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## Minors at risk of von Hippel-Lindau disease: 10 years' experience of predictive genetic testing and follow-up adherence

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1 **Title page**

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3 **Minors at risk of von Hippel-Lindau disease: 10 years ‘experience of predictive**  
4 **genetic testing and follow-up adherence**

5

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32

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34 **Abstract**

35 Von Hippel-Lindau (VHL) disease is one of the most common cancer predisposition  
36 syndromes. Penetrance is high with around 20% of children presenting detectable and  
37 curable manifestations of the disease at 15 years old. VHL predictive genetic testing  
38 (PGT) is recommended during childhood from age 5 years in France. Insufficient  
39 compliance to surveillance of VHL pathogenic variant (PV) carriers is associated with  
40 severe outcome. PGT experienced by children and their parents is probably critical in  
41 influencing future acceptance of the result and adherence to surveillance.

42 We conducted a retrospective study on minors tested (aged 5 to 16 years old) from 2010  
43 to 2020, in a multidisciplinary oncogenetics consultation which follows a 3-step protocol  
44 based on psychological familial support. The objectives were to assess the adherence to  
45 follow-up within the National Expert Center for inherited predispositions to renal tumors  
46 (PREDIR) network of *VHL* PV carriers and its benefit through tumor detection and  
47 medical interventions.

48 A VHL PGT was carried out in 34 children. Among the 16 children diagnosed as *VHL*  
49 PV carriers addressed to the PREDIR network, none had discontinued surveillance after  
50 a median of 41 months. Follow-up examinations detected 11 tumors in 6 children, 4 have  
51 been surgically treated. All had a favorable outcome.

52 Our data suggest that a specific and adapted procedure for PGT in at-risk VHL children  
53 as well as a follow-up, organized within a specialized expert network, fosters a complete  
54 adherence to the surveillance protocol and thus lead to a favorable clinical outcome.

55 **Keywords:** von Hippel-Lindau disease; predictive genetic testing in minors;  
56 psychological support; cancer predispositions; oncogenetics; multidisciplinary  
57 consultation

58

59 **Introduction**

60 von Hippel-Lindau (VHL) disease is a multisystemic familial cancer syndrome, with  
61 dominant inheritance, caused by heterozygous germline pathogenic variant (PV) in the  
62 *VHL* tumor suppressor gene. It represents one of the most common familial cancer  
63 syndromes with approximatively one carrier in 36,000 live births. VHL is implicated in  
64 multiple cellular processes, particularly in the cellular response to hypoxia, explaining  
65 the development of highly vascular tumors. VHL disease tumor spectrum comprises both  
66 benign and malignant tumors including hemangioblastomas of the central nervous system  
67 (CNS, 60-80%) mainly in the cerebellum, retinal hemangioblastomas (60%), clear-cell  
68 renal cell carcinomas (24-70%), renal cysts, phaeochromocytomas and paragangliomas  
69 (10-20%), pancreatic neuroendocrine tumors (8-17%), pancreatic cysts and serous  
70 cystadenomas (17-56%), endolymphatic sac tumors (ELST, 3-15%), epididymal  
71 papillary cystadenomas (25-60%) and broad ligament cystadenomas (very rare)<sup>1-3</sup>. VHL  
72 disease has a high penetrance assessed up to 87% at age 65, with 16% of asymptomatic  
73 and 11 % of symptomatic manifestations at 15 years old estimated on a cohort of 85  
74 Danish VHL patients undergoing surveillance<sup>4</sup>. VHL-related tumors have been  
75 exceptionally reported as early as 2 years of age<sup>5</sup>.

76 Before systematic medical surveillance the median survival of patients affected by VHL  
77 disease did not exceed 50 years of age<sup>1</sup>. Predictive genetic testing (PGT) identifies  
78 asymptomatic PV carriers who are eligible to a medical follow-up, with the aim of  
79 improving prognosis and overall survival, and non-PV carriers for whom surveillance is  
80 unnecessary. Due to the risk of tumors arising during childhood, VHL PGT is  
81 recommended from the age of 5 in France<sup>6</sup>. PGT in minors, defined as all subjects who  
82 have not reached the age of legal majority in health decisions, is allowed by the French

83 bioethics' legislation because VHL disease manifestations occurring in childhood can be  
84 effectively treated or prevented. VHL PGT is associated with an immediate medical  
85 benefit. Potential benefit of early detection of tumors outweighs the harms associated with  
86 the test. Parents or legal guardians should participate in the decision-making process  
87 regarding the health care of their children and are expected to decide to encounter the  
88 genetic test according to "the best interest of the child". Medical genetic units should  
89 take a supportive role in this process <sup>7</sup>. PGT in minors is challenging and requires an  
90 adaptation of genetic counselling and of parents' and children's support throughout the  
91 testing procedure. That procedure is critical for preparing the announcement of the result  
92 of the test as it would influence the proper understanding of the genetic data and, for PV  
93 carriers, the future adherence to medical preventive actions.

94 Families affected by VHL disease encounter psychological, social, and practical  
95 challenges, which can lead to an insufficient compliance to surveillance resulting in  
96 screening delays<sup>8,9</sup>. It has been shown that as many as 60% of identified *VHL* PV carriers  
97 were lost to follow-up 5 years after testing<sup>10</sup>, urging the need for solutions to improve  
98 adherence to surveillance protocols. The French guidelines recommended that a regular  
99 screening for asymptomatic PV carriers begins at 5 years old for retinal lesions and  
100 catecholamine-producing pheochromocytoma (PHEO) or paraganglioma by annual  
101 physical examination and blood pressure measurement, metanephrines measurements,  
102 dilated eye examination and abdominal ultrasonography (until 18 years old and then in  
103 alternance with abdominal MRI). This surveillance also comprises, biennially, an  
104 audiology assessment for searching ELST. A biennially cranial MRI for detecting CNS  
105 hemangioblastomas is performed from the age of 15, Ultrasound of the epididymis is now  
106 only performed in case of symptoms<sup>11</sup>.

107 Since 2010, the oncogenetics multidisciplinary consultation unit (Genetics department of  
108 European Georges Pompidou Hospital in Paris, France) follows a 3-step protocol for  
109 VHL PGT in minors, firstly developed and validated for children at risk of hereditary  
110 paraganglioma/ PHEO<sup>12</sup>. That consultation is the referral genetic unit for the PGT in  
111 minors at-risk of VHL disease of the National Expert Center for inherited predispositions  
112 to renal tumors (the PREDIR network, see <https://predir.org/>), which is in charge of the  
113 medical follow-up of VHL patients and of asymptomatic PV carriers. Herein, we evaluate  
114 the adherence to the surveillance proposed by the PREDIR network to minors after a  
115 positive PGT carried out with the 3-step protocol from 2010 to 2020 and the benefits of  
116 screening through tumor detection and medical intervention.



## 117 **Subjects and methods**

### 118 **Patients**

119 All minor subjects (age under 18 years old) addressed for VHL PGT at the Genetics  
120 department of the European Georges Pompidou Hospital (Paris, France) from 2010 to  
121 2020 were included in our retrospective study.

### 122 **Three-step protocol of PGT**

123 The complete procedure is drawn on Figure 1. The first step is a preparatory step, only  
124 addressed to the parents. During this step, parents receive information on genetic testing,  
125 on the PGT procedure and on the medical preventive actions that will be immediately  
126 recommended in case of a positive test. They first meet the geneticist (A-P.G-R) and  
127 subsequently the psychiatrist (K.L-L) who both provide support during the decision-  
128 making process and help for informing their child. For instance, parents can express their  
129 anxiety about the consequences of the genetic result on their child or, sometimes, their  
130 feeling of guilt about disease transmission. Parents are advised on how to best inform  
131 their child, in tailoring the information to their age-related capacities. The affected parent  
132 is encouraged to talk about his/her own disease and its hereditary transmission.  
133 Personalized advices are given to parents to find the best words for explaining the risk of  
134 transmission and the interest of prevention. An informative booklet written for children  
135 is given to parents as an information support  
136 (<https://www.vhlfrance.org/2018/10/26/vivre-avec-le-vhl/>). More than one preparatory  
137 consultation can be organized if necessary.

138 The second step, leading to the test, is organized when parents are ready to undertake the  
139 testing of their child, who has been properly informed and prepared. The child  
140 accompanied by his parents meet the geneticist and the psychiatrist during a combined

141 consultation. The correct understanding of the genetic test by the minor is checked and  
142 eventually the information is completed. Consent forms are delivered and explained by  
143 the geneticist, who then leaves the consultation room for allowing a dedicated  
144 consultation of both parents and the child with the psychiatrist. During this time,  
145 subjective feelings regarding the result of the genetic test are raised and potential  
146 emotional consequences following the result are anticipated. Lastly the child is seen alone  
147 by the psychiatrist, to give the child the possibility to express personal worries about the  
148 consequences of the genetic result. When the decision to undergo the test is taken, both  
149 parents and the minor if considered mature enough, sign the consent form for genetic  
150 testing in presence of the psychiatrist and blood is withdrawn subsequently.

151 The third step corresponds to the announcement of the genetic test result, by the geneticist  
152 to the minor and his/her parents, in presence of the psychiatrist. Afterwards the child is  
153 seen alone by the psychiatrist, then with his/her parents to provide all family members an  
154 opportunity to express together their immediate reaction to the result. Following a  
155 positive result, a subsequent consultation at the PREDIR reference center (Bicêtre  
156 Hospital, Le Kremlin-Bicêtre, France) is promptly organized. A specific attention is  
157 turned to close relations between the Genetics department and the PREDIR center to  
158 facilitate the booking of the first appointment with the PREDIR physician coordinator  
159 (S.R) who sees VHL at-risk minors in priority.

160 A multidisciplinary meeting between the geneticist and the psychiatrist is organized after  
161 each step of the protocol, in order to precisely prepare the next step. Throughout the whole  
162 procedure, parents and children have the possibility to benefit from additional  
163 consultations with the psychiatrist and/or the geneticist or to postpone appointments. One  
164 of the main objectives of the 3-step protocol is to prepare and to accompany parents and

165 children as best as possible throughout the PGT procedure and appropriately to possible  
166 life events, such as hospitalization of the affected parent, etc.

167 **Genetic testing**

168 Two blood samples are collected during the second step. Each blood sample is processed  
169 independently in order to deliver a single definitive result at the third step. Leucocyte  
170 DNA is extracted from the blood samples in the molecular genetic laboratory of the  
171 Genetics department of European Georges Pompidou Hospital (Paris, France). Targeted  
172 Sanger sequencing or MLPA (SALSA MLPA Probemix P016 VHL- MRC Holland) is  
173 performed for the detection of the VHL PV or of the large VHL deletion previously  
174 identified in the index case of every family.

175

176 **Follow-up of *VHL* PV carriers within the PREDIR network**

177 Our department is part of the PREDIR network, which comprises multiple specialists with  
178 specific skills in charge of establishing a diagnosis and optimizing monitoring and  
179 treatment of VHL patients and at-risk family members. It is composed of a reference  
180 center coordinated by the Bicêtre hospital at Assistance-Publique Hôpitaux de Paris and  
181 11 competence centers spread throughout France. All positive-tested children are  
182 addressed to a PREDIR center for explanation on the recommendations for an initial  
183 screening for VHL disease-related tumors and then an optimal VHL follow-up.  
184 Prescriptions for follow-up exams are sent prior to surveillance consultations. All children  
185 have a follow-up file updated regularly by the reference center and reminder letters are  
186 sent in case of delayed follow-up.

187 **Endpoints**

188 The adherence to medical follow-up has been evaluated with three different criteria: 1.  
189 consultation in the PREDIR center after the genetics result; 2. effective surveillance; 3.  
190 regularity of follow-up.

191 The surveillance benefits have been assessed on the number of lesions detected by follow-  
192 up screening exams and on medical outcome of at-risk VHL minors.

193 **Results**

194 **Population**

195 From 2010 to 2020, a total of 23 parents, from 21 different VHL families, came to  
196 oncogenetics consultation for asking a VHL PGT for their children (Figure 2). The  
197 protocol was stopped after the first step for 4 out of 23 parents. One mother was addressed  
198 to another genetic consultation in a French oversea department, where she lived, for  
199 organizing the PGT of their children. Three additional parents with difficult contexts did  
200 not pursue the procedure. One affected mother had discontinued her medical follow-up  
201 for 7 years when she came for the preparatory consultation. She was encouraged to restart  
202 her own surveillance before organizing the PGT for her child. One patient diagnosed for  
203 VHL disease only one year ago, came alone to receive information on PGT for their child  
204 and finally disagreed with the proposed 3-step protocol. One unaffected mother was still  
205 in mourning of her husband who died of the VHL disease in a context of bilateral renal  
206 cancer. Geneticist and psychiatrist recommended to take more time in order to be  
207 psychologically able to accompany her child during the PGT procedure. The procedure  
208 was thus pursued for 19 parents, from 18 unrelated families, for which the surveillance  
209 had been carried out within the PREDIR network (median of follow-up: 3 years, ranging  
210 from 0 to 19 years). Difficult familial contexts were also encountered among these latter,  
211 including two fathers that had lost their spouse of the VHL disease. Among the 36  
212 children in age of being tested within the families who went along with the procedure,  
213 two had not yet been tested. One was planned to benefit from the PGT during the year  
214 2021. The other, aged of 9 years in 2020, was in second position in the sibling but up to  
215 now his parents did not yet come back to genetic consultation.

216 Thirty-four asymptomatic children, with a median age of 8.5 years old (ranging from 5 to  
217 16), were genetically tested for VHL disease following the 3-step protocol. A positive  
218 VHL status was announced to 20 children (58.8%). Apart from four children that were  
219 living abroad, all the other children (n=16) were subsequently addressed to the PREDIR  
220 center that organized the first screening and then an annual follow-up. All children except  
221 one, who pursued her follow-up within a PREDIR regional competence center (Nantes,  
222 C.A), were followed by the PREDIR national expert center at Kremlin Bicêtre (S.R). All  
223 16 children were seen for a first consultation within the PREDIR center or network and/or  
224 realized a first follow-up exam in a median of one month (ranging from 0 to 10 months)  
225 after the announcement of the positive VHL result.

#### 226 **Adherence to follow-up protocol**

227 All at-risk children who received the result of their PGT before or in 2019 (n=13), pursued  
228 a regular follow-up within the PREDIR center or network. No child was lost to follow-  
229 up with at least one surveillance exam performed during 2020, or at the end of 2019 for  
230 one child. Two individuals tested carriers (patients #1 and #13) had reached adult age at  
231 last follow-up, notably the first child tested in 2010 aged 23 years old at last follow-up,  
232 who had been regularly followed for ten years. The median duration of follow-up of all  
233 16 children addressed to the PREDIR center, calculated from the date of the result of the  
234 genetic test and the last consultation/follow-up exam, was 41 months, ranging from 29  
235 days to 113 months.

#### 236 **Screening results**

237 Follow-up exams have detected 11 tumors (4 PHEO, 4 CNS and 2 retinal  
238 hemangioblastomas, 1 ELST) in 6 children (median age at diagnosis of the first  
239 syndromic tumor of 14.5 years, range 11 to 17) for a total of 687 person-months,

240 representing a theoretical detection of 192 tumors in a population of 1,000 *VHL* PV  
241 carriers followed during a year (Table 1). One child with a 3 cm PHEO had an abnormal  
242 level of metanephrines and the child with ELST had a loss of hearing. In addition,  
243 microcysts (size inferior to 1 cm) were detected in the epididymis (4 patients, at a median  
244 age of 12.5 years old), in the kidneys (2 patients, at age of 12 and 18, respectively) and in  
245 the pancreas (2 patients, at 17 and 18 of age, respectively). All detected tumors were in  
246 line with the expected tumor spectrum according to the affected parent's presumed VHL  
247 subtype (defined by mutation type and clinical manifestations, Table 1).

#### 248 **Medical outcome**

249 All PHEO and the ELST were surgically cured. Laser treatment was applied on the two  
250 detected retinal hemangioblastomas (V.K). Follow-up evaluation after surgery or laser  
251 treatment was normal. Tumor cell growths of the four CNS hemangioblastomas, as well  
252 as of microcysts, were followed regularly. All at-risk VHL children have experienced a  
253 favorable outcome and did not present any new lesions after the last follow-up.

254 **Discussion**

255 VHL is a potentially severe disease associated with premature deaths or severe disabilities  
256 in unscreened and unfollowed members of affected families. Parents, who are  
257 theoretically in favor of prevention by testing their child, face great difficulty in carrying  
258 it out in practice. They find it difficult to expose the hereditary disease during childhood,  
259 fearing to distress the child and harm his development. A supportive procedure to guide  
260 parents throughout the PGT of their children is thus required. Our procedure, based on a  
261 strong psychological familial support, was associated with a complete adherence to the  
262 surveillance protocol. Our genetics department had initially developed a 3-step  
263 multidisciplinary protocol for PGT in minors at risk of paraganglioma or PHEO in the  
264 early 2000s<sup>12</sup>. The procedure has progressively been improved with experience and was  
265 further applied, from 2010, in the PGT in minors at risk of VHL disease. This protocol  
266 was approved by the great majority of parents who came with the aim of testing their  
267 child and said to be reassured by the inclusion and the accompaniment throughout a well-  
268 defined procedure. It should be emphasized that the 3-step protocol was adaptive to each  
269 situation, with the possibility of organizing additional consultations with personalized  
270 advice, depending on the situation of the parent affected by the disease. The main  
271 objective was to ensure a long-life follow-up to PV carriers diagnosed during childhood.

272 The PREDIR network is in charge of French VHL families and patients (adults and  
273 children) as well as of the follow-up of asymptomatic *VHL* PV carriers detected by PGT.  
274 In that situation, the tumors detected by screening exams can benefit from an early  
275 minimal treatment, and /or scrupulous surveillance. These assumptions are in line with  
276 our data, in which all treated children by surgery or photocoagulation did not present new  
277 lesions at last follow-up without any therapeutic sequels. From our data, we have



278 estimated that in a theoretical population of 1,000 *VHL* PV carriers diagnosed and  
279 followed during childhood, 192 curable tumors would be detected, during one year of  
280 follow-up, highlighting the interest and the benefit of *VHL* PGT and subsequent regular  
281 follow-up in children. Furthermore, all detected tumors fell within the expected spectrum  
282 of their parent's presumed *VHL* subtype, suggesting a good match between the parent's  
283 and the child's phenotype, which could help guide management and genetic counselling.  
284 Nevertheless, current French surveillance guidelines do not distinguish between subtypes  
285 for the routine clinical management.

286 Rasmussen et al.<sup>10</sup> had tested individuals for *VHL* PV from 17 unrelated families  
287 including 43 children under the age of 18. Thirty-six individuals were tested positive in  
288 their study and after 5 years only 38.9% of PV carriers continued the tumor surveillance  
289 program. Among these individuals, 8 asymptomatic *VHL* positive children were  
290 diagnosed but only one child had pursued follow-up after five years (14.3%). A  
291 hemangioblastoma was diagnosed in one child that had discontinued follow-up five years  
292 after the test. For their PGT procedure, they used the same procedure for adults and  
293 children, with pre-test counseling including interviews with the geneticist, a social  
294 worker, and a clinical psychologist experienced in PGT. If significant distress was noted,  
295 a further evaluation was performed by an experienced psychiatrist and, if necessary, the  
296 test was postponed. All PV-carriers underwent an initial screening for *VHL* disease-  
297 related tumors and appointments were programmed annually by the social worker upon  
298 completion of the precedent screening. Although the follow-up time in our study was  
299 shorter, of about three and half years, the absence of *VHL* positive child lost to follow-  
300 up emphasizes the importance of a dedicated protocol to children for the PGT, different  
301 from the one of adults, as previously discussed in the literature<sup>14,15</sup>.

302 In agreement with our procedure, it has been recently reported that bibliotherapy using  
303 stories, such as our booklet intended for children, helping children understand inherited  
304 cancer predisposition syndromes, was useful for children aged 5-10 years old at risk of  
305 either Li-Fraumeni syndrome or hereditary PHEO and paraganglioma syndrome, by  
306 improving the process of communication between parents and children<sup>16</sup>.

307 A key value of our work is the validation of our 3-step protocol that can be applied by  
308 other multidisciplinary teams carrying PGT for children at risk of genetic predisposition.  
309 In our case, the protocol was conceived and developed jointly by the geneticist and the  
310 psychiatrist who had been working together for years, based on their experience. To date  
311 several French psychologists have been trained by our team and have integrated other  
312 multidisciplinary teams performing PGT for children according to a similar 3-step  
313 protocol, for different genetic predispositions such as inherited cardiomyopathies. A limit  
314 of our study was the impossibility to consider all parents that could have been referred to  
315 our consultation for the testing of their children but who did not come to our consultation.  
316 Difficult contexts were identified for all parents who did not pursue the PGT procedure  
317 for their child, underlining the importance of detecting this kind of context and possibly  
318 trying to improve the management in these cases. Nevertheless, similar difficult contexts  
319 were also encountered among parents who pursued the procedure. Moreover, all parents  
320 that pursued with our procedure went through the whole process without interruption.

321 In conclusion, our study demonstrates for the first time the benefits of VHL PGT during  
322 childhood, of a specific and adaptive procedure for organizing PGT in children at risk of  
323 VHL, of a follow-up organized within a well-defined specialized network for this rare  
324 predisposition to cancers. A longer follow-up period will be required to examine the  
325 continuation of follow-up during adulthood and the long-time clinical outcome of patients

326 identified as *VHL* PV carriers during their infancy. Finally, our data show that the 3-step  
327 protocol dedicated to PGT in children might be applied for other genetic predispositions.

328 **Data Availability**

329 The datasets generated during and/or analyzed during the current study are available  
330 from the corresponding author on reasonable request.

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### 378 **Author Contributions**

379 RV, KLL, MS, VK, TB, LA, NB, CA, SR, APGR: conceived and designed the work  
380 that led to the submission, acquired data, and played an important role in interpreting  
381 the results. Drafted or revised the manuscript. Approved the final version. Agreed to be  
382 accountable for all aspects of the work in ensuring that questions related to the accuracy  
383 or integrity of any part of the work are appropriately investigated and resolved.

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### 386 **Ethical Approval**

387 The research was approved by the AP-HP Centre Ethics Committee (IRB registration:  
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### 389 **Competing Interests**

390 The authors declare no competing interests.

391

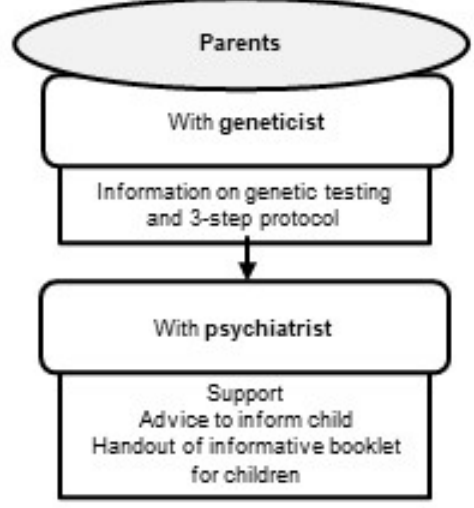
392 **Figure Legends**

393

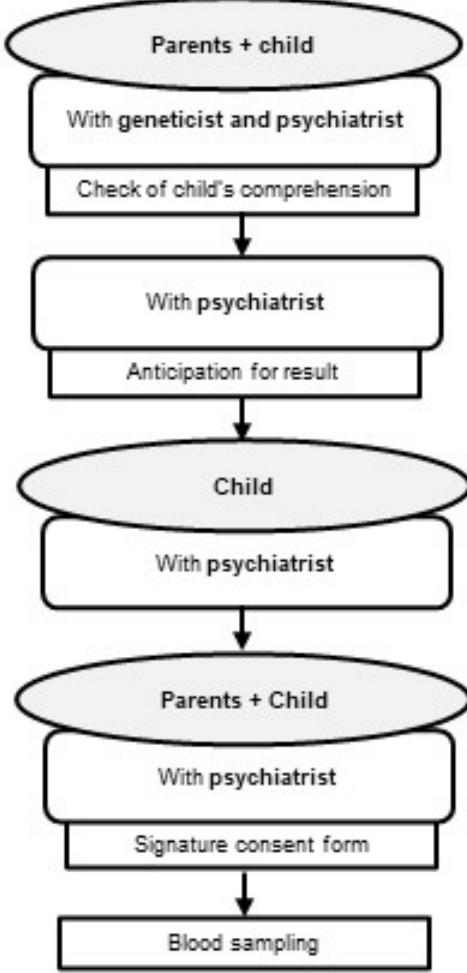
394 **Figure 1.** Design of the 3-step protocol for predictive genetic testing in minors at risk of  
395 Von Hippel-Lindau disease.

396 **Figure 2.** Predictive VHL genetic testing in minors within the oncogenetics  
397 multidisciplinary consultation unit of the European Georges Pompidou Hospital from  
398 2010 until 2020 and follow-up within the PREDIR network.

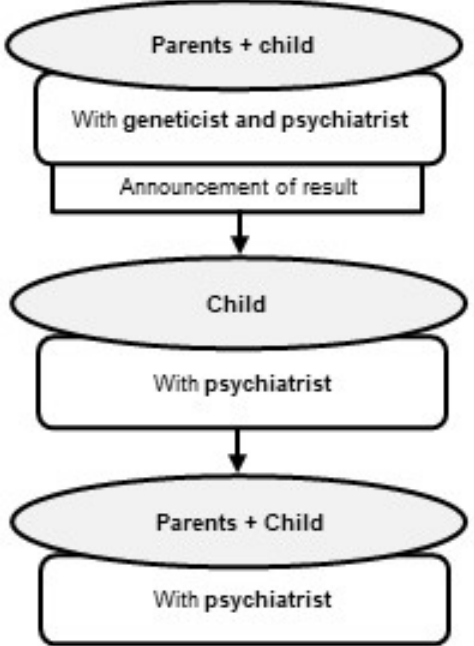
**1<sup>st</sup> step:  
Preparation**



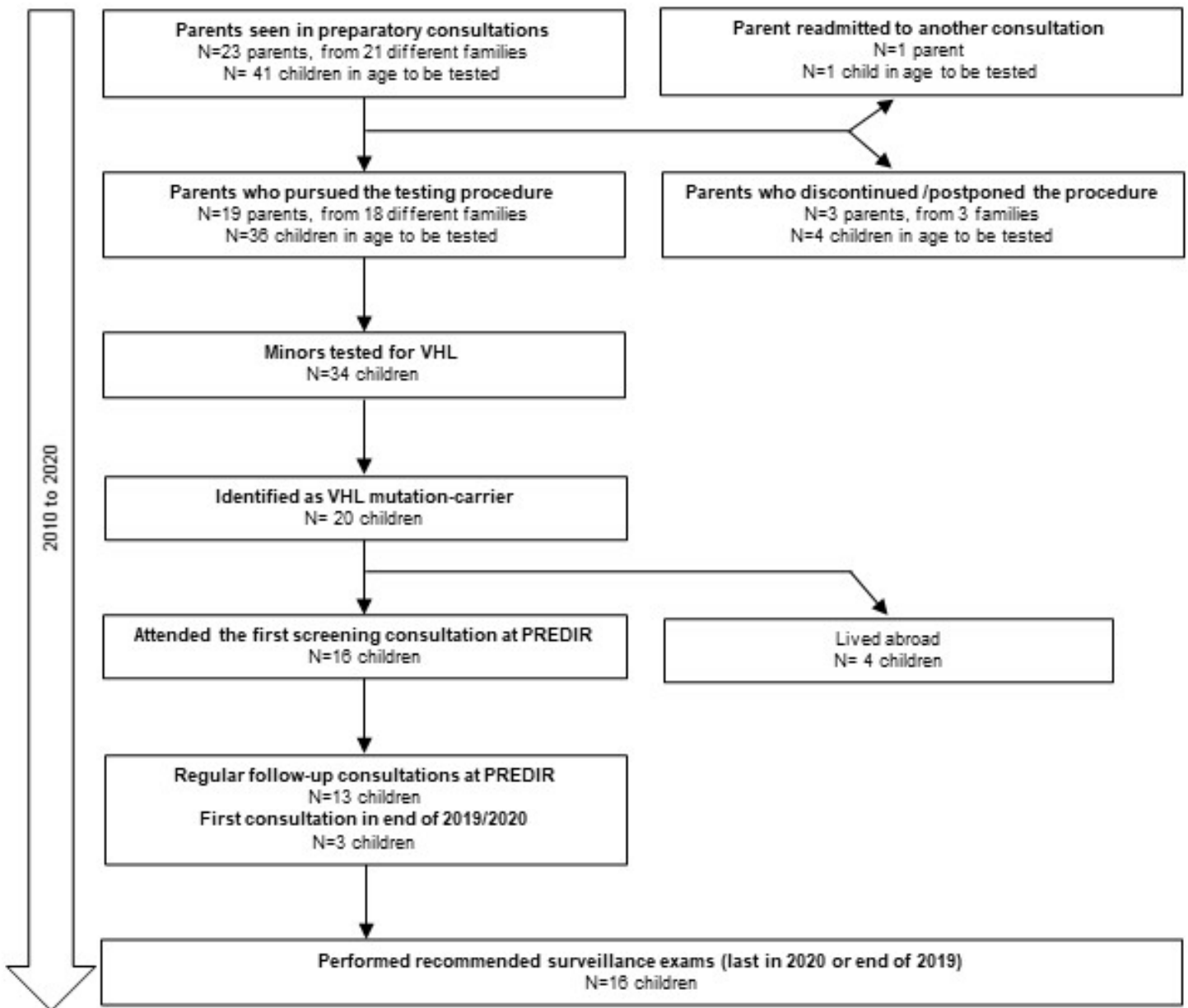
**2<sup>nd</sup> step:  
Genetic testing**



**3<sup>rd</sup> step:  
Announcement**







**Table 1.** Tumors detected during follow-up of the 20 tested carriers children and their outcome.

Patients 2, 7, 8 and 9 lived abroad and were not followed in France.

Parent's presumed VHL subtype is defined according to the type of mutation and clinical manifestations :

The following patients are siblings: 2 and 8 and 7 and 9 (same family); 3 and 14; 5 and 12; 6 and 11; 13 and 15

NA: not available; MRI: Magnetic resonance imaging; MN: metanephrine; NM: normetanephrine; PHEO:

Patient	Year of genetic testing	Type of mutation	Familial clinical manifestations	Parent's presumed VHL subtype	Age at genetic testing (year)	Follow-up duration (month)	Age at first syndromic tumor
1	2010	Missense	CNS HBs, RCC, renal cysts, epididymal cysts	Type I	13	113	-
2	2013	Nonsense	CNS HBs, endolymphatic sac tumor, retinal HBs RCC, pancreatic neuroendocrine tumor	Type I	8	NA	NA
3	2014	Gene deletion encompassing <i>VHL</i>	CNS HBs, PHEO	Type II	9	72	-
4	2014	Missense	CNS HBs, retinal HBs, RCC, PHEOs, pancreatic neuroendocrine tumor	Type IIB	8	62	11
5	2015	Missense	CNS HBs, retinal HBs, RCC, PHEOs, pancreatic neuroendocrine tumor	Type IIB	5	66	-
6	2015	Missense	CNS HBs, retinal HBs, PHEOs	Type II	10	67	16
7	2015	Nonsense	CNS HBs, endolymphatic sac tumor, retinal HBs RCC, pancreatic neuroendocrine tumor	Type I	12	NA	NA
8	2015	Nonsense	CNS HBs, endolymphatic sac tumor, retinal HBs RCC, pancreatic neuroendocrine tumor	Type I	6	NA	NA
9	2015	Nonsense	CNS HBs, endolymphatic sac tumor, retinal HBs RCC, pancreatic neuroendocrine tumor	Type I	5	NA	NA
10	2016	Missense	CNS HBs, endolymphatic sac tumor, retinal HBs, RCC, PHEO, pancreatic cysts	Type IIB	13	47	15
11	2016	Missense	CNS HBs, retinal HBs, PHEOs	Type II	7	42	11
12	2017	Missense	CNS HBs, retinal HBs, RCC, PHEOs, pancreatic neuroendocrine tumor	Type IIB	5	40	-
13	2017	<i>VHL</i> exon deletions	CNS HBs, retinal HBs, RCC, pancreatic cysts	Type I	16	43	17

## pancreatic cysts

14	2017	Gene deletion encompassing <i>VHL</i>	CNS HBs, PHEO	Type II	10	38	-
15	2017	<i>VHL</i> exon deletions	CNS HBs, RCC, pancreatic cysts	Type I	9	34	-
16	2017	Missense	CNS HBs, retinal HBs, RCC, pancreatic cysts	Type II	6	35	-
17	2018	Missense	PHEOs	Type IIC	5	23	-
18	2019	<i>VHL</i> exon deletions	CNS HBs, retinal HBs, pancreatic cysts	Type I	14	2	14
19	2019	<i>VHL</i> exon deletions	CNS HBs, retinal HBs, RCC, pancreatic cysts	Type I	15	3	-
20	2019	Missense	PHEO	Type IIC	6	0	-

according to the classification of Rednam et al.13.

rd 19.

pheochromocytoma; RCC: renal cell carcinoma; CNS: central nervous system; HB: hemangioblastoma

Tumor(s)	Age at diagnosis (year)	Tumor(s) size	Symptomatic at diagnosis	Treatment	Outcome	Cyst(s)	Age at diagnosis (year)	Cyst(s) size
-	-	-	-	-	-	Microcyst of the kidney	18	6 mm
-	-	-	-	-	-	Two cysts of the epididymis	18	1 and 2 mm
NA	NA	NA	NA	NA	NA	NA	NA	NA
-	-	-	-	-	-	-	-	-
PHEO	11	4 cm	No	Surgery	MRI and MN/NM normals 16 months after surgery Complete	Cyst of the epididymis	11	2 mm
Retinal HB	12	Small (no measure)	No	Photocoagulation	destruction at 16 months	-	-	-
-	-	-	-	-	-	-	-	-
Two simultaneous PHEOs of the left adrenal gland	16	2 cm and 1.5 cm	No	Surgery	Normalization of MN and NM levels 7 months after surgery	Five cysts of the epididymis	11	2 to 3 mm
NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA
Endolymphatic sac tumor	15	2 cm	Yes	Surgery	Asymptomatic and improved hearing at 24 months	Bilateral cysts of the epididymis Microcysts of the body and tail of the pancreas	14 17	< 5 mm ≤ 9 mm
PHEO	11	3 cm	Yes	Surgery	Asymptomatic 7 months after surgery	-	-	-
-	-	-	-	-	-	-	-	-
Brainstem HBs	17	4 mm and 6 mm	No	Surveillance	Small increase in size after 38 months	Pancreatic cyst	18	9 mm

