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Review

Human *Papillomavirus* E6 biosensing: Current progression on early detection strategies for cervical Cancer

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ABSTRACT

Prognosis of early cancer detection becomes one of the tremendous issues in the medical health system. Medical debates among specialist doctor and researcher in therapeutic approaches became a hot concern for cervix cancer deficiencies early screening, risk factors cross-reaction, portability device, rapid and free labeling system. The electrical biosensing based system showed credibility in higher specificity and selectivity due to hybridization of DNA duplex between analyte target and DNA probes. Electrical DNA sensor for cervix cancer has attracted too many attentions to researcher notification based on high performance, easy to handle, rapid system and possible to miniaturize. This review explores the current progression and future insignificant for HPV E6 genobiosensing for early Detection Strategies of Cervical Cancer.

Contents

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1. Introduction

Cervix cancer caused by Human *Papillomavirus* (HPV) is one of the most sexually transmitted disease to the women reproductive system [1]. Cervix cancer became the most silent killer after breast cancer that affects the sociability of women condition. Above 290 million was infected by HPV according to the World Health Organization (WHO) at the end of 2013. A very rare virus during 1984 called HPV was discovered by Harald zur Hausen. and ascribed cervical disease to HPV 16 and 18 [2]. HPV got its name because of the strains causes warts that called as *Papillomas* [3,4]. Hundred and fifty HPV strains were distinguished by identifying low and high risk have been perceived. From 150 strains, fifteen was identified as the high danger of cervical malignant.

High risk of 16, 18, 31 and 45 was empowered cervical cancer threat disease [5]. HPV 16 turned into the main strain for the headway of cervical malignant after 18, 31 and 45 [6]. HPV can incorporate into the human genome and human infections through direct skin to skin attachment, sex activity, and resistant concealment. High risk of the HIV-infected individual is at higher chance to get HPV infection from an alternate broad scope of HPV strains [7]. Fatal complication due to late detection of cervical cancer cause a result of tumor or lymph node encroachment, inflammation, or scarring at the pelvic rim [8]. Patients can undergo urinary diversion procedures to relieve obstructive symptoms. Prior to the introduction of the nephrotoxic drug to reduce the inflammation of cancer cells, Lapitan and Buckley undertook a prospective quality of life assessment of cervical cancer patients with hydronephrosis and reported that quality of life did not change over 1 year [9].

As showed up in Fig. 1, HPV infection mechanism system of disease started when the virions enter the cell by means of endocytosis (a) and are trafficked deeply to the core nucleus (b), where they proceed in episomal shape(c) or ligated into the host genome (d). Ligated and episomal viral DNA was made E6 and E7 (e). The association of E6 with p53 and the ubiquitin ligase E6-related protein target p53 for proteasomal degradation (f) and prevent apoptosis. Rb family tumor-suppressor proteins including 'pRb', p130 and p107 interact with E7 (g) and are inactivated, achieve to discharge E2F and advancing cell-cycle development. Fig. 1 outlines the control methodology of HPV and the part of proteins included [10].

HPV is a virus that inherits genomic DNA as genetic material, delegated as a non-enveloped virus which is more firm in term of survival in the harsh environment compared to the enveloped virus. HPV had double-stranded circular DNA genome, secured by an icosahedra capsid forming a molecule with around 55 nm (Fig. 2). Structure of the HPV virus contained virion, capsid, capsomere, genome, nucleocapsid, and envelope (Fig. 2). HPV was guaranteed by a capsid molded by two late proteins, L1 and L2. HPV capsid is made out of 72 capsomeres, each made out of five monomeric 55 kDa units that join to develop a pentamer comparing to the significant protein capsid, L1. The L1 pentamers are framing a system of intra-and interpentameric disulfide interactions which serve to balance out the capsid [11]. Notwithstanding L1, minor capsid proteins with around 75 kDa exist inside the virion, called L2 protein. To amass the viral capsid, pentamers join to duplicates of L2 that blocks the inside for each pentavalent capsomere [12]. Thus, each virion contains 72 copies of L1, the major segment of the capsid, and a variable number of copies of L2, an optional segment of the viral capsid, forming a molecule with icosahedra symmetry of ~50 to 60 nm in diameter measurement [13].

Infection with HPV cause cervical cancer having side effects, for example, vaginal bleeding, contact bleeding, the vaginal mass may demonstrate the existence of malignancy, direct pain during sexual intercourse and vaginal discharge. There are three methods for HPV disease spreading into a human through oral, vaginal and anal sex [14].

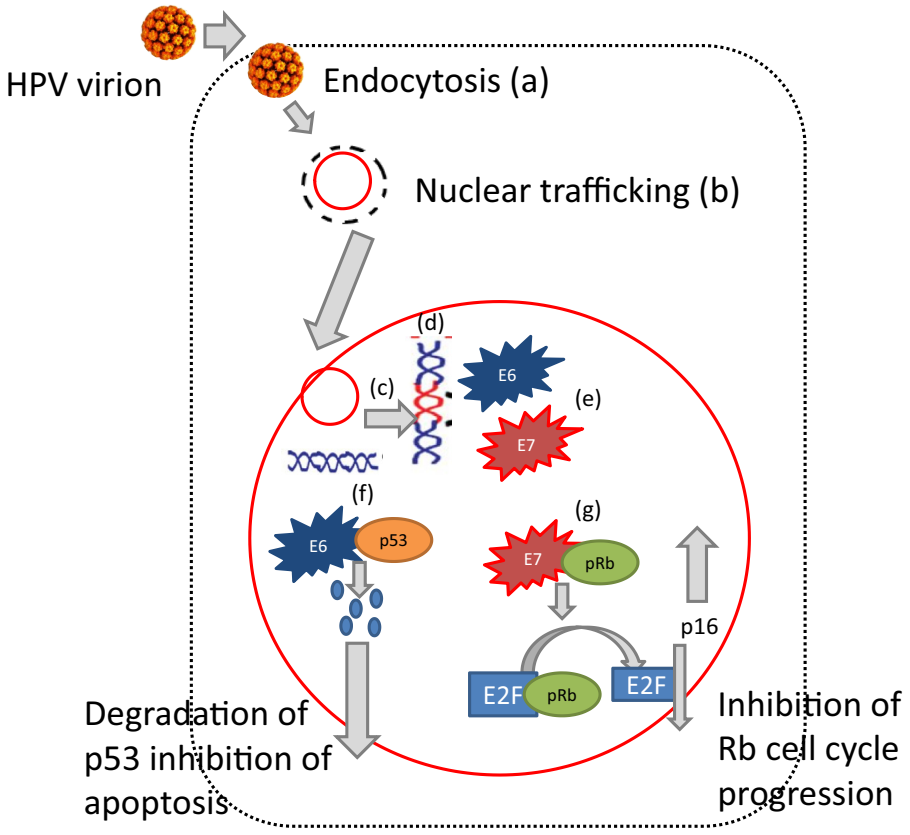

Fig. 1. Steps of HPV regulation in infected cells. (a) Endocytosis (b) trafficked into the host genome (c) episomal form (d) integrated with host genome (e) integrated viral DNA produce E6 and E7 (f) Interaction of E6 with p53 and ubiquitin ligase degraded of p53 protein for proteasomal degradation and apoptosis inhibition (g) Rb family tumor-suppressor proteins including Rb ('pRb'), p130 and p107 interact with E7 and inactivated.

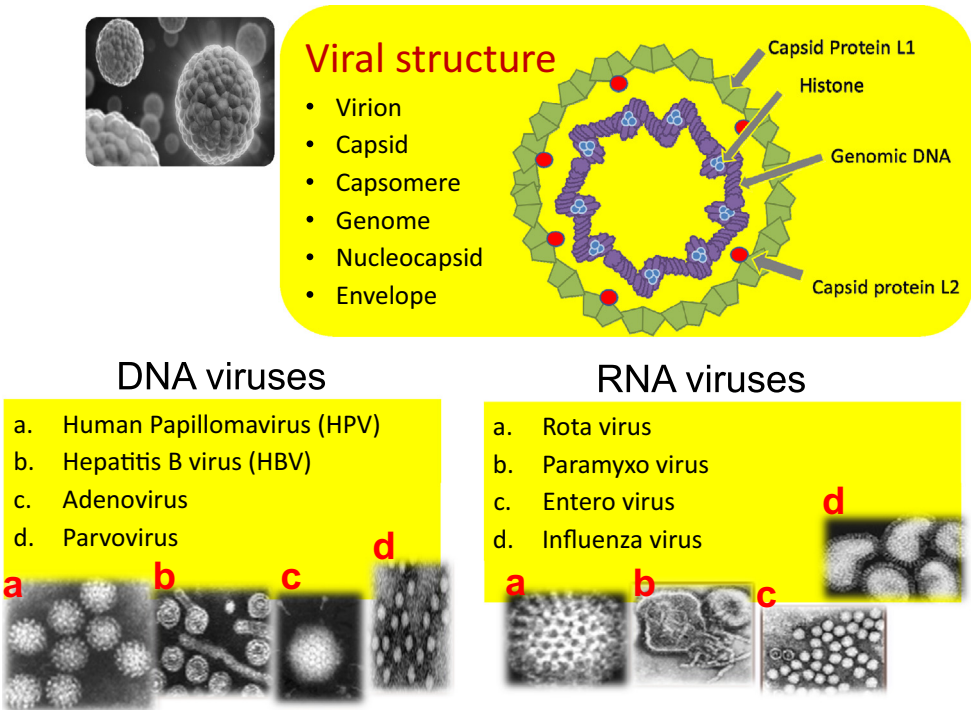

Fig. 2. Structure of viruses and different types of genomic DNA and RNA containing viruses. Most viruses have either RNA or DNA as their genetic material. The entire infectious virus particle, called a virion, consists of the nucleic acid and an outer shell of protein.

Progression model of cervical carcinogenesis was shown in Fig. 3 including normal epithelium infection, HPV infection koilocytosis, cervical intraepithelial neoplasia (CIN) 1, CIN 2, CIN 3 and invasive carcinoma stages. During improvement from HPV infection to high-grade intraepithelial lesions, HPV oncogene expression is significantly expanded, while HPV particle generation goes down. Numerous flare-ups, cases, and deaths connected with HPV infection have happened with expanding frequency [15]. Around the world, cervical cancer is the fourth most regular disease in women [16–18]. An expected 530,000 new cases in 2012 equivalent to 7.5% of all female cancer death [19]. About 270,000 death from cervical disease consistently, which covers 85% of these happen in poor district countries. Early detection forbids up to 80% of cervical cancers in these countries [20]. Thus, high specificity and affectability biosensors, which are a fast and economical strategy for early identification of HPV cause cervical tumor, are definitely required. In this overview, progression in the detection of HPV E6 protein associated with cervical cancer is discussed with currently available strategies.

2. Co-existence of HPV in other cancers

The co-existence of HPV in other cancers involve in the neck, colon, respiratory, digestive tracts, and breast cancer. The relationship between HPV and malignant diseases at various body sites, including the upper respiratory and digestive tracts and the breast is still not clear. About 95% of anal cancers are caused by HPV [21–23]. Most of these are caused by HPV type 16. Oropharyngeal cancers are the cancers of the middle part of the throat, including the soft palate, the base of the tongue, and the tonsils. About 70% of oropharyngeal cancers are caused by HPV. In the United States, more than half of cancers diagnosed in the oropharynx are linked to HPV type 16. HPV causes about 65% of vaginal cancers, 50% of vulvar cancers, and 35% of penile cancers [24]. Most of

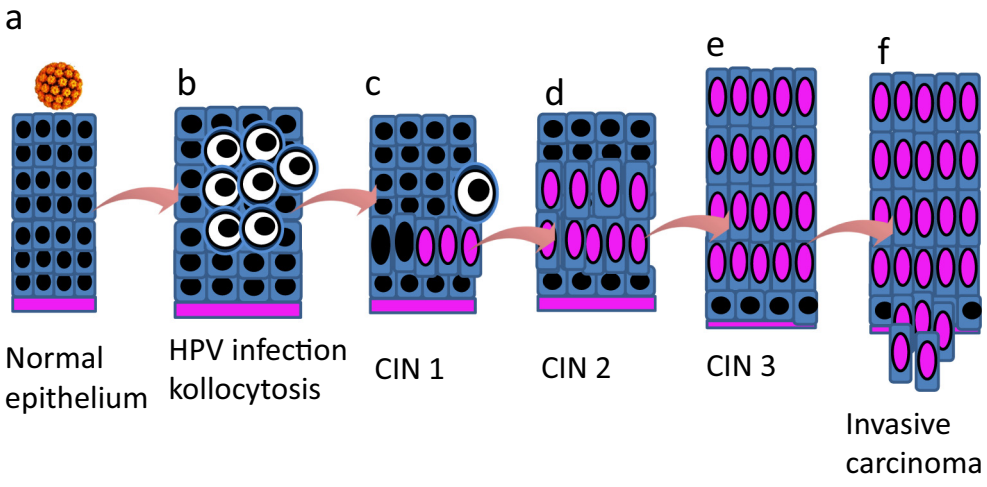

Fig. 3. Progression model of cervical carcinogenesis; (a) normal epithelium infection, (b) HPV infection koilocytosis, (c) Cervical intraepithelial neoplasia (CIN) 1, (d) CIN 2, (e) CIN 3, and (f) invasive carcinoma stages.

these are caused by HPV type 16. High-risk HPV types cause approximately 5% of all cancers worldwide [16,25]. In the United States, high-risk HPV types cause approximately 3% of all cancer cases among women and 2% of all cancer cases among men [25].

3. Current approaches for HPV detection

Clinical techniques for the recognition of cervical cancer include the following fundamental methods: pap smear [26], HPV genotyping [27,28], cytology screening [29] and serological confirmation [30]. All HPV screening tests right now are being used depending on the identification of viral nucleic acids based on the fact that HPV can't be cultured [31,32]. Table 1 showed a sensitivity limit of HPV detection in a clinical sample by using different detection methods.

3.1. Pap smear

Cancer screening techniques incorporate the Papanicolaou test (Pap smear) for women to distinguish cervical cancer disease. Pap smear became current cervical disease screening in industrialized nations [33]. Pap smear was presented in the recent century and has not been changed considerably since the 1940s [34]. Survival of a cancer patient is depending vigorously on early recognition. Advances research technologies for reliable and particular techniques to distinguish tumor are

Table 1
Sensitivity limit of HPV detection in a clinical sample.

Detection method	Advantages	Disadvantages	Biomarker	Sensitivity limit	Detection range	Detection time	Specificity limit	References
Pap smear	Current cervical cancer screening in industrialized countries Presented amidst the most recent century and has not been changed considerably from that since then	The biggest scale of uncertain or abnormal test outcomes that may cover a low number of high-grade precancerous cases Low sensitivity of Pap cytology Lack of reproducibility of the test results	–	Frequently repeated Sensitivity: varied between 34% and 94%	–	One week	Reliably high in most of the review studies	[61–63]
Southern blot hybridization assay	The gold standard for HPV genomic analysis. Iniquitousness of HPV in a relationship with morphology	Low sensitivity Tedious Large amounts of purified DNA Cannot use degraded DNA Limited because of the radioisotope usage	Isomers were used as markers.	Frequently repeated	5–25 ng/ml	2 days	–	[41,64]
HPV DNA genotyping using Polymerase Chain Reaction (PCR)	Decrease false-positive rate High reactivity to genotyping	Not design for genotyping individual strain of HPV Only amplified limited length.	L1 region L2 region	94.1%	12.8 DNA copies	2 h	–	[65,66]
Real-time PCR	Adaptable innovation (viral load and genotype) Bring down amplification signals of some HPV genotypes Very high sensitivity Multiplex analysis	Lower amplification signals of some HPV genotypes Contamination with the previously amplified material can lead to false positives	L1 region L2 region	98%	1 and 10 copies/10 (3) cells	1 h	–	[67–69]
HCII Hybrid Capture based on Enzyme-Linked Immunosorbent Assay (ELISA)	Quantitative FDA-approved test (HCII Hybrid Capture)	Only specific for 13 strain of high risk HPV	E6 protein	98%	5 pg/ml (500,000 copies/ml)	16 h	77–79%	[70–72]
DNA chips based HPV DNA Chip and sequencing	DNA biosensors and gene chips are of extensive recent involvement because of their gigantic guarantee for getting sequence-specific data Rapid, less difficult and less expensive way compared with conventional hybridization assays A recently presented HPV recognition system in cervical lesion HPV DNA Chip test contains 24 different HPV probes Having the ability to distinguish a few HPV types without a moment's delay	–	E6 region	99%	–	2 h	98%	[73]
Electrochemistry DNA Biosensors using thiolated single-stranded (ss) DNA immobilized SPE Au electrode	Suitable for microfabrication technology Low-cost point-of-care (POC) device for detecting specific DNA and RNA Fast and cheap diagnosis of inheritance disease Single-utilize sensors have a few favorable benefits, for example, reduce contamination among samples, steady sensitivity, and reproducibility Simple utilize in the field that no pre-treatment is required. Good calibration range of the target DNA sequence	Suffer from reusability The electrode can be used only once -	E6 region	2 pg mL^{-1}	0.5–5 ng ml^{-1}	30 min		[74,75]

an unavoidable task for cancer specialists. The Pap smear can be utilized as a screening test, however, has false negative up to half of the cases of cervical malignancy [35]. Pap smear became the largest proportion of uncertain or somewhat irregular test outcomes that may veil a low number of high-grade precancerous cases. Unfortunately, it had a low sensitivity of Pap cytology and absence of reproducibility of the test outcomes [36]. Cytological screening utilizing the Pap smear test has prompted to a considerable reduction of the frequency of cervical tumor. In spite of this obvious achievement, screening programs that depend on Pap-stained cytological specimens have a few constraints. Pap smear usually showed irregular test outcomes require expensive set-up by either repeated testing or direct colposcopy and biopsy since a specific rate of high-grade lesions that require fast treatment conceal among these indistinct test outcomes. This work with somewhat abnormal or obscure cytological tests expends an extensive portion of the full costs spent on cervical cancer screening. The detection time for running Pap smear take one week to finish the test sample.

Cytologic screening for precancerous cervical lesions can be done using Papanicolaou-stained smears. Cervical specimens for cytology are generally obtained by blindly inserting a moistened Dacron swab or cytobrush 5 to 6 cm into the ectocervix and rotating the device to sample the mucosa. Since it is important to sample the transition zone, a proctoscope or anoscope may be used to directly visualize the sampling site. Conventional smears or liquid-based cytology can be used. Inflammatory cells, mucus, blood, fecal material, bacteria drying artifacts, and thick preparations can obscure evaluation of the exfoliated cervical cells, and liquid-based cytologic preparations have been shown to increase diagnostic yield.

Discrepancies between cervical cytology and histopathology findings are common, and the severity of disease detected by cytology may not correlate with the severity of disease found on biopsy. Discrepancies can be due to sampling errors and/or interpretation errors for the cervical cytology specimen, the biopsy specimen, or both. Accurate interpretation is important since HSIL is treated and LSIL is followed with annual high-resolution colposcopy. Invasive squamous cell carcinoma is not usually a diagnostic difficulty and is defined by a proliferation of squamous epithelial cells that penetrate the basement membrane and invade the underlying stroma, often with an associated inflammatory response and desmoplastic reaction.

The most common screening test is liquid-based cytology, in which epithelial cells are collected using a cervical sampling broom, brush, or spatula, processed into a thin layer on a glass microscope slide, stained with Papanicolaou stain, and read using a microscope. The sampling method(s) used for the collection of exfoliated cells from the external genitalia, and the sensitivity of the assay used for the detection of HPV DNA. The region used in the past studies including E6 [37], E7 [38], mAb 5051 and HPV 16.

3.2. Southern blot hybridization assay

Southern blotting, where a DNA is being electrophoresed before exchange to a membrane film that is afterward hybridized to a labeled probe [39,40]. The transferred to a membrane support, bringing about immobilization of the DNA fragments, so the membrane film conveys a semipermanent propagation of the banding pattern of the gel [41]. After immobilization, the DNA can be subjected to hybridization analysis, sanctioning bands with sequence correspondence to a labeled probe to be recognized. This unit represents Southern blotting through the upward capillary transfer of DNA from an agarose gel onto a nylon or nitrocellulose membrane layer, and consequent immobilization by UV irradiation (for nylon) or heating (for nitrocellulose). Nevertheless, Southern blotting is work loaded and not reasonable for routine application. Consequently, optional hybridization system has been created such as DNA microarray [40,42,43]. Southern blot hybridization assay got to be a distinctly gold standard method for HPV genomic identification and it additionally proximity of HPV in a relationship with morphology [44]. Southern blot hybridization had their disadvantages; low sensitivity, tedious, a lot of purified DNA, can't utilize DNA which was degraded and limited because of the radioisotope usage [45,46]. The detection time for southern blot hybridization takes 2 days to finish the assay test.

3.3. HPV DNA genotyping

Polymerase Chain Reaction (PCR) is a promising technique for detecting HPV, the right method for high-risk HPV strains, which are in charge of cervical cancer [48]. PCR is being the most well-known method for HPV detection nowadays. Sample clinical preparation using Polymerase chain reaction (PCR) method as shown in Fig. 4 including specimen collection, a thermal cycler for PCR cycles (denaturation, annealing and elongation process), analysis result using gel electrophoresis and DNA sequencing for validation and confirmation. This method can even detect HPV with even one viral copy genome per cell [49]. However, PCR has some disadvantage because it can only amplify the limited length of the target [50], whereas the HPV genome is huge, >7.9 kb. Contrasts in biological properties and sequences typical of various regions are a selection of the target regions can be essential to a dependable result of a PCR with HPV discovery. Oligonucleotides probe usually based on the conserved region of the E6 region [51,52]. L1 region according to PCR with MY09-MY11 primer set, trailed by cycle sequencing of the product is recommendable [53]. PCR is most commonly used, can recognize a lower copy of a target DNA sequence, and therefore, can be utilized to identify a single pathogenic bacterium. It is promising because it identifies the organism by amplifying the target rather than signal, and is hence, less inclined to delivering false-positives. Thus, PCR detection of HPV has different superiority over serological and another standard test [54]. It offered various preferences of specificity, sensitivity, rapidity, precision, and ability to recognize little amounts of target nucleic acid in a specimen. PCR method is known to be responsive and yield both quantitative and qualitative data of the proven HPV strains. PCR amplimers can be identified effectively by standard agarose gel electrophoresis. Sequence particular analysis was significantly increments both the sensitivity and specificity of the measurement. However, this technique is relatively expensive and requires long assay time. Due to the troubles to perform serological test and HPV cultures proficiently, a few apparatuses supported on molecular identification have been produced for the determination of HPV infections [55]. On the common of molecular identification, the discoveries of HPV DNA are being used, in view of the extraction of genomic DNA from clinical specimens with post PCR amplification and recognition [55]. However, because of the high mutation rates in virus DNA amplification, detection by PCR is entangled at some point.

3.4. HCII hybrid capture

In a matter of timing, accessible techniques for identification are principally based on fast immunoassays that require specialist and are tedious and costly. Enzyme-linked immunosorbent assay (ELISA) is the available immunoassays that have been utilized widely to distinguish diverse types of infections with the right antibodies [56]. Fig. 5 showed sample clinical preparation using Enzyme-linked immunosorbent assay (ELISA) method including specimen collection, ELISA plate contained coated with anti-RNA: DNA hybrid antibodies, ELISA plate incubated in microplate heater at 65 °C for 60 min, ELISA plate was mix thoroughly by using microplate shakers, and analysis result by using Digene Microplate Luminometer 2000 (DML 2000™) [57]. The HCII dependably use to be an approval test for recognition of the high risk of HPV [58]. The research laboratory has been used HCII as a part of in-house analytical and clinical approval scrutiny. The HCII was endorsed by FDA as a validation test to test the presence HPV [59,60]. Fig. 6 shows the HCII standard application included 5 main steps. The lysis solution is utilized to break off the virus cells and bring out DNA in the HCII

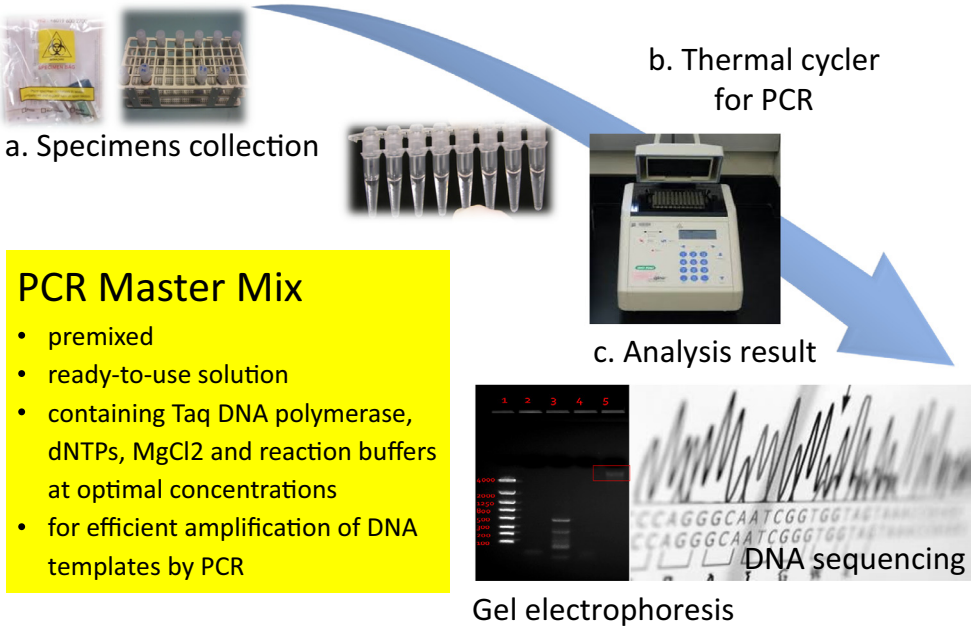

Fig. 4. Sample clinical preparation using Polymerase Chain Reaction (PCR) method (a) Specimen collection (b) A thermal cycler for PCR cycles for denaturation, annealing, and elongation process (c) Analysis result using gel electrophoresis and DNA sequencing for validation and confirmation.

test. The target DNA is complemented with particular RNA. The DNA/RNA hybrid is caught by particular antibodies that acting as capture bioreceptor that immobilized on the microplate. The RNA/DNA hybrid is recognized by the secondary antibody which is conjugated with enzyme alkaline phosphatase. At the point when the substrates are a mix in, the color of the solution was changed into yellow showed the existence of RNA/DNA complement. The indicator signal is enhanced because of enough antibody molecules connected on the hybrid. Hybrid capture systems are available to recognize HPV. The benefit of utilizing HCII compared to PCR is the amplicons were not disturbed in the research set-up. Other than that, the cross-contamination can be deflected.

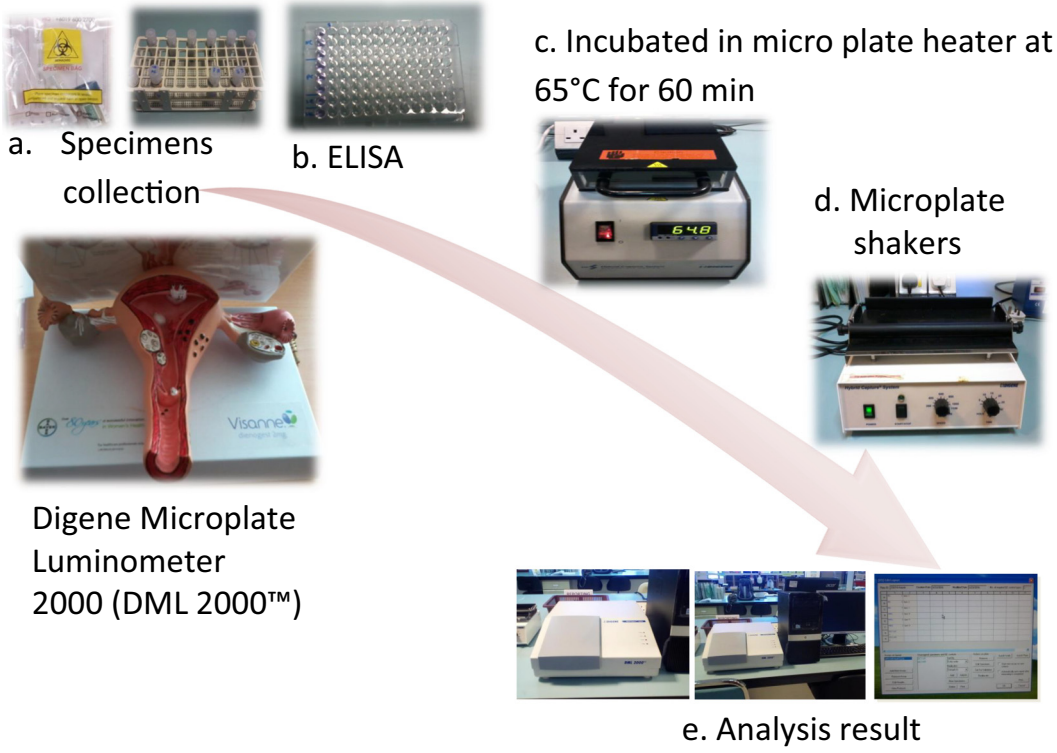

Fig. 5. Sample clinical preparation using Enzyme-linked immunosorbent assay (ELISA) method (a) Specimen collection (b) ELISA plate contained coated with anti-RNA: DNA hybrid antibodies. (c) ELISA plate incubated in microplate heater at 65 °C for 60 min (d) ELISA plate was mix thoroughly by using microplate shakers (e) Analysis result by using Digene Microplate Luminometer 2000 (DML 2000™).

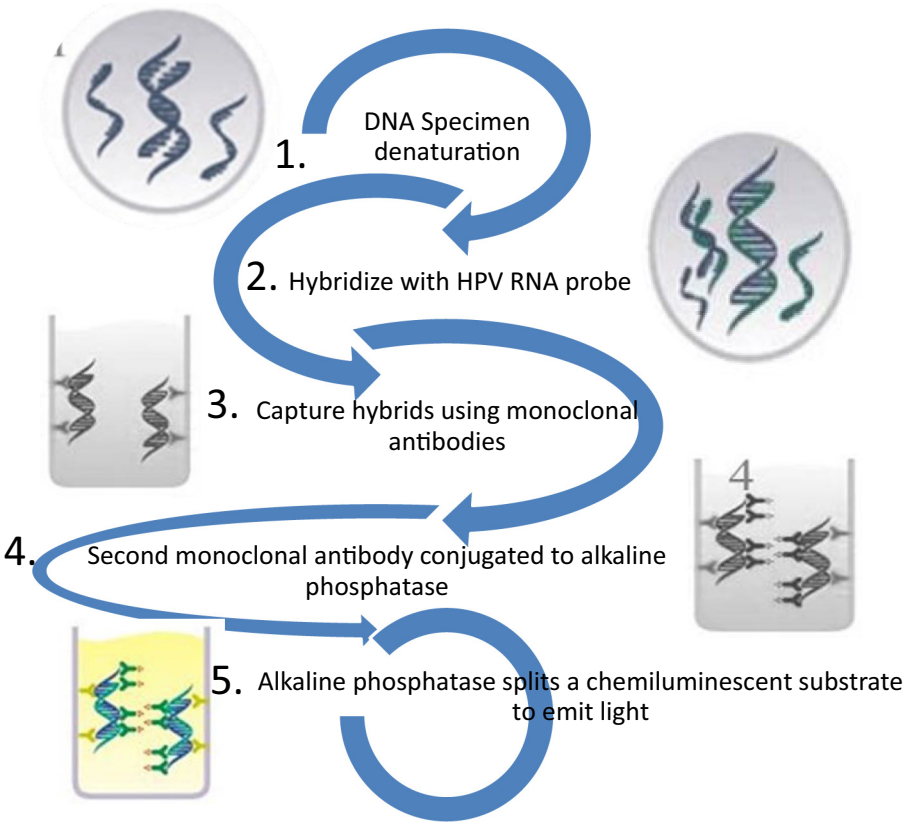

Fig. 6. Schematic diagram of the HCII Hybrid Capture principle application included 5 different steps. (1) DNA specimen denaturation; (2) Hybridize with HPV RNA probe; (3) Capture hybrids using monoclonal antibodies on microtiter plates; (4) Addition of second monoclonal antibody conjugated to alkaline phosphatase, and (5) Alkaline phosphatase splits a chemiluminescent substrate to produce the light.

3.5. Development of biosensor

Currently, the growth of a biosensor for HPV virus diagnosis makes a promise a fast, sensitive and simple to perform. Biosensor comes with the incomparable competency for actual-time and on-spot analysis. On the spot detection of HPV virus is significant since it helps medical doctor especially Obstetrics and Gynecologist (O&G) to diagnose cervical cancer in faster ways. Cervical cancer can be treated if the associated HPV infection detected at an earlier stage before developing a precancerous or cancerous change in the cervix [76]. The lack of a good understanding of the sensing mechanism hampers the further exploitation of these promising nanosensors. The sensing was dominated by a combination of electrostatic gating effect. A small electrostatic disturbance caused by nearby biomolecules can lead to a significant change in device conductance.

The relevance of clinical sample testing using biosensors was used to validate the efficiency of the sensor in the field application. The constructed biosensor was able to detect the extracted genomic DNA indirectly from the clinical sample. The selectivity test by using synthetic target, non-complementary and mismatch to prove that the sensor was working successfully but still have intact purities. The system was found to be highly selective by differentiating complementary and mismatched samples.

Table 2 showed summary of IDE biosensor for detection of HPV virus using different transducer. From previous work, the immobilization was based on the ionic interaction between the negatively charged phosphate group of the DNA and the positively charged amine from L-cysteine that cover the surface electrode [77]. The comparisons with the performance of sensing devices from previous studies had been included in this research to value the impact of the current work in the

Table 2
Summary of IDE biosensor for detection of HPV virus using different transducer.

Probe type	Target	Disease	Detection type	Transducer	Detection limit	Real sample	References
PNA	HPV	Cervical cancer	Direct detection	Piezoelectric QCM	1.21 pg/L	–	[82]
DNA	HPV 16	Cervical cancer	Label-free	Electrochemical DNA biosensor based screen-printed gold electrodes (SPGE)	18.43 nM	Cervix tissue (endocervical swab)	[77]
PNA (14 mer)	HPV 16	Cervical cancer	Label free	Electrochemical DNA biosensor based screen printed carbon electrodes (SPCE)	4 nM	HPV type 16 positive human cancer cell line (SiHa)	[78]
Aptamer	HPV 16-L1	Cervical cancer	Label free	Electrochemical DNA biosensor based screen printed electrodes (SPE); Cyclic voltammetry	490pM	–	[80]
DNA	HPVs 6. 11,16. 18	Cervical cancer	Label-based detection	Genotyping microarrays	0.05 pmol/μL	–	[83]

field of determination of the HPV virus. The biosensor dedicated to molecular detection techniques of HPV strains that prove biosensor methods less complicated and execute from prolong experiment process involve amplification [78,79].

In the major case, 20-mer probe sequence was immobilized on the top of a graphite electrode and utilized for the identification of target L1 of indistinguishable lengthiness by enrolling the varieties in methylene-blue reaction prior and then afterward target identification, accomplishing a limit of detection (LOD) of 1.2 ng/μL (0.5 nM) [55,80]. The other case required to utilize a bioelectronics DNA identification stage earlier known as eSensorTM, for the recognition of HPV sequences depend on thiolate probes immobilized on the surface [80,81]. After the immobilization process, a probe labeled by ferrocene is hybridized and the actual reaction is measured [80].

RNA, DNA, protein and the cancerous cell can be detected by using GNPs based colorimetric assays. Unfortunately, HPV is the most sexually transmitted viruses to the reproductive system and can be transferred through the skin to skin contact [37]. Cancerous cells can be dangerous without proper handling, so DNA biosensor has been chosen in this research study to prevent these circumstances.

Surface modification of inorganic biomaterials has become one of the tremendous research topics in biosensor [84–87]. Surface modification on IDE by using APTES as an assemble monolayer have their own function to limit nonspecific adsorption of other compound comprising the non-complementary DNA or RNA. APTES prevent interaction between the DNA probes and GNPs surface and leaving DNA probes position in the mostly upright state available for DNA hybridization.

The regeneration of the biosensor was beneficial to minimize the cost of the analysis, but only a few publications report reusable electrochemical biosensors [37,38]. The most frequent sensor platform to immobilize the oligonucleotides by using gold electrode, achieving the interaction through thiol-gold covalent bonding. The desired result of AuNPs with single-stranded thiol-modified probe was only achieved if the target is of the same length as the probe [88]. Baptista and coworkers improved this technique to detect long nucleic acids; however, it still depends on either high ionic strength or the pH to induce AuNPs aggregation [89]. Instead of a DNA biosensor, electrochemical microarray based on label-free biosensor has been used extensively for the detection of different HPV16 antibodies [79]. The sensing method based on the interaction between monoclonal antibodies (mAb 5051) and HPV 16.

Biosensor researchers were employed with HPV virus strains as a model to study the interactions between the biorecognition element and the transducer. Table 3 showed biosensor techniques applied for HPV detection and the comparison of GNP/APTES/modified COOH HPV E6 probe based IDE with the available literature on other reported sensing devices for HPV DNA. The comparisons with the performance of sensing devices from previous studies had been included in this research to value the impact of the current work in the field of determination of the HPV virus. The biosensor dedicated to molecular detection techniques of HPV strains that prove biosensor methods less complicated and execute from prolong experiment process involve amplification [78,79].

Instead of a DNA biosensor, electrochemical microarray based on label-free biosensor has been used extensively for the detection of different HPV16 antibodies [79]. The sensing method based on the interaction between monoclonal antibodies (mAb 5051) and HPV 16.

The insertion of GNP on the IDE surface allowed spaced probes at an optimal distance from each other to allow for high hybridization efficiencies and specificity [90]. DNA probes that are too packed and closely cannot participate in hybridization due to electrostatic interaction and steric hindrance (Fig. 4). This is called crowding effect that produced low signal intensity due to the compact arrangement of probes. The DNA targets do not have enough space to hybridize to the immobilized probes. The crowding effect was the main problem in most immobilization methods and can be solved by using GNP integration between surface functionalization [90]. DNA immobilized surface with sufficient distance between the DNA probe produced high hybridization yield. The performance of electrical DNA biosensor using IDE has been investigated by checking the modified probe hybridization with extracted DNA from cervix tissue specimen samples. The extracted DNA samples were directly used on the IDE sensor, different from other previous work that used PCR products for HPV detection.

4. Why the HPV E6 region?

Two early regions, E6 and E7 genes of HPV regions were observed to be the most imperative factors in cellular transformation induced by high-risk HPV [93–95]. A part of the E6 region of HPV genomic has been chosen as a biomarker due to its unique region characteristic [90,96]. E6 region is used for coding for oncoprotein with a high transforming activity [97–99]. It also oncogenic regions of HPV and retained after infection, whereas E2 and L1 can be deleted [100,101]. E6 region is also exhibiting strong sequence conservation, differs between high and low-risk HPV types [47,102–104]. HPV DNA is incorporated by chance amid the cell repair procedures of double-strand denaturation [63,105]. A few techniques exist to distinguish the integration of HPV DNA into the host genome. A basic approach is a real-time PCR-based evaluation of the E2 and E6/E7 gene proportion [63,106–109]. E6 open reading frames are the most plentiful viral transcripts in tumors and tumor cell lines; these oncogenes are fundamental and adequate to incite an HPV-mediated transformation of murine cells 21 and the deification of human fibroblasts [110].

5. HPV DNA as biomarker probes

An easy utilization of biomarkers in cervical tumor screening is the immediate identification of the markers by biochemical characterization in cervical samples [63]. Lately, DNA has used a biomarker probe due to their simple characteristic and denaturation process [111,112]. Zari et al. have fabricated the ssDNA immobilized screen-printed electrode (SPE) for the discovery of short DNA fragments particular to HPV by hybridization [75]. They have utilized guanine oxidation signal to detect the hybridization phenomena by treating DNA with 0.5 M hydrochloric acid and the acid-released purine bases can be detected using SWV [75]. Under optimal conditions, this sensor has a decent calibration scope of target DNA sequence with detection point limit of 2 pg ml^{-1} but suffers from its reusability [75]. As guanine oxidation is monitored, the electrode can be used only once [113]. Civit et al., [55,55] reported a confirmation of-idea of an electrochemical genosensor array for the concurrent identification of two HPV strains, HPV16E7p and HPV45E6 sequences [55]. The detection limit obtained is in the picomolar range that is sufficient for the majority of genuine RNA/DNA tests acquired from PCR amplification [55].

DNA based biosensors have as of late increased much enthusiasm from established researchers because of the conceivable application like gene analysis, human diagnostics or environment monitoring [114]. Recent trends in biosensor innovative research have numerous headings: to enlarge the spectrum of detectable particles by a method for new receptor structures, moreover, to enhance sensor parameters (detection limit, sensitivity, selectivity) utilizing the setup and demonstrated standards, and to coordinate these standards into point-of-care or laboratory devices [115,116].

6. Biosensors

An effective biosensor must have some of the following beneficial characteristics. The biocatalyst must be very particular with the end goal of the analyses, be steady under typical storage conditions and, aside from the colorimetric enzyme strips and dipsticks, demonstrate great dependability and stability over countless assays (i.e. much more prominent than 100) [117]. The reaction in biosensor should have

Table 3
Biosensor techniques applied for HPV detection.

HPV type	Sensor mechanism platform/transducer	Sensing method	Technique	Detection limit	Detection range	Detection time	Reusability	Real Sample	References
HPV 16, 18 and 45	Gold surface/oligoethylene glycol-terminated bipodal thiol/thiolated HPV 16 E7p, HPV 18 E6 and HPV 45 E6 probes	The detection was carried with the target hybridized between a surface immobilized probe and a HRP-labeled secondary reporter probe. The TMB was used as a chromogenic substrate for HRP	Cyclic Voltammetry (CV)	220 pM (HPV 16 E7) 170 pM (HPV 18 E6), and 110 pM (HPV 45 E6),	0.1 nM to 50 nM	20 min	5 tests	Cervix tissue	[37]
HPV 16	Single walled carbon nanotube arrays/GNP/HPV E7 probe	Hybridization between the capture probe and the HPV target, specific to HPV 16 (E7 region)	Electrochemical Impedance Spectroscopy (EIS)	1 aM	1 aM to 1 μM	2 h	6 tests	–	[38]
HPV 16	Gold surface/L-cysteine/HPV 16 oligonucleotide	The measurement based on the reduction signals of methylene blue (MB) before and after hybridization between the probe and the synthetic target or extracted DNA from real samples	Differential Pulse Voltammetry (DPV)	18.13 nm	18.75 nm to 1000 nm	10 min	–	Cervix tissue	[77]
HPV 16	Pencil graphite surface/HPV 16 E6 probe	The hybridization between the capture probe and the HPV 16 E6 gene was directly detected through guanididne oxidation signals	Differential Pulse Voltammetry (DPV)	16 pg/μl	5 pg/μl to 40 pg/μl	5 min	–	–	[91]
HPV 16	Carbon surface/chitosan/antraquinone labeled pyrrolidinyl peptide nucleic acid (acpcPNA) probe	The hybridization with HPV DNA was studied by measuring the electrochemical signal of the label anthraquinone attached to the acpcPNA probe	SWV	4 nm	0.02 nm to 12 nm	15 min	–	–	[78]
HPV 16	Glassy carbon surface/graphene/Au nanorod/polythionine/HPV 16 probe	Besides the capture probe, two auxiliary probes were designed for the hybridization with HPV DNA. 1,10- Phenanthroline ruthenium dichloride ($[Ru(phen)_3]^{2+}$) was used as the electrochemical indicator	EIS and DPV	4.03×10^{-14} mol/L	1×10^{-13} to 1×10^{-10} mol/L	90 min	–	–	[92]
HPV 16	Polymethylmethacrylate substrate/gold nanolayer/4-aminothiophenol/monoclonal antibody (mAB) 5051	Interaction between mAb 5051 and HPV 16	CV and EIS	–	–	1 h	–	–	[79]
HPV 16	GNP/APTES/modified COOH HPV E6 probe based Interdigitated Electrode (IDE)	Hybridization between the modified COOH HPV E6 probe and the HPV synthetic target or extracted DNA from real samples	Electrical biosensor	1.0 pM	1 pM- 1 μM	30 min	5 tests	Cervix tissue	[90]

independent physical parameters, for example, mixing, pH and temperature as is reasonable [118]. This would permit the analysis of tests with insignificant pre-treatment [119]. In the reaction that the response includes cofactors or coenzymes, these ought to, ideally be co-immobilized with the catalyst [119]. The reaction ought to be accurate, precise, reproducible and straight over the analytical range, without dilution or concentration [119,120]. It ought to likewise be free from electrical noise. In the event that the biosensor is to be utilized for intrusive observing as a part of clinical circumstances, the test must be small and biocompatible, having no harmful or antigenic impacts [119,121]. This is ideally performed via autoclaving however, no biosensor enzymes can withstand with intense wet-heat treatment [122]. In either case, the biosensor ought not to be inclined to fouling or proteolysis [123]. The complete biosensor ought to be cheap, small, portable, compact and fit for being utilized semi-skilled operators [124].

6.1. Electrochemical DNA biosensor

Electrochemical DNA biosensor can be utilized for label-free and labeling detections. They recognized changes and measure the current between a probe metal electrode and a sample containing the analyte (target). The electrode potential is connected from the feedback current and the subsequent current can be measured. One strategy utilizing electrochemical detecting incorporates slowly increasing the voltage, bringing the chemical substance at the electrode to be oxidized or reduced. Current versus voltage is plotted, which can distinguish the amount of chemical substance consumed or produced at the electrode [125,126]. Fast detection of viruses has significant inferences for medical services. The available and accessible strategies for identification are basically by using fast immunoassay methods that require a prepared specialist, tedious and costly. In any case, a biosensor encourages a specialist to distinguish the particular virus infection rapidly and recommend a proper course of treatment. Virus infections can be beneficially utilized for the advancement of a continuous detecting to firstly and specifically recognize target in different critical conditions, for example, under acidic or fundamental pH ranges.

Electrochemical DNA biosensors for HPV detection with amperometric labeled detection and impedimetric label-free detection are less explored [55]. Electrochemical biosensors have gotten impressive consideration in regards to the recognition of DNA hybridization because of the flexibility of minimal cost, straightforwardness, high affectability, availability with mass assembling, the plausibility of

microfabrication innovations and versatility, making them the great possibility for point-of-care DNA diagnostics [55]. Electrochemical identification of HPV related sequences have been modifiable for in the past by utilizing methylene-blue as hybridization marker [127] or secondary probes labeled with ferrocene [81]. In the main case, 20-mer probe sequence was immobilized on the surface of a graphite electrode and utilized for the identification of target L1 of indistinguishable length by recording the varieties in methylene-blue reaction prior and then afterward target recognition, accomplishing a limit point of detection of 1.2 ng/μL (0.5 nM) [55,80]. The other case required to utilize a bioelectronic DNA identification stage earlier known as eSensorTM, for the recognition of HPV sequences based on thiolated probes immobilized on the chip surface [80,81]. After target immobilization, a ferrocene-labeled probe is hybridized and the present current reaction is measured [80]. This kind of chips can recognize 86% of HPV targets contained in clinical specimens utilizing a positive or negative type's reaction [55]. In a later report, identification of HPV is done by treating a captured dsDNA duplex with acid and specifically measuring the discharged purine bases by square wave voltammetry [75].

7. Interdigitated electrodes (IDEs)

Interdigitated electrodes (IDE) which are comprised of two independently addressable interdigitated comb-like electrode structures have much of the time been recommended as sensitive nanobiosensors. IDE with an electrode detachment of less than one micrometer is coveted for most signal amplification enhancement. Fabrication of submicron structures can be made by advanced lithography methods. The IDE nanosensor is fabricated on a silicon-on-insulator (SOI) wafer with a 145 nm buried oxide layer [90,96,128,129]. Biosensors using IDE pattern construction usually have functionalization into two types which are capacitive and resistive sensors [130,131]. Fig. 7 showed a basic schematic diagram of fabrication flowchart contained ⟨100⟩Silicon substrate, SiO_2 on Silicon substrate, aluminum coated SiO_2 on a silicon substrate and the IDEs pattern transferred. Fig. 8 showed IDEs biosensor fabrication process involved silicon wafer cleaning, an oxidation process, photolithography, metal deposition, strip photoresist and fabricated IDEs. The sensing layer of the resistive sensor is acted as the resistor. As a capacitive sensor, it is acted as the dielectric between two parallel electrodes. The resistive sensor has measured the changes of resistance in the sensor while the capacitive sensor measures the capacitance [132,133]. IDE biosensor has an advantage of the larger surface area for sensing mechanism, provides low energy consumption to measure the biological changes and easier to manufacturing compared to other biosensors [134,135].

8. Invasive versus non-invasive methods for HPV detection

Invasive method for HPV detection for cervical cancer required the entry of specimen STM swab into the vagina for pap smear test [136]. Women are always afraid and shy to do regular pap smear test because involve expose of their vagina to the medical doctor. Besides that, the blood sample from the patient needs the entry of a needle into the part of body skin. Collection of blood samples for HPV screening test also give bad risks to the patients such as wounding, contamination at the venipuncture, furthermore anemia if a large volume of samples needed for continuous detection assay [137]. Non-invasive strategy implies the body is not occupied or cut open as amid surgical examinations or therapeutics surgery [138]. Saliva is a non-intrusive technique and free from stress diagnostic, another option to invasive strategy utilizing blood [139]. Passive drool samples became the gold quality level standard for examination of saliva that nonstimulated [137]. Replacement of saliva samples instead of blood collection in samples analysis was interesting because saliva collection did not have any risks correlated to blood intake.

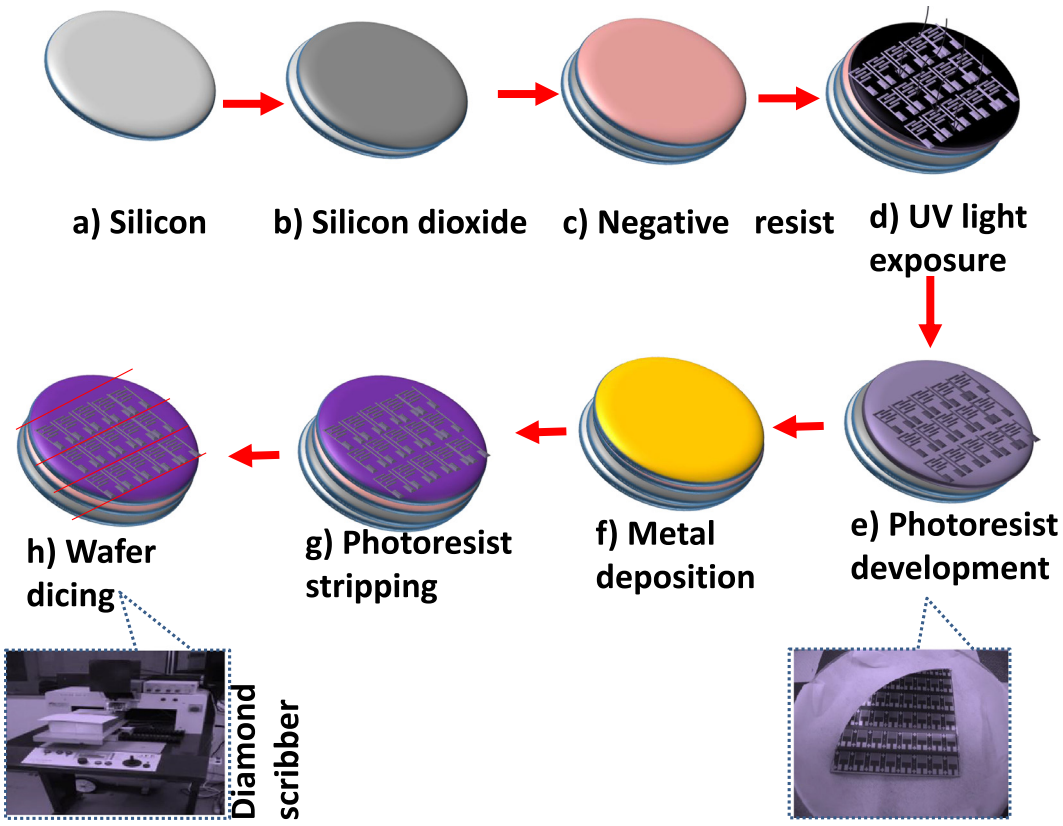

Fig. 7. Schematic diagram of basic fabrication process flowchart. (a) ⟨100⟩Silicon substrate (b) SiO_2 on Silicon substrate (c) Aluminum coated SiO_2 on silicon substrate (d) IDEs pattern transferred.

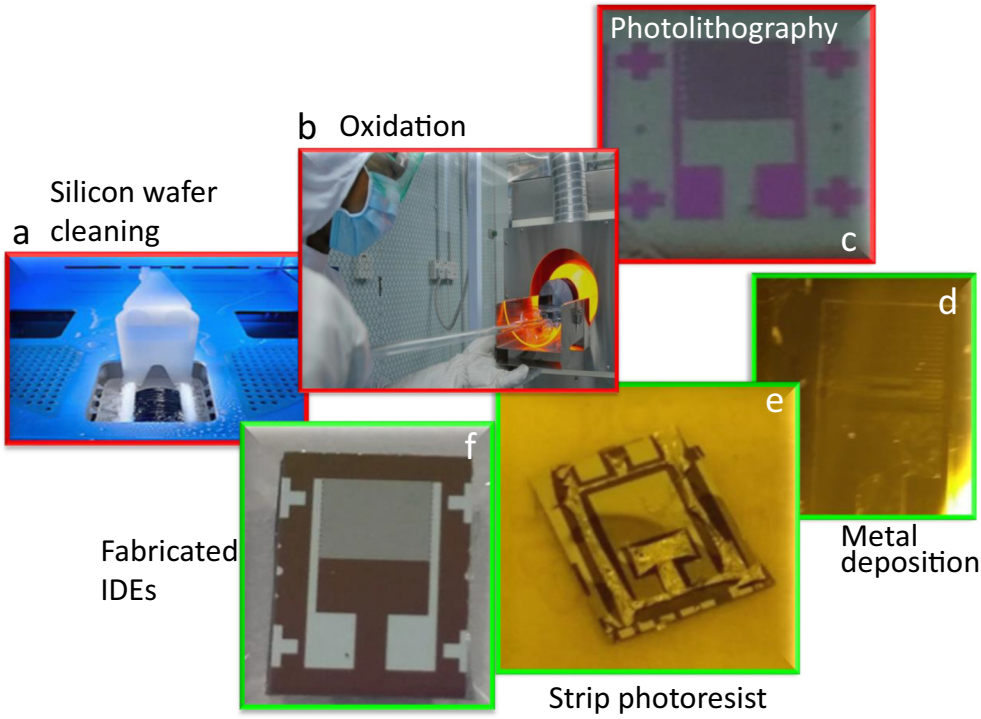

Fig. 8. IDEs Biosensor fabrication process. (a) Silicon wafer cleaning (b) Oxidation process (c) Photolithography (d) Metal deposition (e) Strip photoresist (f) Fabricated IDEs.

Salivation has a few points of interest compared with blood and urine, two of the most utilized demonstrative liquids as a part of a research facility setting. Saliva accumulation is simple and non-invasive requiring generally straightforward guidelines for collection and it has a lower protein content, less complexity and changing structure than serum. Salivary DNA is being routinely utilized as a part of numerous clinical labs for surveying the genetic susceptibility to different diseases. Useful of saliva as a non-invasive diagnostic device such as lab-on-chip [140] for DNA biosensing [141] in bio-behavioral studies has been considered for recognition of HPV that cause cervical malignancy tumor.

9. Conclusion and future perspectives

HPV is sexually transmitted viruses that cause transmitted diseases and cancers such as Cervical. Cervical cancer can be treated if the associated HPV infection detected earlier before developing a precancerous or cancerous change in the cervix. There are as of now many tests accessible for recognition of HPV including Liquid Based Cytology (LBC), HPV genotyping and HCII Hybrid capture that already become commercialized for the laboratory test. However, the main constraint of these commercial detections was time-consuming and it needs an expert to predict and detect the HPV infection that causes cervical cancer. Currently, the gold standard for HPV screening is based on Pap smear integrate with HPV genotyping that called co-testing, which can be used in hospital and clinic. Besides that, the test only can mainly be performed by medical practitioners and specialists due to medical ethics issue. The future goal for HPV screening test is expected to be performed by low cost, simple, reliable and easy to handle.

DNA detection for HPV screening has been extensively studied due to their simple and unique characteristics. Since E6 region has been used as a biomarker which exhibits as strong sequence conservation, differs between high and low-risk HPV types. Previous research demonstrated using a cervical swab and invasive blood-based screening as a collection of the sample prior to detection. Saliva has been utilized as a non-obtrusive strategy for bio-checking and became a higher rate of interesting in sample collection. It is because of a fear attitude with regular check-up with Pap smear associated injection for blood collection.

By 2015 until 2020, the products that were tried in academic and government research facilities will be commercialized into the industrial market. Detection of disease cells in diagnosis would be faster perhaps at the point of a single sick cell while permitting infected cells to be cured without a moment's delay before they spread and influence different parts of the body. Advancement in nanotechnology should be continuous research because it promises great advantages and exposures; in any case, testing ought to be ongoing to guarantee the human-safety. We have summarized the current progression of HPV detection methods for early identification of cervical malignancy tumor. The biosensor method is the most encouraging for the advancement future screening of HPV because of their capacity to create fast and precise measurement information, yet there are numerous changes that ought to be made to enhance their outstanding capacity. Building up a fast and simple identification technique for the early detection turns into a captious issue with a specific end goal to minimize the disease among the human populace. Future research also needed to assess screening program in low-income countries and poor health accommodation to examine the effectiveness of self HPV screening by using saliva as a screening technology strategy.

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