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Review

French recommendations on multi-gene panel testing in renal cell carcinoma

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ABSTRACT

Introduction: Renal cancers are inherited in about 5 % of cases and are associated with several genetic syndromes. Genetic testing is recommended for selected patients suspected of having hereditary syndromes. In the absence of

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guidelines regarding which genes should be included for carrying out genetic screening of these individuals, discrepancies existed among the next generation sequencing (NGS) multi-gene panels (MGP) used in French laboratories. There was therefore a clear need to standardise practices and offer patients with renal cancer a consensus-based genetic testing in France.

Methods: A working group comprising national experts from the French Genetic and Cancer Group Unicancer (GGC) and from the French network on Hereditary PREDIspositions to Renal Cancer (PREDIR) and encompassing medical geneticists, genetic counsellor, molecular biologists and epidemiologists was established. The objective was to define a list of clinically relevant genes that should be included in a "GGC-PREDIR" approved NGS MGP for patients with renal cancer.

A list of 32 genes of interest was compiled following an exhaustive and critical review of the literature. The inclusion or exclusion of each gene was determined based on available data regarding risk, prevalence and analyses published from large studies of patients.

Results: The French group of experts defined a list of 12 genes of clinical and genetic counselling relevance comprising *BAP1*, *FH*, *FLCN*, *MET*, *PTEN*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *TSC1*, *TSC2* and *VHL* to be included in the national recommended "renal cancer" NGS MGP. For each of these genes, recommendations for renal surveillance are proposed.

Conclusion: Unlike hereditary predisposition to breast or colon cancer, hereditary renal cancer predispositions are rare syndromes and risk estimates are lacking for most of them. Prospective studies are needed to improve our knowledge.

The GGC-PREDIR experts retained 12 genes for inclusion in the NGS MGP for renal cancer patients. However, the panel will be expanded on the basis of regularly updated data from the medical literature.

1. Introduction

An increase in incidence of renal cancers is observed in France since 1990 among both men and women, at all ages. The number of new cases was estimated at 17,141 in 2023 of which 69 % were in men (Lapôtre-Ledoux et al., 2023). The median age at diagnosis was 68 years for men and 70 years for women. The cumulative risk of developing renal parenchymal cancer by the age of 75 was estimated to be 1.5 % for men and 0.6 % for women (Defossez et al., 2019).

Renal cell carcinomas (RCC) represent a heterogeneous group of tumours characterized by distinct histological and molecular features. The most common subtype is clear-cell RCC (ccRCC), accounting for approximately 70 % of cases. In addition to ccRCC, there are several rarer subtypes, the most common being papillary RCC (pRCC) and chromophobe RCC (chRCC). RCC can arise sporadically, but it is generally accepted that approximately 5 % of cases are linked to hereditary RCC syndromes (Linehan, 2012; Carlo et al., 2019). However, more recent studies report a higher frequency of patients with pathogenic and likely pathogenic variants when they are tested with large next-generation sequencing (NGS) panel of cancer-related genes. The cumulative frequency of germline pathogenic variants (PVs)/likely pathogenic variants (LPVs) in cancer-related genes can reach 13–17 % but is comprised between 1.4 and 9 % when limited to RCC-associated genes (Truong et al., 2021; Abou et al., 2021; Choudry et al., 2024). Identification of genetic predispositions is essential for adjusting patient's surveillance and treatment and for offering genetic counselling to their relatives. The principal strategy for preventing morbidity and mortality in individuals at risk of inherited RCC is detection of early stage tumours which can then be removed or followed up to a safe size when they are removed (Maher E, 2018). In at-risk individuals, annual renal screening is recommended to detect asymptomatic tumours.

The four major syndromes predisposing to RCC are the von Hippel-Lindau disease (VHL) caused by germline PVs in the *VHL* gene, the hereditary leiomyomatosis and RCC syndrome (HLRCC) linked to germline PVs in the *FH* gene, hereditary papillary renal cell carcinoma syndrome (HPRC) caused by germline PVs in the *MET* gene, and Birt-Hogg-Dubé syndrome (BHD) caused by germline PVs in the *FLCN* gene. Renal cancers have also been reported in patients with tuberous sclerosis (due to germline PVs in the *TSC1* and *TSC2* genes), Cowden syndrome (due to germline PVs in the *PTEN* gene), *SDH*-related tumour syndrome (due to germline PVs in the *SDHA*, *SDHB*, *SDHC* and *SDHD* genes), and *BAP1*-related tumour syndrome. All these syndromes are autosomal dominant disorders.

In addition to these genes regularly associated with an increased risk of RCC, the development of Next Generation Sequencing (NGS) and genomic studies in the recent years led to identify several new (proven or suspected) RCC susceptibility genes. Consequently, more than 30 genes are now presented in literature as possible RCC-predisposing genes (Chakraborty et al., 2021).

There is consensus that muti-gene panel (MGP) testing is the preferred approach for evaluating suspected hereditary RCC when classic syndromic features are absent (Bratslavsky et al., 2021) and given the frequent overlap among clinical syndromes. However, main inconvenients of the use of MGP include a higher rate of variants of uncertain significance (VUS) detection and the risk of identifying mutations associated with unrelated conditions, for which clinical interpretation in this context remains unclear. There was general consensus that when a specific syndrome is suspected—linked to a well-defined gene—single-gene testing should be preferred rather than MGP analysis. Although a standardized approach was lacking, experts agreed that a RCC-specific panel should be favoured to avoid excessively broad testing.

French bioethics laws define best practice standards for the use of genetic testing and the information to be communicated to patients and their relatives. Genetic tests must always be conducted within a medical framework, with appropriate counselling and prior information regarding the potential implications of the results.

Genetic analyses are offered when they are medically or therapeutically relevant to the patient, or when they can support genetic counselling within the family. In cases of hereditary cancer predisposition, testing typically begins with an index case affected by cancer, using a MGP. If a PV or LPV is identified, targeted testing for this specific variant is then offered to the patient's relatives. The objective is to ensure appropriate monitoring for individuals who carry the familial genetic variant, while exempting non-carrier relatives from unnecessary follow-up.

The current guidelines of PREDIR (hereditary PREDIsposition to Renal tumours), a national reference network for rare adult cancers accredited by the French National Cancer Institute, recommend MGP genetic testing in patients with any of the following criteria: ccRCC before the age of 45, or non-ccRCC at any age, or multiple RCC, or a personal or family history suggestive of a syndromic presentation (Verkarre et al., 2020).

In France, 8 out of 26 institutional laboratories perform genetic testing for hereditary predispositions to RCC. However, each laboratory uses custom MGP developed independently, often based on local

interests rather than standardised national recommendations. This has led to inconsistencies in access to genetic diagnosis and genetic counselling across different regions of the country. Furthermore, this situation increases the risk of identifying germline variants in genes whose association with RCC is not well established, then complicating the interpretation of results and the delivery of appropriate genetic counselling.

As it has already been done for breast and digestive cancers (Moretta et al., 2018; Dhooge et al., 2020), the French Genetic and Cancer Group-Unicancer (GGC) decided to set up a working group with the objective to recommend a national NGS MGP for germline screening of patients at-risk for hereditary RCC, based on current clinical utility. This study was carried out in collaboration with the French PREDIR network with the aim of harmonizing genetic diagnosis and management of patients with hereditary predisposition to RCC.

2. Methodology

2.1. Working group of experts

The working group was composed of 22 national experts in the field, belonging to 17 different institutions across 11 cities in France. They were members of the GGC and some of them were members of the PREDIR network. The experts included clinical geneticists, genetic counsellor working in cancer genetics units, molecular geneticists and epidemiologists.

2.2. Selection of genes for evaluation by the experts

First, the working group examined all the 22 genes included in at least one "Renal Cancer" MGP designed by the eight French oncogenetic laboratories affiliated to PREDIR. At the beginning of the study, 5 genes were analysed in all laboratories: *FLCN, FH, MET, SDHB, VHL*. Others were analysed in some laboratories only: *BAP1, SDHC*, *SDHD, TMEM127, TSC1/TSC2* were analysed in five laboratories; *CDKN2B, MITF, PBRM1, PTEN* and *SDHA* were analysed in four laboratories; *CDC73, HNF1B*, *SDHAF2*, *SETD2*, *SMARCB1*, *TP53* were analysed in one or two laboratories.

The working group selected 10 other genes suspected to be of interest in the field of RCC predisposition by reviewing the literature, notably genes with recurrent pathogenic variant found by large NGS studies (Carlo et al., 2018; Kong et al., 2021; Nguyen et al., 2017; Van de BEEK et al., 2023; Wu et al., 2019) and comprising *CDKN2A*, *ELOC*, *EPCAM*, *MAX*, *MLH1, MSH2*, *MSH6*, *NBR1*, *PRDM10* and *PMS2*.

All genes listed in the 'R224 inherited renal cancer – Version 1.27' Genomics England PanelApp (Martin et al., 2019) as having high (*BAP*, *FH*, *FLCN*, *MET*, *SDHB* and *VHL*) and lower (*CDKN2B*, *MITF*, *PTEN*, *SDHC*, *SDHD*, *TMEM127*, *ELOC*, *PRDM10*) level of evidence for gene-renal cancer association have been considered in our reviewing process.

Although germline translocations, mainly involving chromosome 3, have been recognized as a very rare cause of inherited predisposition to RCC (Smith et al., 2020), they have not been considered in the present study as they can't be identified by NGS MGP but karyotyping, genome sequencing or long-read sequencing.

Genes involved in hereditary predisposition to breast cancer, whose alterations are frequently found in genome studies, were excluded because they are not known to be associated with increased risk of RCC (*BRCA1*, *BRCA2*, *ATM* and *CHEK2)*.

The genes involved in predisposition to nephroblastoma were not considered.

Finally, 32 genes were reviewed by the working group with the objectives to 1) evaluate their associated RCC risk; 2) define the pertinence of including them in a national gene panel recommended for patients eligible for "Renal cancer" genetic testing. The evaluated genes were *BAP1, CDC73, CDKN2A, CDKN2B, EPCAM, ELOC, FH, FLCN, HNF1β, MAX, MET, MITF, MLH1, MSH2, MSH6, NBR1, PBRM1, PRDM10, PMS2, PTEN, SDHA, SDHAF2, SDHB, SDHC, SDHD, SETD2, SMARCB1, TMEM127, TP53, TSC1, TSC2* and *VHL*.

2.3. Criteria for selecting or excluding genes from the GGC-PREDIR recommended NGS 'renal cancer' panel

The working group selected genes for which the level of cancer risk associated with genetic variants was considered sufficiently high to justify presymptomatic testing in patient's relatives and to recommend follow-up only for carriers of the familial genetic variant.

Similarly to previous works conducted in breast and colorectal cancer, the GGC-PREDIR working group retained the risk categories defined in the review published by Easton et al. (2015), which focus on breast cancer but are also applicable to other cancers. The goal of the GGC-PREDIR working group was to include genes whose variants confer a high risk of renal cancer, i.e. a relative risk (RR) of renal cancer four times that of the general population.

However, hereditary predisposition to RCC is rare and few data on RCC risk are available in the literature, leading to also taking into account estimated incidence and prevalence of RCC associated with susceptibility genes. We also used data from the national PREDIR database.

2.4. Review of the literature and analyses provide by the working group

Each gene review was initially performed by two or three experts who reported the compiled data for discussion and validation by the whole GGC-PREDIR working group. Population selection and cancer risk estimation were analysed in collaboration with experts in epidemiological studies (NA, VB, SD).

A standardised report in French was produced for each evaluated gene. These reports are available on request and will be integrated in the GGC/Unicancer (www.unicancer.fr/recherche/groupe-genetique-et-cancer) and PREDIR (www.predir.org) websites.

2.5. Selection of guidelines for patient's clinical management

The GGC-PREDIR working group selected the widely accepted national and international recommendations for the management of carriers of PV or LPV in selected genes.

Recommendations for surveillance of the *FH*, *FLCN*, *MET* and *VHL* carriers are those proposed by the national PREDIR network (www.predir.org). Recommendations for *TSC1* and *TSCS2* carriers are based on the French national diagnosis and care program (PNDS, 2021).

International recommendations were selected by the GGC-PREDIR working group for management of *BAP1* (Chau et al., 2019) and *PTEN* (Tischkowitz et al., 2020). Recommendations for *SDHx* carriers are based on the French national diagnosis and care program (PNDS, 2021) and international recommendations (Amar et al., 2021).

2.6. Validation

Data have been discussed during 9 daily working sessions of the GGC-PREDIR working group between January 2022 and May 2023.

This work was presented and discussed during two plenary meetings of the GGC, which brought together more than 60 molecular and clinical experts in oncogenetics and during one plenary meeting of PREDIR.

3. Results and discussion

3.1. Review of studies on the prevalence of germline PV or LPV in RCC-associated cancer genes from NGS RCC series

Nguyen et *al* (Nguyen et al., 2017) reviewed genetic testing results and clinical data from 1235 RCC patients analysed with MGP comprising 19 genes: patients had a median age at diagnosis of 46 years and

altogether, 6.1 % had germline PV in 15 of the genes (Table 1).

Carlo et al. (2018) analysed a series of 254 patients with advanced renal cancer without selection for age or family history, with customised large NGS gene panels targeting 341 or 468 cancer-related genes. A total of 41 patients (16.1 %) carries germline PV or LPV in 17 cancer predisposition genes, among them 14 (5.5 %) had a variant in a RCC-associated gene.

Wu et al. (2019) used an NGS-based panel of 23 genes to analyse 190 unrelated Chinese patients diagnosed with RCC under the age of 45. 18 patients (9.5 %) had germline alteration in 10 genes.

Huang et al. (2021) analysed germline and somatic DNA in 880 Chinese ccRCC patients with large customised NGS panels targeting 381 or 733 cancer-related genes. 95.8 % carried at least one somatic PV. In addition, 52 (5.9 %) were found to carry germline PV or LPV in 22 cancer predisposition genes.

Kong et *al* (Kong et al., 2021) analysed germline and somatic DNA in 322 ccRCC patients with a customised NGS panel targeting 808 cancer-related genes. 9.9 % carried germline PV or LPV variants of which 3.7 % were variants in syndromic RCC-associated genes and 6.2 % were other cancer-predisposition genes.

Truong et al. (2021) analysed germline DNA in 232 patients with RCC diagnosed at age ≤46 years. They used NGS panel MSK-IMPACT including more than 75 genes associated with hereditary cancer predisposition. Germline PV/LPV were identified in 41 patients (17.7 %) of which 21 (9.1 %) were in an RCC-associated gene and 20 (8.6 %) in a non-RCC associated gene.

Yngvadottir et al. (2022) analysed the whole-genome sequencing data on 1336 individuals with RCC recruited in the UK's 100,000 genomes Project. Germline PV/LPV were identified in 85 patients (6.4 %) of which 60 (4.5 %) were in an RCC-associated gene and 28 (2.1 %) in a non-RCC associated genes.

Genes with recurrent genetic variations reported in these studies are listed in Table 1.

3.2. Genes included in the GGC-PREDIR 'renal cancer' panel

3.2.1. VHL

VHL is a tumour suppressor gene encoding an E3 ubiquitin ligase involved in oxygen sensing and regulation of hypoxia inducible factor (HIF) degradation. More than 90 % of ccRCCs have somatic inactivating variants of *VHL*.

VHL germline PVs/LPVs are associated with von Hippel-Lindau disease (VHL), which predisposes to Central Nervous System (CNS) and retinal hemangioblastomas, renal cysts and ccRCC, pancreatic cysts and neuroendocrine tumours, pheochromocytomas and paragangliomas, and endolymphatic sac tumours (Lonser et al., 2003). VHL prevalence is estimated around 1/53.000.

A first series of 104 cases of RCC compared with 109 cases of sporadic renal cancer found that the sex ratio in VHL disease was 1:1 and that the average age at diagnosis of RCC was 44.8 years compared to 61.8 years in patients with sporadic RCC (Maher and al., 1990). In a series of 152 patients with a known VHL disease, the lifetime risk of developing RCC in patients was estimated to be 69 % (Maher and al., 1990a,b). In a French series of 176 patients with a VHL disease consecutively seen in the same hospital from 1988 to 2009, 127 (72 %) were diagnosed with RCC (Joly et al., 2011). The proportion of patients who developed RCC at the age of 60 years is 25–70 % according to studies carried out on series of patients with VHL disease (Lonser et al., 2003; Maher et al., 2011; Ong et al., 2007; Binderup et al., 2017). Finally, in the national series of the PREDIR network, 457 out of 992 patients (46 %) who had at least one renal imaging study presented with RCC (unpublished data).

In regards to these data, the GGC-PREDIR working group concludes that patients with germline *VHL* PVs/LPVs should be considered as at high risk of RCC, despite the fact that there is no recent RCC risk estimate. Consequently, the GGC-PREDIR group of experts has decided to include *VHL* gene in the French recommended "renal cancer" NGS panel.

3.2.2. FLCN

FLCN is a tumour suppressor gene encoding folliculin. Inactivation of *FLCN* leads to upregulation of the mTOR signalling pathway.

FLCN germline PVs/LPVs (Nickerson et al., 2002) are associated with Birt-Hogg-Dubé (BHD) syndrome, which is characterised by benign skin lesions mostly fibrofolliculomas, lung bullae sometimes leading to pneumothorax, and renal tumours. The prevalence was initially estimated at 1/200.000; but the frequency of *FLCN* PV has recently been estimated to 1 in 2710–4190 by large-scale genomic database research studies (Yngvadottir et al., 2025). RCC in BHD patients are most commonly oncocytic tumours, chRCC, hybrid oncocytic chRCC and ccRCC.

There are currently three studies estimating the risk of RCC in BHD patients. The study by Zbar et al., in 2002 (Zbar et al., 2002) is a family

Table 1
Number of germline pathogenic or likely pathogenic variants identified in patients with renal cancer analysed in 7 NGS studies limited to RCC-associated genes. (AML = angiomyolipomas; NA = not analysed).

Study (# patients)	Carlo (254)	Huang (880)	Kong (322)	Nguyen (1,235)	Wu (190)	Truong (232)	Yngvadottir (1,336)
Histology	177 ccRCC 74 non-cc RCC 3 both	ccRCC	ccRCC	459 ccRCC 145 pRCC 82 chRCC 256 others 293 unknown	128 ccRCC 11 pRCC 21 chRCC 29 AML	129 ccRCC 17 pRCC 25chRCC 7 AML 18 FH-deficient RCC 2 SDH deficient RCC 23 others 5 unknown	939 ccRCC 237 non-ccRCC 149 unspecified 61 non available
BAP1	3	0	1	2	3	1	0
CDKN2A	0		0	NA	1	0	0
FH	7	9	2	16	2	12	3
FLCN	0	4	1	22	1	1	4
MET	1		0	2	0	0	0
MMR *MLH1, MSH2, MSH6, PMS2, EPCAM*	2	1	0	7	NA	0	6
MITF	0		0	9	0	0	10
PBRM1	NA		1	NA	1	NA	0
PTEN	0		0	1	0	0	0
SDHx genes	2		0	11	0	2	9
SETD2	NA		0	NA	0	NA	0
TP53	0		1	0	0	1	2
TSC1/TSC2	0		3	3	5	1	0
VHL	1	4	7	2	1	4	5

study of 223 individuals from 33 BHD families which had compared 111 individuals with BHD syndrome (including 16 with renal cancer) with 112 unaffected relatives (including 2 with renal cancer) and reported an OR at 9.3. The study by Houweling et al. (2011) is a family study selected by the "BHD" criterion, performed on 86 mutation carriers belonging to 21 families and reporting a cumulative risk of RCC at age 70 of 16 % (95 % CI, 6–26 %). A more recent study (Bruinsma et al., 2023) assessed the risk of RCC using pooled data from the literature as well as unreported data from 88 families. This study reported 1076 individuals, including 138 carriers of a PV or LPV of *FLCN*, who had developed a renal tumour. By a literature review authors identify studies that had recruited families with PVs/LPVs *FLCN* variants; pedigree data were requested and pooled. By segregation analysis, they estimated the cumulative risk of renal tumour at age 70 of 19 % (95 % CI 12–31) for men and 21 % (95 % CI 13–32) for women.

The other studies published to date only report the prevalence of RCC from series of patients clinically affected by BHD syndrome, which varies between 16 and 34 % depending on the study [Pavlovich et al., 2005; Schmidt et al., 2005; Toro et al., 2008; Benusiglio et al., 2014; Furuya et al., 2016; Sattler et al., 2018; Lagerstedt-Robinson et al., 2022].

In regards to these data on the risk of RCC in people carrying a PV/LPV in *FLCN*, the GGC-PREDIR working group concludes that patients with germline *FLCN* PVs/LPVs should be considered as at high risk of RCC. Consequently, the GGC-PREDIR group of experts has decided to include *FLCN* gene in the French recommended "renal cancer" NGS panel.

3.2.3. *FH*

FH is a tumour suppressor gene encoding fumarate hydratase (Tomlinson et al., 2002). Patients with germline inactivating heterozygous PVs/LPVs in *FH* gene have hereditary leiomyomatosis and RCC (HLRCC) syndrome or Reed syndrome, characterized by cutaneous and uterine leiomyomas, RCC and paragangliomas. Prevalence was initially estimated at 1/200.000; however, data from the 1000 Genomes Project and Exome Agregation Consortium sequencing suggest a frequency of *FH* PV affecting 1/1000 individuals (Shuch B et al., 2020). Classically, RCC in this syndrome were type 2 pRCC, although additional rare subtypes were observed, such as collecting duct carcinoma. Since the last update of the WHO classification (Moch et al., 2022), HLRCC associated RCC are now referred to as FH-deficient RCC; they are often aggressive tumours with a poor prognosis.

Only one study estimating the risk of RCC in people carrying a germline PV/LPV in the *FH* gene has been published (Lehtonen et al., 2006). This study analysed genealogical and cancer data from 868 individuals belonging to *FH* mutation positive families from Finnish family registers. Index patients were excluded. The cohort analysis of the standardised incidence ratios (SIR) was analysed from 256 individuals with complete data. There was a 6.5-fold risk [confidence interval (CI) 2.1–15] for RCC compared with the general population.

Other studies have estimated the prevalence of RCC in series of patients with HLRCC syndrome to be 12–19 % [Muller et al., 2017; Forde et al., 2020] or the cumulative lifetime risk of RCC in carriers of *FH* PVs/LPVs to be 15–21 % (95 % CI 8.2–37.1) [Menko et al., 2014; Lattouf et al., 2016; Forde et al., 2020].

In regards to these data, the GGC-PREDIR working group concludes that patients with germline *FH* PVs/LPVs should be considered as at high risk of RCC. Consequently, the GGC-PREDIR group of experts has decided to include *FH* gene in the French recommended "renal cancer" NGS panel.

3.2.4. *MET*

The *MET* (mesenchymal-epithelial transition) oncogene encodes the hepatocyte growth factor tyrosine kinase receptor. *MET* germline activating PVs/LPVs are responsible for hereditary papillary RCC (HPRCC) without extrarenal manifestations (Schmidt al., 1997). This syndrome is considered to be very rare and the incidence is unknown. Prevalence is estimated to 1/500,000. Classically, RCC in this syndrome were classified as type 1 pRCC; since the WHO 2022 classification, this subtype is now considered as the "classic PRCC". Biphasic squamoid alveolar RCC are classified in this group and have also been reported in *MET* germline PVs/LPVs carriers.

MET function is impaired in 81 % of pRCC, taking into account somatic PVs/LPVs, chromosomal gains and gene fusions (Cancer Genome Atlas Research Network, 2016).

The study by Sebai et al. (2022), reported 158 cases of pRCC type I without other selection criteria (153 independent patients and 5 relatives, mean age 45 ± 13 years): the detection rate of germline PVs/LPVs in *MET* was 12.4 %: 5 % in sporadic presentation and 40.6 % in family history. Patients with PV or LPV had bilateral or multifocal cancer in 84.3 % and 87.5 % of cases, respectively.

There are no large studies estimating the risk of RCC in people carrying a *MET* PV/LPV. Only one study, by Schmidt et al. (1998) estimated the disease penetrance based on 23 individuals from two families carrying *MET* mutations and reported a cumulative risk of RCC at 40 years of age of 19 % (CI 95 %, 5–34 %) and at 60 years of age of 67 % (95 % CI, 46–87 %). Two other studies of large families (Schmidt et al., 1997, 2004) reported cases of renal cancer in 15 of 18 mutation carriers and 14 of 27 mutation carriers, respectively. No cases of RCC were reported in non-mutation carriers in these families, who had, in most cases, a surveillance abdominal CT scan. In these three independent studies, the risk of RCC in people carrying a *MET* PV can be considered high.

Due to the rarity of germline alterations in *MET* gene, there is currently no well-established data on the risk of developing RCC in individuals carrying a *MET* PV/LPV. However, based on the available literature, including the studies cited above showing co-segregation between the presence of *MET* PVs/LPVs and development of renal cancer, the GGC-PREDIR working group has decided to include *MET* in the French recommended "renal cancer" NGS panel.

3.2.5. *BAP1*

The *BAP1* gene is a tumour suppressor gene encoding BAP1 (BRCA1-associated protein-1), a nuclear deubiquitinase that plays an important role in the regulation of DNA double-strand break repair by homologous recombination and cell death. Germline alterations in this gene have been associated with risk of cutaneous melanoma, benign skin tumours (BCC, Spitz tumours), uveal melanoma, mesothelioma (pleural and peritoneal) and RCC (mainly clear cell). This syndrome is considered to be very rare and the incidence is unknown.

Tumour alterations of *BAP1* (homozygous deletions or point mutations combined with loss of heterozygosity) are present in approximately 11–15 % of ccRCC (Peña-Llopis et al., 2012; Ricketts et al., 2018) and less commonly in pRCC (5.6 %). These losses of BAP1 function are associated with high-grade tumours and poor prognosis.

The study by Popova et *al* in 2013 (Popova et al., 2013) reports the first family with 4 relatives presenting with ccRCC, all carrying the family *BAP1* germline VP. Immunohistochemistry (IHC) of 3 tumours from 2 individuals from this family showed loss of BAP1 protein expression which is a major argument in favour of the pathogenicity of the *BAP1* variant and its implication in the tumour's development.

Some studies have reported the prevalence of RCC in *BAP1* VP carriers. The study by Walpole S et *al* (Walpole S et al., 2018), found a RCC rate of 10.5 % in patients carrying a truncating variant and 12 % in those carrying a missense variant. In the cohort study by Chau et al. (2019), only 3 % of patients carrying a *BAP1* VP developed RCC (n = 72). The review by Carbone et al., (2020), finds a 7 % RCC rate in patients carrying a *BAP1* VP (N = 350).

Due to the rarity of germline alterations in *BAP1*, there is currently no well-established data on the risk of developing RCC in individuals carrying a *BAP1* PV/LPV. However, based on the available literature, including the studies cited above, and the observed association between the presence of a PV/LPV and the loss of BAP1 protein expression in

related RCC cases, the GGC-PREDIR working group considers that *BAP1* germline PVs/LPVs may confer an increased risk of developing RCC and has decided to include *BAP1* in the French recommended "renal cancer" NGS panel.

3.2.6. *PTEN*

The PTEN protein is a phosphatase which regulates negatively the intracellular signalling pathway controlled by the phosphatidylinositol-triphosphate (PI3P) kinase. *PTEN* germline PVs/LPVs are associated with Cowden syndrome, corresponding to a complex phenotype associating disorders of tissues derived from the 3 embryonic lineages for which clinical diagnosis can be difficult (Riegert Johnson and al., 2010). Cowden syndrome is also associated with an increased risk of various cancers, particularly of the breast, thyroid and endometrium. The incidence of the disease is unknown but estimated around 1/200,000.

The malignant renal tumours reported in this syndrome correspond to chRCC, pRCC or ccRCC. Loss of PTEN on IHC is frequent in sporadic forms of these tumours (Ricketts et al., 2018).

Studies estimating the risk of RCC in individuals carrying *PTEN* PVs/LPVs report a higher risk than in general population.

The study by Riegert-Johnson et *al* (Riegert-Johnson et al. (2010) reports a cumulative risk at the age of 70 years of 15 % (CI: 6–32)] based on data from 211 patients with clinically Cowden syndrome. The study by Tan et al. (2012) reports a cumulative risk at the age of 70 years (CI: 10.4–56.4) based on data from 368 *PTEN* PVs/LPVs carriers.

The study by Nieuwenhuis et *al* (Nieuwenhuis et al., 2014) reports a RCC cumulative risk at the age of 60 years of 8.5 % for women and 2.5 % for men based on 180 patients with clinically Cowden syndrome. The prospective study by Hendricks et al. (2023) reports a RCC cumulative risk at the age of 60 years of 8.6 % (CI: 3.3–21.6) based on 455 patients (excluding cancers in index cases occurring before diagnosis of Cowden syndrome).

Other studies published to date report SIRs ranging from 4 to 49 (Bubien et al., 2013; Ngeow et al., 2014; Mester et al., 2012).

To date, there is no evidence that a germline *PTEN* PV/LPV can be identified in the context of an inherited predisposition to RCC in the absence of phenotypic manifestations of Cowden disease. However, considering that carrier status for the pathogenic variant is sufficiently discriminative in terms of RCC risk, *PTEN* is included in the French recommended "renal cancer" NGS panel to ensure that potential attenuated forms are not overlooked.

3.2.7. *SDHA, SDHB, SDHC, SDHD*

The *SDHA*, *SDHB*, *SDHC* and *SDHD* genes (commonly referred to as *SDHx*) encode the 4 subunits of the succinate dehydrogenase (SDH). These tumour suppressor genes were identified in 2000–2010 as genes predisposing to paragangliomas/pheochromocytomas and gastrointestinal stromal tumours (GIST) and more recently to pituitary adenomas (Branzoli et al., 2023). The prevalence is estimated to 1–9/1,000,000.

In 2004, Vanharanta et al. (2004) reported the first descriptions of RCC in young patients carrying a germline *SDHB* PV with proven associated loss of heterozygosity at the 1p locus in renal tumours.

In 2011, Gill et al. (2011) showed that SDHB IHC can be used as a screening method to identify SDH-deficient RCC (i.e. with loss of SDHB protein expression) with germline or somatic PV/LPV in one of the *SDHx* genes (*SDHB* or *SDHA* or *SDHC* or *SDHD*).

According to the 2016 WHO classification of renal tumours, SDH-deficient RCC is a specific histological subtype of RCC, which was confirmed in the 2022 WHO classification revision. Therefore, screening by SDHB IHC at the time of the pathological diagnosis of RCC was recommended to facilitate the detection of this subtype. Indeed, SDH-deficient RCC may looks like sporadic RCC as there is no systematic associated history of paraganglioma, pheochromocytoma and/or GIST. *SDHB* germline PVs/LPVs have been reported in 83 % of SDH-deficient RCC (MacFarlane et al., 2020).

Germline VPs in *SDHA*, *SDHC* and *SDHD* genes have also been associated with hereditary SDH-deficient RCC but more rarely.

Only one study has been published estimating the risk of RCC in individuals carrying a PV in one of the *SDHx* genes: Andrews et al. (2018) studied a series of 673 patients with VP in *SDHB*, 43 in *SDHC* and 160 in *SDHD*: 16 RCC were reported (15 in *SDHB* patients and one in *SDHD* patient). The cumulative risk of RCC at age 60 years was estimated to be 4.2 % (0.46–7.8 %, Kaplan Meier non-proband) and 4.71 % (1.65–7.7 %, Kaplan Meier all).

Considering all available data, *SDHx* genes analysis should be preceded by SDHB IHC in renal tumours. In practice, given the increased risk of RCC in patients with germline *SDHx* PV/LPV and the fact that SDHB IHC is not systematically performed in French pathology laboratories, the GGC-PREDIR working group includes the *SDHA*, *SDHB*, *SDHC* and *SDHD* genes in the French recommended "renal cancer" NGS panel.

If a VP/LPV of one of the *SDHx* genes is identified at the germline level in a patient with RCC without prior SDHB IHC, it is recommended to retrospectively assess the involvement of the *SDHx* variant in tumour development by performing SDHB IHC on the renal tumour tissue when available.

3.2.8. *TSC1, TSC2*

The *TSC1* and *TSC2* genes are tumour suppressor genes encoding the proteins hamartin and tuberin respectively, which together regulate cell growth and proliferation by inhibiting the mTOR (mammalian target of rapamycin) pathway.

Alterations in these genes are responsible for tuberous sclerosis complex (TSC) with most commonly *de novo* mutations (60–70 %). TSC is characterised by the possibility of an early disorder in the development of the cerebral cortex with the formation of tubers and by the development of benign tumours in various organs, like facial angiofibromas, retinal hamartomas, cardiac rhabdomyomas and lymphangioleiomyomatosis. The prevalence is estimated at 1/8000 to 1/15,000 births. Its clinical consequences vary greatly from patient to patient.

The most common renal lesions are angiomyolipomas (AMLs). Carlo et al. (2019) reported a 50 % prevalence of AMLs in TSC patients, and described renal cysts, oncocytomas and more rarely malignant angiomyolipomas or RCC with a mean age of 26 years for AMLs, a higher risk of renal damage in patients with a *TSC2* mutation and prevalence up to 5 % for RCC. The review by Henske et al. (2021) included 103 cases of RCC in patients with TSC, with a median age of onset of 36 years. The most commonly reported cancers are ccRCC, but there were also cases of chRCC, hybrid oncocytoma/chRCC, pRCC, unclassified eosinophilic cell tumours and leiomyomatosis stromal tumours. The difficulty of RCC radiological diagnosis compared to AML was mentioned by Carlo et al. and Henske et al. The study by Sauter et al. (2021) looked at rare diseases and cancers using data from the international TOSCA registry, including 2211 patients with a prospective or retrospective diagnosis of TSC. It founds RCC in 31 patients (prevalence = 1.4 %). Ritter's study (Ritter et al., 2022) included data from 1398 thoraco-abdominal scans performed every 2–3 years in 649 patients (47 % men and 53 % women) from 1997 to 2019; prevalence of renal cysts and AMLs was 72 % and 59 % respectively but no RCC has been diagnosed.

According to the current state of knowledge, the risk of benign renal tumours is significant in TSC patients and a slight increase in RCC cancer risk has been reported in women carrying a germline PV/LPV in *TSC1* and *TSC2*. Due to the relatively high penetrance of TSC, the high frequency of *de novo TSC1/2* PV/LPV, the presence of mosaic variants, and the broad variability of TSC expression, renal manifestations may occasionally be the first presentation of TSC, particularly in adults with attenuated or mosaic phenotypes. Because renal surveillance is part of standard TSC follow-up and the differential diagnosis between angiomyolipomas and RCC can be challenging radiologically or histologically, including *TSC1/2* helps avoid diagnostic misclassification. Beyond this risk of confusion, inclusion of *TSC1/2* is further supported by the rare but documented occurrence of *TSC*-associated RCC, which typically presents at a younger age and often displays various histopathological

features and multifocal presentation (Ricketts et al., 2025). Considering all these data, the GGC-PREDIR working group retains the *TSC1* and *TSC2* genes for inclusion in the French recommended "renal cancer" NGS panel.

3.3. Genes not included in the GGC-PREDIR "renal cancer" panel

The GGC-PREDIR working group excluded 20 genes from the "renal cancer" MGP: *ELOC, CDC73, CDN2A, CDKN2B, HNF1β, MAX, MITF, MLH1, MSH2, MSH6, PMS2, EPCAM* (referred to as MMR genes), *PBRM1, PRDM10, NBR1, SETD2, SDHAF2, SMARCB1, TMEM127* and *TP53*.

The reasons of their non-inclusion are summarized in Table 2. In most cases the number of publications and reported cases was insufficient to confirm a risk of RCC linked to these genes. Below, data are more detailed for 4 genes, either because their analysis seems relevant in specific clinical situations (*TP53*, *ELOC*, *PRDM10*) and/or because experts felt they are good candidate genes and that regular bibliographic evaluation of these genes is necessary (*ELOC*, *PBRM1)*.

3.3.1. ELOC

The *ELOC* (formerly known as *TCEB1*) gene encodes the elongin C protein which is part of the E3 ubiquitin ligase complex with VHL, elongin B, cullin 2 and Ing box 1.

Somatic PVs in *ELOC* gene have been reported in 14 % of ccRCC (Batavia et al., 2023).

The *ELOC* gene was firstly reported as potentially associated with predisposition to renal cancer in 2022 (Andreou et al., 2022) following the identification of a *de novo* germline PV in a patient who presented with 2 retinal hemangioblastomas, two central nervous system hemangioblastomas, two ccRCCs and renal cysts, a phenotype strongly evocating VHL disease but without germline or somatic *VHL* alteration.

In the current state of knowledge, *ELOC* is a strong candidate gene to explore in patients suspected of VHL disease without identified VP in the *VHL* gene. However, there are no sufficient data on the risk of RCC associated with germline *ELOC* PVs/LPVs to allow including *ELOC* in the French recommended "renal cancer" NGS panel.

3.3.2. PBRM1

PBRM1 (Poly Bromo-1) is a tumour suppressor gene located at 3p near the *VHL* gene. It encodes the protein BAF180, an ATP-dependent subunit of the chromatin remodelling complex.

Somatic PVs/LPVs of *PBRM1* have been found in 30–45 % of ccRCC (Varela et al., 2011) but germline PVs/LPVs were rarely identified in patients with RCC (Table 1).

The study by Benusiglio et al. (2015) reported the first family with the identification of a germline VP in *PBRM1* in 4 relatives with ccRCC. The variant co-segregated with the disease. BAF180 (PBRM1) IHC of one of the renal tumours in this family showed a loss of PBRM1 protein expression in the tumour tissue with preservation of this protein expression in the adjacent healthy tissue; sequencing of another RCC revealed the *PBRM1* PV associated with loss of heterozygosity.

To date, no study has estimated the risk of RCC in the presence of a germline alteration in the *PBRM1* gene. We only found studies that estimated the prevalence of germline alterations in *PBRM1* in RCC cases or RCC families. Two studies found one germline PV in this gene (Wu et al., 2019; Kong et al., 2021), despite screening of large RCC cohorts.

Due to the small number of published families or cases, there is no sufficient data on the risk of RCC associated with germline *PBRM1* PVs/LPVs to allow including *PBRM1* in the French recommended "renal cancer" NGS panel.

3.3.3. PRDM10

In 2023, a new syndrome overlapping with Birt-Hogg-Dubé syndrome was reported (Van de BEEK et al., 2023) corresponding to a genetic predisposition associated with an increased risk of fibrofolliculomas, lipomas (lipomatosis) and malignant renal tumours (clear cell, type 2 papillary carcinoma or unclassified, etc.), but without pulmonary involvement. This syndrome has been reported in a family without any *FLCN* VP but with a germline missense variant in *PRDM10*, encoding a transcription factor, regulator of *FLCN* expression (Han et al.,

Table 2
Genes not included in the GGC PREDIR 'renal cancer' panel.

Genes	Reasons for studying	Reasons for exclusion	References
CDC73	Case report of RCC or Wilms tumour in *CDC73* VP carriers	Uncertain RCC risk	Van der Tuin K et al. (2017) Bricaire L et al., 2013
CDKN2A CDKN2B	3 cases of germline VP in RCC exome or genome studies	unknown RCC risk	Wu et al. (2019) Maubec et al. (2010) Jafri et al. (2015)
ELOC	One "VHL-like" patient with germline *ELOC* variant	unknown RCC risk	Andreou A et al. (2022)
HNF1β	Two cases of germline variants in patients with chromophobe RCC	Uncertain RCC risk	Rebouissou et al., 2005 Gad et al. (2007)
NBR1	One germline variant identified in a family with clear cell RCC, angiomyolipomas and papillary RCC	Unknown RCC risk	Adolphe et al. (2021)
MAX	Two cases of oncocytoma described in MAX VP carriers	Unknown RCC risk	Burnichon et al. (2012) Korpershoek et al. (2016)
MITF	E318K variant reported in patients with RCC but high frequency of the E318K variant in general population	Uncertain RCC risk	Bertolotto et al. (2011); Nguyen et al. (2017); Oliveira et al. (2021)
MMR	One study on 1445 HNPCC patients reported a Cumulative incidence of RCC at age 75 of 2.06 % in HNPCC patients (0.85 in general population)	Uncertain RCC risk	Therkildsen et al. (2016)
PBRM1	Frequent somatic variants found in RCC One study with germline variants in 4 related patients with RCC	Unknown RCC risk	Varela et al. (2011) Benusiglio et al. (2015)
PRDM10	one germline variant identified in a family suspected of BHD.	Unknown RCC risk	Van de BEEK I et al. (2023)
SDHAF2	Gene belonging to the *SDHx* genes family	No description of association between *SDHAF2* variant and RCC	MacFarlane et al., 2020
SETD2	Frequent somatic variants found in RCC One study with germline variants in patients with both melanoma and RCC	Unknown RCC risk	Hubert JN et al. (2021) Wu J et al. (2019)
SMARCB1	Somatic mutations found in rhabdoid and medullary RCC Two cases of germline variants in RCC patients	Unknown RCC risk	Han E et al. (2021) Hulsebos et al. (2016) Moch et al. (2022)
TMEM127	Cases reports of RCC in germline carriers; one study on 110 patients with germline variants and 6 RCC	Unknown RCC risk	Qin et al. (2014) Armaiz-Pena et al. (2021)
TP53	Reports of RCC in germline carriers; SIR of RCC estimated at 13.2	Risk of RCC much lower than risk of cancer in other organs	De Andrade et al. (2021)

2020). This variant leads to a loss of FLCN expression. Out of eleven people who were carriers of the *PRDM10* VP, two developed a ccRCC at age 54 and a third individual developed an unclassifiable RCC at age 68 and a type 2 papillary at age 75.

There is no data on the risks associated with germline PVs/LPVs in the *PRDM10* gene explaining why *PRDM10* gene is not included in the French recommended "renal cancer" NGS panel. However, analysis of this gene could be suggested in families presenting with evocative clinical conditions involving fibrofolliculomas, lipomas and RCC.

3.3.4. *TP53*

The *TP53* gene is a tumour suppressor gene encoding a transcription factor that controls the expression of numerous genes involved in apoptosis and cell cycle regulation. PVs/LPVs in the *TP53* gene are associated with an increased risk of cancer in various organs (breast, sarcoma, brain tumours, etc.), often at young age.

Two studies have estimated the incidence of RCC in *TP53* PV/LPV carriers. In 24 *TP53* families, Ruijs et al. (2010) estimated the cancer risk in different organs and calculated a RR of RCC of 4.4 [95 %CI 0.9–13], but with only 3 described cases of RCC.

In the NCI series, which included 480 *TP53* carriers from 143 families, 9 cases of RCC were described, including 4 as first tumour: 2 before the age of 30 years, 3 between 30 and 60 years, 4 after 60 years. The SIR of RCC was estimated to be 13.2 [95 %CI 6.0–25.1] (De Andrade et al., 2021).

TP53 appears relatively infrequently mutated in ccRCC.

Although the limited number of available data and the methods used for the risk estimation, current evidence suggests a moderate increased risk of RCC in *TP53* PV/LPV carriers. However, due to the low prevalence of *TP53* germline PV/LPV and the high penetrance of core Li-Fraumeni cancers, identifying a *TP53* germline PV/LPV in cases of isolated RCC is highly unlikely. Therefore, experts do not recommend germline testing for *TP53* in all cases of suspected hereditary RCC but it may be considered in cases of kidney cancer diagnosed before the age of 30, or in cases of personal or family history of tumours suggestive of Li-Fraumeni syndrome.

3.4. *Management recommendations for patients with (likely) pathogenic variants in the genes included in the GGC-PREDIR 'renal cancer' panel*

To support the dissemination and harmonization of clinical management for these rare syndromes, the GGC-PREDIR working group has selected the most widely accepted national and international recommendations for the management of carriers of PV/LPV in the genes included in the GGC-PREDIR 'Renal Cancer' panel (Table 3).

4. Conclusion

For patients with suspected hereditary predisposition to cancer, initial genetic testing is now performed using NGS. This enables the simultaneous analysis of all relevant genes (MGP) at a lower cost and allows for the easy addition of new genes of interest when necessary. However, this MGP NGS approach has also led laboratories to include genes that may be potentially relevant to cancer predisposition, which can result in the identification of genetic variants whose association with a cancer risk is imprecise or unknown. In the absence of international or national guidelines for genetic testing in patients with RCC, significant variability has been observed among the eight French oncogenetics laboratories regarding the list of renal cancer-related genes included in multi-gene panels. To harmonize genetic testing practices for patients with renal tumours, the French, GGC undertook an expert consensus effort, following the same methodology applied to breast and digestive tract cancers (Moretta et al., 2018; Dhooge et al., 2020). In collaboration with the PREDIR network, a review of 32 genes of potential interest was conducted. The gene list was based on current literature and included suggestions from French oncogenetics laboratories involved in the analysis of RCC-associated genes. The aim was to identify genes of validated clinical relevance for family screening, i.e., genes for which

Table 3
Recommendations for renal surveillance in individuals carrying (likely) pathogenic variants in genes included in the GGC-PREDIR 'Renal cancer' panel
CNS-Hb = central nervous system hemangioblastomas, RET-Hb = retinal hemangioblastomas pNET = pancreatic neuroendocrine tumour.

Gene	Age for presymptomatic genetic testing	Abdominal follow-up			Extra renal lesions
		Starting age	Periodicity	Methods	
VHL	≥5 years	5 years	Annual	Ultrasound	CNS-HB and RET-HB
		18 years	Annual	Contrast-enhanced MRI every 2 years alternating with ultrasound in the meantime	Pancreatic cysts and pNET Pheochromocytomas and paragangliomas Endolymphatic sac tumours
FLCN	≥18 years	18 years	Annual	Contrast-enhanced MRI every 3 years alternating with ultrasound in the meantime	Fibrofoliculomas Lung bullae
MET	≥18 years	18 years	Annual	Contrast-enhanced MRI every 3 years alternating with ultrasound in the meantime	
FH	≥10 years	10 years	Annual	Contrast-enhanced MRI	Cutaneous and uterine leiomyomatomas Pheochromocytomas and paragangliomas
BAP1	≥16–18 years (uveal melanoma)	30 years	Annual	Contrast-enhanced MRI every 3 years alternating with ultrasound in the meantime	Uveal melanoma Melanoma Mesotheliomas
SDHB SDHA SDHC SDHD	≥6 years *SDHB* ≥10 years *SDHA/C/D*	6–10 years *SDHB* 10–15 years *SDHA/C/D* >30 years	2–3 years Annual	MRI every 2–3 years Ultrasound if familial RCC (unless MRI the same year)	Pheochromocytomas and paragangliomas Gastro intestinal stromal tumour Pituitary tumours
PTEN	≥10 years (thyroid cancer)	40 years	1–2 years	Ultrasound	Cutaneous lesions/Macrocephaly Thyroid cancer Breast Cancer Endometrial cancer Digestive polyposis Melanoma
TSC1 TSC2	As soon as possible	15 years	1–3 years	Ultrasound	Cutaneous lesions
		15–25 years	1–3 years	Contrast-enhanced MRI	Brain cortical dysplasia
		25 years	1–5 years	Contrast-enhanced MRI	Cardiac rhabdomyomas Lymphangioleiomyomatosis

PVs/LPVs confer a sufficiently increased risk for RCC to justify surveillance in carriers. The expert group also summarized follow-up recommendations for individuals carrying PVs/LPVs in these genes.

Unlike breast or colorectal cancer, definition of RCC-associated genetic risk has been hampered by limited data due to the rarity of the underlying syndromes. Prevalence data were scarce, except for the *MMR* and *FLCN* genes. Experts relied therefore on incidence data available in the literature and in the PREDIR database (unpublished data), recognizing the likely presence of bias due to over-representation of index cases with affected-relatives, probably leading to overestimation of cancer risk. Additional sources of evidence included family segregation studies and somatic data such as the presence of somatic variants, variants associated with loss of heterozygosity or loss of protein expression to support associations with RCC risk.

As a result, ten genes were identified as likely associated with an increased risk of RCC, although precise risk estimates remain uncertain: *BAP1*, *FH*, *FLCN*, *MET*, *PTEN*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *VHL*. The expert group also included *TSC1* and *TSC2* genes because they are associated with a high risk of angiomyolipomas, which are sometimes difficult to distinguish from renal cancer, as well as the high frequency of *de novo* mutations and the variable penetrance of other associated conditions.

Some predisposing syndromes, such as BHD syndrome and HLRCC, are now better understood. It is likely that genetic testing carried out in the context of non-renal clinical symptoms, such as isolated pneumothorax or fibrofolliculomas for *FLCN* gene or cutaneous or uterine leiomyomas for *FH* gene, will help identify more carriers and ultimately lead to refine estimates of RCC risk in these individuals.

Finally, GGC and PREDIR experts emphasized the need for systematic clinical data collection and long-term follow up focused on carcinologic events in patients carrying pathogenic variants in the selected genes. This will be essential for accurately assessing the risk of RCC in these rare diseases.

Apart from syndromic situations, the detection rate for germline PV is low in patients with suspected RCC hereditary predisposition. In cases with high suspicion for a syndromic form of the disease, multiple tumours and/or early onset RCC, tumour genetic analysis may be offered to rule out mosaicism. In addition, in cases of suspected translocation-associated RCC, germline chromosome abnormalities can be specifically searched by karyotyping, genome sequencing or long-read sequencing.

Moreover, a careful genetic counselling is recommended for all patients in order to obtain a comprehensive personal and family medical history, and to ensure that a predisposition to non-RCC cancers or to cancer predisposition syndromes in which RCC is not the primary concern will not be overlooked. This would justify testing a broader panel.

A periodic re-evaluation of this multi-gene panel is planned, including literature reviews of the evaluated genes and others that may emerge in the future as potential contributors to renal cancer predisposition.

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No data was used for the research described in the article.

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