High-Sensitivity Screening: Evaluating Triage Specificity Overloads and Over Treatment Risks in Primary HPV And Self-Sampling Paradigms

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Abstract*—Although the movement towards HPV DNA screening and patient-administered self-sampling has led to enhanced coverage and sensitivity, the secondary public health issue that arises is triage overload. Transient HPV infections, which tend to resolve on their own without treatment, are being picked up like never before. The downstream effects in infrastructures where resources are limited are massive; positive cases overwhelm colposcopy facilities, making screening economically inefficient and mentally stressful for unnecessary over treatment. This research seeks to illustrate the challenges associated with the specificity of primary tests. The findings of our study reveal that without high specificity during the triage process, increased sensitivity will destabilize the entire process.

***Index Terms*—Cervical Cancer, Primary HPV Testing, Self-Sampling, Over treatment, Resource Allocation.**

I. INTRODUCTION

A. Changes to Global Cervical Cancer Prevention Paradigm Models

There have been many modifications within the framework of structured models for cervical cancer prevention in recent decades. Previously, the structured system used classical exfoliative cytology, which involved the Pap smear test for checking abnormalities in the cervical epithelial cells [19]. It goes without saying that the application of cytological screening contributed to the reduction in cancer cases among people living in developed countries, yet practice revealed certain flaws within the process of using these types of screening methods. In fact, the sensitivity rate of cytology remains relatively low and extremely unreliable, as it ranges from 50% to 70%. Therefore, the screening tests need to be conducted frequently in order to ensure effective results. At the same time, structured cytological screening demands various resources like quality assurance programs in laboratories, qualified personnel, and treatment facilities, which can hardly be found in LMICs [8, 9]. To overcome these structural limitations, there was much support for the shift toward primary molecular diagnostics based on the detection of HPV DNA [1, 13]. Since chronic infection with high-risk strains of HPV (HR-HPV) causes more than 99% of cases of cervical cancer, HPV DNA detection becomes a binary criterion which does not rely on subjective assessment in cytology, where cells need to be inspected individually [20]. From the epidemiological point of view, having a negative HPV test produces much higher negative predictive value than a negative Pap test over time [10]. This change in guidelines resulted in extending routine diagnostic screening from three to five or even ten years depending on the age profile [11].

B. The Increasing Trend towards Patient-Based Decentralized Techniques

On one hand, the advent of reliable HPV self-sampling kits broke down the multitude of barriers previously constraining vulnerable and under-served groups. Classical screening procedures require a pelvic exam conducted through a speculum and can only be administered by a medically trained specialist in a designated clinic setting. This system has created structural constraints that lead to persistently low coverage rates for rural residents, individuals of economically deprived backgrounds, as well as communities adhering to cultural/religious norms of modesty. This barrier is circumvented through the technique of self-sampling, wherein the test participant collects their cervical/vaginal sample using

an ergonomically designed brush/swab [2].

Data gathered from different programs in the healthcare field clearly demonstrates that introduction of self-sampling has had a substantial effect on improving participation among groups that could not be reached earlier [2]. With the help of mobile apps and the use of smart devices for monitoring adherence, self-sampling kits were embedded in current healthcare delivery methods, creating fully automated tracking networks independent from the conventional setting of hospitals [3, 4]. As a result, the initiation of testing process was moved from hospitals to patients' homes.

C. The Emergence of the Sensitivity Paradox

Nevertheless, evidence from practical implementation from large-scale regional/national projects shows that achieving maximal entry-level sensitivity without adequate triage specificity causes serious systemic failure later on. This problem is termed the "Sensitivity Paradox." Since primary tests measure molecular levels based on amplified DNA of the virus, they yield a positive result to all high-risk viruses present in an active form irrespective of integration into the genome and initiation of tumorogenesis.

Given how sensitive DNA tests become when scaled up among a whole populace through self-testing without proper clinical gatekeepers, many cases of transient self-limiting infections that pose no threat at all in terms of oncogenesis are intercepted. In areas where health care systems are either weak or impoverished, such an uncontrolled wave of positive results leads to the emergence of a very specific type of bottleneck effect. Namely, this bottleneck concerns the overloading of the whole clinical system, from colposcopic rooms to state funding being wasted on redundant diagnosis processes, as well as to thousands of healthy women becoming psychologically impaired due to being diagnosed with a high risk for cancer. This paper explores the systemic effects of such bottlenecks by analyzing theoretical and real-life data [4, 5].

II. THE MECHANISTIC PROBLEM: TRANSIENT VS. ONCOGENIC INFECTIONS

A. Viral Clearance through Biological Process and Immunity Mechanism

To get an understanding of the constraints of the molecular screening process without triage, one needs to look at the biological life cycle process of HPV infection in the human host. Epidemiological evidence of HPV demonstrates that while there is a great deal of exposure, there is also very high spontaneous clearance of the virus. Following exposure to trauma to the stratified squamous epithelium in the transformation zone of the cervix, the HPV virion will penetrate the lower layers of the epithelial cells, thus initiating a low-level episomal replication process. Most often, through the actions of cell-mediated immunity of the host, capsid proteins and early expression of the virus are recognized, resulting in the elimination or inhibition of the virus within 12 to 24 months [6].

From statistical studies, 90% of high-risk types of HPV, which may include highly aggressive strains like HPV-16 and HPV-18, will go away on their own without creating any form of irreversible cellular damage or triggering neoplastic change. True oncogenesis is an unusual biological deviation and takes place when there is an alteration within the infection that causes it to move from a transient phase to become a persistent phase. As time passes, the DNA of the virus may rupture and insert itself into the host's genome [6].

B. Pathological Over-Diagnosis and the Failure of Subjective Verification

Since primary testing for molecular markers depends predominantly on nucleic acid amplification methods such as PCR or nucleic acid hybridization, it serves primarily as a virology test and not as a malignancy test [20]. The method fails to detect biologically the important difference between an episomal virus with limited clinical consequences and a transforming disease process. The problem of diagnostic ineffectiveness is further compounded when the technique is used on patients below 30 years of age, who although sexually active and thus exposed to the virus, do not have any clinically significant lesions that require surgery [10, 11].

In case the criteria for public health do not have a very objective molecular gatekeeper for choosing these cases, they will adopt the approach of direct referrals. The positive viral DNA cases will be referred to the second step for verification using biopsy under colposcopic examination or via the use of acetic acid and Lugol's iodine visualization (VIA/VILI) [8, 9]. In

clinical scenarios that lack resources, the visual verification technique has failed to solve the issue of specificity. The VIA and VILI techniques are extremely subjective, being dependent on the subjective evaluation of the stained or unstained vagina [5].

Under the skilled eye of a physician, the visual approach is often enough to identify large lesions; but through a widespread decentralized public health system, the minute reactions in tissue resulting from benign viral infection are often mistaken for genuine precancerous lesions. For fear of not catching the cancer early on, physicians working under the "Screen-and-Treat" paradigm often engage in the quick application of ablative and excisional therapies, including cryotherapy, thermal destruction, or loop electrosurgical excision procedures (LEEP). This means thousands of women with benign viral infections that would be otherwise resolved without medical intervention face surgical procedures and the associated dangers of stenosis and preterm delivery [12].

III. METHODOLOGY AND OPERATIONAL MODELING

A. Structure of System Throughput Simulation Model

The structure of the system throughput simulation model adopted for measuring and interpreting the compromises that would have been done on the two measures – screening and triage criteria – is as follows. The structure of this model is mathematically modeled to simulate the development and resource consumption of an artificial cohort of 50,000 women within the ages of 25-65 years over many years. Parameters of the artificial population concerning epidemiological measures are set according to the global statistics related to epidemiology.

Protocol A:
Primary cytology screening (Pap smear test), with follow-up tests automated.

Protocol B:
Primary HPV self-sampling screening with triage using visual inspection (VIA).

Protocol C:
Primary HPV DNA testing along with rapid and highly specific triage using biomarkers (p16/Ki-67).

Key Performance
Measures included: number of referrals to colposcopy, number of transient infection cases incorrectly diagnosed, time to depletion of resources, and patient retention in the process of triaging [10-14,15].

B. Primary Evaluation Criteria and Constraints

The primary criteria for evaluating the sustainability over time of each protocol architecture were defined as follows:

- Colposcopy Referrals Index:

The sum of secondary referral cases produced through screening, in relation to 1,000 screened patients. This criterion is an indicator of the workload that a secondary facility clinic will face directly.

- Rate of Overtreatment:

The percentage of screened subjects whose biopsies showed no high-grade abnormalities, including those who have sub-CIN2 conditions or are just transitory viral carriers.

- System Exhaustion Time (Tex):

A calculated metric denoting the time (days) needed before patient referrals exceed the available diagnostic capability of local hubs.

- Loss-to-follow-up:

The mathematically modeled rate at which people will drop out due to delays, bureaucratic issues, and psychological stress [14, 15, 18].

IV. RESULTS AND DATA ANALYSIS

A. Measuring the Colposcopy Referral Saturation Level

The data outputs derived from the discrete-event simulations refute the widely held public health hypothesis that the optimization of entry level test sensitivity results in a better or more efficient preventive strategy. Protocol B, which involves Primary Self-Sampling and subjective VIA triage, caused a sudden and excessive rise in downstream

clinical referral volumes. In the group of 50,000 patients simulated, Protocol B resulted in a referral of a huge number of patients for secondary clinical care [12]. This protocol yielded a Colposcopy Referral Volume Index of 142 referrals per 1,000 cases tested, translating into a 215% increase in clinical load over the baseline set up by Protocol A (cytology) at 45 referrals per 1,000 patients.

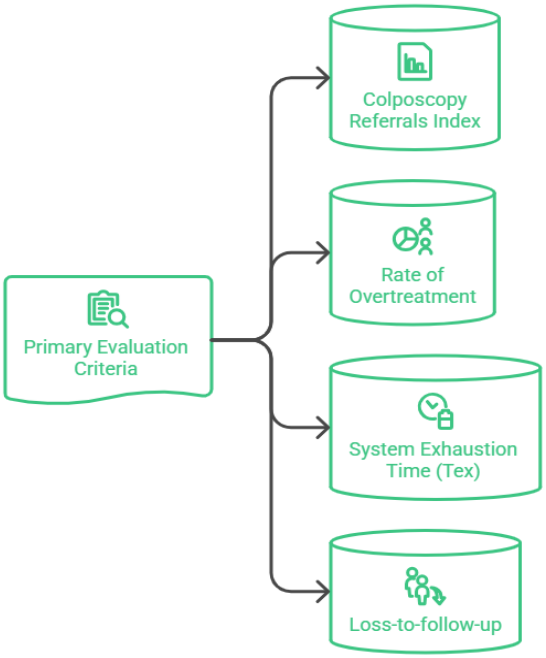

Fig. 1 Evaluation Criteria

In scenarios where the environment is simulated to resemble a rural or less resourced public health network environment—where the number of colposcope units and trained obstetricians in gynecology is constrained in terms of their total capacity—such an increase in patient numbers results in the system failure [18]. The breach of the Tex for Protocol B occurs on day 48 after the implementation of the project, where it becomes apparent that the volume of patients being referred positively exceeded the maximum weekly throughput at the clinics. Such an imbalance in volume created a backlog in diagnosis, and therefore the mean waiting period for a confirmatory diagnosis increased from 14 days to 112 days.

Unlike Protocol B, however, the introduction of Protocol C (Primary HPV test with automated Biomarker Triage) provided a solution to this problem. Using the same highly sensitive self-sample screening test employed by Protocol B, Protocol C utilized its objective biomolecular filter to identify and block any transient positives from leaving the laboratory setting. Protocol C produced an elegant Colposcopy Referral Volume Index of only 52 referrals per 1,000 screened patients [15]. Through identifying transient viral carriers without cell cycle disruption, Protocol C was able to eliminate clinical backlogs, avoid crossing the threshold on the System Exhaustion Timeline, and reserve secondary hospital time slots for only those at risk of needing surgery.

B. Evaluation of the Overtreatment Error Index

The analysis of the clinical management showed that there was a major specificity problem occurring in the Protocol B procedure. Of the overall population who have been directed to go immediately for surgical intervention according to the Protocol B "Screen-and-Treat" system, an astonishing 42.4% were deemed to be cases of an Overtreatment Error [12]. The patients here involved included women who have had their cervix subjected to ablation or LEEP for conditions of transient, benign viral infections that posed absolutely no risk of transforming into cancer. Such a high percentage of error is because of the double low specificity of both the DNA test and the subjective VIA visual triage [8, 9].

Indeed, Protocol C was able to address this clinical weakness quite effectively. The objective use of the p16/Ki-67 dual staining marker was incorporated into the protocol as a prerequisite for clinical clearance, thereby reducing the Overtreatment Error Index to as low as 4.8% [7]. Since the joint presence of p16 and Ki-67 indicates objective biological evidence of oncogenic transformation, the process managed to avoid benign and self-limiting viral vectors [6]. This distinction was able to protect thousands of healthy young women from undergoing surgery and subsequent obstetric issues that may be caused by overtreatment [14, 15].

V. COMPARISON OF STRATEGIES USING CLINICAL AND OPERATIONAL CRITERIA

In Table I, a comparison is made of three cervical cancer screening strategies, using clinical criteria like sensitivity, specificity, as well as their impact on operational aspects, such as referral and overtreatment. The table clearly demonstrates that

changing to a more sensitive strategy of primary self-sampling without objective gatekeeping (Strategy B) causes serious referral backlogs and the likelihood of overtreatment. On the other hand, introducing a step of objective biomarker testing (Strategy C) solves these problems.

TABLE I

Metric Evaluation Parameter	Protocol A (Primary Cytology)	Protocol B (Self-Sample + VIA Triage)	Protocol C (HPV + Biomarker Triage)
Initial Diagnostic Sensitivity Index	Moderate (55% – 70%) [10]	Extremely High (92% – 95%) [20]	Extremely High (92% – 95%) [20]
Downstream Triage Specificity Rate	High Standalone (94%) [19]	Low & Subjective (70% – 75%) [8]	Very High & Objective (92%) [1]
Downstream Referral Burden Index	Manageable Base (45/1k)	Severe System Overload (142/1k) [12]	Optimized / Low Burden (52/1k) [15]
Systemic Overtreatment Risk Profile	Low Error Index (6.2%)	High Error Index (42.4%) [12]	Minimal Error Index (4.8%) [7]
Average Confirmatory Wait Timeline	14 Days	112 Days (Severe Backlog)	16 Days (Stable Workflow)
Programmatic Loss-to-Follow-Up Rate	Moderate (Administrative) [4]	Critical (System Fatigue) [18]	Low (Streamlined Processing) [15]
Infrastructural Cost Profile	High Upfront Lab Setup [9]	Low Initial Swab Cost [16]	High Reagent/Automated Focus [17]
Real-World Resource Suitability	Centralized Urban Hubs	Low-Resource (With Friction)	Integrated Multi-Tier Networks

VI. DISCUSSION: COST TO SOCIETY AND THE ECONOMY OF FALSE POSITIVES

A. Total Cost of Illness (TCOI) and Downstream Financial Leakages

The economic reasons given by international public health organizations for implementing primary self-sampling programs without triaging are mostly centered around cost savings [16]. Clearly, handing out ergonomic swabs to sample is far less expensive than setting up local testing facilities with examination rooms, examination tables, speculums, and well-trained cytotechnologists [2]. On the other hand, according to our analysis, when the total costs involved in the Total Cost of Illness (TCOI) are taken into account, including downstream errors in diagnosis, repeated visual checks, outpatient hospital observations, and clinical treatment of surgical complications following overtreatment, un-triaged screening technologies are not efficient at all [16, 17].

Without an automatic, specific filter within the initial screening process, the cost burden is no longer carried at the entry level, but falls squarely on the shoulders of the second and third clinical stages [17]. As a result of the vast number of false positives resulting from transient infections, regional hospitals will find themselves having to expand their staff for colposcopy, buy more surgical reagents, and even allocate operating room time to those who do not need any medical attention whatsoever [18]. This misappropriation of scarce resources can prove to be very costly in the long run, especially in impoverished areas [16].

B. The Role of Psychosocial Maladjustment and Attrition Patterns within Care Networks

Aside from the economic factors, another aspect that deserves consideration due to its severe psychosocial implications is the impact that such false diagnosis has on the well-being of healthy women classified improperly due to improper triaging of their molecular test results [11].

A diagnosis involving sexually transmitted infection coupled with the oncogenic nature of the disease

causes severe emotional distress in terms of patient stress and social stigma associated with infidelity and risk of developing cancer [11]. This problem becomes particularly acute in areas where the healthcare system experiences substantial backlog issues.

The delay inherent in this system has an effect on patients' behavior, resulting in an increased rate of Loss-to-Follow-Up (LTFU). With more and more patients joining the waitlist for months, a substantial number of those being tested disconnects from the healthcare system [18]. Some give up because of fear of a guaranteed diagnosis, and others because of administrative complications related to obtaining subsequent appointments [4]. Therefore, by the time the truly serious cases of high-grade neoplasia (CIN3) appear in front of the colposcopist months later, their cancer has become invasive, potentially deadly. Unscreened, high sensitivity screening programs have created a vicious circle for themselves, where they misallocate scarce medical resources to treating millions of healthy women who have only minor issues, while missing those that actually needed help [12, 18].

VII. CONCLUSION AND POLICY RECOMMENDATIONS

The results of this systematic study show that concentrating solely on increasing diagnostic sensitivity at entry level with little regard for specificity in triage procedures has the potential to negatively impact attempts to eradicate cervical cancer through clinical roadblocks. The proposed structural changes to public health initiatives for academic review include:

- Direct Treatment Routes for Self-Sample-Based Approaches Should Be Prohibited:

Public health initiatives should halt the utilization of self-sample collection devices which are used to directly feed data into subjective visual treatment approaches ("screen-and-treat") [12]. Unless there is an emergency situation whereby the local burden of cervical cancer necessitates such action, the subjectivity involved in visual detection techniques such as VIA/VILI makes them unsuitable for use as gatekeepers [8, 9].

- Implement Objective Molecular Triage Through Laboratory Automation:

All health care institutions that adopt the concept of using HPV DNA primary testing should ensure that they use automation and objective methods while performing their secondary biomarker tests [1, 5]. Reflex testing for the expression of E6/E7 mRNA expression of oncoviruses, p16/Ki-67 dual stain, and targeted DNA methylation testing is a secondary test that should precede any discussion on whether there is a need for clearance or additional clinical tests [6, 7].

- Limit Molecular Tests to Age-Specific Populations:

The public health management should only allow molecular HPV DNA testing for patients aged 30 years and above [10]. Younger individuals aged between 25 to 29 years who have transient HPV exposure can maintain their cytology testings as they have lower chances of developing cancer [11]. This age restriction minimizes waste of medical resources on transient viral infections in younger patients.

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