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SFE-AFCE-SFMN 2024 Consensus on primary hyperparathyroidism

## Chapter 5: The roles of genetics in primary hyperparathyroidism

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### ABSTRACT

Around 10% of cases of primary hyperparathyroidism are thought to be genetic in origin, some of which are part of a syndromic form such as multiple endocrine neoplasia types 1, 2A or 4 or hyperparathyroidism-jaw tumor syndrome, while the remainder are cases of isolated familial primary hyperparathyroidism. Recognition of these genetic forms is important to ensure appropriate management according to the gene and type of variant involved, but screening for a genetic cause is not justified in all patients presenting primary hyperparathyroidism. The indications for genetic analysis have made it possible to propose a decision tree that takes into account whether the presentation is familial or sporadic, syndromic or isolated, patient age, and histopathological type of parathyroid lesion. Thus, the first consensus recommendation is to propose genetic screening to any patient with a familial form of primary hyperparathyroidism ( $\geq 2$  1st or 2nd degree relatives) or in syndromic presentation or a sporadic isolated presentation if the patient is under 50 years of age, or over 50 with a recurrent or multi-glandular form, carcinoma, atypical parathyroid tumor and/or loss of parafibromin expression. The panel of genes currently recommended for first-line treatment comprises *MEN1*, *CDKN1B*, *CDC73*, *CASR*, *GNA11*, *AP2S1* and *GCM2*. Other genes may also be involved in familial primary hyperparathyroidism, but in a much more rarely and less consistently. The second recommendation is to propose genetic screening, up to and including whole-genome sequencing in the event of inconclusive panel analysis, to patients with proven familial primary hyperparathyroidism and/or pediatric onset. The role of the genetic practitioner is to interpret the sequencing data by categorizing the variants into 5 classes of pathogenicity. The aim of genetic analysis is to identify the genetic variant involved in the patient's phenotype, in order to make or refute a diagnosis of hereditary primary hyperparathyroidism, and to adapt management and monitoring. Appropriate genetic counseling should then be provided for patient and family.

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### 1. Introduction: genetic forms of primary hyperparathyroidism

Genetic causes of hyperparathyroidism account for up to 10% of cases of primary hyperparathyroidism (PHPT) encountered in routine practice [1], and are classified into:

- syndromic forms: multiple endocrine neoplasia type 1 (MEN1), type 2A (MEN2A), type 4 (MEN4) and hyperparathyroidism-jaw tumor (HPT-JT) syndrome;
- isolated forms: isolated familial hyperparathyroidism, severe neonatal primary hyperparathyroidism.

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These forms must be differentiated from familial hypercalcemia-hypocalciuria (FHH) and, exceptionally, from transient neonatal HPT.

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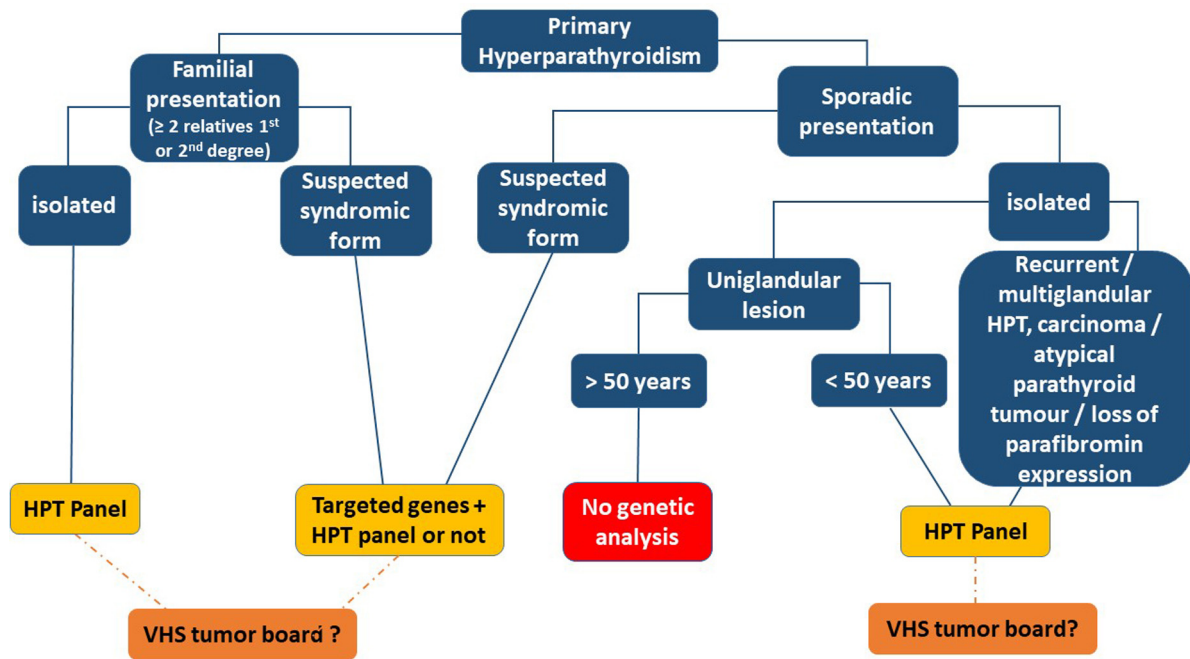


Fig. 1. Decision tree: indications of genetic analysis. HPT: hyperparathyroidism; VHS: very high sequencing tumor board.

## 2. Indications for genetic analysis

The majority of patients with hyperparathyroidism do not require genetic analysis. However, screening for genetic forms is useful not only for identifying affected relatives, but also for the index case itself. Management of patients with familial HPT differs from that of patients with sporadic HPT, and involves screening for associated lesions in the case of a genetic variant involved in a syndromic form.

Few studies have accurately assessed the cost-effectiveness of genetic analysis in an unselected population. In agreement with the French Association of Practitioners of Molecular Genetics (ANPGM), screening for a genetic form of PHPT may be recommended in the following cases (Fig. 1):

- personal and/or family history compatible with an existing syndrome (MEN1, MEN2A, MEN4, HPT-JT). Table 1 summarizes other manifestations that may be associated with syndromic presentations. In particular, patients and relatives should be screened for other endocrinopathies (medullary thyroid cancer, pituitary adenoma, duodeno-pancreatic neuroendocrine tumor, etc.) and lesions associated with the HPT-JT spectrum (jaw tumor, uterine tumor);
- family history compatible with isolated HPT (≥ 2 1st or 2nd degree relatives with PHPT);
- isolated case in a young subject. The age threshold is debated. The 5th International Workshop on HPT set the threshold at 30 or even 35 years of age [1,2]. In a study of 86 patients (age < 45) with isolated presentation, the results of genetic testing showed sequence variations in the predisposing genes in 8 subjects: 4 concerned the *MEN1* gene, 3 the *CASR* gene and 1 the *CDC73* gene [3]. The ANPGM and the Endocrine Tumor Group (GTE) recommendations concerning MEN1 recommend screening for all subjects with isolated PTH under 50 years of age [4]. In a retrospective analysis of a French series of 1258 patients, the mean age at genetic diagnosis for patients with a *CDC73* or *AP2S1* mutation was less than 30 years; it was 46 years for *MEN1* and over 50

years for *CASR* and *GCM2*, the latter being most often responsible for single adenoma-type presentations [5].

If the NGS (next-generation sequencing) panel including the known genes predisposing to hypercalcemia has been implemented (cf. Recommendation 1 below) and is considered non-contributory, and it is a familial form and/or with pediatric onset, then it should be discussed in the Plan France Médecine Génomique (PFMG) tumor board for whole-genome (WGS) very high-throughput sequencing (VHS) of a trio that usually includes the patient and his or her parents, wherever possible (see Recommendation no. 2). The prescriber informs the patient and family in advance of the possibility of sequencing, and must obtain their agreement for sampling and genetic analysis before presenting the file to the tumor board.

Phenotypically, certain presentations are more frequently associated with genetic forms:

- recurrent disease [6];
- multi-glandular involvement, including synchronous or metachronous parathyroid adenoma. Multi-glandular parathyroid involvement is frequently found in MEN1 and FHH;
- parathyroid carcinoma, suggestive of *CDC73* gene variant. There is no definite threshold for hypercalcemia, but parathyroid carcinoma is usually associated with severe hypercalcemia and very high parathyroid hormone concentration (> 500 pg/mL) [7,8]. Similarly, atypical parathyroid tumors or those with loss of parafibromin expression warrant screening for a constitutional variant of *CDC73*;
- hypercalcemia with low calciuria, suggestive of FHH. This differential diagnosis is described in Section 4 "Differential diagnosis".

In some forms of PHPT in which a genetic cause is suspected, molecular study may include a certain degree of emergency, especially in pregnant women or in case of severe hypercalcemia poorly responding to treatment, since genetic results may influence the type of surgery.

**Table 1**  
Specificity of genes involved in primary hyperparathyroidism.

Pathology	Gene	Genetic mechanism	HPT features	Other possible manifestations	Recommended screening age
Genes associated with syndromic presentations					
MEN1	<i>MEN1</i>	Tumor suppressor (AD)	Found in ~90% of MEN1 patients Multi-glandular HPT: hyperplasia/adenoma	Pancreatic NET (~60%), pituitary adenoma (~30–40%), adrenal NET, thymic NET, bronchial NET, etc.	From age 5
MEN2A	<i>RET</i>	Proto-oncogene (AD)	Found in ~20% of MEN2A patients PTH with adenoma/hyperplasia	Medullary thyroid carcinoma (~90–95%), pheochromocytoma (~50%)	Between 0 and 5 years depending on variant
MEN4	<i>CDKN1B</i>	Tumor suppressor (AD)	Multi-glandular HPT: adenoma with or without hyperplasia	Pituitary adenoma, other MEN1-like NETs	Adolescence?
HPT-JT	<i>CDC73 (ex-HRPT2)</i>	Tumor suppressor (AD)	Found in 80–90% of HPT-JT patients PHPT with single or multiple glandular involvement Increased predisposition to carcinoma	Maxillo-mandibular tumor (~30%), kidney lesions, uterine lesions	From age 5
Genes associated with isolated presentations					
FHH type 1	<i>CASR</i>	Calcium-sensing or signal transduction abnormalities (AD; AR)	Permanent elevation of calcium with FeCa $\leq$ 2% suggestive Hyperplasia	If homozygous or compound heterozygous form: severe neonatal HPT with severe osteoporosis, growth retardation	Possible from birth. To be adapted to context
FHH type 2	<i>GNA11</i>	Abnormal calcium-sensing or signal transduction (AD)			
FHH type 3	<i>AP2S1</i>	Abnormal calcium-sensing or signal transduction (AD)		Possible pancreatitis	
Isolated familial HPT	<i>GCM2</i>	Proto-oncogene (gain-of-function) (AD)	Frequently recurrent PHPT		Five years before the age of diagnosis of the index case

AD: autosomal dominant; AR: autosomal recessive; PHPT: primary hyperparathyroidism; NET: neuroendocrine tumor.

### 3. Genes involved

Genes studied in PHPT include those responsible for isolated PHPT and those associated with syndromic presentations, which may be incomplete. Depending on the patient's and family's history, *MEN1*, *CDKN1B*, *RET*, *CDC73*, *CASR*, *GNA11*, *AP2S1* and *GCM2* genes are investigated in first line, either targeted in case of syndromic presentation, or as part of a panel in isolated presentation. Pathologies are autosomal dominant, with except for neonatal forms. Newly described genes, such as *CDKN1A*, *CDKN2B*, *CDKN2C* and *PRUNE2*, can be explored as second-line targets.

#### 3.1. Genes associated with syndromic presentations

##### 3.1.1. *MEN1* gene

The *MEN1* gene is located at 11q13, is 10 kb in size and comprises 10 exons, 9 of which are coding [9]. It is a tumor suppressor gene responding to Knudson's tumorigenesis model [10,11]. It encodes menin, a 610-amino-acid, predominantly nuclear protein. This protein has numerous functions, including transcriptional regulation (differentiation, proliferation, cell cycle, apoptosis) and genome stability (replication, repair). These functions are carried out in a wide range of cell types (ubiquitous expression). This protein exerts its anti-oncogenic role notably by preventing nuclear translocation of  $\beta$ -catenin, blocking the Wnt/ $\beta$ -catenin signaling pathway [12]. To date, over 1300 sequence variants have been described at somatic and/or germline level, distributed throughout the coding part, with no real hot spots. According to the UMD-MEN1 database, the variants can be broken down as follows: missense variants (39% of cases), nonsense variants (9.2%), splice-site variants (9.2%), intronic variants (7.5%), small rearrangements (small insertions/deletions: 33%) and large deletions (2.1%) [13]. Deleterious or probably dele-

rious variants are reported in 90–95% of familial cases and 30–45% of sporadic presentations with the 3 major MEN1 disorders (parathyroid, pancreas, pituitary). Mosaic sequence variants in the *MEN1* gene may account for some cases [14,15].

##### 3.1.2. *CDC73* gene

The *CDC73* gene (homologous to yeast *Cdc73*), formerly named *HRPT2*, is responsible for HPT-JT. It is located at 1q31.2 and comprises 17 exons, with the coding region spanning 1593 bp. It encodes parafibromin, a 531-amino-acid protein. It is a tumor suppressor gene according to the Knudson model [10,11]. Parafibromin is a protein with a predominantly nuclear location (NLS domain in the N-terminal region) and ubiquitous expression. It acts as a transcriptional modulator of histone modifications, chromatin remodeling, initiation and elongation phases. It is part of a protein complex (PAF1) that binds to RNA polymerase. Its role is to modulate the Wnt and Notch intracellular signaling pathways, contributing to the regulation of major cellular functions: proliferation, differentiation, apoptosis and survival. Sequence deleterious variants of the *CDC73* gene in HPT-JT syndrome (120 currently listed) are inactivating: small deletions (a few nucleotides), nonsense or missense sequence variants, splice-site sequence variants, or small insertions. Complete deletions of the gene, or of a few exons, have also been reported [16].

##### 3.1.3. *RET* gene

The *RET* proto-oncogene, responsible for MEN2 [17], is located at 10q11 and encodes a receptor tyrosine kinase involved in the development and survival of neural crest-derived cells. Type 2 MEN results from variants in *RET*-activating sequences, essentially punctual, affecting 8 of the gene's 21 exons and leading to amino acid changes either in the extracellular cysteine-rich domain (exons 5, 8,

10 and 11) or in the intracytoplasmic tyrosine kinase domain (exons 13 to 16). Genotype-phenotype correlations have been reported. In MEN2A, exon 11 followed by exon 10 are the most frequently mutated, and in MEN2B, exon 16 followed by exon 15. In familial medullary thyroid cancer (FMTC), sequence variants concern exons 10, 11, 13, 14, 15 and 8 in order of frequency [18]. In MEN2, PHPT is only exceptionally present as an isolated disorder, and *RET* gene analysis is not recommended in isolated PHPT.

### 3.1.4. *CDKN1B* gene

The *CDKN1B* gene is located in 12p13. It comprises 3 exons, including 2 coding exons, and encodes the p27 protein<sup>kip1</sup> consisting of 198 amino acids [19]. This protein is a cyclin-dependent kinase inhibitor, negatively controlling the cell cycle and limiting the G1-S transition. The promoter of this gene is normally activated by *MEN1* in endocrine tissues to exert its tumor suppressor role [20]. Deleterious sequence variants lead to uncontrolled cell cycle progression. To date, some 30 *CDKN1B* variants have been identified as responsible for MEN4. PHPT and pituitary adenoma are the most frequently associated lesions in MEN4 [21].

## 3.2. Genes associated with isolated presentations

### 3.2.1. *CASR* gene

The *CASR* gene is located at 3q21.1 and codes for the calcium-sensitive receptor (CaSR), a G protein-coupled transmembrane receptor comprising 1078 amino acids. There is a low-abundance functional alternative transcript of 1088 amino acids. The gene comprises 7 exons, with the coding region spanning 3234 bp. Inactivating sequence variants of the *CASR* gene are responsible for FHH type 1, while activating sequence variations are responsible for autosomal dominant hypocalcemia type 1 [22,23].

To date, over 300 inactivating gene sequence variants have been characterized and are responsible for autosomal dominant FHH type 1, or autosomal recessive neonatal HPT.

### 3.2.2. *GNA11* gene

The *GNA11* gene is located at 19p13.3. and encodes the  $\alpha$ -subunit of the G protein<sub>11</sub>, one of the major G proteins activated by the CaSR pathway [24]. To date, only a few inactivating sequence variants have been described as responsible for type 2 FHH [23].

### 3.2.3. *AP2S1* gene

The *AP2S1* gene encodes the adaptor protein AP2  $\sigma$ -subunit, involved in CaSR endocytosis [25]. Three recurrent sequence variants, located on codon 15, which is the area of interaction between the protein and CaSR at the dileucine motif, have been implicated in type 3 FHH. Other sequence variants have more rarely been implicated [26].

### 3.2.4. *GCM2* gene

The *GCM2* gene is located on chromosome 6 (locus 6p24.2) and codes for the GCM2 transcription factor involved in parathyroid gland development and maintenance of PTH secretion [27]. *GCM2* inactivating sequence variants were initially described in association with familial hypoparathyroidism. It was only in 2016 that Guan et al. [28] identified activating sequence variants responsible for PHPT. These are mainly located in a conserved C-terminal inhibitory domain of the protein. Inheritance is autosomal dominant, but penetrance is incomplete [29].

## 3.3. Complementary genes

The *CDKN1A*, *CDKN2B* and *CDKN2C* genes encode the p21, p15 and p18 proteins, respectively. These genes, located at 6p21.2 (10,821 bp), 9p21.3 (6461 bp) and 1p32.3 (13,893 bp), comprise 3,

2 and 3 exons respectively, including 2 coding exons, and code for proteins of 164, 138 and 168 amino acids. They belong to the cyclin-dependent kinase inhibitor (CDKI) complex, and sequence variants, leading to cyclin D1 activation, have been implicated in various tumors, including parathyroid adenoma [30].

The *PRAD1* gene, which encodes cyclin D1, and other genes involved in cyclin D1 activation, such as *CCND1*, *CTNNB1*, *EZH2* or *ZFX*, could also be involved [30,31]. However, the involvement of these genes is exceptional, and they are not systematically included in diagnostic panels.

The *PRUNE2* gene, located on chromosome 9 at position 9.q21.2, is thought to be involved in cases of parathyroid carcinoma. This tumor suppressor gene inhibits the activity of RhoA, a Ras A homolog, by interfering with its protein binding. This reduces the formation of stress fibers and the oncogenic transformation of cells [32,33]. Sequence variants of this gene have been described in prostate cancer, but also in ovarian and thyroid cancer. Somatic sequence variants of *PRUNE2* have been found in parathyroid carcinoma, but also at germline level, associated with loss of heterozygosity of the other allele in the parathyroid tumor. Nevertheless, further studies are needed to determine whether this gene really does play a role in the genetic predisposition to parathyroid carcinoma.

The *TRPV6* gene (transient receptor potential cation channel, subfamily V, member 6) encodes a calcium channel expressed in numerous tissues, notably the placenta and pancreas. It is located at 7q34. Loss-of-function variants have been associated with transient neonatal forms of autosomal recessive HPT [34]. The phenotype includes prenatal skeletal dysplasia suggestive of mucopolysaccharidosis, resulting from defective mineralization of the fetal skeleton secondary to defective transplacental calcium transport. Biology and bone phenotype appear to correct spontaneously within 2 years of birth, without treatment. Heterozygous loss-of-function variants have also been reported in chronic non-alcoholic pancreatitis [35].

## 4. Interpretation of variants

The aim of genetic testing is to identify any genetic variant involved in the patient's phenotype, in order to make or refute a diagnosis of genetic disease, adapt management and propose an appropriate monitoring protocol, potentially including screening for syndromic lesions.

The test is interpreted by a practitioner approved by the French Biomedicine Agency (*Agence de la BioMédecine*), working in a laboratory authorized by the Regional Health Agency. It is based on analysis of the genetic examination and the information provided as part of the prescription.

Variants (relative to the reference genome) present in the genome of the individual are categorized in 5 classes of pathogenicity: benign variants (class 1), probably benign variants (class 2), variants of undetermined or uncertain significance (class 3), probably pathogenic variants (class 4), and pathogenic variants (class 5) [36].

To harmonize and improve this classification of variants, laboratories rely on guidelines from French scientific societies (ANPGM: *Association Nationale des Praticiens en Génétique Moléculaire* <https://anpgm.fr/>; ACLF: *Association des Cytogénééticiens de Langue Française*), international societies (HGVS: Human Genome Variant Society; ACMG-AMP: American College of Medical Genetics & the Association for Molecular Pathology), and specialized laboratory networks (INCa TENGEN network of laboratories specializing in endocrine tumor oncogenetics: <https://www.reseau-gte.org/tengen/>; NGS-DIAG network). The Rare Diseases and NGS-DIAG

networks proposed a consensus for standardized interpretation of sequence variants generated by NGS analysis ([https://anpgm.fr/media/documents/BP-NGSDiag\\_001\\_Interpretation.VentofMedd](https://anpgm.fr/media/documents/BP-NGSDiag_001_Interpretation.VentofMedd)). This consensus is mainly based on the ACMG-AMP classification grid published in 2015 [36]. Pathology-specific adaptations may be proposed by accredited practitioners [37].

In all cases, this classification is based on genomic data and the nature of the variant, literature data, locus-specific databases, epidemiological data (notably databases of variants identified in the general population, such as 1000genomes, ExAC, or gnomAD), analytical data and *in-silico* predictions, and also on personal and family anamnesis, and the segregation of the variant and the disease in the family. Each of these elements is assigned a weighting in favor of the pathogenic or benign nature of the variant. The weighted sum of these elements is used to classify variants into one of the 5 pathogenicity classes above.

Class 1 and 2 variants have no known clinical consequence and are not mentioned in the report. Class 4 and 5 variants have known clinical impact and must be reported so that the person tested can be informed by the prescribing physician when the result is reported. As the clinical consequences of class 3 variants are uncertain, this type of result may be mentioned in the report, specifying that it should not be used to guide management, and in particular that it should not be used for prenatal diagnosis or to inform relatives.

Complementary studies may be necessary in certain cases to reclassify the variant: genetic analysis of the individual's parents, to determine whether the variation is *de novo* or inherited, a family survey to look for cosegregation between genotype and phenotype (screening for the variant and phenotypic characterization of affected or unaffected major individuals in the family), *in vitro* functional analyses (sequencing of the transcript of interest, screening for loss of heterozygosity in a tumor, functional analyses on cell lines), or complementary phenotypic explorations (measurement of calcium excretion fraction, imaging to screen for a syndromic tumor form, dermatological examination). These additional studies are suggested by the approved practitioner, depending on the clinical situation, gene and variant and its presumed consequences at the time the result is delivered. They are particularly necessary in the case of class 3 variants of uncertain significance.

Knowledge in the field of genetics is constantly progressing and, as a result, the interpretation of results may change over time: new arguments may confirm the pathogenicity of a given variant, or invalidate it. Re-interpretation of data can be carried out at the request of the prescribing physician, and is particularly relevant for older interpretations.

## 5. Genetic counseling (including PND [prenatal diagnosis] and PGD [preimplantation genetic diagnosis])

As with all constitutional genetic analyses, genetic testing should be proposed in a dedicated consultation, explaining to the patient the interest of the test, both personally and for his or her relatives, and the implications for the management of his or her pathology if a probably pathogenic or pathogenic variant is identified. Patients should also be alerted to the limitations of genetic analysis: the possibility of identifying a variant of undetermined significance at the time of analysis, or of non-identification of a deleterious variant which, even so, does not necessarily call into question the hereditary nature of the pathology (French Order of May 27, 2013: recommendations of good practice for the examination of the genetic characteristics of persons for medical purposes).

The patient will then sign an informed consent form, specifying that he or she may interrupt the diagnostic process at any time, or refuse to be informed of the results. Under French bioethics law (Act n° 2021-1017 of August 02, 2021; Decree n° 2023-1426 of Decem-

ber 30, 2023), the patient signing the informed consent undertakes to pass on information to potentially concerned relatives in the event of the discovery of a genetic abnormality responsible for a predisposition to a serious disease.

The result of the genetic analysis must be transmitted by the prescribing physician in a dedicated consultation. In the event of identification of a deleterious variant responsible for PHPT, appropriate management and follow-up should be implemented. The age at which relatives can be screened depends on the age at which surveillance begins, according to the gene in question (Table 1). Screening consultations for asymptomatic relatives should be carried out as part of an individual consultation by a physician working as part of a multidisciplinary team dedicated to the care of asymptomatic patients.

In the event of inconclusive genetic analysis or identification of a variant of uncertain significance, further investigations or subsequent re-evaluation may be envisaged, following advances in knowledge or new technical possibilities.

Patients must be given information on the possibilities of prenatal diagnosis (PND) or preimplantation genetic diagnosis (PGD) and the related care pathway. Depending on the pathology, it does not seem legitimate to systematically propose these techniques, but rather to respond to a couple's requests, referring to existing recommendations where they exist. If necessary, a request can be made to the Multidisciplinary Center for Prenatal Diagnosis.

### RECOMMENDATIONS

**R1:** genetic screening should be proposed to any patient presenting a familial form of primary hyperparathyroidism ( $\geq 2$  relatives in the 1st or 2nd degree), or in a syndromic presentation, or a sporadic isolated form if the patient is under 50, or over 50 with a recurrent or multi-glandular form or an atypical parathyroid carcinoma or tumor and/or loss of parafibromin expression. The recommended first-line gene panel comprises *MEN1*, *CDKN1B*, *CDC73*, *CASR*, *GNA11*, *AP2S1* and *GCM2*.

**Grade A+++**

**R2:** patients with familial and/or pediatric onset primary hyperparathyroidism should be proposed genetic screening, up to and including whole-genome sequencing (WGS) in case of inconclusive panel analysis.

**Grade C+**

### Disclosure of interest

The authors declare that they have no competing interest.

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### Références

- [1] Minisola S, Arnold A, Belaya Z, Brandi ML, Clarke BL, Hannan FM, et al. Epidemiology, pathophysiology, and genetics of primary hyperparathyroidism. *J Bone Miner Res* 2022;37:2315–29. <http://dx.doi.org/10.1002/jbmr.4665>.
- [2] Bilezikian JP, Khan AA, Silverberg SJ, Fuleihan GE, Marcocci C, Minisola S, et al. Evaluation and management of primary hyperparathyroidism: summary statement and guidelines from the Fifth International Workshop. *J Bone Miner Res* 2022;37:2293–314. <http://dx.doi.org/10.1002/jbmr.4677>.
- [3] Starker LF, Åkerström T, Long WD, Delgado-Verdugo A, Donovan P, Udelsman P, et al. Frequent germ-line mutations of the *MEN1*, *CASR*, and *HRPT2/CDC73* genes in young patients with clinically non-familial primary hyperparathyroidism. *Horm Canc* 2012;3:44–51. <http://dx.doi.org/10.1007/s12672-011-0100-8>.
- [4] Goudet P, Cadiot G, Barlier A, Baudin E, Borson-Chazot F, Brunaud L, et al. French guidelines from the GTE, AFCE and ENDOCAN-RENATEN (Groupe d'étude des tumeurs endocrines/Association francophone de chirurgie endocrinienne/Réseau national de prise en charge des tumeurs endocrines) for the screening, diagnosis and management of multiple endocrine neoplasia type 1. *Ann Endocrinol (Paris)* 2023;85:2–19. <http://dx.doi.org/10.1016/j.ando.2023.09.003> [S0003-4266(23):00707-2].
- [5] Coppin L, Cuny T, Salim S, Le Bras M, Le Collen L, Guérin C, et al. Isolated primary hyperparathyroidism of genetic origin: lessons

- from a large French series. *Ann Endocrinol (Paris)* 2023;84:544–5, <http://dx.doi.org/10.1016/j.ando.2023.07.109>.
- [6] Park H-S, Lee YH, Hong N, Won D, Rhee Y. Germline mutations related to primary hyperparathyroidism identified by next-generation sequencing. *Front Endocrinol* 2022;13:853171, <http://dx.doi.org/10.3389/fendo.2022.853171>.
- [7] Quinn CE, Healy J, Lebastchi AH, Brown TC, Stein JE, Prasad, et al. Modern experience with aggressive parathyroid tumors in a high-volume New England referral center. *J Am Coll Surg* 2015;220:1054–62, <http://dx.doi.org/10.1016/j.jamcollsurg.2014.10.007>.
- [8] Marini F, Giusti F, Palmigni G, Perigli G, Santoro R, Brandi ML. Genetics and epigenetics of parathyroid carcinoma. *Front Endocrinol (Lausanne)* 2022;13:834362, <http://dx.doi.org/10.3389/fendo.2022.834362>.
- [9] Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 1997;276:404–7, <http://dx.doi.org/10.1126/science.276.5311.404>.
- [10] Knudson AG. Antioncogenes and human cancer. *Proc Natl Acad Sci U S A* 1993;90:10914–21, <http://dx.doi.org/10.1073/pnas.90.23.10914>.
- [11] Knudson AG. Two genetic hits (more or less) to cancer. *Nat Rev Cancer* 2001;1:157–62, <http://dx.doi.org/10.1038/35101031>.
- [12] Matkar S, Thiel A, Hua X. Menin: a scaffold protein that controls gene expression and cell signaling. *Trends Biochem Sci* 2013;38:394–402, <http://dx.doi.org/10.1016/j.tibs.2013.05.005>.
- [13] Romanet P, Mohamed A, Giraud S, Odou MF, North MO, Pertuit M, et al. UMD-MEN1 database: an overview of the 370 MEN1 variants present in 1676 patients from the French population. *J Clin Endocrinol Metab* 2019;104:753–64, <http://dx.doi.org/10.1210/jc.2018-01170>.
- [14] Coppin L, Giraud S, Pasmant E, Lagarde A, North MO, Le-Collen L, et al. Multiple endocrine neoplasia type 1 caused by mosaic mutation: clinical follow-up and genetic counseling? *Eur J Endocrinol* 2022;187:K1–6, <http://dx.doi.org/10.1530/EJE-22-0171>.
- [15] Nelakurti DD, Pappula AL, Rajasekaran S, Miles WO, Petreaca RC. Comprehensive analysis of MEN1 mutations and their role in cancer. *Cancers* 2020;12:2616, <http://dx.doi.org/10.3390/cancers12092616>.
- [16] Le Collen L, Barraud S, Braconnier A, Coppin L, Zachar D, Boulagnon C, et al. A large extended family with hyperparathyroidism-jaw tumor syndrome due to deletion of the third exon of CDC73: clinical and molecular features. *Endocrine* 2021;73:693–701, <http://dx.doi.org/10.1007/s12020-021-02756-4>.
- [17] Takahashi M, Buma Y, Iwamoto T, Inaguma Y, Ikeda H, Hiai H. Cloning and expression of the ret proto-oncogene encoding a tyrosine kinase with two potential transmembrane domains. *Oncogene* 1988;3:571–8 [PMID: 3078962].
- [18] Mulligan LM. RET revisited: expanding the oncogenic portfolio. *Nat Rev Cancer* 2014;14:173–86, <http://dx.doi.org/10.1038/nrc3680>.
- [19] Pellegata NS, Quintanilla-Martinez L, Siggelkow H, Samson E, Bink K, Hofler H, et al. Germ-line mutations in p27Kip1 cause a multiple endocrine neoplasia syndrome in rats and humans. *Proc Natl Acad Sci* 2006;103:15558–63, <http://dx.doi.org/10.1073/pnas.0603877103>.
- [20] Alrezk R, Hannah-Shmouni F, Stratakis CA. MEN4 and *CDKN1B* mutations: the latest of the MEN syndromes. *Endocr Relat Cancer* 2017;24:T195–208, <http://dx.doi.org/10.1530/ERC-17-0243>.
- [21] Chevalier B, Coppin L, Romanet P, Cuny T, Maiza JC, Abeillon J, et al. Beyond MEN1, when to think about MEN4? Retrospective study on 5600 patients in the French population & literature review. *J Clin Endocrinol Metab* 2024;109:e1482–93, <http://dx.doi.org/10.1210/clinem/dgae055>.
- [22] Brown EM. Mutations in the calcium-sensing receptor and their clinical implications. *Horm Res* 1997;48:199–208, <http://dx.doi.org/10.1159/000185516>.
- [23] Hannan FM, Kallay E, Chang W, Brandi ML, Thakker RV. The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. *Nat Rev Endocrinol* 2018;15:33–51, <http://dx.doi.org/10.1038/s41574-018-0115-0>.
- [24] Nesbit MA, Hannan FM, Howles SA, Babinsky VN, Head RA, Cranston T, et al. Mutations affecting G-protein subunit  $\alpha_{11}$  in hypercalcemia and hypocalcemia. *N Engl J Med* 2013;368:2476–86, <http://dx.doi.org/10.1056/NEJMoa1300253>.
- [25] Nesbit MA, Hannan FM, Howles SA, Reed AA, Cranston T, Thakker CE, et al. Mutations in *AP2S1* cause familial hypocalciuric hypercalcemia type 3. *Nat Genet* 2013;45:93–7, <http://dx.doi.org/10.1038/ng.2492>.
- [26] Gorvin CM, Metpally R, Stokes VJ, Hannan FM, Krishnamurthy SB, Overton JD, et al. Large-scale exome datasets reveal a new class of adaptor-related protein complex 2 sigma subunit (*AP2 $\sigma$* ) mutations, located at the interface with the *AP2* alpha subunit, that impair calcium-sensing receptor signalling. *Hum Mol Genet* 2018;27:901–11, <http://dx.doi.org/10.1093/hmg/ddy010>.
- [27] Günther T, Chen ZF, Kim J, Priemel M, Rueger JM, Amling M, et al. Genetic ablation of parathyroid glands reveals another source of parathyroid hormone. *Nature* 2000;406:199–203, <http://dx.doi.org/10.1038/35018111>.
- [28] Guan B, Welch JM, Sapp JC, Ling H, Li Y, Johnston JJ, et al. GCM2-activating mutations in familial isolated hyperparathyroidism. *Am J Hum Genet* 2016;99:1034–44, <http://dx.doi.org/10.1016/j.ajhg.2016.08.018>.
- [29] Coppin L, Dufosse M, Romanet P, Giraud S, North MO, Cardot Batters C, et al. Should the GCM2 gene be tested when screening for familial primary hyperparathyroidism? *Eur J Endocrinol* 2020;182:57–65, <http://dx.doi.org/10.1530/EJE-19-0641>.
- [30] Thakker RV. Genetics of parathyroid tumours. *J Intern Med* 2016;280:574–83, <http://dx.doi.org/10.1111/joim.12523>.
- [31] Arnold A. Major molecular genetic drivers in sporadic primary hyperparathyroidism. *Trans Am Clin Climatol Assoc* 2016;127:235–44.
- [32] Yu W, McPherson JR, Stevenson M, van Eijk R, Heng HL, Newey P, et al. Whole-exome sequencing studies of parathyroid carcinomas reveal novel PRUNE2 mutations, distinctive mutational spectra related to APOBEC-catalyzed DNA mutagenesis and mutational enrichment in kinases associated with cell migration and invasion. *J Clin Endocrinol Metab* 2015;100:E360–4, <http://dx.doi.org/10.1210/jc.2014-3238>.
- [33] Soh UJ, Low BC. BNIP2 extra long inhibits RhoA and cellular transformation by Lbc RhoGEF via its BCH domain. *J Cell Sci* 2008;121:1739–49, <http://dx.doi.org/10.1242/jcs.021774>.
- [34] Suzuki Y, Sawada H, Tokumasu T, Suzuki S, Ninomiya S, Shirai M, et al. Novel TRPV6 mutations in the spectrum of transient neonatal hyperparathyroidism. *J Physiol Sci* 2020;70:33, <http://dx.doi.org/10.1186/s12576-020-00761-2>.
- [35] Masamune A, Kotani H, Sörge FL, Chen JM, Hamada S, Sakaguchi R, et al. Variants that affect function of calcium channel TRPV6 are associated with early-onset chronic pancreatitis. *Gastroenterology* 2020;158:1626–41.e8, <http://dx.doi.org/10.1053/j.gastro.2020.01.005>.
- [36] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405–24, <http://dx.doi.org/10.1038/gim.2015.30>.
- [37] Romanet P, Odou MF, North MO, Saveanu A, Coppin L, Pasmant E, et al. Proposal of adjustments to the ACMG-AMP framework for the interpretation of MEN1 missense variants. *Hum Mutat* 2019;40:661–74, <http://dx.doi.org/10.1002/humu.23746>.