Many researchers are urgently working to develop precision oncology, a process to personalize a patient’s treatment based on the specific biology of their cancer. On the surface, kidney cancer (renal cell carcinoma, RCC) appears ideally suited to precision oncology approaches. More than 25 yr ago, the role of VHL loss in hypoxia signaling and RCC development was discovered [1,2]. In 2013, The Cancer Genome Atlas project published a comprehensive molecular evaluation of clear cell RCC [3]. Our deeper understanding of RCC biology has accelerated development to the point that there are now ten approved systemic therapies. Yet these new discoveries and therapies have resulted in only modest improvements in patient survival. Patients now live long enough to matriculate through multiple treatments, increasing their exposure to significant side effects before ultimately succumbing to their disease.

Currently, the potential of precision oncology to minimize futile toxicity and maximize patient survival remains unfulfilled. There are no established biomarkers for metastatic RCC and a number of reasons why candidate biomarkers fail to improve patient outcomes [4]. Careful evaluation suggests that applying precision oncology in metastatic RCC may be more challenging than anticipated, as RCC patients are less likely to have a genetic alteration that suggests a druggable target when approved treatments fail [5].

The development of next-generation sequencing technology has allowed researchers to detect mutations in circulating cell-free DNA. The significance of these genomic alterations in RCC is not known. Can circulating tumor DNA be used to select treatment, or identify early treatment response or progression, or elucidate specific mechanisms of resistance? In this issue of European Urology, Pal et al [6] begin to address these questions in a large cohort of 220 patients with metastatic RCC. For each patient, the number and type of genomic alterations identified were assessed and correlated with receipt of either first-line or subsequent systemic therapies.

1. Applying circulating tumor DNA assays to RCC

The circulating tumor DNA assay used in the report applies targeted sequencing of 73 common genomic alterations. While this generic approach trades sensitivity for portability across cancer types, it is notable that at least one genomic alteration was found in nearly 80% of patients. However, an RCC-specific assay would probably identify additional genetic alterations, as this assay does not include four of the nine most frequent tissue-based mutations described by the TCGA [3] (PBRM1 32.9%; SETD2 11.5%; BAP1 10.1%; KDM5C 6.7%) or seven of the ten most frequent mutations described by Scelo et al [7] (PBRM1 39.4%; SETD2 19.1%; BAP1 11.7%; ZFHX3 9.6%; CSMD3 8.5%; FAT3 7.5%; KDM5C 7.5%). In addition, the frequency of VHL genomic alterations (23%) is much lower than expected, as multiregion sequencing of metastatic RCC consistently identified VHL loss as the truncal event [8]. Furthermore, additional VHL alterations will be missed, as this approach is not designed to detect epigenetic changes (eg, inactivation by hypermethylation) or gene loss (eg, loss of chromosome 3p), which are thought to be a common events in clear cell RCC [9].

The specificity of the genomic alterations identified is also not yet well characterized. Previous reports on specific circulating tumor DNA mutations (eg, KRAS mutations)
showed excellent agreement with tissue analysis [10], while comparisons of commercially available tissue-based and circulating tumor DNA assays have found low concordance rates [11]. It is interesting that in this study the most common genomic alteration identified in patients with metastatic RCC was TP53, occurring in 35% of patients. This is markedly higher than tissue-based analyses and may reflect the selection of these clones or the detection of unrelated background p53 mutations.

Moreover, the precision of the assay (the ability to detect the same genomic alterations on repeat tests) is also not known. In this study, only 17 patients had serial samples, and these showed decreasing agreement with increasing time between tests (illustrated in Supplementary Fig. 2 in [6]). This could illustrate a new challenge: temporal genetic heterogeneity. Analogous spatial heterogeneity is seen when multiple locations within a primary tumor or metastasis are sequenced, for which as many as five biopsies are required for an 80% likelihood of identifying 80% of genetic mutations [12]. However, the loss of initially detected genomic alterations in subsequent tests is difficult to reconcile with this branched evolution model for metastatic RCC, which would suggest that the number of alterations increases with tumor progression [8].

2. Does circulating tumor DNA detect tumor evolution?

It is important to note that the circulating tumor DNA was analyzed at one time point for the vast majority of patients. As a result, it is not possible to know if the signature of genomic alterations evolved while receiving therapy. The total number of genomic alterations was not significantly different when comparing patients receiving first-line versus subsequent therapies. While several specific genomic alterations (TP53, p = 0.02; NF1, p = 0.01) were more common in patients receiving subsequent therapies, this did not account for multiple comparisons, and may not be reproducible in future studies.

3. The future of precision oncology in RCC

Metastatic RCC, like all cancers, employs myriad strategies to grow, invade, metastasize, and evade the host immune response. These actions are orchestrated via a unique genomic landscape, with several frequent mutations and a long right tail of rare variants. The report by Pal et al [6] illustrates the potential of circulating tumor DNA in evaluating an additional dimension of genomic diversity to monitor therapeutic response, and suggests a future in which a blood test can be used to help guide therapy. While a single blood test to deliver precision oncology would be remarkable, successful biomarker development will probably require multiple emerging technologies and complementary approaches. Building on this initial report by Pal et al [6], future efforts to optimize circulating tumor DNA analysis using RCC-specific panels, or even panels tailored to mutations identified at the time of surgery, will further increase the sensitivity of these assays. Circulating tumor DNA will require robust validation before routine clinical use, but is a promising technology poised to help overcome the challenges in applying precision oncology to RCC.

Conflicts of interest: The author has nothing to disclose.

References