simplest way is to functionalize the surface in

order to coat it with the biological elements. This can be done by polylysine, aminosilane, epoxysilane or nitrocellulose in the case of silicon chips/silica glass. Subsequently the bound biological agent may be for example fixed by layer by layer deposition of alternatively charged polymer coatings [4]. Alternatively three dimensional lattices (hydrogel/xerogel) can be used to chemically or physically entrap these (where by chemically entrapped it is meant that the biological element is kept in place by a strong bond, while physically they are kept in place being unable to pass through the pores of the gel matrix).

The most commonly used hydrogel is sol-gel, a glassy silica generated by polymerization of silicate monomers (added as tetra alkyl orthosilicates, such as TMOS or TEOS) in the presence of the biological elements (along with other stabilizing polymers, such as PEG) in the case of physical entrapment [5]. Another group of hydrogels, which set under conditions suitable for cells or protein, are acrylate hydrogel, which polymerize upon radical initiation. One type of radical initiator is a peroxide radical, typically generated by combining a persulfate with TEMED (Polyacrylamide gel are also commonly used for protein electrophoresis) [6]. Alternatively light can be used in combination with a photo initiator, such as DMPA (2, 2-dimethoxy-2-phenylacetophenone) [7]. Smart materials that mimic the biological components of a sensor can also be classified as biosensors using only the active or catalytic site or analogous configurations of a biomolecules [8]. There are many potential applications of biosensors of various types. The main requirements for a biosensor approach to be valuable in terms of research and commercial applications are the identification of a target molecule, availability of a suitable biological recognition element, and the potential for disposable portable detection systems to be preferred to sensitive laboratory-based techniques in some situations. Some examples are

- Glucose monitoring in diabetes patients ←historical market driver
- Other medical health related targets
- Environmental applications e.g. the detection of pesticides and river water contaminants such as heavy metal ions
- Remote sensing of airborne bacteria e.g. in counter-bioterrorist activities.

In spite of above advantages there are also some disadvantages of biosensors, they are

1. Heat sterilization is not possible because of denaturation of biological material,

2. Stability of biological material (such as enzyme, cell, antibody, tissue, etc.), depends on the natural properties of the molecule that can be denaturalized under environmental conditions (pH, temperature or ions)

3. The cells in the biosensor can become intoxicated by other molecules that are capable of diffusing through the membrane.

#### Different types of implantable medical sensors-

1. Implantable continuous hemodynamic monitor
2. Swan-ganz catheter
3. Radio frequency based wireless pressure sensor
4. Echo
5. Chemical sensors
6. Miniature pressure sensors
7. Implantable cardioverter defibrillators
8. Electrochemical sensor
9. Implantable glucose biosensor
10. Left ventricular assist devices
11. Right ventricular hemodynamic.

#### Hybrid cathode lithium batteries

The use of practical implantable cardiac pacemakers dates back to 1950s, powered by Zn/HgO batteries [9]. In the late 1960s, scientists made efforts to develop nuclear batteries based either on the Seebeck effect or the beta voltaic effect [10]. However by the mid-1980s, most of the industries had settled on using lithium/iodine for implantable pulse generators (IPGs) requiring less than about 200 $\mu$ m. IPGs such as the implantable neurological stimulators which required the power range 200-500 $\mu$ m were mainly supported by Li/SOCl<sub>2</sub> batteries. Implantable Cardioverter defibrillators (ICDs) were initially powered by Li/V<sub>2</sub>O<sub>5</sub> batteries and later by silver vanadium oxide of Ag<sub>2</sub>V<sub>4</sub>O<sub>11</sub> composition [11-13]. These devices help to capture and store information about the electrical activity of the heart.

#### Characteristic features of hybrid cathode batteries electrolyte

To minimize secondary intercalation reactions, most commercial Li/CF<sub>x</sub> cells use electrolyte consisting of LiBF<sub>4</sub> dissolved in  $\gamma$ -butyrolactone. Ag<sub>2</sub>V<sub>4</sub>O<sub>11</sub> cells for ICDs use a high-conductivity electrolyte containing 1M LiAsF<sub>6</sub> dissolved in equal volumes of propylene carbonate and dimethoxyethane. Electrolyte composition can affect solubility of Li-Ag<sub>2</sub>V<sub>4</sub>O<sub>11</sub> discharge products, leading to undesirable side reactions, particularly for high-rate ICD batteries. Thus, a key element of hybrid-cathode battery technology is selection of an electrolyte composition that gives stable performance over the long service life.

#### Comparison with other implantable battery systems

Models describing both design of practical hybrid cathode batteries and the expected long-term discharge behavior were developed. These models incorporate data from cell discharge experiments lasting from 5 to 7 years. Lithium batteries with hybrid cathodes of Ag<sub>2</sub>V<sub>4</sub>O<sub>11</sub> and CF<sub>x</sub> combine the best features of both cathode components. They can offer power density and energy density that are competitive with or superior to other developed battery chemistries, along with the stability and reliability needed for implantable medical applications.

#### Heart failure management-

Heart failure (HF), often called congestive heart failure (CHF) or congestive cardiac failure (CCF), occurs when the heart is unable to provide sufficient pump action to maintain blood flow to meet the needs of the body [14-16]. The symptoms include shortness of breath, leg swelling and exercise intolerance. It is treated with implanted devices (pacemakers or ventricular assist devices) and

occasionally a heart transplant is required. In developed countries, around 2% of adults suffer from heart failure, but in those over the age of 65, this increases to 6-10%[17-18] Acute decompensated heart failure (ADHF) is a worsening of the symptoms, typically shortness of breath (dyspnea), edema and fatigue, in a patient with existing heart disease [19].

Patients with CHF have a diminished ability to excrete free water load. Hyponatremia frequently develops in decompensated heart failure due to the effects of excess circulating neuroendocrine hormones. Generally water intake should be limited to 1.5 L daily or less in patients with hyponatremia, though fluid restriction may be beneficial regardless in symptomatic reduction. The rate of HF hospitalization has been as high as 1 million annually in the United States among all the other medical conditions needing hospitalization (20). Given the aging population and growing economic burden, improved management of the patient with HF at home and prevention of hospital admissions have become national priorities. Rehospitalization rates for HF are now the target of publicly reported performance measures, national improvement initiatives, and government incentives [21]. Standard management of the ambulatory HF patient involves office-based follow-up 2 to 12 times a year, with physical examinations supplemented by laboratory tests and echocardiograms as needed. Patients are instructed to monitor their weight and symptoms.

#### Telemonitoring-

Telemonitoring involves the transfer of physiological data such as blood pressure, weight, electrocardiographic signals, or oxygen saturation through technology such as telephone lines, broadband, satellite, or wireless networks. By incorporating more data, Telemonitoring also promises to detect HF deterioration earlier, allowing for more prompt and effective intervention.

Information about the patient's condition would be gathered through a structured telephone conversation, and patients would be directed to follow up with their physician if there was evidence for deterioration. Structured telephone support can help with monitoring, self-care management, or both.

#### PPMs and ICDs -

To avoid the unreliability of patient-reported or patient-collected data, the invention of implantable devices proved a boon to the human kind as conventional methods of detecting change in fluid status such as weight and symptom monitoring do not provide sufficient warning and hence there is a necessity of additional metrics.

These implantable devices can take the form of permanent pacemakers (PPM), implantable cardioverter-defibrillators (ICD), or cardiac resynchronization therapy devices that have been placed for other indications. Or, they can be specially designed implantable hemodynamic sensors and monitors that can measure such parameters as intracardiac pressures. Remote monitoring of these devices generally involves the transmission of recorded data through an external transmitter to the manufacturer's central database. Information is transferred on a regular basis, and alerts are forwarded to the physician [22]. Another measure provided by some of these devices is intrathoracic impedance, which is the impedance measured between the right ventricular lead tip and the generator. An increase in pulmonary vascular congestion is reflected by decreased impedance, which can be recorded and reported by the device before symptom development[23]. Remote monitoring of PPM and ICD data may allow for the more timely recognition of serious arrhythmias, device problems, or worsening HF.

#### Implantable hemodynamic monitors-

Elevations in left ventricular filling pressures and pulmonary artery pressures are closely correlated with clinical congestion, functional limitation, and prognosis in patients with HF[24]. Ambulatory hemodynamic monitoring could provide an early warning of potential decompensation as well as facilitate the day-to-day management of patients with HF by allowing for the titration of medications on the basis of reliable physiological data. Several

systems are therefore currently under development that measure pressures directly in the right ventricle (RV), left atrium, and pulmonary artery. The RV pressure sensor system is similar to a pacemaker generator with a modified unipolar pacemaker lead (Chronicle, Medtronic, Minneapolis, Minnesota). Information includes continuous heart rate, body temperature, and hemodynamic such RV systolic and diastolic pressures and ePAD (RV pressure at maximal RV dP/dT), which correlates with pulmonary artery diastolic pressures and thus approximates left-sided filling pressures [25].

A device to directly measure left atrial pressure has also been developed (Heart POD, St. Jude Medical, Minneapolis, Minnesota). This device has a sensor lead placed intra-atrially through a transseptal puncture, which is then linked to a coil antenna placed subcutaneously. A pulmonary artery sensor (CardioMEMS Heart Sensor, CardioMEMS, Inc., Atlanta, Georgia) is a silicone, pressure-sensitive capacitor that is implanted in the pulmonary artery via right heart catheterization. It is powered externally by an antenna that is placed on the back or side of the patient when readings are conducted, and it provides accurate pulmonary artery pressure assessment when compared with both Swan-Ganz catheterization and echocardiography [25-26].

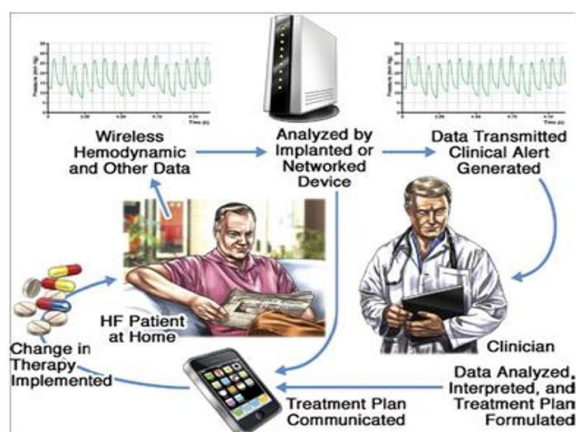


Fig. 2: Home Hemodynamic monitoring of Chronic HF [27]

### Cardiac resynchronization therapy-

The clinical success of Cardiac Resynchronization therapy (CRT) led to increased implantation rate of CRT devices. In normal individuals, electrical activation of both ventricles is preceded by depolarization of the His-Purkinje system resulting in rapid activation of both ventricles. In patients with left bundle branch block (LBBB), the total activation of the LV is prolonged with delayed activation and contraction of the lateral wall. However, even in the presence of LBBB, endocardial activation may be prolonged only minimally [28]. Various studies have evaluated the effect of CRT on myocardial perfusion and metabolism. In order to assess small differences in a quantitative manner, positron emission tomography (PET) was used. In mild heart failure, LV efficiency of forward work is reduced, whereas RV oxidative metabolism is increased [29]. Resting perfusion may be normal, but the perfusion reserve is typically reduced. With more severe heart failure, LV oxidative metabolism becomes also compromised [30].

### Efficacy of implantable biosensors

A major drawback to the widespread application of implantable biosensors is that they gradually lose their function with time. This progressive in vivo failure may be caused by a change in the properties of some of the components of the biosensor and/or a change in the local biological microenvironment surrounding the implanted biosensor. However, the effect of the biological environment on the physical and chemical properties of Nafion is mostly unknown. Because Nafion is the outermost coating of sensor, and thus the most susceptible to the rigorous biological environment, it is likely that a change in the properties of the Nafion coating leads to eventual sensor failure. According to the Mercado

et.al, [31]. In a recent paper [31] author has demonstrated calcification of Nafion occurs both in vitro and in vivo. The surface topography (SEM), surface composition (EDX) and permeability to

glucose of thermally annealed Nafion membranes were assessed for up to 4 weeks under both in vitro and in vivo conditions. Nafion membranes thermally annealed at 120°C and kept in culture medium or implanted subcutaneously in rats showed extensive cracking. Membranes kept in water did not crack. In membranes annealed at 150°C, cracking was reduced, but not eliminated. An analysis of surface composition and a fluorescent dye for Ca<sup>2+</sup> clearly showed deposits of calcium phosphates in the membranes. These deposits appeared to be responsible for the cracking of the membranes. The permeability to glucose of Nafion membranes annealed at 120°C and kept in culture medium or implanted in rats increased at one week and then decreased during the three following weeks. This study revealed that mineralization of Nafion occurs in the biological environment, resulting in cracking and changes in permeability. This study shows that modifications to prevent the mineralization of Nafion are necessary to make it suitable for use in implantable biosensors. Many experiments were carried out to bring in a new method that could possibly limit the rate of calcification of Nafion.

### Working of a typical biosensor

The basic principle by which a biosensor works similar to that of electronic sensors. Their performance criteria is based upon - sensitivity, selectivity, accuracy, precision, repeatability and noise tolerance. Like other sensors, biosensors transduce or translate one kind of energy into another and must be placed into a chain of components that detect, translate and modify an original „sign of life“ into a useful signal. Biosensors are usually classified into various groups either by type of transducer employed (electrochemical, optical, piezoelectric, and thermal) or by the kind of bio recognition element utilized (antibody, enzymes, nucleic acids, and whole cells). Both components of the biosensor, namely, bio recognition element (referred as a receptor) and transduction platform (referred as a transducer) play an important role in the construction of a sensitive and specific device for the analyte of interest (referred as a target). Biosensor operations are dependent on the details of the sensor design, just as chemical sensors are. Chemical sensor is a device that transforms chemical information into an electrical signal. This principle is based on the fact that a constant potential applied between a working and a reference electrode promotes a redox reaction, which produces a current.

The magnitude of this current is proportional to the concentration of electro active species present. Biosensors use a biochemical recognition mechanism, such as an analyte concentration, in direct contact with a transducer. In all cases the binding of an analyte changes the physical chemical properties of the sensor. The transducer, analyte and the binding mechanism are chosen such that the changes are measurable. For example, the measurement of small changes in mass is a transduction form that has been used for biosensor development. More generally; a biosensor recognizes and converts a biological event into a detectable signal by the action of a receptor, transducer and a processor.

Following are some of examples of Biosensors.

### Electrochemical Biosensors

Electrochemical biosensors are mainly used for the detection of glucose concentration, etc. The underlying principle for this class of biosensors is that many chemical reactions produce or consume ions or electrons which in turn cause some change in the electrical properties of the solution which can be sensed out and used as measuring parameter. Electrochemical biosensors can be classified based on the measuring electrical parameters as: (1) conductimetric, (2) amperometric and (3) potentiometric

### Conductimetric

The measured parameter is the electrical conductance / resistance of the solution. When electrochemical reactions produce ions or electrons, the overall conductivity or resistivity of the solution changes. This change is measured and calibrated to a proper scale.

Conductance measurements have relatively low sensitivity. The electric field is generated using a sinusoidal voltage (AC) which helps in minimizing undesirable effects such as Faradaic processes, double layer charging and concentration polarization. Amperometric: This high sensitivity biosensor can detect electro active species present in biological test samples. Since the biological test samples may not be intrinsically electro-active, enzymes are needed to catalyze the production of radio-active species. In this case, the measured parameter is current.

#### Potentiometric

In this type of sensor the measured parameter is oxidation or reduction potential of an electrochemical reaction. The working principle relies on the fact that when a ramp voltage is applied to an electrode in solution, a current flow occurs because of electrochemical reactions. The voltage at which these reactions occur indicates a particular reaction and particular species.

#### Glucose Biosensors

The most commercially successful biosensors are amperometric glucose biosensors. These biosensors have been made available in the market in various shapes and forms such as glucose pens, glucose displays, etc. The first historic experiment that served as the origin of glucose biosensors was carried out by Leland C. Clark. He used platinum (Pt) electrodes to detect oxygen. The enzyme glucose oxidase (GOD) was placed very close to the surface of platinum by physically trapping it against the electrodes with a piece of dialysis membrane. The enzyme activity changes depending on the surrounding oxygen concentration. Glucose reacts with glucose oxidase (GOD) to form gluconic acid while producing two electrons and two protons, thus reducing GOD. The reduced GOD, surrounding oxygen, electrons and protons (produced above) react to form hydrogen peroxide and oxidized GOD (the original form). This GOD can again react with more glucose. The higher the glucose content, more oxygen is consumed. On the other hand, lower glucose content results in more hydrogen peroxide. Hence, either the consumption of oxygen or the production of hydrogen peroxide can be detected by the help of platinum electrodes and this can serve as a measure for glucose concentration. The current and future applications of glucose biosensors are very broad due to their immediate use in diabetic self-monitoring of capillary blood glucose. These types of monitoring devices comprise one of the largest markets for biosensors today and their existence has dramatically improved the quality of life of diabetics.

#### Thermal-detection Biosensors

This type of biosensor is exploiting one of the fundamental properties of biological reactions, namely absorption or production of heat, which in turn changes the temperature of the medium in which the reaction takes place. They are constructed by combining immobilized enzyme molecules with temperature sensors. When the analyte comes in contact with the enzyme, the heat reaction of the enzyme is measured and is calibrated against the analyte concentration. The total heat produced or absorbed is proportional to the molar enthalpy and the total number of molecules in the reaction. The measurement of the temperature is typically accomplished via a thermistor, and such devices are known as enzyme thermistors. Their high sensitivity to thermal changes makes thermistors ideal for such applications. Unlike other transducers, thermal biosensors do not need frequent recalibration and are insensitive to the optical and electrochemical properties of the sample. Common applications of this type of biosensor include the detection of pesticides and pathogenic bacteria.

#### Applications of biosensors

##### Glucose detection *in-vivo*

One of the main clinical applications of biosensors is to develop point-of-care glucose concentration measuring devices for patients suffering from diabetes. Originally introduced in the early 1980s the latest generation of hand held glucose sensors has revolutionized the lifestyles of those suffering from diabetes. Patients are now able to self-monitor their glucose concentrations and self-administer

insulin injections as required. Most enzyme-based biosensors to detect glucose concentrations use enzymes known as oxidoreductases [30]. The most common enzymes used for glucos detection are glucose oxidase and glucose dehydrogenase.

#### Biosensors in cardiovascular disease

Biosensors for cholesterol measurement comprise the majority of the published articles in the field of cardiovascular diseases. In the fabrication of cholesterol biosensor for the estimation of free cholesterol and total cholesterol, mainly cholesterol oxidase (ChOx) and cholesterol esterase (ChEt) have been employed as the sensing elements [30]. Electrochemical transducers have been effectively utilized for the estimation of cholesterol in the system Based on number and reliability of optical methods, a variety of optical transducers have been employed for cholesterol sensing, namely monitoring: luminescence, change in color of dye, fluorescence and others Other cardiovascular disease biomarkers are also quantified. CRP measurement rely mainly on immunosensing technologies with optical, electrochemical and acoustic transducers besides approaches to simultaneous analytes measurement incorporated streptavidin polystyrene microspheres to the electrode surface of SPEs in order to increase the analytical response of the cardiac troponin T and used an assay based on virus nanoparticles for troponin I highly sensitive and selective diagnostic, a protein marker for a higher risk of acute myocardial infarction.

Early and accurate diagnosis of cardiovascular disease is crucial to save many lives, especially for the patients suffering the heart attack. Accurate and fast quantification of cardiac muscle specific biomarkers in the blood enables accurate diagnosis and prognosis and timely treatment of the patients. It is apparent that increasing incidences of cardiovascular diseases and cardiac arrest in contemporary society denote the necessity of the availability of cholesterol and other biomarkers biosensors. However, only a few have been successfully launched in the market. One of the reasons lays in the optimization of critical parameters, such as enzyme stabilization, quality control and instrumentation design. The efforts directed toward the development of cardiovascular disease biosensors have resulted in the commercialization of a few cholesterol biosensors. A better comprehension of the bioreagents immobilization and technological advances in the microelectronics are likely to speed up commercialization of the much needed biosensors for cardiovascular diseases.

#### CONCLUSION

The advancement of technology has allowed for the development of more advanced home-monitoring techniques, including implanted hemodynamic sensors, which are particularly promising. Continuous monitoring of ambulatory RV pressures is feasible, accurate, and safe. Furthermore, RV pressure changes reflect the patient's volume status, which provides meaningful information to guide day-to-day management of CHF. More research in these fields is needed. And also economic considerations are important, and cost-effectiveness of CRT needs further research required to ascertain its feasibility Mineralization of the Nafion was minimal when treated with FeCl<sub>3</sub>. As a result, there were less calcium phosphate deposits, less cracking and the permeability remained virtually unchanged. TEM data also proved to be quite useful in visualizing the crystals of calcium phosphate in Nafion. Pre-incubation in FeCl<sub>3</sub> has proved to be a useful, inexpensive and quick mean to prevent the calcification of Nafion.

Besides Heart Failure management, Biosensors are widely used in medicine to monitor or detect biological molecules for applications ranging from diabetes to cancer. The new Heart Failure Sensors provide accurate method for pulmonary Artery Pressure (PAP) assessment in the patients when compared to Swan-Ganz Catheter and ECHO. Left Ventricular Assist Devices (LVAD) is safe and provides improved quality of life of patients who are to undergo transplantation. Long-term ambulatory pressure measurements from an Implantable Hemodynamic Monitor (IHM) may prove helpful in day-to-day clinical management with a favourable impact on Chronic Heart Failure (CHF) hospitalizations. Additional advantages of implantable devices include the ability to track measures longitudinally over time, average these

values over the course of a day, and more accurately reflect a patient's clinical status.

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