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Germline *HSD3B1* Genetics and Prostate Cancer Outcomes

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Abstract

Dihydrotestosterone synthesis in prostate cancer from adrenal DHEA/DHEA-sulfate requires enzymatic conversion in tumor tissues. 3β-hydroxysteroid dehydrogenase-1 (3β-HSD1) is an absolutely necessary enzyme for such dihydrotestosterone synthesis and is encoded by the gene *HSD3B1* which comes in two functional inherited forms described in 2013. The adrenal-permissive *HSD3B1*(1245C) allele allows for rapid dihydrotestosterone synthesis. The adrenal-restrictive *HSD3B1*(1245A) allele limits androgen synthesis. Studies from multiple cohorts show that adrenal-permissive allele inheritance confers worse outcomes and shorter survival after castration in low-volume prostate cancer and poor outcomes after abiraterone or enzalutamide treatment for castration-resistant prostate cancer. Here, we review the clinical data and implications.

Introduction:

Over the last 30 years an increasing ability and decreasing cost of performing genetic sequencing has driven oncologic treatment towards precision medicine. Sequencing of somatic (tumor-based) and germline (present in all patient tissues) genetics in prostate cancer have both been performed and have helped identify mutations which predict response to therapies. A focus of our research has been the function of genes and enzymes regulating androgen synthesis pathways, and how certain genetic variants predict response to androgen deprivation therapy (ADT). A particular focus is a germline missense-encoding variant in the gene *HSD3B1,* which codes for the enzyme 3β-hydroxysteroid dehydrogenase-1 (3βHSD1) and has been shown to predict outcomes for prostate cancer patients treated with ADT in a variety of clinical situations.

In this review we discuss the current clinical relevance of a functional variation in *HSD3B1.* We start by reviewing the relevant biology of androgens and prostate cancer in the normal

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physiologic state and under conditions of androgen deprivation therapy. We then summarize the current evidence that *HSD3B1* variation predicts outcomes for prostate cancer patients treated with ADT. Additionally, we discuss the emerging evidence regarding *HSD3B1* variation and outcomes under intensified treatment of metastatic prostate cancer. Finally, we discuss the current clinical role of *HSD3B1* testing, and potential future directions and questions regarding the role of this common variant.

Biology of Steroids and Prostate cancer

Androgens, particularly testosterone (T) and 5α-dihydrotestosterone (DHT), have been known to play a biologically and clinically significant role in prostate cancer since the Nobel prize winning work of Huggins and Hodges[1]. In this seminal work, patients with metastatic prostate cancer were treated with androgen-deprivation therapy (ADT) in the form of surgical or medical castration. Prostatic-acid phosphatase and alkaline phosphatase levels were measured serially and marked declines in phosphatase levels along with clinical improvement were observed with castration. This work was the first to demonstrate the critical role of androgens in metastatic prostate cancer and showed the potential of inhibiting androgens to slow the disease. These observations form the basis of modern hormonal treatments for prostate cancer

Over the subsequent 80 years, while the role of ADT in treating metastatic prostate cancer has been firmly established, further work has helped establish the multi-faceted role of androgens in prostate cancer. Clinical studies have demonstrated that inhibition of formation of DHT by 5-alpha-reductase inhibitors like finasteride and dutasteride reduce the risk of development of prostate cancer (in particular, low grade prostate cancer),[2,3] that addition of conventional ADT to external beam radiation therapy improves oncologic outcomes,[4,5,6] and that intensive neoadjuvant androgen deprivation therapy can lead to appreciable rates of pathologic complete response or minimal residual disease in patients with high-risk localized prostate cancer.[7] Additionally, new intensified hormonal treatments such as the CYP17A1 inhibitor abiraterone acetate and potent and direct androgen receptor (AR) antagonists (enzalutamide, apalutamide, and daralutamide) have shown efficacy in metastatic castrate resistance prostate cancer (mCRPC)[8,9], non-metastatic CRPC[10-12], and metastatic castrate sensitive prostate cancer (mCSPC)[13-15]. Basic science work from the laboratory has helped elucidate important mechanisms driven by ADT including direct activation of apoptosis, inhibition of tumor angiogenesis, inhibition of DNA repair, and promotion of host immune function.[16,17,18] Furthermore, while work by the Cancer Genome Atlas (TCGA) Research Network on molecular drivers of prostate cancer has demonstrated the heterogeneity of localized prostate cancer, many of the most common alterations are in androgen-driven pathways including fusions of androgen-regulated (ARE) elements with ETS family transcription factors (with TMPRSS2-ERG being the most common ARE-ETS fusion), and SPOP mutations.[19] Recent in-vitro work has suggested that androgens may even play a role in development of some of these mutations.[20] Finally, research into mechanisms of castrate-resistance have demonstrated numerous ways in which AR signaling persists despite ADT.[21,22] Generally, androgens are playing a critical role in all forms of prostate cancer, from early oncogenesis, to response to treatment of localized disease, to metastatic castrate-sensitive disease, and finally in metastatic castrate resistant disease. Thus, individual

genetic variations in androgen metabolism and biology may affect any or all of these different disease states.

Androgens in the normal physiological state and under androgen deprivation therapy

In the normophysiologic state, the vast majority of androgens are synthesized in the Leydig cells of the testes. In the mitochondria various enzymes catalyze a series of sequential reactions to modify cholesterol as a starting substrate to generate testosterone (Figure 1). Testosterone is then released into circulation and perfused to the prostate where it is converted to DHT by steroid-5-alpha-reductase enzymes (SRD5A), which is predominantly SRD5A2 in prostate. DHT is the primary driver of prostatic AR activity, and germline mutations in SRD5A2 result in abnormal development of the external genitalia and the prostate.[23] Similarly, drugs inhibiting SRD5A (finasteride and dutasteride) result in ductal atrophy and a reduction in prostate size, as well as a reduction in the development of prostate cancer.[2,3,24]

Under ADT testicular androgen production is blocked. However, a major secondary source of androgen production leads to persistently present circulating androgens. The most notable secondary source is from the adrenal reticularis. In the normal physiologic state, the adrenal reticularis produces the majority of certain androgen precursors including dehydroepiandrosterone and its respective sulfate (DHEA and DHEAS), and a substantial fraction of Δ^4-androstenedione (AD). These precursors are weakly agonistic of AR and thus termed “weak androgens”. However, their associated AR agonist activity may be attributable in large part to metabolism to T/DHT and therefore the term “weak androgen” is probably better substituted with “precursor steroids”. The adrenal reticularis also produces a small amount of testosterone, under normal physiologic conditions; however, this is outweighed by far higher DHEAS concentrations. Adrenal precursor steroids are a major source of T/DHT and thus prostate cancer stimulation during ADT and efforts to further inhibit androgen production or directly inhibit AR binding form the basis for intensified hormonal therapies. Two agents which inhibit adrenal androgen production are ketoconazole (now rarely used) and abiraterone acetate. Ketoconazole is a non-steroidal antifungal agent which also inhibits CYP11A1 and CYP17A1. These two enzymes are critical for synthesis of DHEA and AD, and their inhibition results in markedly reduced production of androgen precursors by the adrenal glands.[25] Abiraterone acetate (cleaved to abiraterone as the active drug) is a more specific steroidal CYP17A1 inhibitor. Trials with abiraterone have demonstrated significant further testosterone suppression in men on ADT.[26] Blockade of the formation of androgen precursors limits both adrenal and peripheral tissue generation of testosterone and DHT, and thus effectively reducing AR signaling.[27,28]

Biology of *HSD3B1*

3βHSD1 is an enzyme mainly located in peripheral tissues which metabolizes DHEA to androstenedione, and thus provides a route to DHT synthesis from adrenal precursor steroids (Figure 1). In fact, the activity of 3βHSD1 is necessary for synthesis of any non-testicular testosterone or DHT. A specific germline missense-encoding variant (1245A→C) of the

gene *HSD3B1* renders the 3βHSD1 protein resistant to ubiquitination and degradation, and thus leads to increased build-up of the enzyme and resultant increases in downstream potent androgens[29]. We have termed the *HSD3B1*(1245C) allele the "adrenal permissive" allele, as it results in a phenotype of increased androgen synthesis from adrenal precursors and *HSD3B1*(1245A) the "adrenal restrictive" allele because it limits generation of potent androgens.[30,31]

HSD3B1 Inheritance and Prostate Cancer Outcomes with ADT

Some of the earliest clinical evidence for the importance of *HSD3B1* inheritance in prostate cancer outcomes with ADT came from Hearn et al work examining three retrospective cohorts.[32] The first was a cohort of 118 men from the Cleveland Clinic who had undergone radical prostatectomy with or without adjuvant or salvage radiation and had a subsequent biochemical recurrence treated with ADT. Progression-free (PFS), metastasis-free (MFS), and overall survival (OS) from ADT were all worse with increasing number of the adrenal permissive alleles inherited (Table 1) Similarly, a 137 patient post-prostatectomy cohort from the Mayo Clinic demonstrated shorter PFS from ADT with increasing number of adrenal permissive alleles (Table 1). Due to a short duration of follow-up, MFS and OS could not be assessed. Finally, a cohort of 188 patients with metastatic prostate cancer from the Mayo Clinic was also analyzed. PFS, MFS, and OS from ADT were all reduced with increasing adrenal permissive allele number. (Table 1)

These findings were confirmed in three additional independent cohorts treated with ADT. First, by Agarwal et al, who examined a cohort of 102 men with mCSPC. The cohort included both patients with prior definitive treatment (42%) and those who were metastatic. After adjustment for Gleason score and PSA, a significant difference in median PFS was identified between the patients who were homozygous adrenal restrictive and those who were homozygous adrenal permissive (21 vs 11 months). No significant difference was identified between the heterozygous individuals and the men in the homozygous adrenal restrictive group (adjusted median PFS of 19 and 21 months).[33] Contemporaneously, a study by Shiota et al examined a cohort of 104 Japanese men with mCSPC treated with primary androgen deprivation therapy.[34] The cohort was notable for having a high baseline PSA (median 244ng/mL), high rate of Gleason ≥8 disease (67.4%), and high rate of clinical T4 disease (27.8%). While the frequency of the adrenal permissive allele was substantially less than in the predominantly Caucasian cohorts of Hearn and Hahn (Table 2), PFS was still significantly shorter in patients with at least one adrenal permissive allele (either heterozygous or homozygous). OS, however, was not significantly different, possibly secondary to the small number of patients with adrenal permissive alleles. Last, Garcia-Gil et al reported on a cohort of 44 patients with metastatic prostate cancer treated with ADT. They separated the cohort into two groups based on presence or absence of any adrenal permissive alleles. PFS was 24mo and 57mo for those with adrenal permissive alleles and without respectively.[35]

Expanding on the previous work, Hearn et al analyzed outcomes for a cohort of prostate cancer patients who underwent ADT treatment for PSA progression after definitive radiotherapy.[36] While OS and PFS were not significantly different between the groups, MFS

after ADT was significantly shorter in patients with adrenal permissive alleles (5.8 and 4.4 years with 1 and 2 alleles respectively vs 7.4 years with 0 alleles). The finding that adrenal permissive alleles lead to more rapid development of metastases but not decreased survival may have been due to the moderate length of follow-up (median 7.9 years). However, the clinically relevant difference in MFS confirms the importance of adrenal permissive variants in predicting post-radiation progression outcomes after ADT.

These four studies, encompassing seven independent cohorts, demonstrate the significance of adrenal-permissive *HSD3B1* inheritance in predicting outcomes in some of the common clinical situations where ADT is utilized including post-prostatectomy recurrence, post-radiotherapy recurrence, and metastatic disease. In each of these settings, the presence of a homozygous adrenal permissive genotype was predictive of shorter PFS, and in two of the cohorts with longer follow-up, was associated with decreased OS. One area of difference between the studies is in the outcomes of heterozygous patients. In regard to PFS, the Cleveland Clinic post-prostatectomy cohort demonstrated differences in PFS between patients with the homozygous adrenal restrictive genotype and who were heterozygous. However, the Mayo post-prostatectomy validation cohort and metastatic cohort did not demonstrate a significant difference between these two groups, although numerically the heterozygotes had intermediate outcomes in the metastatic cohort. In Agarwal et al, the heterozygous patients had adjusted PFS rates similar to the homozygous adrenal restrictive arm (19 vs 21months respectively). Conversely, Shiota et al and Garcia-Gil et al analyzed the heterozygous and homozygous adrenal permissive patients as one group and noted a difference in PFS as compared to patients with the homozygous adrenal restrictive genotype. Thus, the cohorts are somewhat unclear on if there is a significant difference between heterozygous patients and either those in the homozygous adrenal restrictive or homozygous adrenal permissive cohorts. The overall survival data is more consistent, showing the heterozygous patients as having worse overall survival than the homozygous adrenal restrictive patients in both the Cleveland Clinic post-prostatectomy cohort and the Mayo Clinic metastatic cohort. Comparisons to the homozygous adrenal permissive groups are limited, as the homozygous adrenal permissive groups are generally smaller (~8-10%). Overall survival analysis was not performed by Agarwal et al and was limited by cohort size in Shiota et al and the Mayo post-prostatectomy cohort. Generally, the three genotypes appear to be distinct, with heterozygous patients having outcomes in between the homozygous adrenal permissive and homozygous adrenal restrictive patients. However, due to the small number of patients in each arm (particularly the homozygous adrenal permissive arms), such differences can be hard to elucidate statistically. Biologically, research from Chang et al has shown somatic (tumor-based) mutations leading to loss of heterozygosity in individuals with a germline heterozygous phenotype, suggesting that heterozygous individuals may be at risk for developing a adrenal permissive phenotype resistant to androgen deprivation therapy.[29]

HSD3B1 and outcomes with ADT +/− docetaxel in mCSPC

Recently, Hearn et al retrospectively analyzed data from the phase 3 Chemohormonal Therapy vs Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) study.[37] CHAARTED was a randomized-controlled trial of patients with

mCSPC randomized to either ADT or ADT and docetaxel chemotherapy. Patients were stratified based on a number of factors including presence of high volume (visceral metastases or >4 bone metastases including one outside of the pelvis/vertebrate) or low volume disease. Hearn and colleagues combined the experimental and control arms and analyzed the data by presence or absence of at least one adrenal permissive allele in white patients, in whom the adrenal-permissive allele frequency is highest. For patients with low-volume disease, the presence of ≥1 adrenal permissive allele was associated with development of CRPC (HR 1.89, 2-year rates of 49.0% and 29.5%% for ≥1 and 0 adrenal permissive alleles, respectively) and increased risk of mortality (HR 1.74, 5-year rates of 42.5%% and 29.2% for ≥1 and 0 adrenal permissive alleles, respectively). Conversely, in patients with high-volume disease, presence of an adrenal permissive genotype did not lead to worse outcomes. An additional analysis looking at the possibility of differential benefit of docetaxel in patients with *HSD3B1* variants did not show any difference in outcomes. These findings support the role of *HSD3B1* variants in driving outcomes for mCSPC patients undergoing ADT therapy even when additional therapy (docetaxel in this case) is added to the regimen. The findings of differential responses between patients with low volume and high volume disease is interesting, and may be indicative of the fact that patients with high-volume disease have increasing degrees of genomic alteration which may lead to less dependence on extra-gonadal androgens.[38] Studies of *HSD3B1* in other intensified therapies in the mCSPC space (such as abiraterone or enzalutamide) have not been performed at this point.

HSD3B1 and next-generation hormonal therapies in mCRPC

While the above studies all address the power of *HSD3B1* variation to predict prostate cancer outcomes in men with advanced CSPC undergoing ADT, an additional major question is how *HSD3B1* variation interacts with hormonal therapies in the mCRPC patient. The earliest work looking to answer this question was done by Almassi et al who examined outcomes of mCRPC patients undergoing treatment with the older drug ketoconazole, which is a non-steroidal inhibitor of CYP17A1 and CYP11A1. This study suggested that inheritance of the adrenal-permissive *HSD3B1* allele is associated with longer PFS, supporting the hypothesis that mCRPC in men with adrenal permissive alleles is dependent on adrenal androgens and thus may be more responsive to treatments which block adrenal androgen production.[39]

Unfortunately, extending the findings on ketoconazole to other CYP17A1 blockers such as Abiraterone is not straightforward. Abiraterone is a steroidal CYP17A1 inhibitor (as opposed to non-steroidal like ketoconazole) which is converted to multiple downstream metabolites by 3βHSD1. An early metabolite, Δ^4-abiraterone (D4A), strongly inhibits steroidogenic enzymes (CYP17A1, 3βHSD) and even AR itself. However, further metabolites of D4A have pro-androgenic activity. Work by Alyamani et al has demonstrated that presence of adrenal permissive alleles is associated with significantly more generation of the pro-androgenic abiraterone metabolites.[40,41] Thus, while abiraterone itself may be beneficial in inhibiting adrenal androgen synthesis in patients with adrenal permissive alleles, increased metabolism of abiraterone by those same adrenal permissive enzymes to pro-androgenic metabolites may limit or blunt the efficacy of the drug.

Two early studies of *HSD3B1* genotype and response to abiraterone were performed by Hahn et al and Shiota et al. Hahn et al examined a cohort of 76 men with mCRPC treated with first-line abiraterone, and noted similar PFS times among patients of all three genotypes. Shiota et al, however, reported on a similarly treated cohort of Japanese men (lower adrenal-permissive gene frequency) and found longer times to progression among those with adrenal permissive alleles. While interesting, these early studies were limited by small cohort sizes, especially of the uncommon homozygous adrenal permissive genotype (5 patients in the Hahn study, 0 in the Shiota study).[42,34]

Two new studies have helped clarify the role of *HSD3B1* in response of mCRPC to abiraterone or enzalutamide. These larger studies both examined mCRPC patients treated with either abiraterone or enzalutamide and assessed the association between homozygous adrenal permissive *HSD3B1*(1245C) allele inheritance and outcomes with abiraterone or enzalutamide. Lu et al reported on two cohorts combined of 266 CRPC patients and examined PSA response rates, time on treatment, and overall survival, in two groups (homozygous adrenal restrictive + heterozygotes vs homozygous adrenal permissive). The groups had very similar PSA response rates (>30% PSA decline in 68% of both groups, and >50% decline in 58% of adrenal permissive and 60% of adrenal restrictive groups) and times on treatment (10.3 months for the adrenal restrictive and 7.1 months for the adrenal permissive). However, survival was significantly shorter with homozygous adrenal-permissive allele inheritance (23.6 vs 30.7 months), even after adjustment for pre-defined risk factors (Gleason score, PSA, etc.). Sub-group analyses separating patients into groups based on if they received abiraterone or enzalutamide demonstrated numerical differences in survival for both groups by genotype (23.6mo vs 32.8mo for abiraterone treated adrenal permissive and restrictive respectively, and 16.6mo vs 26.9mo for enzalutamide treated adrenal permissive and restrictive respectively) though the enzalutamide difference was not statistically significant (possibly because of the small cohort size of 56 patients) and neither was the abiraterone difference after adjustment for pre-treatment risk factors. Lu et al also retrospectively examined the mCSPC outcomes for this cohort and found a shorter time on initial ADT treatment (14 vs 18mo for adrenal permissive and restrictive respectively), though the difference was not statistically significant (HR 1.51, p=0.11) after adjustment for baseline characteristics.[43]

Similarly, Khalaf et al examined outcomes from a combined two cohorts of mCRPC patients being treated with either enzalutamide or abiraterone. They examined time-to-progression, PSA response, and overall survival. They also retrospectively examined time from ADT initiation to development of CRPC. Patients with the homozygous adrenal permissive genotype were less likely to have a PSA response than heterozygous or homozygous adrenal restrictive patients, and had a shorter time-to-progression. However, overall survival was not significantly different in the combined cohort. Interestingly, when analyzed individually the two cohorts had markedly different results. In the 1st cohort (from an RCT of enzalutamide vs abiraterone performed in British Columbia), homozygous adrenal permissive genotype was a significant predictor of overall survival on univariate analysis (and showed a large numeric difference in time to progression and PSA progression). However, in the 2nd cohort (from a prospective study of mCRPC patients in Spain), homozygous adrenal permissive genotype was not a significant predictor of OS, time-to-progression, or PSA progression.

The Spanish cohort had much higher levels of prior taxane use and the analyses suggested that homozygous adrenal permissive genotype is associated with worse outcomes with first-line abiraterone or enzalutamide.[44]

The studies of Lu and Khalaf both suggest that homozygous adrenal permissive phenotype may impair response to both abiraterone and enzalutamide in mCRPC. However, neither study convincingly showed that one agent was superior to another for any genotype. Importantly, these studies together suggest that resistance to abiraterone or enzalutamide in homozygous adrenal permissive patients may be dependent on extragonadal androgen synthesis stimulation of AR.

Clinical Relevance:

While the numerous studies described above (encompassing many different cohorts) have generated consistent evidence that *HSD3B1* inheritance is an important player in determining outcomes for prostate cancer patients being treated with ADT in a variety of settings, in particular with low-volume prostate cancer, it remains to be determined whether and how *HSD3B1* status can be used to inform clinical decision-making. However, there are several situations where it could potentially be useful.[45]

HSD3B1 status may be informative in decision making for patients with recurrence following definitive therapy. For example, a patient with recurrence after primary treatment and an adrenal restrictive phenotype, may elect to forgo the salvage treatment knowing that he is likely to have a longer more durable response to androgen deprivation therapy, or conversely, one with an adrenal permissive phenotype may accept the morbidity of salvage treatment knowing that his response to future non-curative ADT and subsequent abiraterone or enzalutamide will likely be poor. Such decisions have to be made in the context of numerous variables including patient performance status, oncologic status (PSA kinetics, Gleason score, etc), and desire to avoid salvage treatment. However, choices regarding salvage therapy are often made on the margin, and further biologic information about response to systemic therapies may better inform these tough decisions.

Similarly, there is increasing interest in targeted therapy (typically SBRT) and treatment of oligometastatic prostate cancer with curative intent.[46] For patients with an adrenal restrictive phenotype, aggressive treatment of oligometastatic disease may offer marginal benefit over ADT alone, while for those with a homozygous adrenal permissive genotype it may be the best chance for preventing progression and mortality. Generally speaking, *HSD3B1* status may help inform intensity of prostate cancer therapy for patients with low-volume mCSPC. In their investigation of *HSD3B1* status on abiraterone and enzalutamide outcomes for mCRPC patients, Lu et al[43] also looked back at overall survival from time of initial ADT initiation. Patients with a homozygous adrenal permissive genotype had OS of 58 months compared to 81 months for those with a homozygous adrenal restrictive or heterozygous phenotype. An ability to prognosticate a 2-year difference in survival could influence many decisions for physicians and patients alike. Ultimately, definitive answers for the role for *HSD3B1* in clinical decision-making will require additional prospective clinical trials.

Future Directions

Androgen deprivation therapy is currently part of the armamentarium for treatment of localized prostate cancer (in conjunction with radiation) and is the treatment backbone for metastatic castration-sensitive prostate cancer. In addition, numerous trials have examined (or are examining) the role of ADT regimens as neoadjuvant treatment for high-risk prostate cancer. *HSD3B1* status could potentially play a role in any of these disease states. ADT plays a role in limiting repair of DNA damage caused by radiation therapy and is typically recommended as part of primary external beam radiation treatment.[18] Less effective ADT due to an adrenal permissive phenotype might thus lead to adverse outcomes with radiation/ADT as primary therapy, or may indicate the need for additional hormonal therapy (such as an AR receptor antagonist like apalutamide or enzalutamide). However, current studies have not addressed this possibility. Similarly, *HSD3B1* status may predict response to neoadjuvant hormonal therapy regimens, potentially identifying a cohort of patient most likely to benefit from such therapies. Currently, our group is examining the role of *HSD3B1* status in predicting response to neoadjuvant ADT/apalutamide therapy prior to prostatectomy for patients with high-risk prostate cancer. Such studies are particularly appealing as immediate pathologic outcomes (like complete response or minimal residual disease) can be used as early signs of clinically important differences. In the metastatic castrate sensitive and castrate resistant space, there is a possibility that *HSD3B1* status could help differentiate which agents would be most beneficial for certain patients. However, further studies are clearly necessary, as the current studies do not directly compare different regimens.

Conclusions

Androgens play a critical role in prostate cancer, and ADT is currently part of treatment of localized prostate cancer, mCSPC, and mCRPC. The adrenal-permissive *HSD3B1* (1245C) allele enables increased generation of T and DHT from adrenal precursor steroids. This increase in androgens under conditions of ADT leads to shorter PFS, MFS, and OS in a variety of clinical settings. *HSD3B1* status may also predict poor outcomes with intensified hormonal therapies, and thus serve as a biomarker to determine treatment strategy in a variety of clinical situations. However, further studies to elucidate the ability of *HSD3B1* to predict differential responses with intensified regimens are needed.

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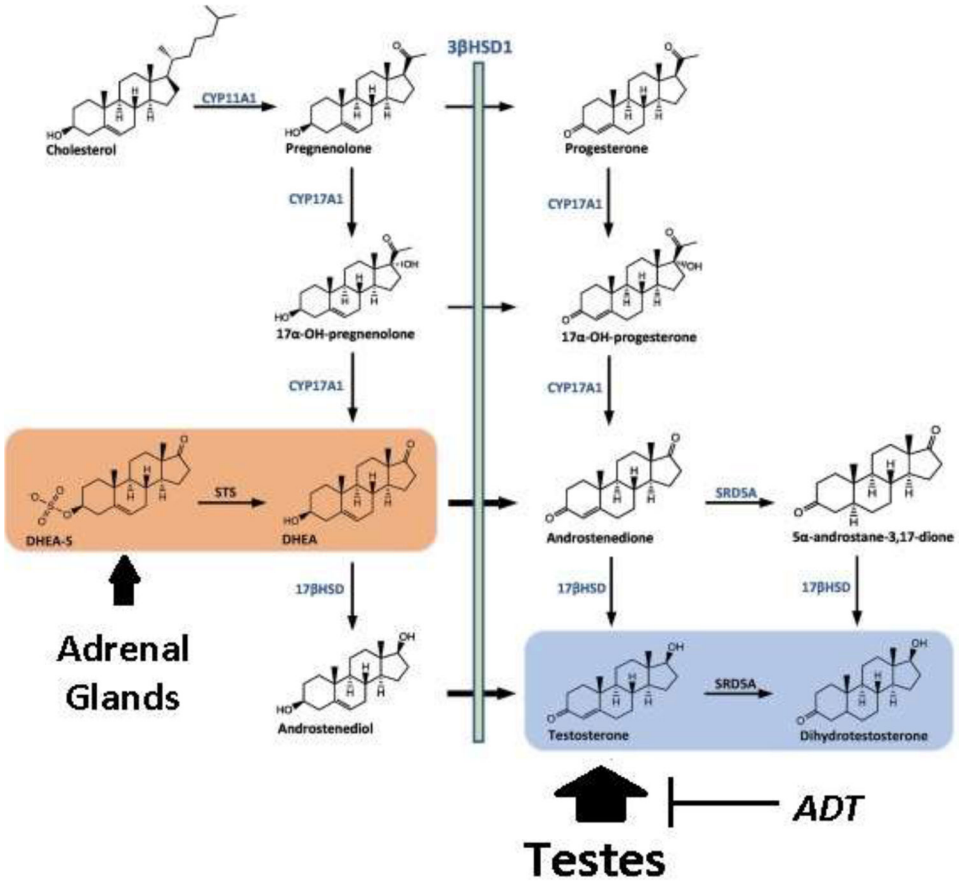

Figure 1:

Common sources of androgens. In the normophysiologic state, the majority of testosterone is produced in the testes and released into circulation. Under conditions of ADT, testicular testosterone production is suppressed. Precursor androgens (notably DHEA and DHEA-S) are generated by the adrenals and released into circulation. Conversion to androgenic testosterone occurs in peripheral tissues with 3β-HSD1 (protein product of *HSD3B1*) playing a pivotal step.

Table 1:

Relevant outcomes of various published cohorts stratified by HSD3B1 grouping. Of note, different studies have used different groupings of the three genotypes in their analyses.

Hearn et al Cleveland Clinic Prostatectomy Cohort (n= 118)	**Homozygous Adrenal Restrictive**	**Heterozygous**	**Homozygous Adrenal Permissive**
Progression Free Survival	6.6yr	4.1yr	2.5yr
Metastasis Free Survival	9.1yr	6.8yr	3.6yr
Overall Survival	16.7yr	7.4yr	7.3yr
Frequency	37%	53%	10%
Mayo Clinic Prostatectomy Cohort (n=137)			
Progression Free Survival	3.3yr	2.8yr	0.9yr
Frequency	56%	37%	7%
Mayo Clinic De Novo Metastatic Cohort (n=188)			
Progression Free Survival	1.8yr	1.4yr	0.8yr
Overall Survival	9.7yr	6.8yr	4.6yr
Frequency	52%	42%	6%
Hahn et al mCSPC Cohort (n=102)			
Progression Free Survival	21mo	19mo	11mo
Frequency	47%	43%	10%
Hearn et al Post-Radiation ADT Cohort (n=213)			
Progression Free Survival	2.3yr	2.3yr	1.4yr
Metastasis Free Survival	7.4yr	5.8yr	4.4yr
Overall Survival	7.7yr	6.9yr	7.2yr
Frequency	46%	45%	9%

Garcia-Gil et al mCSPC Cohort (n=44)	**Homozygous Adrenal Restrictive**	**Heterozygous/Homozygous Adrenal Permissive**
Progression Free Survival	57mo	24mo
Frequency	59%	41%
Hearn et al CHAARTED Analysis (n=475)		
Low Volume Disease, 2yr CRPC Free Rate	71%	51%
Low Volume Disease, 5yr OS Rate	71%	58%
High Volume Disease, 2yr CRPC Free Rate	27%	27%
High Volume Disease, 2yr OS Rate	33%	37%

Lu et al mCRPC treated with Abiraterone or Enzalutamide (n=266)	**Homozygous Adrenal Restrictive/Heterozygous**	**Homozygous Adrenal Permissive**
PSA response >30%	67.70%	68.40%
PSA response >50%	59.50%	57.90%
Time on Treatment All	10.3mo	7.1mo
Time on Treatment Abiraterone	10.4mo	5.2mo
Time on Treatment Enzalutamide	10.1mo	7.2mo

Hearn et al Cleveland Clinic Prostatectomy Cohort (n= 118)	**Homozygous Adrenal Restrictive**	**Heterozygous**	**Homozygous Adrenal Permissive**
Overall Survival All	30.7mo		23.6mo
Overall Survival Abiraterone	32.8mo		23.6mo
Overall Survival Enzalutamide	26.9mo		16.6mo

Table 2:

HSD3B1 genotype and overall allele frequencies in various published cohorts

	Homozygous Adrenal Restrictive	Heterozygous	Homozygous Adrenal Permissive	Overall Adrenal Permissive Allele Frequency
Hearn et al				
Cleveland Clinic Prostatectomy Cohort (n= 118)	44 (37%)	62 (53%)	12 (10%)	37%
Mayo Clinic Prostatectomy Cohort (n=137)	77 (56%)	50 (36%)	10 (8%)	26%
Mayo Clinic De Novo Metastatic Cohort (n=188)	98 (52%)	79 (42%)	11 (6%)	27%
Hahn et al				
Metastatic Hormone Sensitive Cohort (n=102	48 (47%)	44 (43%)	10 (10%)	31%
Shiota et al				
Metastatic Hormone Sensitive Cohort (n=104)	95 (91.3%)	7 (6.7%)	2 (1.9%)	5%
Metastatic Castrate Resistant Cohort (n=99)	85 (86%)	14 (14%)	0 (0%)	7%
Hearn et al				
Post-Radiation ADT Cohort (n=213)	97 (46%)	96 (45%)	20 (9%)	32%
Khalaf et al				
mCRPC cohort (n=546)	249 (45.6%)	215 (39.4%)	82 (15%)	35%
Lu et al				
mCRPC cohort (n=266)	143 (54%)	101 (38%)	22 (8%)	27%