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Potential Impact on Clinical Decision Making via a Genome-Wide Expression Profiling: A Case Report

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ABSTRACT

Management of men with prostate cancer is fraught with uncertainty as physicians and patients balance efficacy with potential toxicity and diminished quality of life. Utilization of genomics as a prognostic biomarker has improved the informed decision-making process by enabling more rationale treatment choices. Recently investigations have begun to determine whether genomic information from tumor transcriptome data can be used to impact clinical decision-making beyond prognosis. Here we discuss the potential of genomics to alter management of a patient who presented with high-risk prostate adenocarcinoma. We suggest that this information help selecting patients for advanced imaging, chemotherapies, or clinical trial.

Case presentation

A 66-year old male with a family history of prostate cancer (PCa) presented with weakened urinary stream, urinary tract infection (UTI) and elevated PSA level of 51.8 ng/mL. Digital rectal examination (DRE) revealed a large nodule involving the entire left gland. Biopsy was recommended but not performed due to noncompliance. Continued blood work demonstrated a rising PSA (Fig. 1A).

Transrectal ultrasound guided biopsy performed a year after presentation demonstrated 2/12 cores with Gleason 9 (5 + 4) and 3/12 cores with Gleason 9 (4 + 5). Preoperative pelvic MRI and bone scan were negative for metastatic disease. The patient underwent robotic-assisted laparoscopic prostatectomy and bilateral pelvic lymphadenectomy with pathology demonstrating Gleason 9 (5 + 4) acinar adenocarcinoma involving 70% of the gland, positive surgical margins, lymphovascular invasion, extracapsular extension, and 13 negative nodes (pT3a pN0).

Light microscopy revealed poorly differentiated areas of tumor with neuroendocrine (NE) appearance (Fig. 1B), but immunohistochemistry was negative for traditional NE markers such as chromogranin and synaptophysin, and markers for small cell carcinoma (CD56 [NCAM1] and TTF-1).

The Decipher PCa classifier (GenomeDx Biosciences, San Diego, CA) prognostic test showed a 5-year risk of distant metastasis of 45.4%.[1] Previous studies[2] have indicated that patients with such Decipher scores would experience 80% reduction in metastasis if adjuvant as opposed to salvage radiation was administered, and accordingly adjuvant radiation therapy was recommended.

Prior to initiation of post operative therapy, the patient presented with lower back pain and pancytopenia. CT revealed multiple lytic lesions throughout the lumbar spine and visualized

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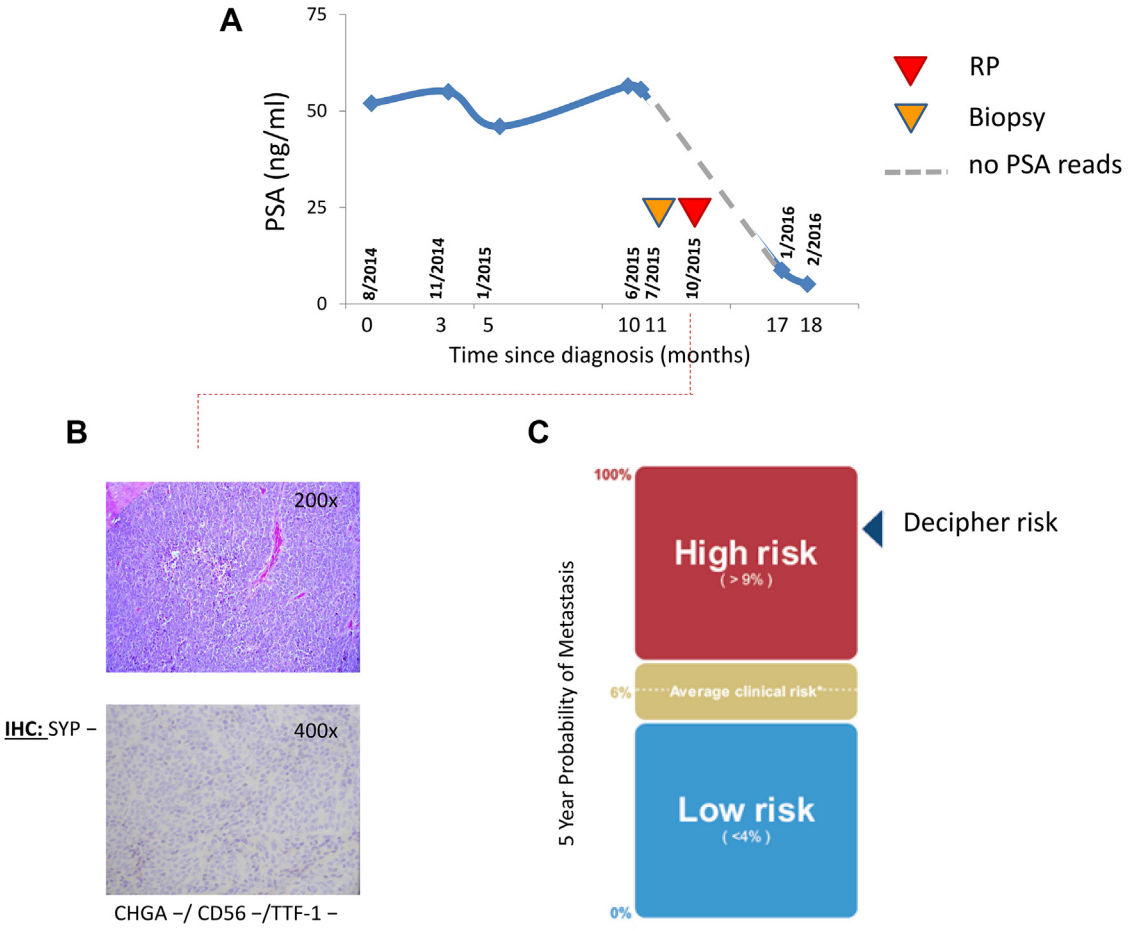

Figure 1. Clinical course of patient. A) Timeline delineating PSA kinetics and surgeries in association with diagnostic testing. B) H&E and synaptophysin negative staining of prostatectomy specimen. C) The Decipher test result showing a high risk of metastatic disease at 5 years.

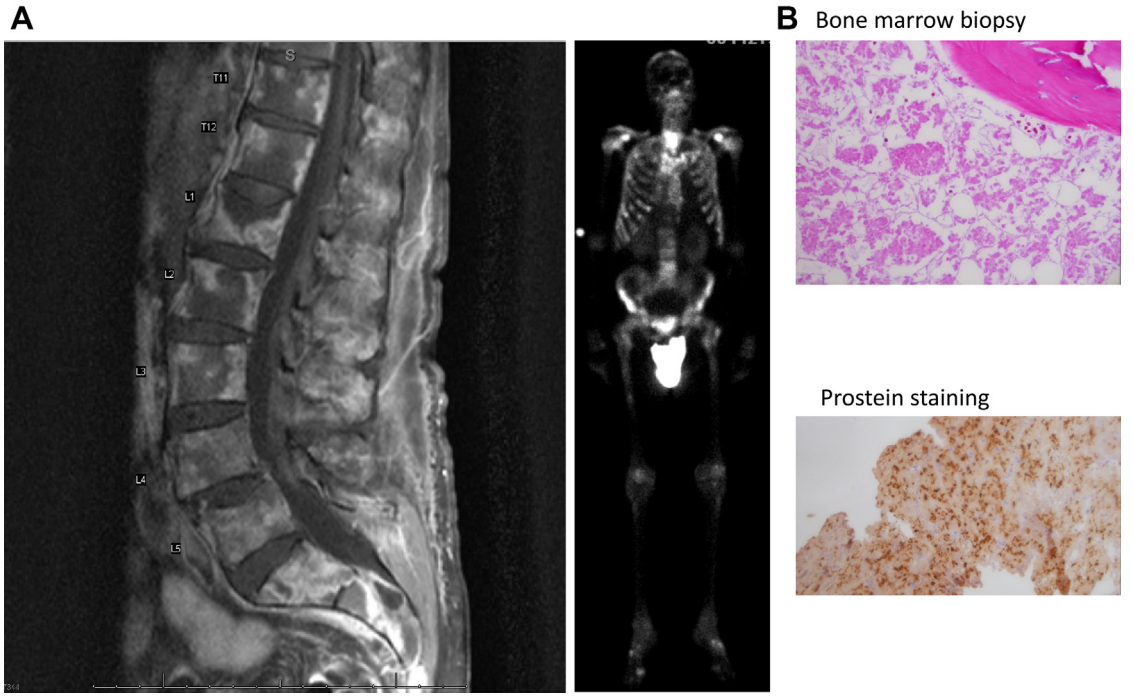

Figure 2. A) MRI and nuclear medicine bone scan demonstrating diffuse widespread osseous metastases. B) Bone marrow with extensive necrosis, consistent with infiltrating tumor.

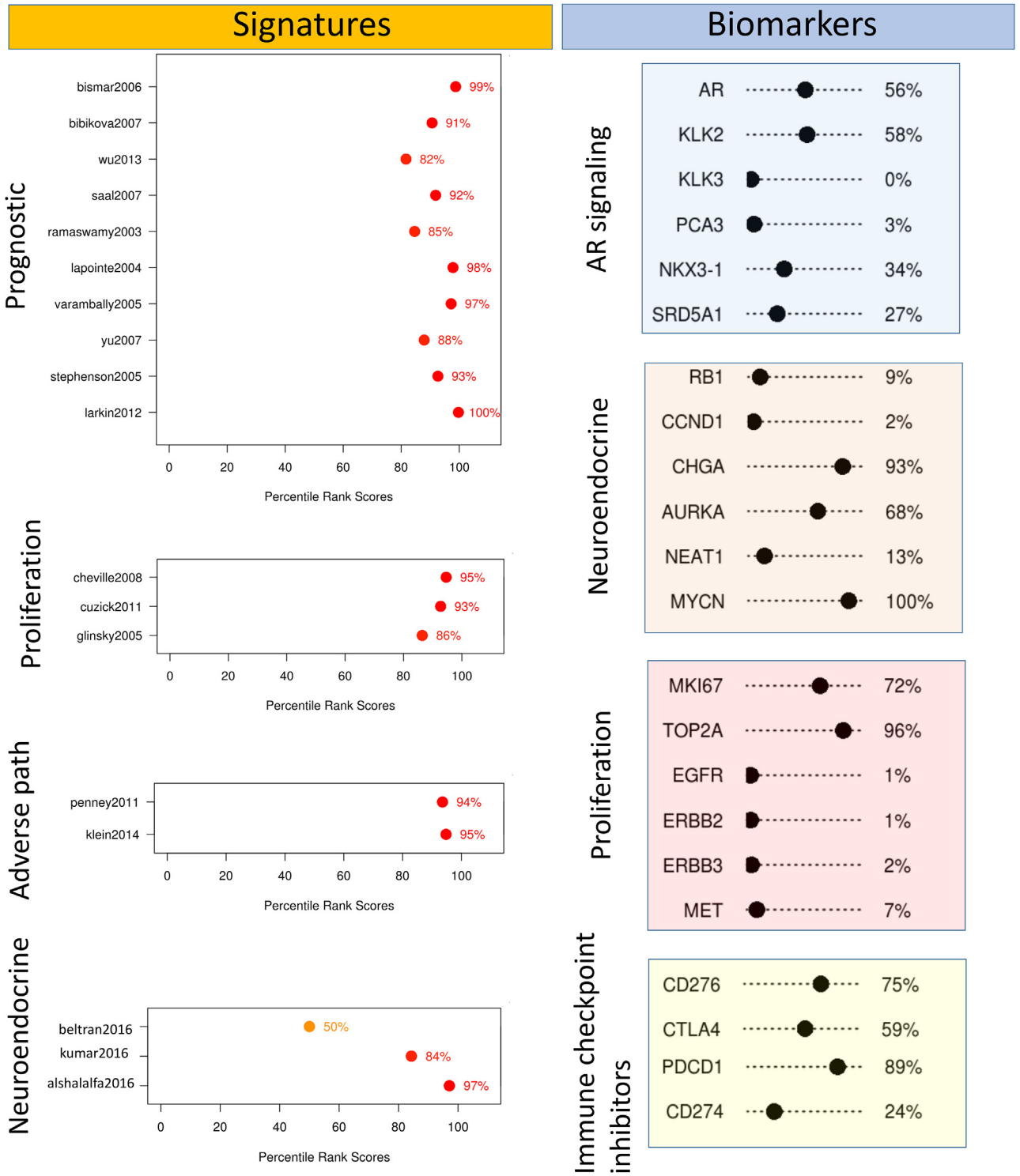

Figure 3. GenomeDx GRID assay. Prognostic signatures and genes implicated in prostate cancer demonstrating aggressive proliferation and neuroendocrine features of prostatectomy specimen.

skeleton (Fig. 2A), without nodal or visceral disease. MRI demonstrated diffusely enhanced marrow replacement throughout the thoracic and lumbar spines, visualized pelvis and ribs. Bone scan showed diffuse metastatic bone disease in the axial and appendicular skeleton. Bone marrow biopsy demonstrated extensive necrosis, consistent with metastatic carcinoma (Fig. 2B). The patient received Degarelix but developed progressive thrombocytopenia. Pulse steroids were prescribed and his thrombocytopenia began to stabilize. Palliative radiation therapy to L1-L5 was delivered and his PSA decreased to 5.1 ng/mL.

This case highlights the concern with under-treatment of men at high-risk for metastatic progression. There are numerous points regarding management to consider that in retrospect could have altered his clinical course. First, his prognostic score showed an

extremely high metastatic potential, yet standard imaging were negative. This is the ideal patient for whom to integrate novel imaging such as PSMA or NaF-PET. Although these are costly tests, with proper patient selection they may prove to be cost effective. Second, this case highlights the importance of obtaining prognostic features in the pre-treatment setting as opposed to post-prostatectomy. This is the type of patient for whom a neoadjuvant approach with either intensive androgen deprivation therapy or chemotherapy may have been beneficial. Clearly, this patient's case represents the cohort of men in whom aggressive pre-operative approaches are critical. Third, this case highlights the potential for treating very aggressive localized disease using a metastatic paradigm.

DNA sequencing of a panel of 315 pan-oncology genes was performed and revealed equivocal amplification of MDM4, MCL1 and PI3KC2B genes (FoundationOne™, Foundation Medicine, Cambridge, MA). These were not clinically actionable targets.

Comprehensive RNA expression analysis (Decipher GRID®, GenomeDx Biosciences, San Diego, CA, ClinicalTrials.gov number NCT02609269) was used to evaluate 41 PCa disease signatures reported in literature and the expression of 698 pan-oncology genes. The results for this patient's tumor were percentile ranked relative to the GRID population of patient PCa expression profiles ($n = 2293$). Analysis of a panel of 17 prognostic signatures showed the patient's tumor had among the highest scores (Fig. 3).

Low expression of AR regulated genes such as KLK3 (0th percentile), PCA3 (third), SRD5A1 (27th), NKX3.1 (34th) but average expression of AR (56th) and KLK2 (58th) were observed. AR signaling signatures proposed by Faisal et al[3] (sixth) showed low AR activity.

In contrast, high expression of neuroendocrine/small cell genes such as CHGA (93rd), NKX2.1 (96th), MYCN (99th) but loss of CCND1 (second) and RB1 (ninth) were observed. In addition, three neuroendocrine/small cell signatures proposed by Kumar et al[4] (84th) and Alshalalfa et al[5] (97th) suggest a tumor expression profile consistent with neuroendocrine disease.

Among the panel of putative druggable targets in PCa, only the target of checkpoint inhibitor PD1 (PDCD1, 90th) was found at high expression. Finally, high expression of AKT3 (99th) detected on the GRID and PIK3C2B amplification on Foundation One, suggested amplification of chromosome 1q. Analysis from cBioPortal showed that AKT3 is known to be amplified in 30% of castrate-resistant and 22% of neuroendocrine PCa.

Discussion

Genomics have advanced our understanding of the molecular underpinnings of prostate cancer, but have just begun to influence clinical decision making. This case illustrates how genomic analysis can provide critical information regarding precision medicine clinical trials that is not available from clinicopathologic features and highlights that despite the availability of genomics to identify potentially actionable mutations, the breadth of clinical trials and availability of molecular therapeutics is lagging. This chasm may be mitigated through clinical trial designs such as the NCI-MATCH trial (NCT02465060).

One of the promising tools generating genome-wide data for PCa patients is the GRID®. The GRID assessment evaluates the relative expression of genes compared to a radical prostatectomy population (>2000 patients) whose expression data has been de-identified and anonymized. Currently, this is a tool for research purposes, but as this case highlights has the opportunity to assist physicians in rational selection of both clinical trials and standard of care approaches for management in men with very high-risk disease. The findings from GRID and other such genomic assessments will require validation, but as the 'N of 1' approach is increasing in utilization within oncology, this platform provides a framework to integrate it into localized prostate cancer.

Conclusion

This case report demonstrates how genomics and sequencing are becoming available and can provide valuable data, while highlighting the lack of current translation into clinical applicability due to (1) limited clinical trials available and (2) rapid clinical progression. Genomic data provide further evidence for rational treatment approaches for selection of imaging, therapy, and informed patient decision making.

Conflict of interest

MA, ED, NE, JL, HA, MT, AO, LL are employees of GenomeDx Biosciences Inc. FF, ED, RD are on the advisory board of GenomeDx.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.eucr.2016.08.010.

References

1. Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate Cancer, Version 1.20: featured updates to the NCCN guidelines. *JNCCN*. 2016;14(1):19–30.
2. Freedland SJ, Choeurng V, Howard L, et al. Utilization of a genomic classifier for prediction of metastasis following salvage radiation therapy after radical prostatectomy. *Eur Urol*. 2016. pii: S0302-2838(16)00059-2.
3. Faisal FA, Sundi D, Tosoian JJ, et al. Racial variations in prostate Cancer molecular subtypes and androgen receptor signaling reflect anatomic tumor location. *Eur Urol*. 2015;70(1):14–17.
4. Kumar A, Coleman I, Morrissey C, et al. Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer. *Nat Med*. 2016;22(4):369–378.
5. Alshalalfa M, Tsai H, Haddad Z, et al. Deciphering the genomic fingerprint of small cell prostate cancer with potential clinical utility. *J Clin Oncol*. 2016;34(Suppl 2S; Abstr 303).