

Editorial

The Pros and Cons of “Machination of Medicine” in Genitourinary Oncology Practice

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Abstract. The increasing availability of genomic sequencing of tumor tissue in oncology provided valuable insights into tumor evolution and offered clinicians the unprecedented opportunity to tailor therapies on each individual patient, according to the treatment-impacting alterations identified in the tumor cells. In addition to the characterization of somatic alterations in tumor samples, the identification of germline (i.e., constitutional) pathogenic variants can provide additional information to guide informed and personalized therapeutic planning for patients and to enable risk-based screening protocols for at-risk relatives. In genitourinary malignancies, only a few associations between germline mutations and cancer risk and behavior have been thoroughly investigated (e.g., alterations in DNA repair genes in prostate cancer or mutations in Lynch syndrome genes in upper tract urothelial carcinoma). To achieve a wider use of both tumor genomic and germline genetic testing, an integrative approach led by scientific societies is necessary to involve physicians, patients and advocacy groups, to develop a shared strategy to advance the field and provide value-based and reproducible standards of care for patients and their families.

Keywords: Genitourinary tumors, molecular alterations, targeted therapy, next-generation sequencing, biomarkers

The availability of genomic sequencing data from patient’s tumor samples in routine oncology practice

is rapidly increasing at an unprecedented pace, thanks to the wider accessibility to next-generation sequencing technologies at a relatively affordable cost, and to the use of such tests as companion diagnostics for an increasing number of approved targeted drugs [1]. In most cases, data are generated from tumor-only analysis, performed either by utilizing a panel

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of specific hotspot mutations or by more comprehensive approaches (e.g., larger panels testing full genes/conspicuous length of genes, whole exome sequencing, etc.). Tumor-tissue based sequencing is primarily performed to help clinicians offer patients the most effective personalized therapies. On occasion, the sequencing of the somatic DNA from the patient’s tumor tissue sample can, when customized predictive algorithms are employed, provisionally identify unexpected germline genetic alterations in patients who do not have a clear personal or family history of cancer. The provisional identification of suspected germline variants from the somatic tumor tissue can subsequently trigger formal germline genetic testing using a subsequently obtained germline sample [2, 3]. The importance derived from the recognition of germline pathogenic alterations, either from direct germline testing or derived from tumor-only sequencing, is twofold. On one hand, it can help address the risk of future cancer development in patients and their relatives, making their enroll in tailored prevention/early diagnosis protocols possible. On the other, distinct germline mutations may change the therapeutic strategies regardless the tumor-specific somatic alterations [3, 4]. While offering both testing to all novel cancer patients is not always feasible and may end up creating confusion both among patients and treating physicians, it is important to develop evidence-based testing algorithms that combine both germline and somatic testing with formal genetic counseling, to provide patients and their relatives with the best care possible, as well as potentially decreasing the economic burden at the level of healthcare systems, thanks to implementation of *ad hoc* screening and prophylactic protocols.

In the field of genitourinary (GU) malignancies, germline genomic alterations have been largely investigated in prostate cancer [5]. For instance, germline mutations in the tumor-suppressor genes *BRCA1* and *BRCA2* carry a four-to-ninefold higher risk to develop prostate cancer, and germline mutations in DNA repair genes, like *ATM*, *BRCA2*, and *MSH2*, have been found associated with Gleason grade 5 prostate cancer histology [6, 7]. Moreover, the presence of specific germline mutations may influence the therapeutic plan, as suggested for mutations in *BRCA2* and other DNA damage repair (DDR) genes [8, 9]. As an example, those patients who are found harboring a *BRCA2*-mutated prostate cancer usually face a more aggressive disease course, are younger and potentially more suited for aggressive therapeutic

possibilities upfront and inclusion in clinical trials compared to the majority of prostate cancer patients harboring a *BRCA2* wild-type tumor [10–12]. To refine patient selection for poly (ADP-ribose) polymerase (PARP) inhibitors, better stratification assays are likely needed, combining different genomic and, eventually, clinical data. For instance, the homologous recombination deficiency (HRD) score – computed by combining three DNA-based measures of genomic instability – has been recently tested in three cohorts of primary prostate cancer, showing an interesting patient stratification potential [13, 14]. While different professional societies provide spurious indications for germline and/or somatic testing in prostate cancer patients, they generally agree on recommending testing in patients with high-risk or advanced/metastatic disease, irrespectively of a positive familiar history [15, 16].

Upper tract urothelial carcinoma (UTUC) represents another well-known example of a GU malignancy linked to a hereditary cancer syndrome (i.e., Lynch Syndrome, LS) caused by germline mutations in one of the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6* and *PMS2* [17]. Genomic profiling comparing LS-UTUC and sporadic UTUC found overlapping but distinct mutational landscapes, with some alterations (*CIC*, *NOTCH1*, *NOTCH3*, *RBI*, and *CDKN1B*) found almost exclusively in LS cases [18]. Moreover, LS patients with mutations in the *MSH2* gene are also at increased risk of developing urothelial carcinoma (UC) of the bladder [19]. Beyond the well-known link between UTUC and LS, more recent epidemiological and genomic evidence supports a role of hereditary germline mutations in a small but important proportion of bladder UC patients, and positive family history for bladder cancer carries a twofold higher risk for UC [20–22]. By tumor-germline DNA sequencing using a targeted exome sequencing platform (MSK-IMPACT) on a cohort of 586 patients with UC, Carlo and colleagues [21] identified pathogenic/likely pathogenic germline variants in 80 (14%) cases, most of them (66; 83%) having mutations in DDR genes. Of note, 26% of patients with high-penetrance germline variants would have not been tested for germline mutations according to current guidelines, highlighting how traditional criteria to identify patients at risk for hereditary syndromes miss a fraction of patients with germline alterations. Moreover, the relatively high frequency of germline alterations in DDR genes, also confirmed by other reports [23–25], paves the ways to clinical trials testing PARP inhibitors in UC patients.

Germline alterations associated with cancer predisposition can be found in approximately 5–10% of kidney malignancies [26], and several hereditary cancer syndromes or rare genetic diseases include kidney tumors among their clinical manifestations (e.g., von Hippel-Lindau syndrome, hereditary leiomyomatosis and renal cell carcinoma (HLRCC), Birt-Hogg-Dube syndrome, Beckwith–Wiedemann syndrome). Of note, the number of genetic alterations causing renal neoplasms is steadily increasing with the increasing access to sequencing, and well-known and less well-known syndromes have been described in relation to germline pathogenic variants including *VHL*, *MET*, *FH*, *BAP1*, *CDC73*, and *MITF* genes [27]. However, current guidelines from professional societies are quite variable in the recommendations for germline genetic testing and counselling for kidney cancer patients and their families, and, even when testing is recommended, the current criteria for germline testing eligibility are likely to miss a fair proportion of patients with hereditary cancer variants [28]. Germline testing in kidney cancer appears to be of great importance for several reasons. Firstly, identification of patients affected by hereditary cancer syndromes at the diagnosis of a kidney tumor may help patients and physicians design a tailored protocol to plan the best surgical approach (e.g., radical vs. nephron-sparing procedures) and to prevent and/or follow-up for the associated high morbidity and mortality linked to extrarenal manifestations [27, 29]. Moreover, germline testing results may also influence the therapeutic strategy (e.g., germline *MET* alterations in papillary renal cell carcinoma patients were highly predictive of response to foretinib [30]).

In testicular germ-cell tumors (TGCTs), data about germline alterations and cancer susceptibility are limited, and the roles that hereditary factors may play in the development and progression of TGCTs are not fully established. Recently, Ramamurthy and colleagues [31] analyzed a cohort of 250 patients with testicular cancer subjected to different germline testing protocols and found pathogenic/likely pathogenic variants in 45 (18%) of enrolled subjects. Alterations in moderate-to-high penetrance genes were found in *CHEK2*, *BRCA1/2* and *LS* genes, which may also represent actionable therapeutic targets. *CHEK2* germline alterations were also observed in another large, multicenter study [32]. However, a third large study on 919 cases of TGCTs failed to identify single validated genetic defects underlying the predisposition to germ-cell cancer development, suggesting that the heritable risk in TGCTs is likely to be polygenic

[33]. Familial associations have also been described in non-germ cell testicular tumors, such as large cell calcifying Sertoli cell tumor in Carney complex syndromes, generally characterized by mutations in the *PRKARIA* gene, and Peutz-Jeghers syndrome, characterized by mutations in *STK11/LKB1* [34, 35].

Finally, one consequence that usually undermines the widespread use of technology in routine clinical practice is overcoming the gap of patients' access to these tests, and potentially to newer drugs, based on their affordability in each geographical area. This gap will become increasingly critical if the number of targeted compounds resulting in a significant survival improvement would become available in genomically-selected GU cancer patients.

This is the reason why developments in the area of “machination of medicine” should be closely monitored and controlled by academic Societies. Lost this type of control, there may be a significant risk that the scientific advances that have had as their objective the providing clinical benefit for patients dramatically raise as recently happened in the United States [36]. In summary, while the advantages of combining germline testing along with somatic tumor analysis are recognized for some cancer types such as breast cancer, much remains to be discovered and implemented in GU malignancies. Findings derived from germline testing would have wide impact not only on the affected patients, who may be directed towards specific therapeutic protocols, but also on their relatives, who may be enrolled in dedicated cancer screening programs. Moreover, professional societies must promote a fruitful cooperation with advocacy groups to promote the establishment of embracing cancer risk assessment and counseling programs, during which physicians and healthcare associates not only provide traditional genetic counselling and discuss management options, but also provide genetic education to improve informed decisions and adaptation to the risk for patients and their relatives. Of no less importance, this continuous discussion must promote improvements in the ethical, legal, public health and social implications of wider genomic testing in oncology. To this end, the Global Society of Rare Genitourinary Tumors (GSRGT) [37] has been established to develop practical criteria for physicians and patients aligned with advocacy groups and other major stakeholders to highlight the most valuable advances in medical and scientific knowledge, while simultaneously ensuring both affordability by the healthcare systems and ease of patient access.

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CONFLICT OF INTEREST

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