Finally, with the availability of techniques such as ctDNA sequencing, it is now easier than ever to track tumor evolution and study how ITH changes dynamically over time, without the need for risky and invasive biopsies. These approaches are likely to lead to the development of novel therapeutic strategies.

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Precision, complexity and stigma in advanced prostate cancer terminology: it is time to move away from 'castration-resistant' prostate cancer

The treatment of men with advanced prostate cancer (APC) is changing rapidly, with several new therapeutic options leading to longer survival. Categorizing clinical states that reflect the cancer biology and prior therapy in men with APC has become more complex. The Prostate Cancer Clinical Trials Working Group (PCWG) developed guidelines that harmonized inclusion, monitoring and outcome definitions for clinical trials in APC [1–3]. PCWG2 guidelines were seminal in changing the terminology from 'hormone-refractory' or 'androgen-independent' to 'castration-resistant prostate cancer (CRPC)', based on evidence of men responding to further hormonal manipulations after primary androgen deprivation therapy (ADT). Both of the approved next-generation endocrine agents, abiraterone acetate and enzalutamide, have shown an overall survival benefit for men with progressive cancer despite castrate levels of testosterone [4, 5]. Thus, adopting the term 'castration-resistant' improved the biological accuracy of disease characterization compared with 'hormone refractory'. The term CRPC, although not unanimously accepted, has become embedded in research and clinical practice.

However, the expression 'castration' has strong negative connotations, even if biologically appropriate [6]. The term is used more commonly in veterinary medicine, and it has punitive associations among a variety of cultures, where castration has been used in the past as a means of inducing punishment and/or submission. Many clinicians have experienced negative responses from men and their families when using the term castration-resistant prostate cancer. As the clinical and research communities strive to maximize patient-centered care and involve men in treatment decision making [7], it is time to acknowledge that the label we have assigned to their disease state may be alienating to the very men we are trying to engage.

Upfront use of docetaxel with ADT as chemo-hormonal therapy has become a standard of care for men with newly diagnosed metastatic prostate cancer [8–11]. Recently, abiraterone has been proved to provide similar survival benefits when administered from commencement of ADT [12, 13]. Additionally, there are a number of ongoing clinical trials investigating earlier use of enzalutamide and other AR-targeted therapies or combinations before the onset of 'castration resistance'. According to PCWG3 criteria, a patient treated upfront with ADT/docetaxel or ADT/abiraterone would theoretically be in the same first-line metastatic CRPC category upon progression as a man treated with ADT alone, but it is unlikely that the resistant tumours that eventually emerge are biologically similar. Resistance mechanisms to AR targeting agents have been described in the castration resistant setting and it seems likely that similar and perhaps additional mechanisms of resistance may occur when these agents are used earlier [14, 15].

It is evident that the term CRPC currently encompasses diverse populations; this diversity will only increase as the therapeutic approach evolves and an expanding range of treatment combinations and sequences become available. The time is ripe to update the terminology. The ideal terminology may best be identified by engaging not only clinicians, but by also involving patient and advocacy groups to identify terms that will simultaneously satisfy men with APC, as well as reflecting the biology and prior treatment of the disease.

One possible option for the prostate cancer community would be to begin by referring to metastatic or APC, specifying each line

of treatment and molecular subtype, analogous to terminology used in defining subtypes and treatment lines in breast cancer [16]. The description would therefore include 'metastatic prostate cancer' followed by treatments received/receiving. Additionally, if appropriate this can be complemented by a defined molecular state, e.g. 'with germline *BRCA2* truncating mutation'. This will also allow greater flexibility if gonadal suppression is one day replaced by novel treatments that do not act by suppressing testosterone levels, such as advanced single agent androgen receptor blockade [17]. Most importantly, the term would not reflect upon the gonadal status of the individual, but would serve to describe the disease without implications about the virility of the individual.

'CRPC' was terminology that was aligned with our interventions and registration strategies, when our therapeutic approach to non-localized prostate cancer was linear. However, the rapid development of new agents and approaches that are no longer used in a fixed order, and which undoubtedly will be used in an increasingly complex non-linear fashion, make the term less relevant. This process reflects a movement towards precision oncology, where the imperative is no longer to group men in large homogenous groups, but rather, to acknowledge the diversity of biology and therapies available.

Thus, we advocate discontinuing the use of the term 'CRPC' and replacing it with more descriptive nomenclature, in an effort to simultaneously increase the precision in our terminology, acknowledge the complexity of APC, and move away from stigmatizing language. Importantly we propose partnering with patients and advocates to develop appropriate terminology that is not viewed negatively by the men who entrust us with their care. It is time to make this change.

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Cancer drug costs—the case for a thoughtful discussion of a manageable problem

Rapid advances in our understanding of the biology driving the neoplastic process are translating into a dramatic increase in the number of available treatment options for cancer. These therapies can lead to longer duration and better quality of responses, even in patients with advanced disease. Concern about the cost of cancer drugs and the value they provide has existed for a long time, even during the era when chemotherapy drugs were largely the only systemic modality of cancer therapy for most patients. Ironically, these concerns have assumed a greater urgency, in part, because the superior efficacy of newer drugs is translating to more lines of therapy as well as greater duration of each line of therapy. In parallel, the generally rising cost of healthcare, and certain high-profile pharmaceuticals in particular, in oncology and elsewhere has shone a spotlight on the costs to society of the current healthcare economic paradigms [1, 2].

The cancer drug fund experience

In this issue of *Annals of Oncology*, Aggarwal et al. [3] analyze the experience with the National Health Service (NHS) Cancer Drug Fund (CDF) in the UK. This fund was set up in 2010 as a mechanism to provide cancer patients in the UK with access to novel drugs that had either not yet been appraised by The National Institute for Health and Care Excellence (NICE) or had been appraised but not recommended for reimbursement. Approximately £1.3 billion was spent between 2010 and 2016 before the CDF was rationalized back into the NHS. The authors reviewed the 47 indications for 29 drugs that were approved by the CDF for reimbursement and concluded that based on the pivotal clinical trial data underlying the decision, professional society criteria for clinical benefit thresholds and the likely real world performance of these drugs, the CDF did not deliver any meaningful value to the patients or the society.

The authors are to be commended for undertaking a systematic analysis of the CDF decisions, decisions that inevitably had to occur in an environment of politics and heightened emotions in the context of a disease that is nearly uniformly fatal in relatively short order. The critics would contend that considerations other than the strength of the scientific data played a significant role in the decision making for CDF reimbursement. At the time the CDF was created, there was considerable concern that decision making by NICE was based mostly on mathematical formulae for cost–effectiveness and did not fully consider the nature of the disease and the needs of individual patients. It was felt that the UK was falling behind other western countries in providing access to new life-extending therapies.

The authors' conclusions are substantially correct in that the vast majority of indications covered by the CDF were for drugs that provided only a marginal OS (overall survival) benefit or lacked OS data at the time of reimbursement decisions. Of the 47 indications approved, survival benefit was reported for only 18 indications with a median OS benefit of 3.1 months (range 1.4–15.7 months). Only 9 of the 47 indications met the ESMO criteria for clinical benefit [4]. Many of these indications were later removed by the CDF itself due to insufficient evidence of clinical benefit. A key shortcoming of the analyses (through no fault of the authors) is that the actual outcome data from patients who received the drugs as part of this scheme is lacking. Such data were supposed to have been collected routinely starting in April 2012 but this apparently did not happen. In the absence of such data, the authors had to rely on other published data about the performance of cancer drugs in real world situations. This has obvious limitations in that we do not know if the physicians and patients who made the decision to access these drugs made wise data-driven choices or simply wasted precious resources.

This raises an obvious question: is the concept of a dedicated CDF (or for that matter any rare/orphan disease fund) inherently a bad idea [5]? The authors clearly state this to be the case and recommend adherence to standard, universal processes employed to assess other health technologies, such as the NICE assessments. However, an important distinction must be made between the goal of the CDF program, which was quite laudable, and the execution, which was clearly deficient both in terms of decision making for coverage and collection of relevant data on utilization and outcomes to justify continuation or termination of the program. While no one would argue that using such a fund to reimburse a drug with 1.4 months (HR 0.82) survival benefit (aflibercept) is warranted, equally, it is hard to justify not reimbursing a drug such as