Introduction
Prostate cancer is the second leading cause of cancer death in the USA and the number of cases is rapidly increasing in Japan. Patients presenting with advanced disease typically receive hormonal therapy using medical or surgical castration as initial treatment. However, most prostate cancer patients acquire resistance to the initial hormonal therapy over 2–3 years, thus progressing to a castration-resistant disease state.

Since docetaxel was introduced in 2004 to prolong the survival of patients with castration-resistant prostate cancer (CRPC), there has been a rapid increase in the number of effective systemic agents for CRPC, including novel androgen receptor (AR)-directed, immunotherapeutic, chemotherapeutic and radiopharmaceutical drugs. Concomitant docetaxel treatment at the beginning of hormonal therapy for metastatic castration-sensitive prostate cancer (CSPC) has resulted in longer overall survival than with hormonal therapy alone. Elucidating an appropriate treatment sequence using these therapies is important for maximizing clinical benefit in castration-sensitive and castration-resistant prostate cancer patients. The development of advanced high-throughput ‘omics’ technology has enabled the use of novel markers to guide prognosis and treatment of this disease. In this review, we outline the genomic landscape of prostate cancer and the molecular mechanisms of castration-resistant progression, and how these affect the development of new drugs, and their clinical implications for selecting treatment sequence. We also discuss many of the potential tissue-based or liquid biomarkers that may soon enter clinical use, with the hope that several of these prognostic or predictive markers will guide precision medicine for prostate cancer patients in the near future.

Keywords: prostate cancer, biomarker, treatment, castration-resistant prostate cancer

Received: 9 March 2017; revised manuscript accepted: 13 June 2017.

Abstract: Advances in our understanding of the mechanisms driving castration-resistant prostate cancer have promoted the development of several new drugs including androgen receptor-directed therapy and chemotherapy. Concomitant docetaxel treatment at the beginning of hormonal therapy for metastatic prostate cancer has resulted in longer overall survival than with hormonal therapy alone. Elucidating an appropriate treatment sequence is important for maximizing clinical benefit in castration-sensitive and castration-resistant prostate cancer patients. The development of advanced high-throughput ‘omics’ technology has enabled the use of novel markers to guide prognosis and treatment of this disease. In this review, we outline the genomic landscape of prostate cancer and the molecular mechanisms of castration-resistant progression, and how these affect the development of new drugs, and their clinical implications for selecting treatment sequence. We also discuss many of the potential tissue-based or liquid biomarkers that may soon enter clinical use, with the hope that several of these prognostic or predictive markers will guide precision medicine for prostate cancer patients in the near future.
Table 1. Potential prognostic or predictive biomarkers in prostate cancer.

| Biomarker                                      | Source  | Clinical relevance                                      | Prog versus Pred |
|-----------------------------------------------|---------|--------------------------------------------------------|------------------|
| Metastatic status                             | Clinical| Number of bone mets (EOD), viseral mets                | Prog/Pred        |
| Performance status                            | Clinical| ECOG performance status [0–4]                          | Prog/Pred        |
| Time to CRPC                                   | Clinical| Time from ADT to CRPC                                  | Pred             |
| Prior treatment                               | Clinical| Number of antiandrogens or steroid                      | Pred             |
| PSA                                           | Blood   | Protein specifically extracted from prostate gland     | Prog              |
| PSA kinetics                                  | Blood   | PSA decrease rate under treatment                      | Prog              |
| Gleason score                                 | Tissue  | Pathological features strongly correlated prognosis     | Prog/Pred        |
| Lactate dehydrogenase                         | Blood   | Elevated by injuries and various disease including cancer| Prog/Pred        |
| Alkaline phosphatase                          | Blood   | Elevated by cancer spreading to bones or liver          | Prog              |
| Albumin                                       | Blood   | An index of nutritional status                          | Prog              |
| Hemoglobin                                    | Blood   | Decreased by anemia                                     | Prog/Pred        |
| Neutrophil-lymphocyte ratio (NLR)             | Blood   | Elevated NLR predicted poorer OS in various cancer patients | Prog              |
| Testosterone                                  | Blood   | Ligand of AR associating prostate cancer proliferation | Prog/Pred        |
| Number of circulating tumor cells (CTCs)      | Blood   | Increased number of CTCs associating with worse cancer prognosis | Prog              |
| AR splice variants in CTC (esp. AR-V7)        | Blood   | Correlating with poor response to ENZA and ABI but good response to Chemo | Pred             |
| Concentration of cell-free DNA (cfDNA)        | Blood   | Increased abundance of cfDNA associating with worse cancer prognosis | Prog              |
| AR mutation and copy number in cfDNA          | Blood   | Correlating with worse efficacy of ENZA and ABI        | Pred             |
| Somatic DNA repair mutations                  | Tissue  | Correlating with poor response to ADT, but good response to PARP inhibitors | Prog/Pred        |

ABI, abiraterone; ADT, androgen-deprivation therapy; AR, androgen receptor; cfDNA, cell-free DNA; CRPC, castration-resistant prostate cancer; CTC, circulating tumor cell; ECOG, Eastern Cooperative Oncology Group; EOD, extent of disease; ENZA, enzalutamide; mets, metastases; NLR, neutrophil-lymphocyte ratio; OS, overall survival; PARP, poly-ADP ribose polymerase; Pred, predictive marker; Prog, prognostic marker; PSA, prostate-specific antigen.

Pretreatment clinical parameters as prognostic or predictive biomarkers

The currently used biomarkers are defined as prognostic and predictive (Table 1). Prognostic markers aim to evaluate objectively the patient’s overall outcome, such as the probability of cancer recurrence after standard treatment. The presence or absence of a prognostic marker can be useful for the selection of patients for treatment but does not directly predict the response to treatment. Predictive markers aim to evaluate objectively the likelihood of benefit from a specific clinical intervention, or the differential outcomes of two or more interventions, including toxicity. The discovery of prostate-specific antigen (PSA) as a serum tumor marker has revolutionized prostate cancer diagnosis, and is the only widely used biomarker for diagnosis and prognosis of this disease. However, PSA is organ- but not cancer-specific. Moreover, it is not able to differentiate between indolent and aggressive forms of prostate cancer. Many men may harbor aggressive prostate cancer despite having low initial levels of serum PSA. The Gleason grading system is also used with prostate biopsy samples to help evaluate the prognosis of men with prostate cancer. Recently, the new, simplified prostate cancer grading system with five grades has shown more accurate grade stratification.
compared with current Gleason grading systems.11 Together with other parameters, it is incorporated into a strategy of prostate cancer staging that predicts prognosis and helps to guide treatment.

The majority of other clinical and biological prognostic biomarkers of prostate cancer have been validated, which helps physicians to estimate survival using tumor and patient characteristics. Originally, PSA-based test results, performance status (PS) score and hemoglobin level were combined with age, albumin, lactate dehydrogenase (LDH) or alkaline phosphatase levels, Gleason score, pain intensity and metastases characteristics in different prognostic models.12,13 After the emergence of new treatment options in CRPC, an updated nomogram for predicting survival in men with metastatic CRPC receiving first-line chemotherapy was developed and validated.14 More recently, metastatic site and opioid analgesic use,15 as well as serum androgen levels,16 have been reported to correlate with prognosis. We analyzed pretreatment parameters predicting enzalutamide efficacy by Cox proportional hazard analyses for PSA progression-free survival in 345 patients. Enzalutamide treatment was effective for patients with low Gleason scores, good PS, absence of bone or visceral metastasis and no prior steroid or docetaxel treatment.17 In subgroup analysis of the PREVAIL study, the treatment effect of enzalutamide for increasing progression-free survival time was more significant in patients with good PS, low Gleason score, no visceral metastasis, low LDH levels and high hemoglobin levels.18 For metastatic CRPC, the benefit of chemohormonal therapy was more apparent in the subgroup with high-volume than low-volume disease, indicating that the clinical benefit was more pronounced among patients with a higher burden of disease.5 The neutrophil-to-lymphocyte ratio is also correlated with prognosis in patients with metastatic prostate cancer.19 By using these known baseline clinical parameters, we can predict the prognosis and efficacy of novel treatments for prostate cancer. However, they are not perfect for selecting the best treatment sequence. Achieving precision medicine will require more precise tissue- or liquid-based biomarkers with prognostic and predictive value beyond these clinical parameters.

### Treatment selection based on the mechanisms of castration resistance

Most advanced prostate cancers treated with androgen-deprivation therapy (ADT) acquire castration resistance by various mechanisms, including AR overexpression, AR mutation, AR activation by other signals and non-AR pathways.20 Novel mechanisms such as de novo androgen production in cancer cells21 and the generation of AR splice variants22 have recently been associated with castration resistance and poor prognosis. We have previously reported that a prostate cancer cell line, LCaNAP, comprises a heterogeneous group of cells with different androgen-deprivation sensitivities and potential for invasiveness.23 Therefore, we need to consider the heterogeneity of CRPC cells when we choose therapy for each prostate cancer patient.

The mechanisms of castration resistance and the treatment selection based on them are summarized in Table 2. AR overexpression was associated with castration resistance in a study using mouse xenograft models of prostate cancer, and enzalutamide suppressed tumor growth,24 indicating that enzalutamide is effective for CRPC patients with increased AR expression. AR mutations might also be induced by ADT or specific antiandrogens.25–27 For patients with CRPC harboring mutant AR, antiandrogen withdrawal or alternative antiandrogen treatment might be effective.28 Enzalutamide-refractory mutant AR has been reported recently and might be one mechanism for acquired enzalutamide resistance.29 The testosterone concentration of metastatic prostate cancer tissues is higher than in nonmetastatic tissues, caused by the increased expression of enzymes for androgen synthesis such as cytochrome P450 17alpha-hydroxylase/17,20-lyase (CYP17).21 Abiraterone might be effective for these CRPC patients. Recently, the metabolites of abiraterone have been demonstrated to have antagonistic effects on AR and considered to have a further potential mechanism of action.30 AR splice variants including AR-V7 have been shown to provide an important mechanism for CRPC and treatment resistance.31 They are AR isoforms coding only for the DNA binding and transactivation domains of AR, and lack the C-terminal ligand-binding domain.32 These truncated AR species are resistant to conventional AR-targeting agents as well as abiraterone and enzalutamide.33,34 Taxane chemotherapy might be a better treatment option for AR-V7-positive prostate cancer patients.35–37 Therefore, detection of AR-V7 might represent a prognostic and predictive (i.e. treatment selection) marker in men with CRPC.38 Other than AR overexpression, mutation and splice variants,
various additional AR bypass pathways are associated with androgen-independent AR activation and might represent future treatment options for CRPC. We previously reported the association of a prostaglandin receptor, EP4, in CRPC as a potential treatment target. Historically, steroid and estrogen treatment has resulted in subjective and objective responses in patients with CRPC. Glucocorticoid receptor (GR) and progesterone receptor (PR) are considered to be AR bypass pathways associated with castration resistance. The actions of these receptors under treatment with steroids or estrogen differ among cell types and their concentrations. Recently, GR overexpression was reported to be associated with enzalutamide resistance. The interaction of GR or PR and AR is complicated and elucidation of their true function and clinical implication in CRPC needs further examination. Non-AR pathways such as neuroendocrine differentiation and DNA repair are also important. As androgen-targeting therapy is not effective in these cells, platinum-based chemotherapy or other molecular targeted therapy such as poly-ADP ribose polymerase (PARP) inhibitor may be treatment options.

Circulating tumor cells and cell-free DNA as novel liquid biomarkers
Prostate biopsies are almost always performed at the time of prostate cancer diagnosis, therefore, tissue markers such as Gleason grade are useful to determine prognosis and select first-line treatment. However, for patients who fail first-line therapy, treatment is often changed without performing another tumor biopsy. Therefore, other biomarkers using samples easily obtained for predicting subsequent treatment efficacy are urgently needed. Recent advances in high-throughput technology provide new and powerful platforms to find novel biomarkers from body fluids such as blood or urine.

We have previously examined the gene expression profiles using transcriptome analyses of prostate cancer tissues and found that cysteine-rich angiogenic inducer (Cyr)61 is highly expressed in prostate cancer, and its expression is correlated with cancer aggressiveness. Serum Cyr61 protein expression levels are correlated with biochemical recurrence after surgery. Proteomic analyses have recently uncovered several candidate biomarkers from tissue or serum samples. We have examined the lipid expression profiles of prostate cancer tissues using high-resolution imaging mass spectrometry and found that decreased expression of lysophosphatidylcholine independently predicts biochemical recurrence. We have also found, using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, that a C-terminal PSA fragment composed of 19 amino acid residues is a potential novel urine biomarker for diagnosis of prostate cancer. However, it was difficult to establish the method to measure the concentration of these lipids or proteins. Therefore, none of them could be commercially available biomarkers.

The blood of some patients with advanced prostate cancer contains circulating tumor cells (CTCs) derived from the primary tumor and metastatic sites. It is also known that CTCs can be detected in peripheral blood before the occurrence of clinically detectable metastases. Several CTC isolation methods have been investigated. The most extensively investigated target in the context of CTC characterization in prostate cancer is the AR. We reported that the detection of AR-V7 in CTCs was associated with resistance to

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**Table 2.** Mechanisms of castration resistance and the treatment selections.

| Mechanism                        | Treatment                                                        |
|----------------------------------|------------------------------------------------------------------|
| AR mutation                      | Alternative antiandrogen [e.g. bicalutamide→flutamide]           |
| AR overexpression                | Novel antiandrogen [enzalutamide]                                |
| Novel androgen synthesis         | CYP17 inhibitor [abiraterone]                                    |
| AR splice variant                | Taxane chemotherapy [docetaxel/cabazitaxel]                      |
| AR activation by other signals   | Steroid/estrogen/molecular target therapy                       |
| Non-AR pathways                  | Chemotherapy [platinum]/molecular target therapy [PARP inhibitor]|

AR, androgen receptor; CYP17, cytochrome P450 17alpha-hydroxylase/17,20-lyase; PARP, poly-ADP ribose polymerase.
abiraterone and enzalutamide.\textsuperscript{33} AR-V7-positive CTCs were identified in 39\% of patients receiving enzalutamide and 19\% of those receiving abiraterone in our initial study of 62 patients. The PSA response rate was 0\% for AR-V7-positive patients in the context of both therapies. These results have now been expanded to a larger sample of 202 patients, in whom the negative prognostic impact of CTC-specific AR-V7 detection has been confirmed.\textsuperscript{57} These results suggest that the presence of AR-V7 might explain the mechanism of primary resistance to abiraterone and enzalutamide in many cases. By contrast, the presence of AR-V7 does not appear to correlate with poor treatment responses in patients receiving docetaxel or cabazitaxel.\textsuperscript{35,37,58}

One of the shortcomings of CTC analysis is difficulty in cell isolation and subsequent nucleic acid extraction (blood samples need immediate preparation soon after extraction from patients). In addition, CTC capture methods based on epithelial cell adhesion molecule or other cell-surface markers may miss mesenchymal cells undergoing epithelial–mesenchymal transition. Cell-free DNA (cfDNA) has recently been recognized as a potential biomarker in advanced tumors. cfDNA is composed of small fragments of nucleic acid that are not associated with cells or cell fragments.\textsuperscript{59,60} cfDNA might be more stable than CTCs and can be stored for several days after extraction. In several solid malignancies, analysis of cfDNA has been used to characterize and monitor disease, as well as predict outcome and treatment response.\textsuperscript{61} Similar to CTCs, ARs represent an important target in the context of cfDNA analysis. AR copy number variations and activating mutations in the ligand-binding domain are correlated with resistance to abiraterone and enzalutamide.\textsuperscript{26,27} In addition, analysis of AR-V7 from whole-blood RNA is feasible\textsuperscript{62,63} and may correlate with inferior outcomes to abiraterone and enzalutamide.\textsuperscript{64}

**Novel molecular biomarkers based on genomic landscape of prostate cancer**

ARs are the most important molecules for prostate cancer progression, and their overexpression, mutation or splice variance can be useful predictive biomarkers. However, other genomic changes in prostate cancer might also be useful in the recent advances of CTC and cfDNA isolation technology.

Gene fusions, specifically E26 transformation-specific fusions such as the \textit{TMPRSS2:ERG} translocation, are associated with early onset of prostate cancer.\textsuperscript{65} \textit{TMPRSS2:ERG} gene fusion might predict cancer-specific and overall survival based on immunohistochemistry in metastatic patients undergoing palliative transurethral resection of the prostate.\textsuperscript{66} However, there seems to be no association between \textit{TMPRSS2:ERG} expression and response to ADT.\textsuperscript{67,68} Phosphatase and tensin homolog (PTEN) loss activates PI3K/AKT signaling, thus controlling cell proliferation and growth\textsuperscript{69} and is associated with poor prognosis.\textsuperscript{70} The prognostic value of PTEN deletion combined with \textit{TMPRSS2:ERG} fusion in prostate cancer has been investigated in several studies.\textsuperscript{71–73} PTEN loss is independently associated with increased risk of lethal progression, particularly in the ERG fusion-negative subgroup.\textsuperscript{74} It is also reported that PTEN-negative tumors are associated with worse survival and shorter time on abiraterone treatment in CRPC.\textsuperscript{15} \textit{TMPRSS2:ERG} fusions and PTEN gene in CTCs have been evaluated,\textsuperscript{75} but the results are not consistent.\textsuperscript{76} After these initial publications, several more recent reports fail to show the value of these parameters as potential predictive biomarkers. Other prostate-cancer-associated gene mutations such MYC, RB1 and MET have also been detected in cfDNA; genomic aberrations in these genes are associated with poor prognosis.\textsuperscript{77}

It is increasingly recognized that mutations in genes controlling DNA repair pathways, especially homologous recombination repair and mismatch repair, may be relevant in many cancer types including prostate cancer.\textsuperscript{78} In recent genomic sequencing efforts, the prevalence of somatic DNA repair gene mutations (primarily involving the \textit{BRCA1/2} and \textit{ATM} genes) in biopsies from patients with CRPC is in the order of 15–25\%.\textsuperscript{79} About half of these patients with somatic DNA repair aberrations also have germline defects in these same DNA repair genes (8–12\% of the total).\textsuperscript{80} The presence of a germline or somatic mutation in a DNA repair gene may have prognostic and therapeutic implications. For example, one study has suggested that these patients have poorer responses to ADT.\textsuperscript{81,82} Conversely, such patients may have a favorable response to alternative therapies including PARP inhibitors such as olaparib.\textsuperscript{48} Intriguingly, patients with tumors that harbor DNA repair defects may exhibit higher sensitivity to platinum-containing chemotherapy,\textsuperscript{83} immune checkpoint inhibitors,\textsuperscript{84} radiopharmaceutical products\textsuperscript{85} or a novel approach involving high-dose testosterone treatment.\textsuperscript{86}
the next few years, several ongoing studies will conclusively determine the predictive impact of DNA repair mutations in the context of these and other therapies.

**Future perspective**
There have been rapid advancements in the treatment of CRPC, with a resulting improvement in prognosis of patients. Further research is needed with respect to selection and sequencing of treatments for an individual patient. A role for biomarkers to select patients that may benefit from a particular therapy will need to be elucidated further, but the detection of the AR-V7 splice variant and DNA repair mutations appear promising candidates in the quest for biomarkers that will allow the precision medicine revolution to take place. The future of precision oncology is upon us.

**Funding**
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Conflict of interest statement**
ESA has served as a paid consultant/advisor to Janssen (Raritan, NJ, USA), Johnson & Johnson (New Brunswick, NJ, USA), Medivation (San Francisco, CA, USA) and Astellas (Northbrook, IL, USA); he has also received research funding to his institution from Janssen (Raritan, NJ, USA), Johnson & Johnson (New Brunswick, NJ, USA), Medivation (San Francisco, CA, USA) and Astellas (Northbrook, IL, USA). No other author reports any conflicts of interest.

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