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Recent Advancement in Nanosensors with Special Reference To Biomedical Applications

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Abstract – Nanosensors are making big impact already changing the world in fields of medical, food, aerospace , environmental fields and are gaining increasing attention due to the need and ability to detect and measure chemical and physical properties in difficult to reach biological and industrial systems that are nanoscale region. Recently the use of such nanosensors with sensitivity and selectivity can offer different advantages in biomedical applications like earlier detection of disease, toxins or biological threats and create significant improvements in clinical as well as environmental and industrial outcomes. This paper aims to recent advancement in nanosensors with special reference to biomedical applications.

Keywords : Advancement in nanosensors, Applications of nanosensors, Nanosensors, Various biomedical application

I. INTRODUCTION

Nano sensors are like all other sensors who work to detect all kind of signal from variety of environments with one difference that they use nanomaterial as their active sensing element and are very very small. Nano sensor is a device that communicates information about the behavior of particles at Nano scale level to macroscopic level. Nano sensor is a sensing device whose purpose is to convey data and information from the Nano scale to the macroscopic scale. Various chemical, mechanical and optical properties possessed by nanoparticles which is used by biological sensors, Nano scale sensors, and other optical electronic devices.

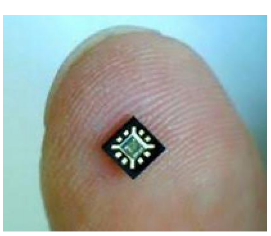

Fig. 1 Nanosensor
Source: www.medium.com

Nanosensors are sensing devices with at least one of their sensing dimensions being no greater than 100 nm. In the field of Nano technology, nanosensors are instrumental for (a) monitoring physical and chemical phenomena in regions that are difficult to reach, (b) detecting biochemical in cellular organelles, and (c) measuring nanoscopic particles in industry and environment. This helps scientists and researchers to utilize the unique physical, chemical, mechanical and optical properties that naturally occur at that scale. Nanosensors require less power to operate and hence are used in different fields. Also they have greater sensitivity which means they give more accurate result data. Nanosensors are important in biomedical field as the future of medicine is at nanoscale . Nanosensors operates on small scale that allow them to go places that sensors didn't have the ability to go before. Not only in biomedical field, these are important in different fields as well. In addition to their sensitivity, nanosensors offer significant advantages in cost and response time, making them suitable for high-throughput applications. Nanosensors provide real time monitoring which does not require days or weeks like traditional detection methods. [1]

II. WORKING OF NANOSENSOR

Nanosensor measures electrical changes in the sensor material. The basic process include binding in which the analyte binds selectively to the nanosensor and then based on the interaction of the sensor with the bio-element , a signal is generated. This signal then processed further into useful metrics.

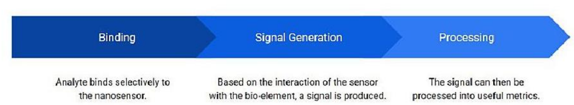

Fig.2 Nanosensor workflow
Source:https://en.wikipedia.org/wiki/File:Overview_of_Nanosensor_Workflow.jpg

Different sensors use different mechanisms. Electrochemical sensors measures resistance changes in nanosensors upon the binding of an analyte. The changes are due to accumulation of charge barriers, changes in scattering. Carbon nanotubes are used to detect atmospheric

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concentration of gases at molecular level and they are also used to sense ionization of gaseous molecules.

Mechanical nanosensors measures electrical changes. They are used to sense changes in capacitance and are used in car airbags as MEMS.

Biological sensors consist of a bioreactor and a transducer. These are analytical device which produce chemical signals. These signals are in proportion to the concentration of the target analyte.

Photonic nanosensors operates on the basis of chemical modulation of a hydrogen film volume as hydrogen swells or shrinks upon chemical stimulation. The hydrogen film volume incorporates a Bragg grating that changes color and diffracts light at different wavelength and this diffracted light is correlate with the concentration of a target analyte.

III. CLASSIFICATION OF NANOSENSOR

Nanosenors are classified into several ways. Let's have a look at some of them. They can be classified depending on its energy source, structure and applications.

1. According to energy source: In this case the nanosensors are classified as

1.1. Active nanosensors: These types of nanosensors need an energy source such as a thermistor.

1.2. Passive nanosensors: These type of nanosensors need no source of energy, such as a thermocouple, and piezoelectric sensor.

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2. Classification based on structure: Basically four types of sensors are classified based on structure
   (i) Optical nanosensors,
   (ii) Electromagnetic nanosensors
   (iii) Mechanical and/or vibrational nanosensors.
   (iv) Chemical Nanosensors[2]

3. Classification based on application: There are four types of sensors based on application
- Chemical sensors,
- Deployable nanosensors,
- Electrometers
- Biosensors [3]

1. Classification of Sensors According its Energy Source

Active Nanosensors: These types of nanosensors need an energy source such as a thermistor. An active nanosensor would have the ability to send a signal that could be received remotely. For example, an embedded nanosensor in a stationary position in a water reservoir, lake, or stream could detect the presence of a dangerous pathogen and send a signal. [4]

Passive Nanosensors: A passive nanosensor would rely on observation of a change in color, opacity, or fluorescence.[5]

2. Classification of Sensors According its Structure

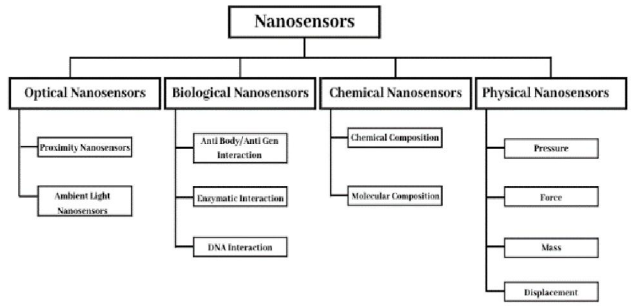

Fig. 3 Types of Nanosensors

2.1 Optical nanosensors: In different industries such as chemical industry, medicine, human protection, biotechnology and environmental sciences optical sensors are used due to their capability of monitoring chemical analysis which depends on optical properties of nanomaterials.
The first reported optical nanosensor was based on fluorescein which is trapped within a polyacrylamide nanoparticle, and was used for pH measurement. [6]

Optical nanosensors are of two types:

(i)Proximity sensors: These are designed for use in detecting the presence of an object or motion detection in various industrial mobile electronic appliances and Retail automats.

(ii)**Ambient light sensors:** Due to the property of providing precise light section for a wide range of ambient brightness they are commonly used in LCD backlight control in Mobile phones, this was example of the many types of nanosensors. [7]
Recently a technique for two-dimensional localization based on position-dependent directional scattering of a single dipolar nanoantenna has been demonstrated. [8]

2.2 Biological sensors: These include a large variety of biosensors, such as enzyme-modified electrodes for determination of glucose, immunosensors, and DNA sensors. These are the most commonly used nanosensors due to the ability to detect early possibility of diseases like cancer etc. The biosensor can usually be considered a subset of chemical sensors because the transduction methods or the so called sensor platforms, are similar to those for chemical sensors. [9]
A biological nanosensor is usually composed of a biological recognition system or bio receptor, such as an antibody, an enzyme, a protein or a DNA strain, and a transduction mechanism, e.g., an electrochemical detector, an optical transducer, voltaic or magnetic detector

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Antibody-based biosensors are based on the principle that antigen–antibody interactions can be transduced directly into a measurable physical signal. Antibody-based electrochemical systems allow the rapid and continuous analysis of a binding event without requiring added reagents or separation/washing steps. Combining the sensitivity and specificity of the antigen–antibody binding interaction with the high sensitivity and relative simplicity of modern electro analytical techniques has produced immune electro chemical sensors that have a potential in such areas as clinical diagnostics, environmental monitoring, food and water quality control, and bioprocess analysis. [10]

DNA is a major target for a wide range of small molecules that may specifically or non·specifically interact with double stranded DNA and affect its functions. A large number of inorganic and organic compounds are able to bind to DNA and form complexes. According to their structural characteristics, DNA targeted drugs that can interact non-covalently with DNA, are mainly intercalators, but also minor and major groove binders. When drug·DNA complex is occurred, some conformational changes at the structure of both drug as well as DNA could be observed.[11] Enzyme interactions in biological nanosensors are based on the principle of enzyme interaction. Like so many of the cell's regulatory systems, this takes place through a series of enzyme–enzyme interactions.

2.3 Chemical Nanosensors: Chemical nanosensors as the name suggests are used to detect various chemicals in drugs, in residue from environment samples, in monitoring pollution. They are also used in measuring some properties like pH or ion concentration and to detect the presence of nanoparticles and chemical species. In addition to that chemical nanosensors are also used for diagnosis purpose and are applied to analyze a single chemical or molecule. It consist of a identification part and a transducer part, the identification part interacts with the target molecules or ion in the sample and the transducer converts the chemical interactions into measurable signals. Moreover, chemical nanosensors are also used to measure magnitudes such as presence of a specific type of molecules, concentration of a given gas or the molecular composition of a substance.

2.4 Mechanical \Physical nanosensors: Mechanical nanosensors are used to sense change in capacitance. They have several advantages over optical and electromagnetic nanosensors when it comes to detection of nanoscale mechanical properties. There are many types of mechanical nanosensors carbon nanotube based fluidic shear stress sensor and the nano mechanical cantilever sensors. Different physical nanosensors like mass, pressure, force or displacement are based on the fact that the electronic properties of both nanotubes and nanoribbons change when they are bent or deformed. For example, a carbon nanotube can be used to build a nano size field effect transistor, the dimensions of nanotube are main effective for on /off threshold on, shape and temperature among others.[12]

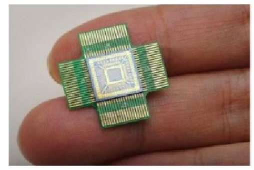
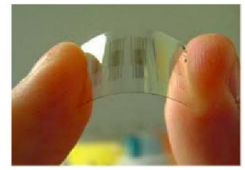

Fig 4: Chemical Nanosensor (left) (Source: NASA) and a Mechanical Nanosensor (right) (Source: Nanotechnics14)

Nanosensors are of wide range and one of nanosensors based on structure is mentioned below. This is also structure based nanosensor.

Electromagnetic nanosensors: On the basis of detection mechanisms there are two types of sensors in this category.

a) Monitoring via electrical current measurement.
b) Monitoring via magnetism measurement.

Electrical current measurement: In this the advantage of this approach is the label-free methodology over the use of dye.

Magnetic measurement: Magnetic nanosensors consist of magnetic nanoparticles (iron oxide). When these magnetic nanoparticles bind to their intended molecular target, they form stable nanoasemblies. This leads to a corresponding decrease in the spin-spin relaxation time of surrounding water molecules, which consequently can be detected by magnetic resonance techniques. [13]

3 Classification of Sensors According its Applications

1. Chemical nanosensors
2. Biosensors.
3. Deployable nanosensors
4. Electrometers

Some of these fall in this category according to their applications as well. As discussed above chemical sensors and biosensors are widely used in biomedical application and are famous in research field.

3.1 Deployable Nanosensors: Deployable nanosensors are portable chemical detection system which are light weight and combines nanomaterials for sample collection and a concentration with a micro electromechanical detector. Due to its nature and features it is used in military or in other national securities.

3.2 Electrometers: It has mechanical resonator, a detection electrode, and a gate electrode which are used to couple charge to the mechanical element.

IV. APPLICATIONS OF NANOSENSORS IN BIOMEDICAL FIELD

There are many different applications where nanosensors are used due to their sensitivity and small size. They are widely used in biomedical fields and in the fields of medical technology, agriculture, plant nanobiotics, and many industrial applications. Many industries are using nanosenosr and this holds great potential for future profitability in the field of robotics, biomedical, medical and the internet of things, environmental monitoring, military etc. From sources recently nanosensor marked was valued at USD 133.69 million in 2017, and it is expected to be USD 4,621.71 million by 2023. Moreover advanced technologies have been proved to be a driving force of new opportunities and further development. [14]

Nanosensors include:

- Carbon Nanotube–Based Fluorescent Nanosensors
- Quantum Dot–Based Fluorescent Nanosensors
- DNA-Based Fluorescent Nanosensors
- Peptide-Based Fluorescent Nanosensors
- Plasmon Coupling–Based Nanosensors
- Plasmonic Enhancing–/Quenching–Based Nanosensors
- Magnetic Resonance Imaging-Based Nanosensors
- Photoacoustic-Based Nanosensors
- Multimodal Nanosensors (synergistic nanosensors with multiple modalities to overcome individual challenges) [15]

Although nanosensors are widely used in every field whether its military or chemical. Nanosensors has provided major advancement in development of military grade active sensing packages to detect damage(corrosion, substrate integrity, etc) also the development of medical portable nanosensing devices to detect the disease and sending signals to base station gave so much ease and relief to military and the people living in remote areas. In addition, nanotechnology will have impact on battle space systems concerned with information and signal processing, autonomy and intelligence.[16]

They are also used in a detecting various chemicals in biomedical and for medical diagnosis purposes such as bloodborne sensors or in lab on a chip type devices, these are widely used in this field. Nanosensors are also used in monitoring plant signaling and metabolism to understand plant biology and also used in study of neurotransmitters in brain for understanding neurophysiology.

1. DNA biosensors

In the field of biomedical, biosensors are one of the most largely funded areas of research. This is because of their capability to lead in early stage detection of various diseases. Cancer detection is one of them and there are many. Biosensors can also be used to detect specific types of DNA. Following image on the left shows nanobarcode particles and on the right is an example of carbon nanotubes used as biosensor. Nanobarcode is used to sense different biomaterials and DNA using encoding antibodies on them. Whereas in right image the DNA molecules attach to the ends of the vertical carbon nanotubes that were grown on a silicon chip. Other types of nanosensors are also used for detection of specific disease like detection of asthma attack up to three weeks before it happens. These are just two major applications of nanosensors. [17]

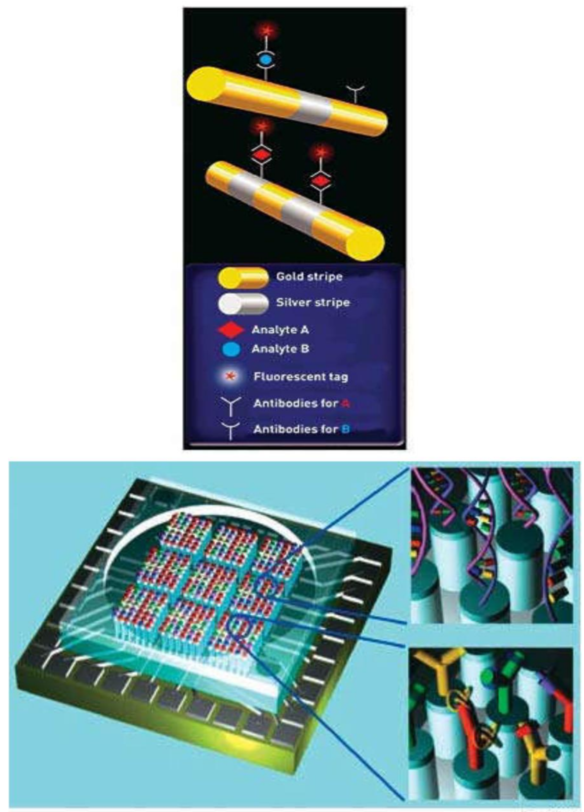

Fig. 5
Source: Nasa

2. Wearable Vitamin C nanosensor

Recently nanosensors are used in testing of the COVID-19 - the disease caused by the novel SARS-CoV-2 virus. Vitamin C is an essential component for body and it helps in supporting the immune system as well as plays vital role in wound healing, improving iron absorption from plant-based foods. This vitamin is being studied whether it can help in recovery of the disease and found useful. A wearable vitamin C nanosensor is developed by a team at the University of California San Diego which could provide a new, highly

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personalized option for users to track their daily nutritional intake and dietary adherence.

This might be a helping hand for doctors if vitamin C does help patients to recover from disease. This wearable sensor can help doctors in tracking patient's vitamin C level during treatment and recovery. This wearable technology ***uses*** an enzyme-based approach to track changes in the level of a necessary vitamin. According to *a PhD Candidate in nanoengineering* in Joseph Wang's lab at the UC San Diego Jacobs School of Engineering this is the first demonstration of using an enzyme-based approach.[18]

Fig. 6
Source:https://www.printedelectronicsworld.com/articles/20737/new-wearable-tracks-vitamin-c-levels-in-sweat

3. *Paper based nanosensor for early detection of cancer*

Scientists at Washington State University (WSU) stated that they have designed a technology that is 30 times more sensitive compared to the existing lab-based tests in determining early-stage cancer biomarkers in blood. Cancer is one of the disease which is responsible for death of most of the people hence this type of technology can be helpful in saving many lives.

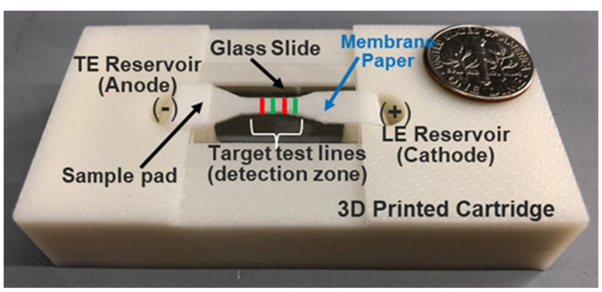

Fig. 7 Image of the paper-based isotachophoresis (ITP) device that isolates, enriches, and detects exosomes from a prostate cancer cell line.
Source: Washington State University.

The technology involves using an electric field to concentrate and isolate cancer biomarkers onto a paper strip. Researchers have found that one of the way cancer cell spread is through tiny exosome vesicles in blood with ranging a size from 40 to 120 nanometers. Moreover cancer cells secrete more exosome bubbles than blood and it is quite difficult to detect cancer filled exosomes in blood while testing as they look same as normal cell exosomes, The team of WSU for the first developed a technology that uses electric field to concentrate and rapidly isolate, enrich and detect the exosomes taken from a prostate cancer cell line. [19]

4. Biosensors Embedded Mask

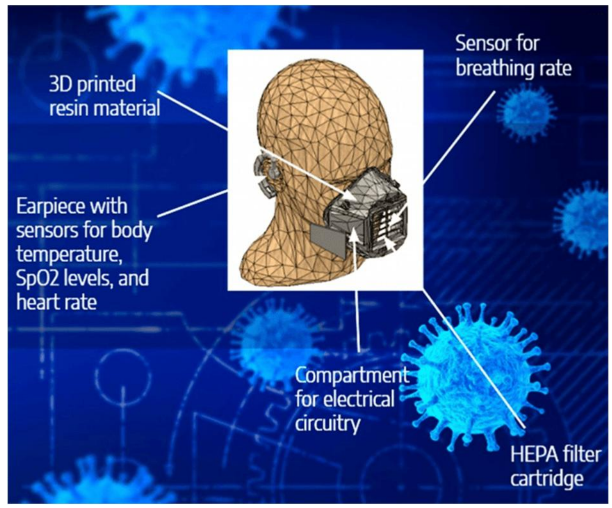

Fig. 8. VitalMask, a "smart" respiratory mask that prevents the spread of airborne diseases and monitors the wearer's vital signs.
Source: Cornell University.

As the disease COVID -19 was spreading all around the world, the students of Cornell University designed a vital mask which prevents the airborne diseases with the help of embedded nanosensor. The VitalMask is made up of 3D-printed resin, with sensors placed near the nose, mouth, and earlobes of the wearer to monitor heart rate, body temperature, respiratory rate, and blood oxygen levels. Kristin Ong '21 stated that "These vital signs are transferred in real time to a mobile or desktop app, not only does the mask help busy medical personnel prioritize patients, it also offers a washable, reusable alternative to standard disposable masks."
The team including Chen, Liu, Ong, Ray Wei '21, and Allison Fleisher '21 was awarded the grand prize of $2,000 and a $500 third-place win in a special category, sponsored by IBM, for coronavirus innovations.[20]

5. Nanosensor Probe

As the need for early detection of diseases are increasing, new inventions are also taking place. One of the major disease on which research is continue going on is cancer. Recently an ORNL nanosensor is used which detects the early signs of DNA damage that can cause cancer. A "nanoneedle" with a tip about one-thousandth the size of a human hair pokes a living cell, causing it to quiver briefly. Once it is withdrawn from the cell, the sensor detects the DNA damage.

This nanosensor of high selectivity and sensitivity was developed by a research group led by Tuan Vo-Dinh and his coworkers Guy Griffin and Brian Cullum. The group believes that, by using antibodies targeted to a wide variety of cell chemicals, the nanosensor can monitor in a living cell the presence of proteins and other species of biomedical interest.[21]

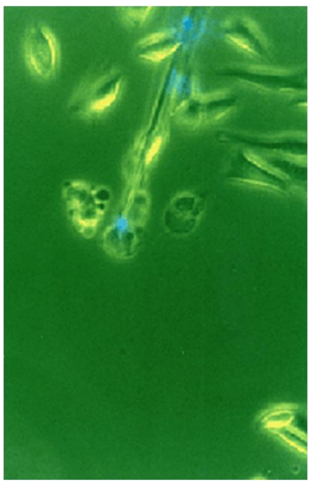

Fig. 9 ORNL
Source: https://www.thoughtco.com/inventions-using-nanotechnology-1992181

6. Bioelectronics ammonia gas sensors

A team of scientists at the University of Massachusetts Amherst stated that they have developed bioelectronics ammonia gas sensors that are among the most sensitive ever made. It uses electric-charge-conducting protein nanowires derived from the bacterium Geobacter to provide biomaterials for electrical devices. They grow hair-like protein filaments that work as nanoscale "wires" to transfer charges for their nourishment and to communicate with other bacteria.[22]

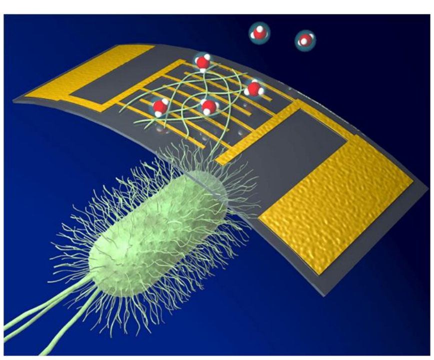

Fig. 10 Protein nanowires (light green) harvested from Geobacter (background) are sandwiched between electrodes (gold) to form bioelectronic sensor for detection of biomolecules (red). Image

Source: Photo courtesy of University of Massachusetts Amherst/Yao lab.

7. Nanosensor can alert a smartphone when plants are stressed

MIT engineers have develop a way to track how plants respond when they are stressed, this may include infection, injury, and minor damage. They used sensors made up of carbon nanotubes to track. Plants use hydrogen peroxide to communicate with their different parts such as leaves sending out a distress signal to them which stimulates the leaf cells that produce compounds. This compound helps plants in repairing the damage or to defend the predators such as insects. These sensors can be embedded in plants leaves, where they report to hydrogen peroxide signaling waves. These new sensors can use these hydrogen peroxide signals to distinguish between different types of stress in plants as well as in different species of them. This kind of sensor could be used to study how plants respond to different types of stress, also helping agricultural scientists develop new strategies to improve crop yields. **[23]**

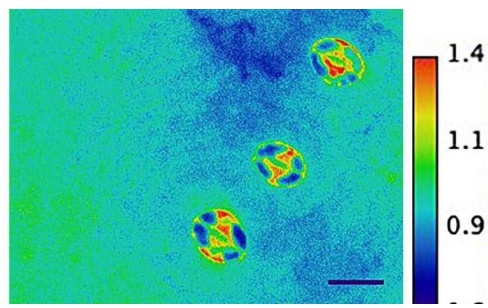

Fig. 11 The image depicts three Arabidopsis leaf surface pores, or stomata, expressing the new SNACS stress nanosensor

Source: Schroeder Lab, UC San Diego

8. Researchers develop experimental rapid covid-19 test using nanoparticle technique

Team of scientists from the University Of Maryland School Of Medicine (UMSOM) developed an experimental diagnostic test for COVID-19 that can visually detect the presence of the virus in 10 minutes. It uses a simple assay containing plasmonic gold nanoparticles to detect a color change when the virus is present. The test does not require the use of any advanced laboratory techniques, such as those commonly used to amplify DNA, for analysis.[24]

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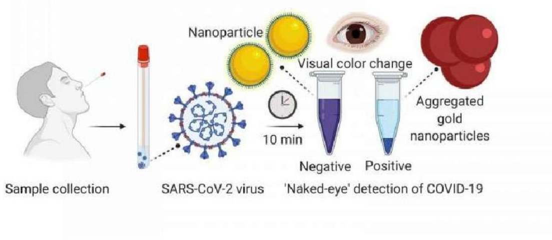

Fig. 12 A nasal swab containing a test sample is mixed with a simple lab test. It contains a liquid mixed with gold nanoparticles attached to a molecule that binds to the novel coronavirus. If the virus is present, the gold nanoparticles turns the solution a deep blue color (bottom of the tube) and a precipitation is noticed. If it is not present, the solution retains its original purple color.

Source : University of Maryland School of Medicine

9. In –Ear Sensor to help in fight against COVID-19

A team at technical University of Munich developed an ear wearable sensor to help in fight against COVID-19 which uses a high-tech biometric sensors for 24-hour monitoring of COVID-19 patients in home isolation. This in-ear wearable sensors use optical processes, among other technologies, to capture biodata. These devices can measure all of the parameters needed and transmit them to a small computer via a Bluetooth connection. From there they are forwarded to the central office for analysis in compliance with data protection regulations. This in ear wearable senor can speed up the detection of worsening symptoms in **COVID-19** patients.

These will ease the workload of intensive care units by eliminating the need for intensive treatment, including mechanical ventilation, in some cases. This will keep a track on them and will ensure that they can be transported to the hospital immediately without any further delay.[25]

Fig. 13 In-ear sensors
Source: Andreas Heddergott / TUM

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