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Is Knowledge Power or Is Ignorance Bliss: Screening and Management of Familial Renal Cell Carcinoma Syndromes

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The discovery of hereditary renal cell carcinoma (RCC) syndromes has had a major impact on modern understanding and management of renal malignancy. Yet, as more familial syndromes and genetic predispositions are described, numerous clinical questions arise. (1) Who should be screened and when? (2) Is a diagnosis of a genetic predisposition to RCC an actionable finding? (3) How does such a diagnosis change immediate and downstream management for a given patient? (4) How should the patient's family members be counseled regarding the finding?

In this issue of *European Urology*, Carlo et al [1] present an updated review of the recognized familial RCC syndromes and describe several previously unknown genetic pathologies that have been discovered since the last review in the Platinum Journal in 2010 [2]. The authors offer a thorough analysis of current knowledge of the genetic abnormalities, clinical phenotypes, and pathologic features of each syndrome.

Importantly, the implications of germline genetic abnormalities for the management of metastatic RCC are comprehensively addressed. The authors highlight how knowledge of the molecular mechanisms specific to each familial RCC syndrome is being exploited to develop rational treatment strategies for that syndrome. Such applications include use of multitargeted receptor tyrosine kinase inhibitors and the HIF-2α inhibitor PT2977 for management of patients with von Hippel-Lindau (VHL) syndrome; glycolysis inhibition, bevacizumab/erolotinib, and PARP inhibitors for patients with hereditary leiomyomatosis and RCC (HLRCC); foretinib for treatment of patients with hereditary papillary RCC (HPRCC); vandetanib/metformin for succinate dehydrogenase (SDH)-deficient RCC and HLRCC; and everolimus for patients with tuberous sclerosis complex–associated angiomyolipoma.

With regard to management and understanding of patients with familial syndromes and localized disease, the application of the "3 cm rule" to VHL, Birt-Hogg-Dubé, and HPRCC patients—and the contrasting uncompromising and immediate management of HLRCC-associated tumors—are the clinical innovations that have perhaps had the greatest impact on the care of patients with familial RCC. Since the 2010 review, SDH-deficient RCC has been added to the latter aggressive management category, and the addition of BAP1-related tumors is likely on the horizon. The clinical relevance of this information to actionable risk stratification in all-comers with renal masses and to family members of those with known mutations is undeniable.

Screening of patients with known hereditary syndromes and their family members for RCC poses a unique challenge. Low sample sizes and long follow-up time from diagnosis to mortality ensure that high-level data will almost certainly never exist to inform optimal surveillance regimens. This leaves clinicians to largely guess at the optimal intensity and timing of the initiation of screening based on observed rates of disease progression, ages of onset, and patient/physician preferences. This is especially problematic in high-risk syndromes such as HLRCC for which the clinical stakes are high, the costs are nontrivial, and the effectiveness of surveillance is largely unknown.

Finally, the question of perhaps the greatest pertinence to the greatest number of patients is germline genetic screening of patients without a known familial syndrome at the time of RCC diagnosis. As with any testing, determina-

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tion of the pretest probability is important; however, as the cost of testing drops, screening may become more ubiquitous. Thus, although a physician who is managing a patient with RCC must be familiar with the pathognomonic signs and symptoms of familial syndromes, patients for whom there are no suspicions regarding harboring of germline mutations may be increasingly tested in the future. Carlo et al cite data from The Cancer Genome Atlas to point out that germline pathogenic variants were identified in 6%, 9%, and 6% of cases of clear cell ($n = 387$), papillary ($n = 289$), and chromophobe RCC ($n = 66$), respectively. However, the percentages of these cases with germline variants in genes related to known RCC syndromes were significantly lower, at 1.8%, 2.4%, and 0%, respectively. The cases included four patients with VHL and three with *BAP1* mutations in the clear cell RCC cohort, as well as four patients with *FH* and three with *MET* mutations in the papillary cohort. The majority of germline variants in this population were not previously recognized to be associated with RCC [3].

This reality, combined with the increasing number of recognized syndromes and the growing availability of inexpensive testing for multiple pathogenic germline variants, affords a significant opportunity for a shift in clinical approach. Despite the romantic image of the astute Oslerian urologist who identifies a fibrofolliculoma or cutaneous leiomyoma in the patient they are seeing for a renal mass, the clinician who benefits their patient the most may be the one who relies on more obvious data. A crude assessment of family history along with age [4], multifocality, stage [5], and histology on presentation may be the best indications for genetic testing independent of findings suggestive of any individual syndrome. Indeed, the current American Urological Association guidelines make age <46 yr at presentation the basis for their strongest recommendation for genetic screening, mentioning other clinical factors only as reasons to "consider" referral [6]. Disease stage—currently a major trigger for genetic testing for prostate cancer patients [7] but not mentioned at all in the guidelines for genetic testing for patients with RCC—may also take on an increasingly important role as data emerge showing germline variants that are enriched in populations with advanced RCC [5].

Although the costs of genetic testing are decreasing, ignorance may remain bliss for patients for whom results are not readily actionable. Yet, as the implications of germline testing for screening, local or systemic therapy, and surveillance become increasingly clear, knowledge—as it has done through the ages—will grow in power.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Carlo MI, Hakimi AA, Stewart GD, et al. Familial kidney cancer: implications of new syndromes and molecular insights. Eur Urol 2019;76:754–64.

[2] Verine J, Pluvinage A, Bousquet G, et al. Hereditary renal cancer syndromes: an update of a systematic review. Eur Urol 2010;58:701–10. http://dx.doi.org/10.1016/j.eururo.2010.08.031.

[3] Huang K-L, Mashl RJ, Wu Y, et al. Pathogenic germline variants in 10,389 adult cancers. Cell 2018;173:355–70. http://dx.doi.org/10.1016/j.cell.2018.03.039, e14.

[4] Shuch B, Vourganti S, Ricketts CJ, et al. Defining early-onset kidney cancer: implications for germline and somatic mutation testing and clinical management. J Clin Oncol 2014;32:431–7. http://dx.doi.org/10.1200/JCO.2013.50.8192.

[5] Carlo MI, Mukherjee S, Mandelker D, et al. Prevalence of germline mutations in cancer susceptibility genes in patients with advanced renal cell carcinoma. JAMA Oncol 2018;4:1228. http://dx.doi.org/10.1001/jamaoncol.2018.1986.

[6] Campbell S, Uzzo RG, Allaf ME, et al. Renal mass and localized renal cancer: AUA guideline. J Urol 2017;198:520–9. http://dx.doi.org/10.1016/j.juro.2017.04.100.

[7] Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17:479–505. http://dx.doi.org/10.6004/jnccn.2019.0023.