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RISK-STRATIFIED SCREENING FOR UROGENITAL MALIGNANCIES: CURRENT EVIDENCE AND FUTURE PERSPECTIVES

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Abstract: Urogenital malignancies, including prostate, bladder, kidney, and testicular cancers, are major contributors to global cancer morbidity and mortality. Early detection improves treatment outcomes; however, universal screening has limitations such as over diagnosis, false-positive results, and unnecessary interventions. Risk-stratified screening has emerged as a personalized approach that identifies individuals most likely to benefit from screening based on factors such as age, family history, genetic predisposition, lifestyle, and environmental exposures. Recent advances in multiparametric magnetic resonance imaging (mpMRI), molecular biomarkers, liquid biopsy, and artificial intelligence (AI) have further improved the accuracy of early cancer detection. This review summarizes current evidence on risk-based screening strategies for major urogenital malignancies, highlights emerging diagnostic technologies, discusses current challenges, and explores future directions toward precision oncology. Personalized screening has the potential to improve early diagnosis, reduce unnecessary procedures, and optimize healthcare resources while improving patient outcomes.

Keywords: Urogenital malignancies; Risk-stratified screening; Early detection; Biomarkers; Artificial intelligence; Precision medicine.

Introduction

Urogenital malignancies comprise cancers of the prostate, bladder, kidney, testis, and upper urinary tract. Together, they represent a significant global health burden, with prostate cancer being the most commonly diagnosed malignancy among men in many countries, while bladder and kidney cancers continue to increase in incidence due to aging populations, smoking, obesity, and improved imaging techniques (1,2). Although advances in surgery, systemic therapy, and immunotherapy have improved survival, prognosis remains closely related to the stage at diagnosis.

Screening aims to detect cancer before symptoms develop, allowing timely intervention and improved survival. However, unlike screening programs for cervical or colorectal cancer, universal screening for most urogenital cancers remains controversial. Widespread prostate-specific antigen (PSA) testing has reduced prostate cancer mortality but has also increased the diagnosis of clinically insignificant tumors, leading to unnecessary biopsies and treatment-related complications (3). Similarly, there is insufficient evidence to support routine population-based screening for bladder, kidney, or testicular cancers because of their relatively lower prevalence and concerns regarding cost-effectiveness.

These limitations have shifted attention toward risk-stratified screening, a personalized strategy that targets individuals with the highest probability of developing clinically significant disease. Risk assessment incorporates factors such as age, family history, inherited genetic mutations, ethnicity, smoking, obesity, occupational exposure, and previous medical conditions

(4,5). By focusing on high-risk individuals, clinicians can improve the balance between the benefits and harms of screening.

Technological advances have further strengthened this approach. Multiparametric MRI has improved the detection of clinically significant prostate cancer, while novel urinary and blood-based biomarkers have enhanced diagnostic accuracy. In addition, liquid biopsy and artificial intelligence are increasingly being integrated into clinical practice, offering more precise and less invasive methods for early cancer detection (6,7). These innovations support the transition from a "one-size-fits-all" model toward precision-based screening tailored to an individual's risk profile.

This review summarizes current evidence regarding risk-stratified screening for urogenital malignancies, with emphasis on organ-specific screening strategies, emerging biomarkers, artificial intelligence, current limitations, and future prospects.

Principles of Risk-Stratified Screening

Risk-stratified screening is based on the principle that cancer risk varies considerably among individuals. Instead of recommending identical screening protocols for everyone, this approach tailors screening according to each person's estimated risk of developing clinically significant cancer (5).

Important risk factors include increasing age, family history of cancer, inherited genetic mutations such as BRCA1, BRCA2, and Lynch syndrome, ethnicity, smoking, obesity, occupational exposure to carcinogens, chronic inflammation, and certain hereditary cancer syndromes (4,5). Individuals with multiple risk factors are more likely to benefit from earlier or more intensive screening than those at average risk.

Risk prediction models increasingly combine clinical information with laboratory biomarkers and imaging findings. In prostate cancer, PSA level, PSA density, PSA velocity, digital rectal examination, and multiparametric MRI are integrated to improve patient selection for biopsy (6). Similar approaches using urinary biomarkers and imaging are under investigation for bladder and kidney cancers.

The primary goal of risk-stratified screening is to maximize early detection of aggressive cancers while minimizing over diagnosis and unnecessary procedures. Shared decision-making between clinicians and patients is essential, ensuring that individuals understand both the benefits and limitations of screening before testing is undertaken (3,5). As molecular diagnostics and artificial intelligence continue to evolve, personalized screening strategies are expected to become increasingly accurate and clinically relevant.

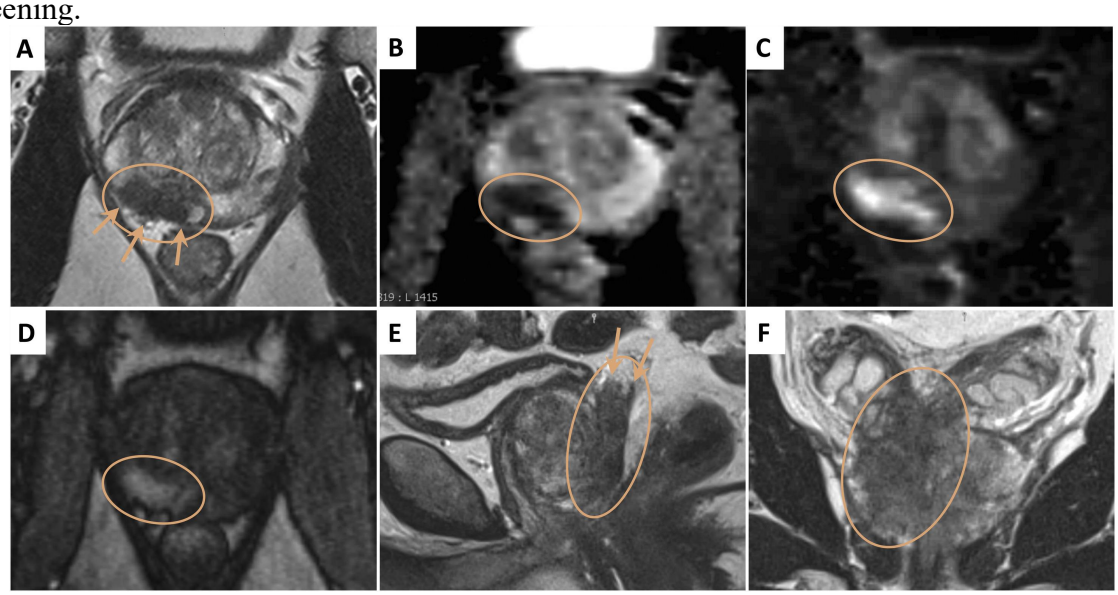
Screening Strategies for Major Urogenital Malignancies

Prostate Cancer

Prostate cancer has the strongest evidence supporting risk-stratified screening. Although prostate-specific antigen (PSA) testing has reduced prostate cancer mortality, indiscriminate screening may lead to over diagnosis and unnecessary treatment of low-risk disease (3). Current guidelines recommend individualized decision-making rather than universal PSA screening. Men aged 50–69 years with a life expectancy greater than 10 years are the primary candidates, while screening should begin earlier (40–45 years) for individuals with a strong family history, African ancestry, or pathogenic BRCA2 mutations (4,8).

Risk assessment incorporates PSA level, digital rectal examination (DRE), PSA density, PSA velocity, family history, and multiparametric magnetic resonance imaging (mpMRI). MRI-targeted biopsy has significantly improved the detection of clinically significant prostate cancer while reducing unnecessary biopsies (9). Consequently, combining clinical risk factors with MRI and

validated risk calculators has become the preferred strategy for individualized prostate cancer screening.

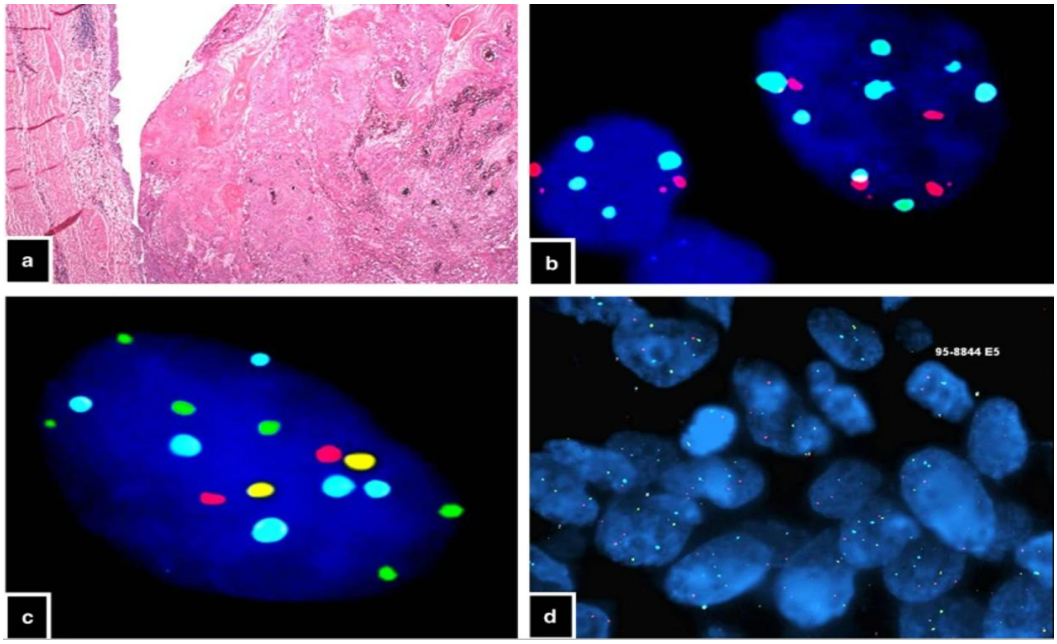


Fig; Prostate multiparametric magnetic resonance imaging

Bladder Cancer

Routine screening for bladder cancer is not recommended in the general population because evidence for mortality reduction is limited (10). However, selected high-risk individuals may benefit from targeted surveillance.

The strongest risk factor is cigarette smoking, followed by occupational exposure to aromatic amines, chronic bladder inflammation, previous pelvic radiotherapy, cyclophosphamide therapy, and exposure to arsenic-contaminated water (10). Screening methods include urine cytology, cystoscopy, and urinary biomarkers such as NMP22, bladder tumor antigen (BTA), and UroVysion fluorescence in situ hybridization (FISH). Although these biomarkers improve sensitivity, none currently possess sufficient accuracy to replace cystoscopy (10). Future screening programs are expected to combine clinical risk assessment with molecular biomarkers to improve early diagnosis.



Fig; Urovysion™ fluorescence in situ hybridization (FISH)

Kidney Cancer

There is currently no recommendation for population-based screening for kidney cancer because of its relatively low prevalence and the absence of a validated screening test (11). Nevertheless, surveillance is appropriate for individuals with hereditary syndromes such as von Hippel–Lindau disease, Birt–Hogg–Dubé syndrome, and hereditary papillary renal carcinoma.

Additional risk factors include obesity, hypertension, smoking, chronic kidney disease, and long-term dialysis. In these high-risk populations, renal ultrasonography offers a practical and non-invasive screening tool (11). Emerging biomarkers, including circulating tumor DNA, kidney injury molecule-1 (KIM-1), microRNAs, and metabolomic signatures, have shown promise but require further validation before routine clinical use (12).

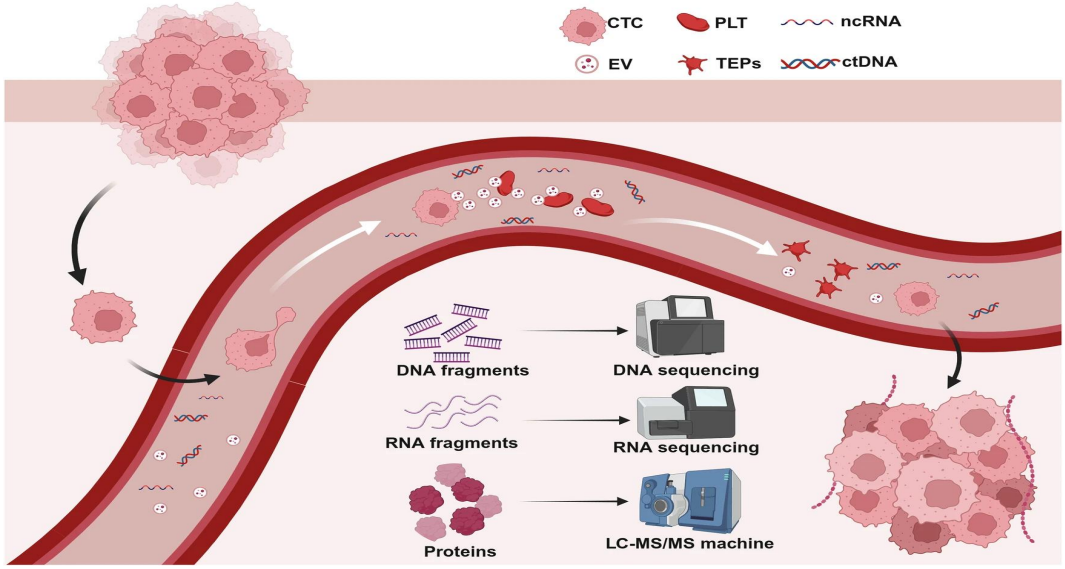
Testicular Cancer

Testicular cancer predominantly affects young men between 15 and 40 years of age. Despite increasing incidence, routine population screening is not recommended because the disease is relatively uncommon and highly curable, even when diagnosed after symptom onset (13). Risk-based surveillance is appropriate for men with cryptorchidism, previous testicular cancer, infertility, family history, or testicular atrophy. Public education regarding testicular self-examination and prompt medical evaluation of painless scrotal masses remain important strategies for early diagnosis (13). Ultrasonography remains the imaging modality of choice, while serum tumor markers (AFP, β-hCG, and LDH) are primarily used for diagnosis and follow-up rather than screening.

Emerging Biomarkers and Artificial Intelligence

Advances in molecular diagnostics have substantially improved the accuracy of risk-stratified screening. Beyond total PSA, newer biomarkers such as the Prostate Health Index (PHI), 4Kscore, PCA3, SelectMDx, and ExoDx Prostate IntelliScore improve the identification of clinically significant prostate cancer and reduce unnecessary biopsies (14). Similarly, urinary biomarkers including NMP22, BTA, and UroVysion FISH may complement conventional diagnostic methods for bladder cancer, although their role in routine screening remains limited.

Liquid biopsy represents one of the most promising developments in precision oncology. Analysis of circulating tumor DNA (ctDNA), circulating tumor cells, exosomes, and other cell-free nucleic acids enables non-invasive detection of molecular alterations associated with malignancy. These technologies may facilitate earlier diagnosis, monitor disease progression, and identify recurrence with minimal patient discomfort (15).



Fig;Liquid biopsy in cancer

Artificial intelligence (AI) is increasingly being incorporated into cancer screening. Machine learning algorithms can integrate clinical characteristics, imaging findings, pathology, and genomic data to estimate an individual's cancer risk with greater precision. In prostate cancer, AI-assisted interpretation of multiparametric MRI has improved lesion detection, biopsy targeting, and risk classification. As validation studies continue, AI is expected to support personalized screening intervals and clinical decision-making, contributing to more efficient and accurate early cancer detection (15).

Challenges and Future Perspectives

Despite significant advances, several challenges limit the implementation of risk-stratified screening for urogenital malignancies. One of the major concerns is overdiagnosis, particularly in prostate cancer, where screening may identify indolent tumors that would never become clinically significant. This can result in unnecessary biopsies, overtreatment, psychological stress, and treatment-related complications (3).

Another limitation is the lack of universally validated biomarkers. Although several blood- and urine-based biomarkers have shown promising diagnostic performance, many require further validation before they can be incorporated into routine screening programs (14). In addition, advanced technologies such as multiparametric MRI, genomic testing, and liquid biopsy remain costly and are not readily available in many low- and middle-income countries.

Artificial intelligence (AI) offers exciting opportunities for precision screening but also presents challenges related to data quality, algorithm validation, privacy, and ethical considerations. Large prospective studies involving diverse populations are required before AI-based models can be routinely implemented in clinical practice (15).

Future screening strategies are expected to integrate clinical risk factors, imaging findings, biomarkers, and genomic information into comprehensive risk prediction models. Polygenic risk

scores, liquid biopsy, and AI-assisted diagnostic systems may allow clinicians to personalize screening intervals and identify aggressive cancers at an earlier stage while minimizing unnecessary investigations. Such precision-based approaches have the potential to improve patient outcomes and optimize healthcare resource utilization.

Conclusion

Risk-stratified screening represents a major shift from conventional population-based screening toward personalized cancer prevention. By incorporating individual risk factors such as age, family history, genetic susceptibility, lifestyle, and environmental exposures, this approach improves the early detection of clinically significant urogenital malignancies while reducing over diagnosis and unnecessary interventions. Emerging technologies, including multiparametric MRI, molecular biomarkers, liquid biopsy, and artificial intelligence, are further enhancing the accuracy of risk assessment and early diagnosis. Although additional validation and cost-effectiveness studies are needed, current evidence supports the integration of risk-based screening into future clinical practice. Continued research and equitable access to innovative diagnostic technologies will be essential for improving survival and reducing the global burden of urogenital cancers.

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