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PCa Commentary

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GENOMIC SEQUENCING FOR PROSTATE CANCER – Which Men Gain a Clinical Benefit from Genomic Testing.

The commonly cited goal of 'personalized medicine' in regards to treatment selection based on genomic testing is early in the 'work in progress' stage. Breathtaking advances in next generation sequencing are very promising, but currently there are only limited options for therapeutic guidance. This was acknowledged by Dr. Oliver Sartor in the recent NEJM review, Metastatic Prostate Cancer, Feb 2018: "The use of advanced genomic analysis is now feasible to a greater extent than ever before. Whether its use improves treatment decisions is not yet clear."

The intent of this Commentary is to highlight where in the course of cancer progression genomic information *might* have a beneficial impact on clinical management. The focus will be on 'predictive biomarkers', i.e., those which indicate the likelihood that a certain treatment will provide benefit … or no benefit.

Currently the predominant clinically informative mutations are BRCA1/2, ATM, CHEK2, PALB2 and a few others whose function is to repair damaged DNA. A second group is the androgen receptor splice-variants, predominantly AR-V7, overexpression of which predicts for little or no responses to agents targeting the androgen receptor (AR), e.g., Zytiga and Xtandi and others. A third class is the family of 'mismatch repair genes' (MMR) and CDK12. These mutations increase responsiveness to immunotherapy.

All of these mutations are found at low levels at the onset of the disease, but their expression increases significantly during the course of progressive cancer as an adaptive response to the pressure of treatment, i.e., androgen deprivation therapy and chemotherapy.

❖ *Testing for germline (inherited) and somatic (acquired) mutations:*

Germline mutations can be diagnosed from blood, saliva, scrapings of buccal mucosa or skin biopsies. Currently, somatic mutations are diagnosed by sequencing circulating tumor cells. Tests using blood plasma assaying for cell-free DNA are available and being refined. Multiple tests are available to identify mutations in MMR genes.

❖ *Genomic testing in men with low- or favorable intermediate-risk prostate cancer:*

Currently there is little utility in germline genomic analysis for men in this category. The low percentages of predictive markers, such as mutations in BRCA 2 (~6%) and in the family of mismatch repair genes (MMR) (~1.5%), do not merit the search. It is unlikely that at this early stage, knowledge about predictive mutations would change standard therapy.

Of note, mutated BRCA2 is both predictive and prognostic - prognostic for greater disease aggressiveness; predictive as to response to PARP inhibitors and platinum-based chemotherapy.

❖ *Germline genomic testing in men with high-risk and locally advanced and metastatic disease:*

Men in this group (i.e. Gleason 8-10, PSA>20 ng/mL, locally advanced tumor stage or nodal spread, >50% positive cores) may well benefit from *foreknowledge* of their mutational landscape since they are at risk for shorter durations of response to standard androgen suppression, earlier development of CRPC and metastasis. Knowledge of a man's genomic status will then be on record to guide future therapy choices.

The National Cooperative Cancer Network recommends germline testing of men with these characteristics and those with metastatic disease.

❖ *Genomic testing for germline mutations in DNA damage repair genes:*

- BRCA2 and other members of the DNA damage repair gene family predict for more aggressive disease. Recently reported results (*J Clin Oncol.* Feb 2019, Castro et al.) from the PROREPAIR-B protocol found that in men with metastatic CRPC germline mutations in BRCA 1/2 and ATM conferred a significant negative impact on treatment outcome compared to non-carriers.

- When a man has developed metastatic castration-resistant prostate cancer (mCRPC) and already had been found on germline testing to have mutated BRCA1/2 (or mutations in ATM, CHEK2,RAD51D and PALB2) he then is a candidate for the many protocols open for treatment with PARP inhibitors. In the metastatic state the likelihood of being positive for DNA damage repair mutations increases to ~12 % (16% if ATM and BRCA1 are included).

  In a small study of 50 men, heavily pretreated and unselected for mutations, Mateo *et al., NEJM* 2015 Oct, reported a >50% decline in PSA in 33%; in 16 men showing mutations in the DNA repair genes the response was 88%.

  In another study 6 of 8 men carrying a BRCA2 mutation showed a >50% decline in PSA within 12 weeks when treated with carboplatin/Taxotere).

- When a man has developed mCRPC it becomes informative to submit blood for assessment of *somatic mutations,* i.e., those mutations that have evolved in adaptation to suppressed testosterone. Assays for somatic mutations increased the total number of mutations in DNA repairs genes to ~25%, thereby expanding the eligibility for protocol-based PARP inhibition.

❖ *Testing for overexpression of the splice-variant AR-V7:*

AR-V7 is a modified form of the basic androgen receptor. It is continuously active in promoting tumor growth, and is not suppressed by agents targeting the AR such as Zytiga and Xtandi. Although AR-V7 is minimally expressed at the onset of prostate cancer, in the metastatic setting AR-V7 expression increases so that it is found in ~30 - 40% of men. A positive assay for acquired (i.e., 'somatic') overexpression of the AR-V7 splice variant predicts the unlikelihood of a response to drugs such as these.

- A study by Antonarakis *et.al. (J Clin Oncol.* 2017 Jul) examined the clinical significance of AR-V7 found in the circulating tumor cells (CTC) of 202 men with mCRPC progressing on ADT and were about to start therapy in either Zytiga or Xtandi. Three cohorts were established: those who were CTC negative (and therefore not testable for cellular AR-V7); those CTC+ and AR-V7 negative and those both CTC+ and AR-V7 positive. Before therapy with either drug 36 men (17.8%) were already CTC+ and AR-V7+ and those men were more likely to have Gleason score $\geq$ 8, a higher PSA and metastases at diagnosis. In men who had previously received Zytiga or Xtandi 27% were CTC+ and AR-V7+.

- Response to treatment was defined as a >50% decline in PSA. Only 14% of CTC+/AR-V7+ group met that criteria for response. After first-line therapy the PSA median progression-free survival in this group was 2.9 months; after second-line hormone therapy and 4.1 months, compared to >21.6 months and 6.2 months, respectively, for the CTC- group. The Antonarakis study did not have chemotherapy treatment arm, however the superiority of taxane therapy over (say) Zytiga and Xtandi in men CTC+/ARV7+ was indicated in the study by Scher *et al., (JAMA Oncology* Nov 2016).

- Knowledge of the CTC/AR-V7 status in men newly diagnosed with metastatic disease has therapy implications. Currently treatment in this group of men is customarily an LHRH inhibitor (Lupron or Firmagon) combined with Zytiga, Xtandi, or chemotherapy. A positive test of AR-V7 might favor chemotherapy. In men who have progressed to mCRPC after initial hormone suppression, knowledge of the AR-V7 status could influence the choice of the next therapy and also the choice of the subsequent second-line therapy after progression.

- Unfortunately testing for AR-V7 is limited by the cost: QIAGEN's AdnaTest ProstateCancerPanel AR-V7 lists at $2784. Epic Sciences OncotypeDx Nuclear Detect employs a different technology and is commercially available through Genomic Health (included into the NCCN Guidelines for MCRPC and Medicare is covering it List price, $3950). It is still available at Johns Hopkins. The recent PROPHESY study found both assays to be equivalent. 'Liquid Biopsy' tests for AR-V7 are already available.

❖ *Mismatch repair gene mutations - A predictive biomarker for response to immunotherapy:*

Although minimally expressed in the primary tumor, as with other mutations, mutations in these genes (MSH2, MSH6, MLH1, PSM2) increase in metastatic disease, e.g. to 5 to 10%. "Clinically, due to the high number of neoantigens generated by this hypermutation phenotype, patients with mismatch repair defects are prime candidates for checkpoint blockade…," Isaac *et al., Asian J of Urol* Nov 2018.

In 2018 the FDA approved the PD-1 blocker pembrolizumab, KETRUDA, for treatment of metastatic prostate cancer exhibiting these mutations. Men expressing PD-1 In the Keynote study had a 17% response to KETRUDA.

BOTTOM LINE:

Genomic research for clinical relevant mutations is producing an immense quantity of data. Currently for efficiency, the practicing clinician and interested patients can focus on identifying mutations in three important genomic areas: the mutations in the DNA repair family of genes, overexpression of the AR-V7 splice variant, and mutations in MMR genes. These data can have important bearing on treatment choices.

Your comments and requests for information on a specific topic are welcome.
Please e-mail ecweber@nwlink.com.

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