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after progression on vascular endothelial growth factor-targeted therapy. Cancer 2012; 118: 6055–6062.
16. Kim J, Jonasch E, Alexander A et al. Cytoplasmic sequestration of p27 via AKT phosphorylation in renal cell carcinoma. Clin Cancer Res 2009; 15: 81–90.
17. Lin A, Piao HL, Zhuang L et al. FoxO transcription factors promote AKT Ser473 phosphorylation and renal tumor growth in response to pharmacologic inhibition of the PI3K-AKT pathway. Cancer Res 2014; 74: 1682–1693.
18. Gordan JD, Lal P, Dondeti VR et al. HIF-alpha effects on c-Myc distinguish two subtypes of sporadic VHL-deficient clear cell renal carcinoma. Cancer Cell 2008; 14: 435–446.
19. Roberts AM, Watson IR, Evans AJ et al. Suppression of hypoxia-inducible factor 2alpha restores p53 activity via Hdm2 and reverses chemoresistance of renal carcinoma cells. Cancer Res 2009; 69: 9056–9064.
20. Feng C, Ding G, Jiang H et al. Loss of MLH1 confers resistance to PI3Kβ inhibitors in renal clear cell carcinoma with SETD2 mutation. Tumour Biol 2015; 36: 3457–3464.
21. Chen F, Zhang Y, Şenbabaoğlu Y et al. Multilevel genomics-based taxonomy of renal cell carcinoma. Cell Rep 2016; 14: 2476–2489.

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Acquiring evidence for precision prostate cancer care

In the current issue of Annals of Oncology, Romero-Laorden et al. [1] report the case of a patient with metastatic castration-resistant prostate cancer (mCRPC) who achieved a significant tumour response to the PARP inhibitor veliparib administered as a single agent. Molecular studies on this patient's primary and metastatic tumour tissue samples revealed a homozygous deletion of *BRCA2* as the putative mechanism determining PARP inhibitor sensitivity, although the authors describe genomic heterogeneity for this event within the primary tumour.

The use of PARP inhibitors against BRCA1/BRCA2 defective tumours, based on applying the biological concept of synthetic lethality to cancer treatment, has been a clinically important advance in precision cancer medicine [2–4]. Defects in DNA repair genes, particularly in those involved in double-strand error-free homologous recombination (HR) mediated repair (i.e. *BRCA1, BRCA2, ATM, PALB2, CDK12, FANCA* and others), have been identified in a proportion of advanced prostate cancers [5, 6]. While this disease is primarily driven by androgen-signalling, emerging data over the last few years indicate that BRCA1/2-defective metastatic prostate cancers, representing ~10–14% of the overall mCRPC population, could respond to alternative approaches such as PARP inhibitors or platinum chemotherapy [7, 8]. Tumour responses in cases harbouring other HR gene aberrations have also been described. Some of these mutations have been also reported to confer worse prognosis from prostate cancer [9, 10]. These data are currently being explored in several clinical trials with four different compounds, and the PARP inhibitor olaparib has been given Breakthrough Designation by the FDA based on data in this disease.

Despite multiple recent advances in prostate cancer care, with several new therapies approved for advanced disease based on survival benefit in randomized trials, molecular stratification strategies have not been incorporated into prostate cancer patient care so far. Presently, stratification of patients for Androgen Receptor (AR)-targeting agents based on AR aberrations [11–14] and treatment with DNA repair targeting agents for patients harbouring DNA repair defects constitute two promising opportunities for more precise care of advanced prostate cancer. Randomized trials need now to prove the benefit of such approaches to transfer these into clinical practice. Implementation of such multiplexed molecular testing to patient care does however present challenges that will have to be addressed towards guaranteeing clinical qualification of these biomarkers.

The first challenge arises from the need for rigorous validation of assays used at each centre and homogenization of biomarker assays across centres. Panel or more comprehensive whole exome sequencing requires laborious bioinformatic analyses, which are not yet standardized. Collaboration between regulatory agencies, academics and industry is critical for success, and all parts need to be involved in the design of clinical trials focused on testing precision medicine approaches. In the particular case of DNA repair defects and prostate cancer, we envision a multiplexed biomarker assay may be necessary, as different genes have been shown to associate with sensitivity to PARP inhibition. The FDA has already started considering how to adapt the regulatory framework to this new scenario and how to efficiently integrate post-marketing data review [15].

Intra-patient genomic heterogeneity represents a second major challenge for precision medicine [16]. Molecular studies to date predominantly using single site tissue biopsies, either from the primary tumour or metastases, are insufficient to comprehensively integrate temporal or spatial tumour evolution data. In the case reported here, the authors identified a somatic *BRCA2* homozygous deletion in bone metastatic tissue sample by targeted next-generation sequencing. They then studied the prostatectomy specimen collected 2.5 years before and identified areas of homozygous and heterozygous loss of the *BRCA2* gene region by FISH. The questions arising then are: would the *BRCA2* loss have been missed if this patient had been assessed based on standard random biopsies of the original prostate tumour? Moving forward, can we rely on archival prostate tumour samples, normally small blocks that have been in paraffin for years, to stratify mCRPC patients for somatic DNA repair defects?

Primary prostate cancers are essentially multifocal tumours, so spatial genomic heterogeneity in primary tumours is inherent [17] Treatment-mediated selective pressure before, or during, the development of metastatic disease facilitates the selection of the resistant clone or clones [18]. Also, polyclonal seeding and seeding between metastases has been described and may contribute to this selection process [19]. All these elements may confer a lower degree of heterogeneity for advanced disease, but this would still be a relevant feature to consider when stratifying patients.

Circulating biomarkers such as circulating-free DNA (cfDNA) and circulating tumour cells (CTC) are promising sources for obtaining tumour genomic material through a minimally invasive form of a liquid biopsy that can be repeated over time to account for tumour evolution. Sequencing of cfDNA can provide mutational data from different metastases represented in cfDNA and can be used to monitor evolution in response and resistance to

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treatment [11, 20]. However, only a fraction of cfDNA comes from tumour cells, and therefore in cases with low tumour content, particularly in earlier stages of the disease, assessment can be challenging, particularly for copy number alterations. Assay development should permit, within a few years, the addressing of these issues. Circulating tumour cell analyses also permits single-cell molecular characterization and therefore represent another possible biomarker for spatial heterogeneity assessment; however, the costs and complexity of these assays still prevent population-wide testing outside academic institutions. Moreover, not all clones or metastases may be contributing equally to circulating tumour genomic material. The key question then is: how much of this heterogeneity is clinically relevant in defining sensitivity to a certain treatment?

In conclusion, this case reported by Romero-Laorden et al. is in line with previously published data, supporting evidence that a molecularly defined subset of prostate cancer patients could benefit from PARP inhibitors. Large clinical trials are ongoing to validate these promising data. This case also highlights some of the challenges that need to be addressed to successfully advance the more precise care of mCRPC patients. We envision sequencing circulating tumour genomic material, in the forms of cfDNA and CTC, to circumvent the limitations of single site biopsies.

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Disclosure

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References

1. Romero-Laorden N, Piñeiro-Yañez E, Gutierrez-Pecharroman A et al. Somatic *BRCA2* bi-allelic loss in the primary prostate cancer was associated to objective response to PARPi in a sporadic CRPC patient. Ann Oncol 2017; 28(5): 1158–1159.
2. Farmer H, McCabe N, Lord CJ et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005; 434(7035): 917–921.
3. Bryant HE, Schultz N, Thomas HD et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 2005; 434(7035): 913–917.
4. Fong PCP, Boss DDS, Yap TA et al. Inhibition of poly (ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 2009; 361(2): 123–134.
5. Robinson D, Van Allen EM, Wu Y-M et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015; 161(5): 1215–1228.
6. Pritchard CC, Mateo J, Walsh MF et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016; 375(5): 443–453.
7. Mateo J, Carreira S, Sandhu S et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015; 373(18): 1697–1708.
8. Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 2016; 69(6): 992–995.
9. Castro E, Goh C, Olmos D et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013; 31(14): 1748–1757.
10. Castro E, Goh C, Leongamornlert D et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol 2015; 68(2): 186–193.
11. Romanel A, Tandefelt DG, Conteduca V et al. Plasma AR and abiraterone-resistant prostate cancer. Sci Transl Med 2015; 7(312): 312re10–312re10.
12. Henzler C, Li Y, Yang R et al. Truncation and constitutive activation of the androgen receptor by diverse genomic rearrangements in prostate cancer. Nat Commun 2016; 7: 13668.
13. Antonarakis ES, Lu C, Wang H et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014; 371(11): 1028–1038.
14. De Laere B, van Dam P-J, Whitington T et al. Comprehensive profiling of the androgen receptor in liquid biopsies from castration-resistant prostate cancer reveals novel intra-AR structural variation and splice variant expression patterns. Eur Urol 2017 [Epub ahead of print], doi: 10.1016/j.eururo.2017.01.011; pii: S0302-2838(17)30018-0.
15. Evans BJ, Burke W, Jarvik GP. Special Report: The FDA and Genomic Tests—Getting Regulation Right 2015; 372: 2258–2264.
16. Gerlinger M, Rowan AJ, Horswell S et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012; 366(10): 883–892.
17. Boutros PC, Fraser M, Harding NJ et al. Spatial genomic heterogeneity within localized, multifocal prostate cancer. Nat Genet 2015; 47(7): 736–745.
18. 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.
19. Gundem G, Van Loo P, Kremeyer B et al. The evolutionary history of lethal metastatic prostate cancer. Nature 2015; 520(7547): 353–357.
20. Carreira S, Romanel A, Goodall J et al. Tumor clone dynamics in lethal prostate cancer. Sci Transl Med 2014; 6(254): 254ra125.

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