Whole-genome sequencing identifies homozygous BRCA2 deletion guiding treatment in dedifferentiated prostate cancer

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Abstract Whole-genome sequencing (WGS) has transformed the understanding of the genetic drivers of cancer and is increasingly being used in cancer medicine to identify personalized therapies. Here we describe a case in which the application of WGS identified a tumoral BRCA2 deletion in a patient with aggressive dedifferentiated prostate cancer that was repeat-biopsied after disease progression. This would not have been detected by standard BRCA testing, and it led to additional treatment with a maintenance poly ADP ribose polymerase (PARP) inhibitor following platinum-based chemotherapy. This case demonstrates that repeat biopsy upon disease progression and application of WGS to tumor samples has meaningful clinical utility and the potential to transform outcomes in patients with cancer.

[Supplemental material is available for this article.]

INTRODUCTION

The role of whole-genome sequencing (WGS) in identifying targetable mutations in cancer remains one of the greatest hopes in achieving personalized cancer therapy. Its role in patients with advanced treatment-resistant cancer by rebiopsyng patients at the point of progression has not been fully explored.

Most prostate cancers are adenocarcinomas, which are sensitive to androgen-deprivation therapy. It is thought that androgen receptor–depleted neuroendocrine cells, which
are few in number and normally lie quiescent, can flourish because of a cascade of molecular events, resulting in neuroendocrine dedifferentiation and androgen therapy–resistant prostate cancer (Li et al. 2013, 2016). Dedifferentiation from adenocarcinoma to small-cell carcinoma is also recognized in EGFR-mutant lung cancer (Sequist et al. 2011).

Mutations in DNA repair genes are an important feature of many cancers and are associated with an advanced, aggressive phenotype in prostate cancer (The Cancer Genome Atlas Research Network 2015; Mateo et al. 2015; Robinson et al. 2015). Germline BRCA mutations and their clinical association with breast and ovarian cancer are well-known, although there is an associated increased risk of other malignancies such as stomach and pancreatic cancer (Friedenson 2005). The increased prevalence of prostate cancer in patients with germline BRCA1 and BRCA2 mutations has prompted consideration of prostate cancer screening in such patients by the IMPACT screening study (Bancroft et al. 2014). Identification of somatic BRCA mutations in breast and ovarian cancer has been driven by the option of poly ADP ribose polymerase (PARP) inhibitor therapy for patients with BRCA mutations (Hennessy et al. 2009; Winter et al. 2016). Most BRCA mutations identified in patients with prostate cancer are somatic, and, compared with low mutation levels in early prostate cancer, ∼15% of patients with metastatic androgen therapy–resistant prostate cancer harbor functionally relevant somatic mutations or deletions in BRCA1 or BRCA2 (Robinson et al. 2015).

Current recommendations regarding the role for rebiopsy in prostate cancer focus on patients for whom an active surveillance approach is being pursued, although the most recent European Association of Urology (EAU)–European Society for Radiotherapy & Oncology (ESTRO)–International Society of Geriatric Oncology (SIOG) Guidelines note the importance of biopsy at the point of biochemical relapse in prostate cancer, ideally 18–24 mo after treatment (Cornford et al. 2016). Early rebiopsy or genome sequencing either at initial biopsy or rebiopsy on disease progression do not have a standard role in management. Here we present a case report of a patient with prostate cancer in whom rebiopsy and WGS at the point of disease progression had a significant and ongoing clinical impact because of the identification of a tumoral BRCA2 deletion not present in the initial biopsy.

RESULTS

Clinical Presentation and Family History

A 63-yr-old previously well man presented with a history of weight loss and hip pain. The family history was relevant for breast cancer only with the patient’s mother, maternal aunts, and sister having developed breast cancer. Blood tests demonstrated an elevated prostate-specific antigen (PSA) of 2900 µg/l (<4.0 µg/l), alkaline phosphatase (ALP) 2361 IU/l (44–147 IU/l) and a reduced Hb 10.8 g/dl (13.5–17.5 g/dl). A computed tomography (CT) scan of his body and whole-body magnetic resonance imaging (MRI) imaging demonstrated a primary prostate cancer with bone and pulmonary metastases (Fig. 1A). A prostate biopsy confirmed adenocarcinoma with a Gleason score of 8 (4 + 4) (Fig. 2A,B). He was referred to oncology and started androgen-deprivation therapy (ADT) with bicalutamide and goserelin (Zoladex) injections. The patient had an initial PSA response to testosterone deprivation, and within 3 mo the patient had gained weight with an unchanged performance status (PS) of 1. His PSA fell to 189.6 µg/l and alkaline phosphatase (ALP) to 1516 IU (Fig. 3). However, over the following weeks he clinically deteriorated with increasing pain in his right hip and upper leg. MRI imaging of his spine indicated progression of the bony metastases causing L4 nerve root compression (Fig. 1B). He was treated with five fractions of radiotherapy to his thoracic (20 Gy, five fractions) and lumbar (18 Gy, five fractions) spine and, given the radiographic progression, he commenced palliative docetaxel chemotherapy.
In the subsequent weeks, the patient’s clinical condition deteriorated despite the docetaxel treatment. His PS quickly declined from 1 to 3. He experienced increasing pain from bony metastases and developed urinary retention requiring the insertion of a urinary

**Figure 1.** Computed tomography (CT) and magnetic resonance imaging (MRI) images demonstrating disease course. (A) Initial staging CT scan. Axial section of lumbar spine, soft tissue window, demonstrating mild bone erosion (arrow) indicating bone metastasis. (B) Image at month 2.5 (see Fig. 3 for ALP/PSA correlation)—MRI spine, axial section, demonstrating L4 lesion invading into right pedicle. (C) Image at month 4—MRI spine, axial section, demonstrating further increase in L4 lesion with extensive metastatic marrow infiltration. (D) Image at month 10.5—CT scan, bone window, demonstrating significant reduction in the lesion at L4.
catheter. Despite a fall in his ALP and PSA (Fig. 3), an MRI performed at this time indicated further progressive bony metastatic disease (Fig. 1C).

Given the rapid clinical progression was atypical for adenocarcinoma, a further biopsy was taken from an expanding rib metastasis. This demonstrated metastatic small-cell carcinoma positive for pan-cytokeratin (panCK) and thyroid transcription factor 1 (TTF1), but negative for other traditional markers of small-cell carcinoma such as 34BE12, CD56, synaptophysin, and chromogranin (Fig. 2C,D).

**Genomic Analysis**

An established research programme at the Oxford Molecular Diagnostics Centre, a CPA (Clinical Pathology Accreditation; http://www.oxford-translational-molecular-diagnostics.cshs.org) rebiopsy and WGS in personalized cancer care.
Rebiopsy and WGS in personalized cancer care

Within the tumor, WGS identified two large genomic regions of copy neutral loss of heterozygosity, 41 genomic regions with acquired copy-number gains (10/41 with more than one additional copy) and 56 with acquired copy-number losses, including four separate regions displaying homozygous loss in copy number. One such homozygous loss was observed spanning ~1.68 Mb of Chromosome 13 from 13q12.3-q13.1. This large homozygous deletion includes 21 separate genes or noncoding RNAs including BRCA2 (Fig. 4). Despite the family history of breast cancer, no known pathogenic BRCA1 or BRCA2 germline variants were identified. A summary of the mutation analysis is shown in Table 1, and a more detailed variant table for the gene of interest, BRCA2, in Table 2.

Figure 3. Timeline of prostate-specific antigen (PSA) and alkaline phosphatase (ALP) levels and management interventions from diagnosis. LHRH, leutinizing hormone-releasing hormone; MRI, magnetic resonance imaging.
Given the transition in histopathology from adenocarcinoma to small-cell carcinoma of the prostate the patient commenced a trial of etoposide and carboplatin chemotherapy. This resulted in a rapid improvement clinically, biochemically (Fig. 3) and radiologically (Fig. 1D). Aside from treatment for neutropenic sepsis following the third cycle, the patient was able to complete six cycles of chemotherapy.

Tumors with mutations in genes involving homologous recombination such as \textit{BRCA2} are sensitive to PARP inhibition, with a recent phase II study demonstrating biochemical, radiological, and survival benefits in patients with \textit{BRCA2}-mutant prostate cancer (McCabe et al. 2006; Mateo et al. 2015). After completion of chemotherapy, the patient was started on the PARP inhibitor rucaparib, which was generously provided by Clovis Oncology for use on a compassionate basis outside of a clinical trial. The patient continues on rucaparib with clinical benefit at the time of submission (13 mo).

**DISCUSSION**

This case highlights the potential value of rebiopsy and utility of WGS in personalized treatment of prostate cancer. The further biopsy of the rib lesion was performed in the face of progressive disease despite falling PSA levels, revealing a \textit{BRCA2} deletion not present in the germline. To our knowledge, this is the first case study demonstrating the identification of a \textit{BRCA2} deletion in dedifferentiated prostate cancer.

The dedifferentiation of cancers from adenocarcinoma to small-cell carcinoma is more commonly observed in \textit{EGFR} mutated lung cancer and may confer sensitivity to platinum-
based therapies (Sequist et al. 2011). Such dedifferentiation with small-cell recurrence has similarly been described in breast adenocarcinoma in a germline BRCA2 mutation carrier (Niravath et al. 2015). The induction of neuroendocrine transformation in adenocarcinoma of the prostate is recognized and is associated with loss of tumor-suppressor genes (such as TP53, which was mutated in this case), loss of androgen-related pathways, and activation of mitotic pathways such as aurora kinase A thought to play significant roles (Li et al. 2013; Vlachostergios and Papandreou 2015). Typically this transformation is thought to occur after a more prolonged duration of androgen deprivation than reported here (Beltran et al. 2012).

### Table 1. Mutation analysis of tumor genetic sequence

| Gene   | Mutation | Chromosome | Start   | Finish   |
|--------|----------|------------|---------|----------|
| CDC73  | CN gain  | 1          | 170,479,674 | 198,492,877 |
| VHL    | CN gain  | 3          | 0       | 16,153,088  |
| PDGFRA | CN gain  | 4          | 52,652,733  | 65,798,728  |
| C-KIT  | CN gain  | 4          | 52,652,733  | 65,798,728  |
| NFkB   | CN loss  | 4          | 65,798,728  | 191,154,276 |
| FBXW7  | CN loss  | 4          | 65,798,728  | 191,154,276 |
| PIK3R  | CN loss  | 5          | 49,405,693  | 97,198,579  |
| APC    | CN loss  | 5          | 101,904,635 | 130,674,136 |
| JAK2   | CN loss  | 9          | 64,626    | 10,139,240  |
| CDKN2A | CN gain  | 9          | 10,320,113 | 26,205,565  |
| PTCH1  | CN gain  | 9          | 73,037,883 | 112,950,586 |
| NOTCH1 | CN gain  | 9          | 134,275,097 | 141,213,431 |
| PTEN*  | CN loss  | 10         | 85,557,432 | 105,804,295 |
| APC    | CN loss  | 11         | 0        | 11,638,440  |
| HRAS   | CN loss  | 11         | 11       | 34,694,617  |
| KIT    | CN loss  | 12         | 8,485,813  | 32,425,114  |
| FLT3   | CN loss  | 13         | 19,020,013 | 32,178,877  |
| BRCA2  | Homozygous copy loss | 13 | 32,178,877 | 33,860,144 |
| RB1    | CN loss  | 13         | 33,860,144 | 109,025,409 |
| CDH1   | CN loss  | 16         | 46,455,960 | 90,354,753  |
| TP53*  | CN loss  | 17         | 7,506,837  | 7,671,804  |
| PAK7   | CN loss  | 20         | 0        | 14,782,559  |

Additional mutations that are commonly mutated in prostate cancer are identified through whole-genome sequencing (The Cancer Genome Atlas Research Network 2015). CN, copy number. *These are recognized mutations in primary prostate cancer.

### Table 2. Summary of BRCA2 mutation

| Gene   | Chromosome | HGVS DNA Reference | HGVS protein reference | Variant type | Predicted effect | dbSNP/dbVar ID | Genotype    |
|--------|------------|--------------------|------------------------|--------------|-----------------|----------------|-------------|
| BRCA2  | 13         | g. 32178877–33860144del | n/a                   | Copy loss    | Loss of function | n/a            | Homozygous   |

HGVS, Human Genome Variation Society; dbSNP, Database for Short Genetic Variations; dbVar, Database of Genomic Structural Variation; n/a, not applicable.
New guidelines regarding the immunohistochemical classification of small-cell carcinoma of the prostate emphasize the need for accurate classification of this aggressive subtype of prostate cancer, which is known to be particularly platinum-sensitive (Epstein et al. 2014).

WGS of the rib lesion found a homozygous deletion of BRCA2 leading to successful treatment with a PARP inhibitor. It is important to note that, despite the family history, this patient was not found to carry a known pathogenic BRCA1 or BRCA2 mutation, and this observation was only made through sequencing tumoral DNA. WGS promises to offer a new level of personalized therapy, as illustrated here and in other cases such as the recent use of WGS to identify BCL2 inhibitors as a therapeutic option for a patient with chronic myeloid leukemia (CML) resistant to ponatinib therapy (Korfi et al. 2015). Here we demonstrate that adoption of a lower threshold for repeat biopsy and consideration of WGS can have a significant and beneficial impact on patient treatment and outcomes. Although we would not advocate repeat biopsies and sequencing for all patients, our report suggests this may be particularly pertinent in cases with rapid progression on standard treatment or an unusual clinical phenotype. This study, among others, supports the notion that as the costs of WGS falls, clinicians should increasingly consider this approach as it may reveal avenues to personalized cancer treatment.

**METHODS**

**DNA Extraction**

Germline DNA was isolated from 1.5 ml peripheral blood using the QIASymphony DSP DNA Midi kit (QIAGEN), according to the manufacturer’s protocol. Tumor DNA was extracted from fresh frozen tissue using the All Prep Mini DNA Extraction kit (QIAGEN), as described in the manufacturer’s protocol.

**Library Preparation and Whole-Genome Sequencing**

Libraries of 350-bp fragments were generated from 1 µg sheared genomic DNA using the TruSeq PCR-Free library preparation kit (Illumina). Of note, 2 × 126 bp paired-end sequencing was performed using the HiSeq2500 HTv4 (Illumina). WGS was performed at a coverage of 30× for the germline and of 75× for the tumor (Supplemental Table S1).

**Bioinformatic Data Analysis—SNV Calling**

Paired-end alignment of sequencing data against the reference genome hg19 (GRCh 37) was performed using the Whole Genome Sequencing Application v2.0, based on the Isaac Alignment Tool (Raczy et al. 2013) within BaseSpace, a cloud-based analysis tool suite (Illumina).

Somatic single-nucleotide variant (SNV) and insertion/deletion (indel) variant calling analysis was performed using the Tumour-Normal Application v1.0, based on Strelka (Saunders et al. 2012), within BaseSpace. Calls were annotated using the Variant Effect Predictor v2.8 (McLaren et al. 2016), COSMIC v77 (Forbes et al. 2015), and 1000 Genomes v3 (The 1000 Genomes Project Consortium 2015). The SIFT (Kumar et al. 2009) and PolyPhen-2 (Adzhubei et al. 2010) algorithms were used to evaluate the impact of a mutation on protein structure or function as predicted by Ensembl (v84) (McLaren et al. 2016). All variants of interest were manually inspected using Integrative Genomics Viewer (IGV) (Robinson et al. 2011).

**Copy-Number Analysis—Structural Variants and Translocation Detection**

Structural variant (SV) calling analysis was performed locally using BreakDancer [v1.4.5] (Chen et al. 2009). Analysis was limited to a set of disease-specific genes, as defined in
Atlas of Genetics and Cytogenetics in Oncology and Haematology (Huret et al. 2013), accessed at the time of analysis. The coverage of the aligned sequence data was determined by the total number of aligned bases divided by the genome size. This information is provided by the Whole Genome Sequencing Application v2.0 (Raczy et al. 2013).

Manual inspection in IGV is essential for each of the translocations reported by BreakDancer in order to view the complexity and quality of the sequence alignment of the regions that were reported and to verify whether the event is somatic or germline.

Clinical Interpretation

All SNVs, indels, and copy-number variants (CNVs) identified within the COSMIC Cancer Genes Census (v77) (Forbes et al. 2015) ranked with respect to their pathogenicity and clinical actionability (Futreal et al. 2004). A number of different sources, including COSMIC (Forbes et al. 2015), “MyCancerGenome” (www.mycancergenome.org), and ClinicalTrials.gov (www.clinicaltrials.gov) were used to determine whether genetic alterations were clinically relevant.

Table 1 and Supplemental Table S2 contain details of this analysis.

ADDITIONAL INFORMATION

Data Deposition and Access

The reported variants are deposited in the ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/) under accession numbers SCV000493829, SCV000493830, and SCV000493831.

Ethics Statement

Written consent for this case study, sequencing, and publication thereof was obtained from the patient and ethical approval granted in line with the Biomedical Research Centre (BRC) Cancer Pilot (Ref: 14/SC/1165 South Central Berkshire B REC). Written consent did not include WGS archiving or raw data deposition.

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Author Contributions

K.P. and B.P.F. wrote and revised the manuscript, and K.P. created the table and figures. A.S., S.K., P.A., H.D., N.P., and J.C.T. performed the WGS and subsequent analysis. A.P. edited the manuscript and was involved in the clinical management of the patient. I.R., L.B., Z.T., D.K., C.V., K.G., and M.T. were involved in the clinical diagnosis and management of the patient.

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