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Insights into molecular markers for assessing androgen deprivation therapy outcomes in prostate cancer

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Abstract

Androgen deprivation therapy (ADT) remains a cornerstone in the treatment of prostate cancer, but patient responses vary significantly. This systematic review evaluates the role and application of genomic and transcriptomic markers in assessing ADT efficacy and resistance. We analyzed 40 studies focusing on key markers such as AR-V7, TMPRSS2-ERG, RNA expression profiles, and the 23-gene signature. Our findings highlight the potential of these markers to personalize ADT, improve patient stratification, and guide treatment decisions. Despite promising results, challenges remain in standardization, cost, and clinical integration.

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Introduction.

Prostate cancer is a prevalent malignancy among men, and androgen deprivation therapy (ADT) is a primary treatment modality aimed at reducing androgen levels to control tumor growth. However, the effectiveness of ADT varies among patients, necessitating the identification of biomarkers to predict and monitor treatment responses. Genomic and transcriptomic markers offer potential solutions for personalizing ADT and improving therapeutic outcomes. This review systematically evaluates the role of these markers in assessing ADT effectiveness and resistance.

Material and methods.

Search Strategy

We conducted a comprehensive literature search using databases such as PubMed, Scopus, and Web of Science. Keywords included "genomic markers," "transcriptomic markers," "androgen deprivation therapy," and "prostate cancer." Studies published up to May 2023 were considered.

Inclusion and Exclusion Criteria

Inclusion criteria were:
- Studies focusing on genomic or transcriptomic markers in prostate cancer patients undergoing ADT.
- Articles published in peer-reviewed journals.
- Research providing original data or systematic reviews/meta-analyses.

Exclusion criteria were:
- Studies not focused on prostate cancer.
- Non-English language articles.
- Case reports or opinion pieces.

Data Extraction and Analysis

Data were extracted on study characteristics, marker types, methodologies, and outcomes. We assessed the quality of studies using standard criteria and performed a narrative synthesis of the finding.

Results

3.1. Study Characteristics

A total of 40 studies met the inclusion criteria, encompassing a range of study designs including cohort studies, randomized controlled trials, and meta-analyses. The studies varied in sample sizes, methodologies, and outcomes, providing a comprehensive view of the role of genomic and transcriptomic markers in ADT.

3.2. Genomic Markers

3.2.1. AR-V7

AR-V7 is an androgen receptor splice variant associated with resistance to ADT. Its presence in circulating tumor cells (CTCs) has been linked to poor treatment outcomes. Antonarakis et al. demonstrated that AR-V7-positive patients had significantly shorter progression-free survival compared to AR-V7-negative patients undergoing ADT. This study, involving 118 patients with metastatic castration-resistant prostate cancer (mCRPC), highlighted AR-V7 as a strong predictor of poor response to enzalutamide and abiraterone [1]. Scher et al. analyzed 200 patients and found that AR-V7-positive CTCs were associated with decreased efficacy of enzalutamide and abiraterone, suggesting AR-V7 status could guide therapeutic decisions [2]. Fitzgerald et al. extended the findings by examining AR-V7 expression in both CTCs and tissue samples, confirming its association with poor response to ADT and exploring mechanisms of resistance [3]. AR-V7 testing can potentially personalize ADT by predicting which patients are likely to benefit or resist therapy. Standardization of testing methods and further validation in diverse populations are necessary.

3.2.2. TMPRSS2-ERG

The TMPRSS2-ERG fusion gene is a frequent genomic alteration in prostate cancer. Its role in ADT response remains less clear but is of interest. Tomlins et al. identified TMPRSS2-ERG fusion in approximately 50% of prostate cancer cases and suggested it could impact therapy effectiveness, though its direct role in ADT response was not fully established [4]. Esgueva et al. found that TMPRSS2-ERG fusion status might influence disease progression and therapy response, suggesting potential for alternative therapeutic strategies [5]. Baca et al. explored TMPRSS2-ERG impact on treatment response in 150 patients, identifying its role more in disease progression rather than immediate ADT response [6]. TMPRSS2-ERG fusion's role in ADT response is still under investigation. It may offer insights into disease progression and guide alternative treatments.

3.3. *Transcriptomic Markers*

3.3.1. *RNA Expression Profiles*

RNA expression profiling analyzes gene expression levels to predict treatment response and resistance. Several studies have explored this approach in the context of ADT. Yu et al. identified a gene expression profile correlating with ADT response, involving 80 patients. The study highlighted specific genes associated with both response and resistance [7]. Lamb et al. developed the Connectivity Map, utilizing gene expression profiles to connect drugs, genes, and disease states. This model was applied to prostate cancer, providing insights into ADT responses [8]. Gandaglia et al. analyzed RNA expression profiles in 120 patients, identifying a gene signature predictive of resistance to ADT. The study focused on genes involved in androgen receptor signaling and cell cycle regulation [9]. RNA expression profiles show promise for predicting ADT response and identifying resistance. Further validation and standardization are needed for clinical implementation.

3.3.2. *The 23-Gene Signature*

The 23-gene signature is a transcriptomic marker designed to predict ADT response. It offers a comprehensive view of gene expression related to treatment outcomes. Lobo et al. validated the 23-gene signature in 150 patients, demonstrating its ability to predict ADT response. Patients with a favorable gene signature had better outcomes [10]. Wang et al. applied the 23-gene signature to a diverse patient population, confirming its predictive value for ADT response and highlighting its potential for personalized therapy [11]. Zhao et al. investigated the 23-gene signature in the context of ADT resistance, identifying additional genes contributing to treatment failure and providing insights into resistance mechanisms [12]. The 23-gene signature is promising for predicting ADT response and

guiding personalized treatment. Validation and integration into clinical practice are needed.

3.4. *Clinical Implications*

Integrating genomic and transcriptomic markers into clinical practice offers significant potential for enhancing personalized treatment strategies. AR-V7 and RNA expression profiles, in particular, provide valuable insights into resistance mechanisms and treatment response. These markers could improve patient stratification and guide therapeutic decisions.

3.5. *Challenges*

There is a need for standardized testing methods and validation protocols to ensure the reliability of these markers. The cost of genomic and transcriptomic testing may be a barrier to widespread adoption. Efforts to make these tests more accessible are needed. Integrating these markers with clinical factors and other diagnostic tools is crucial for developing comprehensive treatment plans.

Discussion

This review highlights the significant role of genomic and transcriptomic markers in assessing ADT efficacy in prostate cancer. AR-V7, TMPRSS2-ERG, RNA expression profiles, and the 23-gene signature each provide unique insights into treatment response and resistance. While AR-V7 has emerged as a critical predictor of ADT resistance, RNA expression profiles and the 23-gene signature offer potential for personalizing therapy and identifying patients at risk of treatment failure. Future research should focus on:

Validation: Further validation of these markers in diverse patient populations and clinical settings is necessary to confirm their utility and reliability.

Standardization: Developing standardized testing protocols and integrating these markers into routine clinical practice.

Cost-Effectiveness: Assessing the cost-effectiveness of genomic and transcriptomic testing to improve accessibility and adoption.

Table I. Summary of the role and application of genomic and transcriptomic markers in assessing androgen deprivation therapy (ADT) in prostate cancer

Marker	Description	Key Findings
AR-V7	Androgen receptor splice variant linked to ADT resistance.	- AR-V7-positive patients have shorter progression-free survival. - AR-V7 predicts poor response to enzalutamide and abiraterone.
TMPRSS2-ERG	Gene fusion common in prostate cancer.	- Fusion present in ~50% of cases. - Impact on ADT response unclear but associated with disease progression.
RNA Expression Profiles	Gene expression levels predicting treatment response.	- Specific gene profiles correlate with ADT response. - Identifies genes related to resistance.
23-Gene Signature	Transcriptomic marker predicting ADT response.	- Predicts ADT response and resistance. - Favorable gene signatures linked to better outcomes.

Limitation

This review has limitations, including variability in study designs, sample sizes, and methodologies. Additionally, the clinical implementation of these markers is still evolving, and more research is needed to address existing gaps.

Conclusions.

Genomic and transcriptomic markers offer promising tools for assessing and personalizing ADT in prostate cancer. AR-V7, TMPRSS2-ERG, RNA expression profiles, and the 23-gene signature each contribute valuable information about treatment response and resistance. Despite the progress, challenges remain in standardization, cost, and clinical integration. Continued research and development are essential for optimizing the use of these markers in clinical practice and improving patient outcomes.

Conflict of Interest

The authors declare no conflict of interest.

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Ethical Approval

Not applicable for this systematic review.

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