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From clinical epidemiology to practice recommendations: Knowledge gaps and uncertainty in management of anal precancers

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Precis

We discuss the existing data on anal precancers and demonstrate the impact of evidence gaps and uncertainty on a clinical decision model developed to provide clinical guidance for management of anal precancers.

Keywords

Anal precancer; cost effectiveness; clinical epidemiology; uncertainty; clinical recommendations

The article by Deshmukh et al. presents a clinical and cost-effectiveness analysis on management of anal high-grade squamous intraepithelial lesions (HSIL) in HIV-positive men who have sex with men (MSM) (Reference for primary manuscript). Based on a decision analytic model of the natural history of anal cancer and precancer, the authors concluded that younger HIV-positive MSM might benefit from a conservative HSIL management approach, whereas for older patients, treatment was more favorable. Like cervical cancers, most anal cancers are caused by human papillomavirus (HPV) infections [1]. The success of cervical cancer screening is based on detection and removal of cervical precancers to prevent invasive cancers from occurring. While detection of anal HSIL is possible with similar tools that have been established for cervical cancer, such as high-resolution anoscopy (HRA) or anal cytology, there are currently no guidelines for anal cancer screening and management of anal cancer precursors in HIV-positive MSM.

The translation of etiologic understanding of disease processes to clinical and public health recommendations is complex and involves many of the components summarized in the Table. Here, we use the example of anal precancer management to illustrate how these components can be used to identify important questions and knowledge gaps that need to be addressed.

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(1) Public health burden

Quantifying the public health burden of disease in terms of prevalence, incidence and mortality is important to estimate the potential benefit and the cost of population-wide implementation of interventions. Demographic analyses can point to specific sub-populations (e.g., age groups) that an intervention may be targeted to. Information on disease trends can be useful to estimate the future burden of disease and to evaluate changes in important exposures over time that may impact interventions. Although there is no fixed threshold of disease burden in a population above which screening is justified, anal cancer prevalence in the general population is clearly too low to consider screening[2]. While there has been a slight increasing trend among men, this seems to be mainly driven by HIV-positive MSM.

(2) High-risk populations

Even when the population-wide burden is not high, there may be specific subgroups in the general population with high risk of disease that could be targets for clinical or public health interventions. Several high-risk populations for anal cancer exist, including women with cervical precancers, MSM, and particularly HIV-positive MSM in whom cancer rates approach levels high enough to warrant evaluation of screening strategies [3].

(3) Natural history

Natural history encompasses the complete disease process from initiation to progression through preclinical stages until clinical manifestation. Important features of natural history relevant for clinical and public health interventions are disease stages, transition probabilities, and the timing of these transitions. The natural history of anal cancer appears to be similar to cervical cancer, starting with an HPV infection that may progress to HSIL and ultimately to cancer[4–6]. However, most HPV infections clear and a subset of HSILs regress spontaneously. It has been suggested that the progression rates of anal HSIL are lower compared to cervical precancers [1], but data are limited. To what extent natural history of anal cancer differs between HIV-positive and HIV-negative individuals is currently not known.

(4) Risk assessment

While relative risk estimates are the mainstay in etiologic research, clinical and public health decisions require absolute risk estimates for a given exposure, genetic predisposition, screening test, or diagnostic test [7]. Absolute risks are needed to quantify the benefits and harms of an intervention in the target population and can be used to establish risk thresholds for clinical action. Accurate risk-prediction models can be used to identify individuals who would most benefit from clinical and public health interventions. Several biomarkers and diagnostic tests have been evaluated for anal precancer detection, but data on management of anal precancers in larger populations are scarce[8, 9].

(5) Current clinical standards

The current clinical standard provides important benchmarks and reference standards for improving practice with new approaches. Depending on the variability of clinical practice and the perspective of involved stakeholders, establishing uniform references may be difficult. There is currently no standard approach for screening for and management of anal HSIL. While some centers perform anal cancer screening and treatment of HSIL in HIV-positive MSM [10, 11], other experts have cautioned against that practice [1]. Importantly, treatment of HSIL in the anal canal is associated with higher morbidity compared to excisional treatment of the cervix, and there is some evidence that recurrence rates are higher [12]. An ongoing trial (ANCHOR) was designed to evaluate treatment of anal precancers versus watchful waiting to address some of the major unresolved questions related to progression of HSIL and clinical outcomes[13].

(6) Clinical, societal, and public health implications

While a strong evidence base is necessary for clinical decision-making and translation of evidence, other important factors need to be considered from the perspective of the society, providers, and patients. These include individual and societal risk tolerance, value judgments regarding the magnitude of benefits and harms, and patient preferences. For example, communicating risk estimates and associated uncertainties in an understandable, unbiased way to patients is challenging[14]. Further, the risk perception and value judgment regarding possible benefits of anal precancer treatment (e.g. prevention of cancer) and possible harms (e.g. disturbance of anal function) may vary substantially between individual patients and affect treatment decisions. Finally, availability of healthcare resources plays an important role in the decision-making process.

Importantly, the individual components described above are highly interdependent. Rarely does a single component drive a decision about implementation of a new intervention, nor do all components need to be considered equally. When considering these components in the context of implementation of screening and management strategies for anal cancer precursors, it becomes clear that large evidence gaps currently exist in important areas that inform the tradeoff of benefits and harms, such as precancer progression rates, treatment efficacy, risk of treatment and comorbidities, and risk of overtreatment. Similarly, there is not much data on patient and societal preferences regarding various interventions. As outlined above, filling these evidence gaps is crucial towards improving secondary prevention of anal cancers in HIV-positive MSM.

Several types of evidence can be utilized to address these gaps and inform clinical and public health decision-making. Clinical trials are usually considered the highest level of evidence to inform clinical practice. However, it is impossible and sometimes unethical to conduct randomized clinical trials for all clinical questions, and there are currently no randomized trial data on anal cancer screening. Data from high-quality observational studies and electronic medical records can address important clinical epidemiology questions. Systematic reviews and meta-analyses pool evidence from multiple sources to generate robust summary estimates of observed data and to identify important sources of

heterogeneity between studies that can inform future research. Finally, clinical decision and cost-effectiveness models, like the anal cancer model developed by Deshmukh and colleagues, can help to address questions based on simulated, not-directly-observed, data and include cost to inform decisions about optimal use of resources.

Importantly, clinical decision and cost-effectiveness models require an accurate underlying disease model, informed by a sufficient understanding of natural history (Table). The disease model simulates the disease process and various interventions in a specific population and can generate estimates to fill in gaps between directly observed data. Models are particularly well-suited to address the effects of cancer screening under a range of plausible scenarios that cannot be directly evaluated in observational studies or trials (e.g., varying intervals, age to start and stop, differences in test performance, etc). In 2009, the U.S. Preventive Services Task Force (USPSTF) used evidence generated from six independent models to evaluate screening strategies that varied in terms of interval and ages of initiation and cessation to support the recommendation for biennial mammography screening [15]. Similarly, in a study designed to inform the cervical screening guidelines update in 2012, Kulasingam et al., used simulation modeling to evaluate age of screening initiation and cessation, comparing the benefits and harms associated with strategies that incorporate HPV DNA testing versus cytology alone at different screening intervals [16]. These models were based on extensive high-quality evidence covering essential components presented in the Table, and directly supported evidence from clinical trials and observational studies.

The quality of a disease model depends on the underlying evidence: models typically integrate data from multiple, heterogeneous sources, and rely on assumptions about biologic processes and disease natural history with inherent uncertainty. Uncertainty affects all aspects of health-decision making, from the generation of evidence to communicating findings and clinical recommendations [14, 17]. Most researchers and clinicians are familiar with uncertainty measures used for clinical trials and observational studies, like confidence intervals around measured effect sizes. While individual studies can provide strong and precise estimates, these estimates may differ across study populations, limiting their generalizability. Systematic reviews and meta-analyses summarize multiple individual studies and allow to evaluate heterogeneity of results across populations, providing important information about uncertainty, and pointing to areas that require additional research. The uncertainty influencing clinical decision and cost-effectiveness models is multifactorial and highly complex; in contrast to epidemiologic studies, there is no simple measure like a confidence interval or a heterogeneity index that can be reported and easily understood by the target audience. Given the large gaps in evidence on anal cancer natural history, screening, and management, the recommendations derived from the decision model developed by Deshmukh and colleagues need to be evaluated carefully. The authors thoroughly evaluated the uncertainty in the values assigned to specific parameters (i.e., parameter uncertainty) by conducting sensitivity analyses for 15 model parameters individually and in combination, using a probabilistic sensitivity analysis approach. However, it is unclear how the parameters and value ranges were selected for detailed evaluation, given the limited availability of evidence for many measures. Two parameters, HSIL progression and regression, were most influential on determining the optimal age at which treatment plus vaccination became cost-effective, and there is a

high level of uncertainty surrounding these measures. In addition to parameter uncertainty, decisions regarding the appropriate sources of evidence, population characteristics, disease states, risk factors, and outcomes, can also introduce uncertainty into the model particularly in the absence of high-quality data (i.e. structural uncertainty). For example, the starting point within the natural history model of anal carcinogenesis can strongly affect progression rates. Some HIV-positive MSM may be aggressively screened and have HSIL detected earlier, others are under constant, but less aggressive surveillance, while some may only be diagnosed when presenting with clinical symptoms at later stages when HSIL is more likely to progress. The baseline population of 40-year-old, HIV-positive MSM with a first-time diagnosis of HSIL defined by Deshmukh et al., implies a population that is undergoing screening and thus may not be generalizable to all HIV-positive MSM with HSIL. Similarly, in the do-nothing scenario, access to care and health seeking behavior may influence the timing of detection of anal cancer, and could have a strong impact on cancer stage and survival. Individual risk factors, adherence to HIV medication, and variability in treatment may also have an important impact on these estimates; yet, most parameter values used in the model are derived from studies carried out at highly-specialized centers that may not reflect the range of clinical care.

To enable stakeholders and users to better evaluate model applicability and identify areas of uncertainty that require additional evidence, it is important to provide non-technical documentation on model parameters and model uncertainty, and to qualify model-derived recommendations accordingly. Several approaches to standardize this reporting have been proposed [17–19]. While Deshmukh and colleagues describe their uncertainty assessment in the discussion, the clinical recommendation that they present is not qualified by the possible impact of uncertain model parameters. Thus, clinicians, patients, and policy makers may interpret the recommendations as stronger and more certain than they are given the limited evidence.

A recommendation that is likely to change with more evidence has less certainty and should be implemented more cautiously, and signifies important areas for additional research. On the contrary, if additional evidence is not likely to change the recommendation, it indicates a high level of certainty and enables implementation of the clinical recommendations with less reservation [20]. In the example of anal cancer screening, it appears that additional evidence could have a major impact on many important parameters underlying the disease model and thus the uncertainty is high (e.g., HSIL progression/regression estimates informed by results of ANCHOR). Relevant stakeholders involved in the process from generating evidence to implementing and acting on recommendations must be aware of the uncertainties in order to implement optimal public health and clinical guidelines. The implications and associated uncertainties of clinical recommendations need to be discussed with and understood by patients so that they can make informed decisions [14]. Although beyond the scope of this editorial, there is an obvious lack of research in areas related to patient-centered, sociologic, and qualitative aspects of screening and management of anal precancers. Ultimately, the goal of evidence-based recommendations is to maximize the tradeoff between benefits and harms of clinical and public health interventions for individuals and for the society as a whole.

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Table

Considerations for translating evidence to clinical and public health interventions. These considerations can guide the translation of etiologic understanding of disease processes to clinical and public health interventions.

Component	Important Considerations
Public health burden	- Prevalence - Incidence and mortality rates and trends - Demographics - Geographic distribution
High-risk populations	- Subgroups defined by genetics, demographics, exposures, and diagnoses - Temporal changes in exposures and diagnoses - Proportion of disease in high-risk populations (etiologic fraction)
Natural history	- Disease stages, transition probabilities, and timing - Clinically relevant subtypes (morphologic/molecular) - Detectable and treatable precursors or preclinical states
Risk assessment	- Absolute risk estimates - Risk markers (exposures, genetics, biomarkers) - Risk prediction or early detection
Current Standards	- Established clinical practice (reference standards) - Risk thresholds - Practice guidelines and recommendations
Clinical, societal, and public health implications	- Different perspectives of society, providers, and patients - Risk tolerance - Benefits and harms - Healthcare resources - Options for primary prevention (modifiable risk factors, clinical interventions, chemoprevention) - Communication of risk and uncertainties