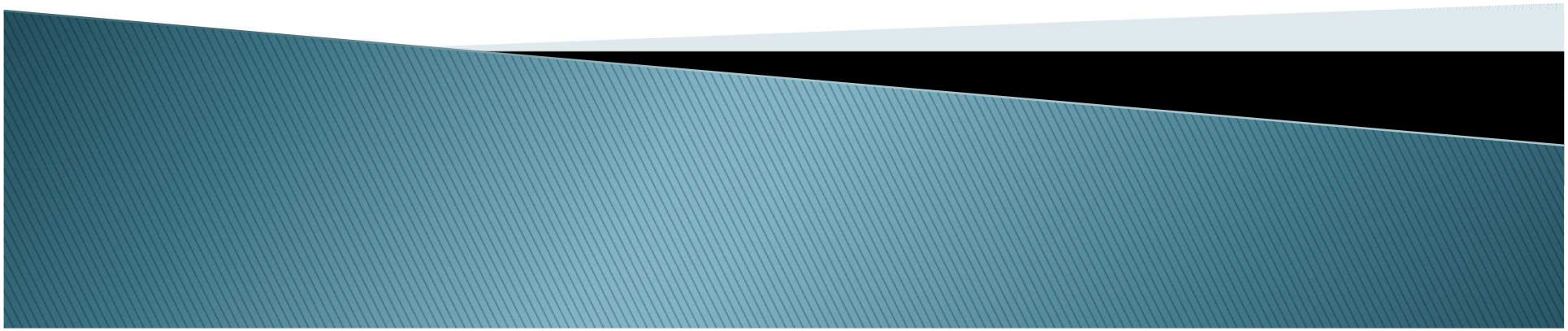
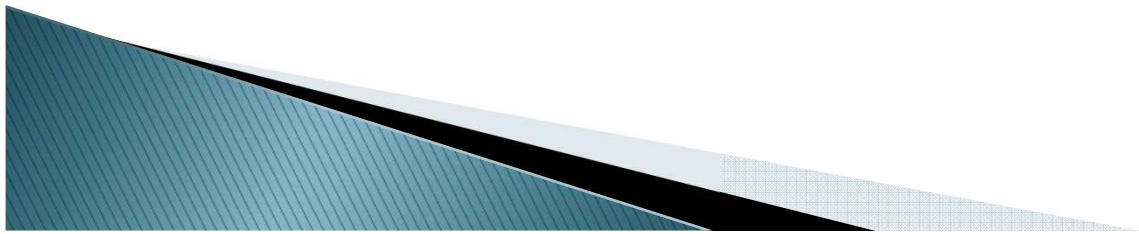
TNE et Tests Génétiques

Journée RENATEN
20/09/2019
I.MORTEMOUSQUE



Plan

- Les principales prédispositions aux TNE
  - Néoplasie Endocrinienne Multiple type 1: NEM1
  - Néoplasie Endocrinienne Multiple type 2 : NEM2
  - Prédispositions Paragangliomes et Phéochromocytomes : PGL et PHEO
  - Maladie de Von Hippel Lindau : VHL
  - Neurofibromatose de type 1 : NF1
- Les indications d'analyses génétiques
- La réalisation des tests génétiques



Les prédispositions aux TNE

- NEM 1
  - Rare : 3/100 000
  - Pénétrance élevée : 90% à 40 ans
  - Risques cumulés :
    - **Hyperparathyroïdie : 95 %**
    - Adénome pituitaire : 20 à 40 %
    - TNE pancréas/duodénum : 30 à 70 %
      (gastrinomes 40%, insulinomes 10%)
    - Tumeurs corticosurrénale : 40 %
    - Carcinoïde bronchique ou thymique : 5 %

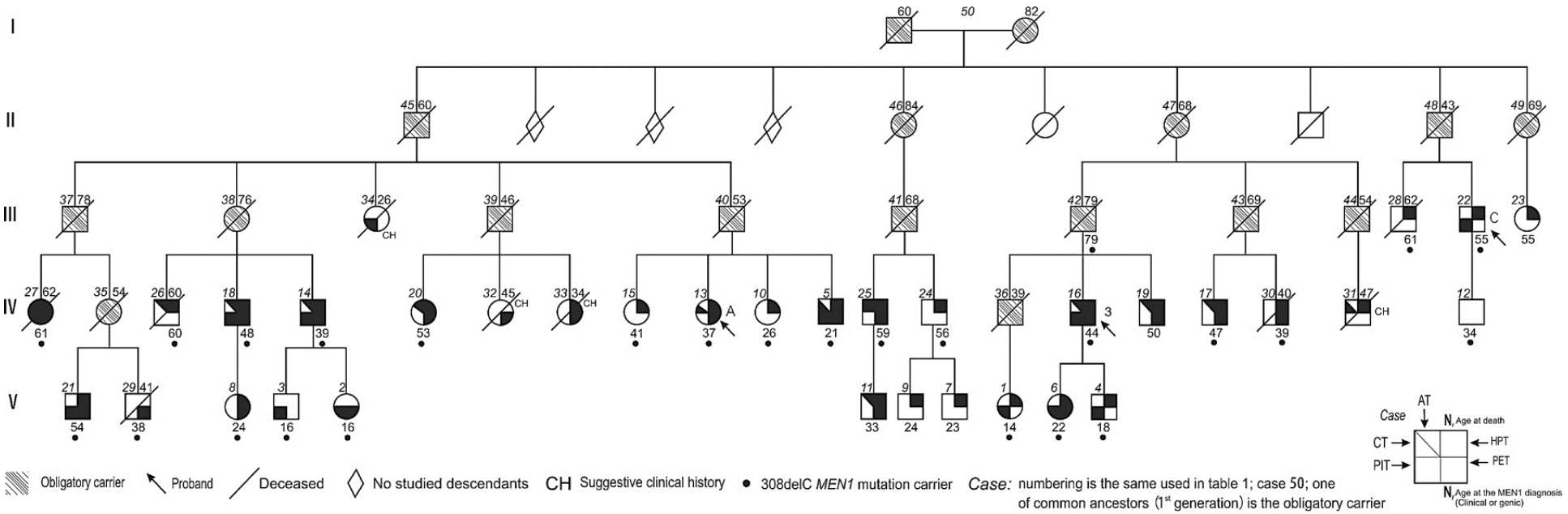
Les prédispositions aux TNE

- NEM 1
  - Gène *MEN1*, code pour la ménine
  - Mutation identifiée dans plus de 80% des cas
  - Mutation *de novo* : 10 %

  - Transmission autosomique dominante : probabilité de 50 % pour les apparentés du 1er degré
  - Expressivité variable même en intrafamilial
  - Surveillance dès 5 ans (adénome hypophysaire)

Les prédispositions aux TNE

- NEM 1



European Journal of Endocrinology (2008) 159 259–274 ISSN 0804-4643

CLINICAL STUDY

Multiple endocrine neoplasia type 1 in Brazil: *MEN1* founding mutation, clinical features, and bone mineral density profile

D M Lourenço Jr, R A Toledo, I I Mackowiak, F L Coutinho, M G Cavalcanti, J E M Correia-Deur, F Montenegro[1], S A C Siqueira[2], L C Margarido[3], M C Machado[4] and S P A Toledo

Unidade de Endocrinologia Genética, Laboratório de Investigação Médica (LIM 25), Endocrinologia, Faculdade de Medicina da Universidade de São Paulo (FMUSP), Av. Dr. Enéas de Carvalho, 455 – 5° Andar, Cerqueira Cesar, São Paulo 01246-903, SP, Brasil, [1]Departamento de Cirurgia de Cabeça e Pescoço da FMUSP, São Paulo, Brasil, [2]Departamento de Patologia Cirúrgica da FMUSP, São Paulo, Brasil, [3]Departamento de Dermatologia da FMUSP, São Paulo, Brasil and [4]Departamento de Cirurgia geral da FMUSP, São Paulo, Brasil

AT : adrenal tumor
HPT : hyperparathyroidism
PET : enteropancreatic endocrine tumor
CT : carcinoid tumor
PIT : pituitary adenoma

Les prédispositions aux TNE

- NEM 2
  - 1/35 000
  - Pénétrance élevée > 90%
  - Risques cumulés
    - **Carcinome médullaire de la thyroïde > 90 %**
    - Phéochromocytome : 50 %
    - Adénome parathyroïde : 20 %

Les prédispositions aux TNE

- NEM 2
  - Gène *RET*, proto-oncogène
  - Mutation identifiée dans plus de 98 % des cas
  - Mutation *de novo* : 5 %

  - Transmission autosomique dominante : probabilité de 50 %
  - Thyroïdectomie parfois très précoce, fonction de la mutation

Les prédisposition

- NEM 2
  - Prise en charge en fonction du type de mutation

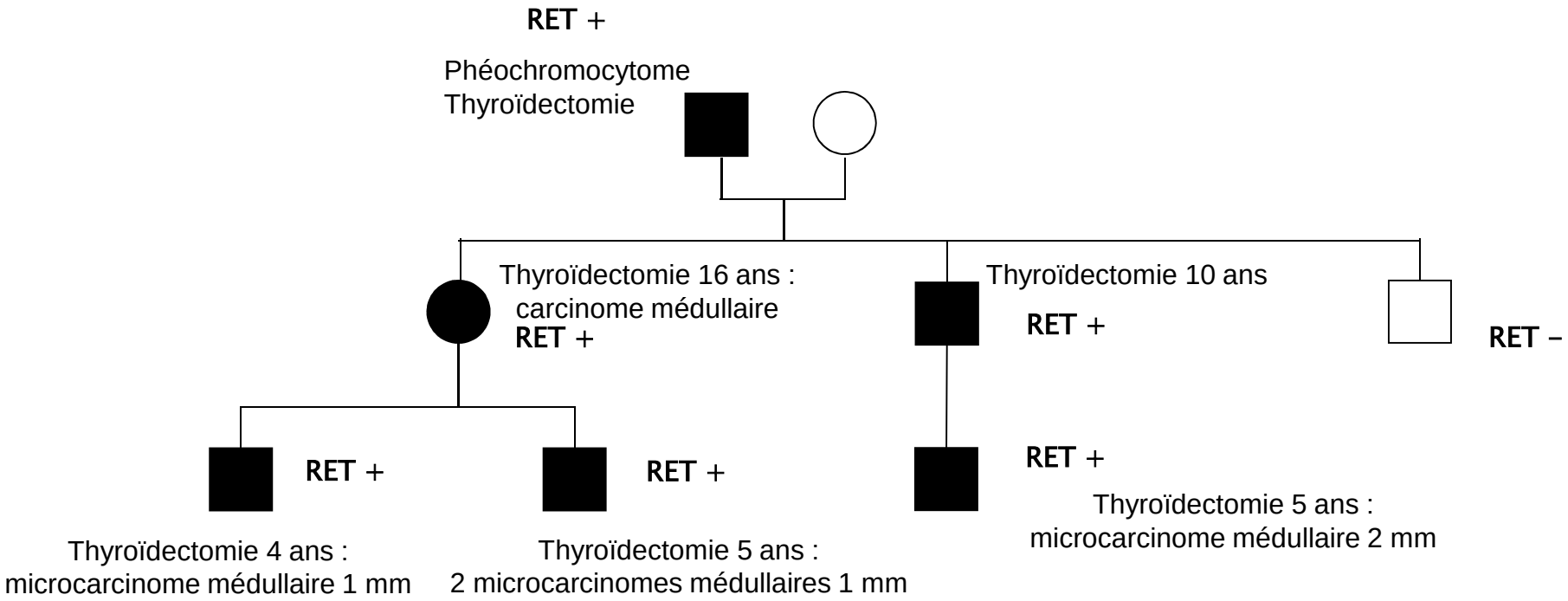
Table 3. Risk for Aggressive MTC Based on Genotype and Recommended Interventions

ATA Risk Level	Pathogenic Variants [1]	Age of Prophylactic Surgery	Age to Begin Screening	
			For PHEO	For HPT
Level D (highest risk)	p.Ala883Phe p.Met918Thr p.[Val804Met;Glu805Lys] [2] p.[Val804Met;Tyr806Cys] [2] p.[Val804Met];Ser904Cys] [2]	As soon as possible in 1st year of life	8 yrs	NA
Level C	p.Cys634Arg p.Cys634Gly p.Cys634Phe p.Cys634Ser p.Cys634Trp p.Cys634Tyr	<5 yrs	8 yrs	8 yrs
Level B	p.Cys609Phe p.Cys609Arg p.Cys609Gly p.Cys609Ser p.Cys609Tyr p.Cys611Arg p.Cys611Gly p.Cys611Phe p.Cys611Ser p.Cys611Trp p.Cys611Tyr p.Cys618Arg p.Cys618Gly p.Cys618Phe p.Cys618Ser p.Cys618Tyr p.Cys620Arg p.Cys620Gly p.Cys620Phe p.Cys620Ser p.Cys620Trp p.Cys620Tyr p.Cys630Arg p.Cys630Phe p.Cys630Ser p.Cys630Tyr p.Asp631Tyrp.Cys634_Thr636dup (p.633/9 bp dup [3]) p.Lys634_Arg635insHisGluLeuCys (p.634/12 bp dup [3]) p.[Val804Met;Val778Ile] [2]	Consider <5 yrs; may delay if criteria met [4]	Codon 630 pathogenic variant: 8 yrs All others: 20 yrs	Codon 630 pathogenic variant: 8 yrs All others: 20 yrs
Level A	p.Arg321Gly p.Glu529_Cys531dup (p.531/9 bp dup [3]) p.Gly532dup p.Cys515Ser p.Gly533Cys p.Arg600Gln p.Lys603Glu	May delay beyond age 5 yrs if criteria met [4]	20 yrs	20 yrs
	p.Tyr606Cys p.635/insert ELCR;p.Thr636Pro p.Lys666Glu p.Glu768Asp p.Asn777Ser p.Leu790Phe p.Val804Leu p.Val804Met p.Gly819Lys p.Arg833Cys p.Arg844Gln p.Arg866Trp p.Ser891Ala p.Arg912Pro			

4. Criteria: normal annual basal and or stimulated serum calcitonin; normal annual neck ultrasound examination; family history of less aggressive MTC

Les prédispositions aux TNE

- NEM 2



Les prédispositions aux TNE

- Prédisposition aux Paragangliomes et Phéochromocytomes

Table 2 Germline mutations implicated in the development of phaeochromocytoma/paraganglioma (PPGL)

Gene	Location	PPGL syndrome	Secretory Pattern (all may be non-secretory)
RET	10q11.21	Adrenal, frequently bilateral.	Adrenergic
VHL	3p25.3	Commonly adrenal, frequently bilateral. Occasionally extra-adrenal, may be malignant	Noradrenergic
NF1	17q11.2	Adrenal, may be bilateral	Adrenergic
SDHA	5p15.33	Rare, reports of extra-adrenal disease	Dopaminergic/Noradrenergic
SDHB	1p36.13	Adrenal or extra-adrenal disease (frequently abdominal), often malignant	Dopaminergic/Noradrenergic
SDHC	1q23.3	Rare; reports of adrenal and extra-adrenal disease. Occasional reports malignancy.	Dopaminergic/Noradrenergic
SDHD	11q23.1	Frequently head and neck PGL, also associated with adrenal disease	Dopaminergic/Noradrenergic
SDHAF2	11q12.2	Rare, reports of adrenal and extra-adrenal PPGL	Dopaminergic/Noradrenergic
MAX	14q23.3	Adrenal disease or extra-adrenal reported. May be malignant.	Noradrenergic/Adrenergic
TMEM127	2q11.2	Adrenal, rare reports of head and neck PGL	Adrenergic

50% NEM2A et 2B

10 à 20%

< 5%

When should genetic testing be performed in patients with neuroendocrine tumours?

Triona O'Shea[1] · Maralyn Druce[1]

Rev Endocr Metab Disord (2017) 18:499–515
DOI 10.1007/s11154-017-9430-3

Les prédispositions aux TNE

- Prédisposition aux Paragangliomes et Phéochromocytomes

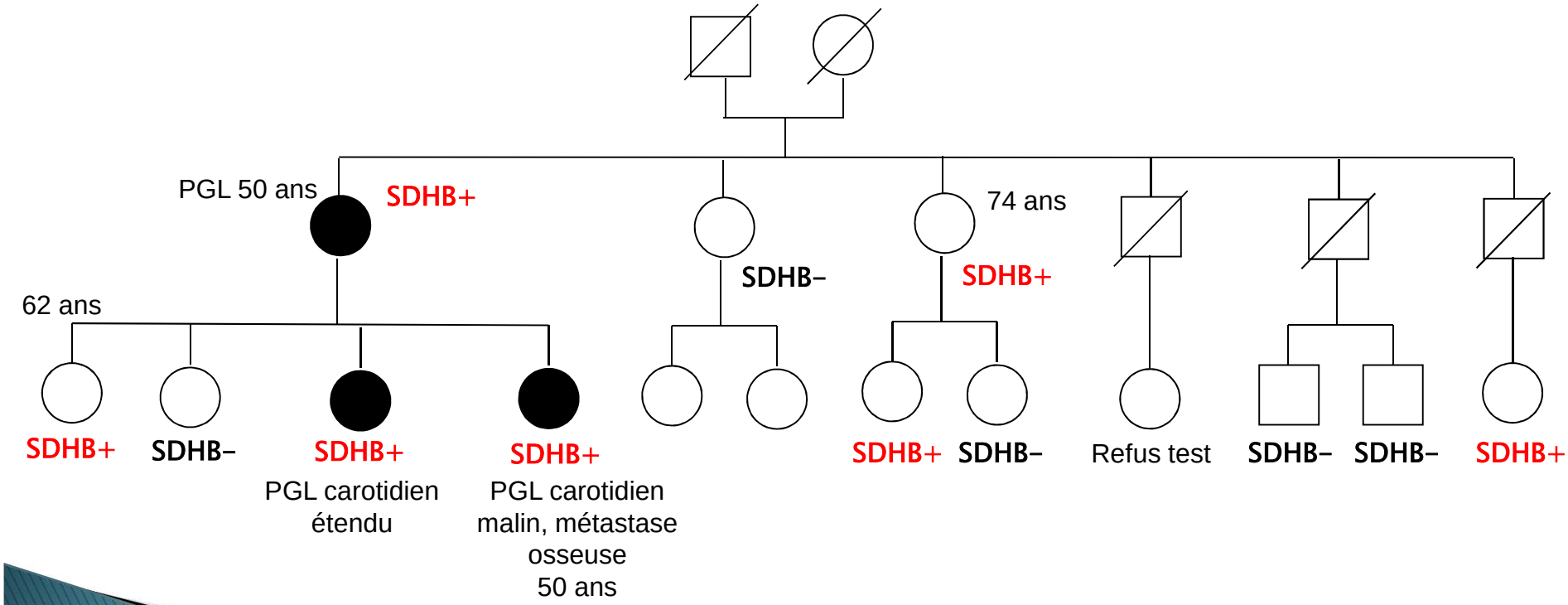
Table 1.

Molecular Genetic Testing Used in Hereditary Paraganglioma-Pheochromocytoma Syndromes

Gene [1, 2]	Proportion of Hereditary PGL/PCC Syndromes Attributed to Pathogenic Variants in This Gene
MAX	~1% [6]
SDHA	0.6%-3% [6, 9]
SDHAF2	<0.1% [6]
SDHB	12%-20% of HNPGL [13] 24%-44% of chest, abdomen, pelvic PGL/PCC [14]
SDHC	2%-8% [12, 14]
SDHD	~40%-50% of HNPGL [13] ~15% of chest, abdomen, pelvic PGL/PCC [14]
TMEM127	~2% [6]
Unknown [20]	

Les prédispositions aux TNE

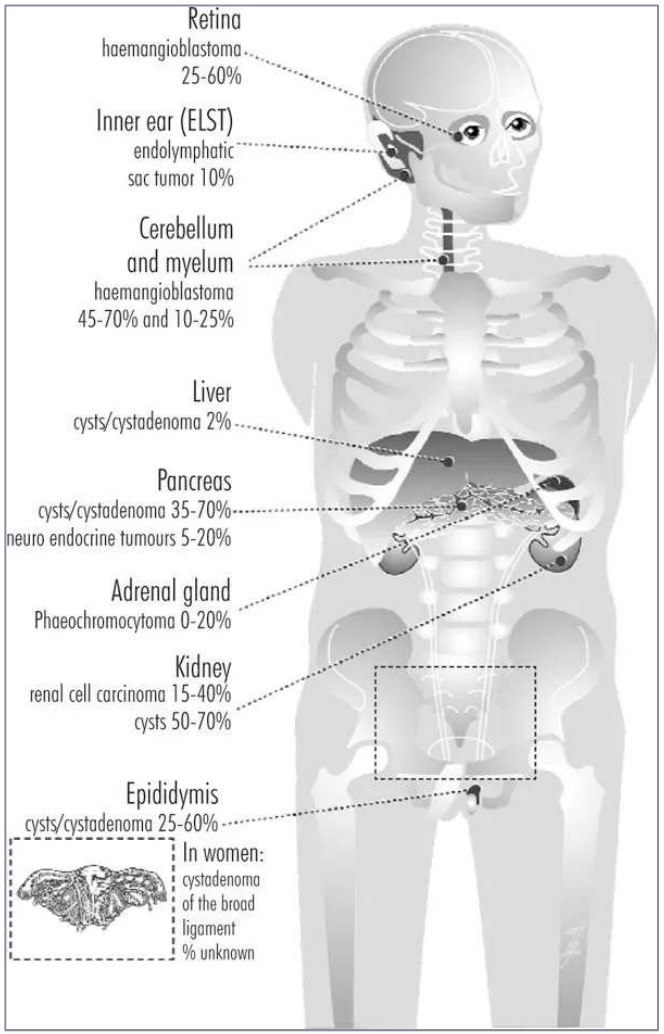
- Prédisposition aux Paragangliomes et Phéochromocytomes



Les prédispositions aux TNE

- VHL
  - 1/53 000
  - Pénétrance élevée > 80%

  - Gène *VHL*
  - Autosomique dominant
  - Mutation *de novo* 20%
  - Surveillance dès 5 ans



Von Hippel-Lindau Disease

Frederik J Hes, Jo WM Höppener, Rob B van der Luijt & Cornelis JM Lips

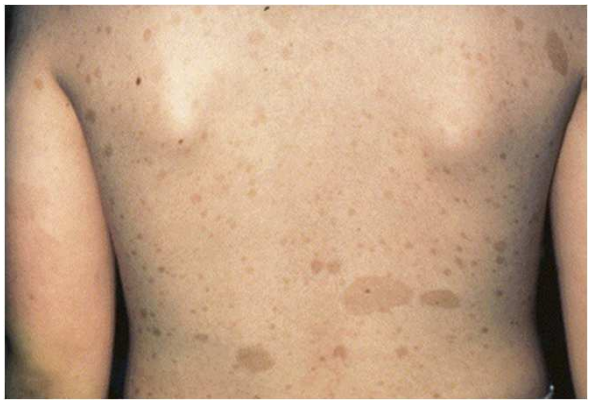
Hereditary Cancer in Clinical Practice **3**, Article number: 171 (2005)
2881 Accesses | **9** Citations

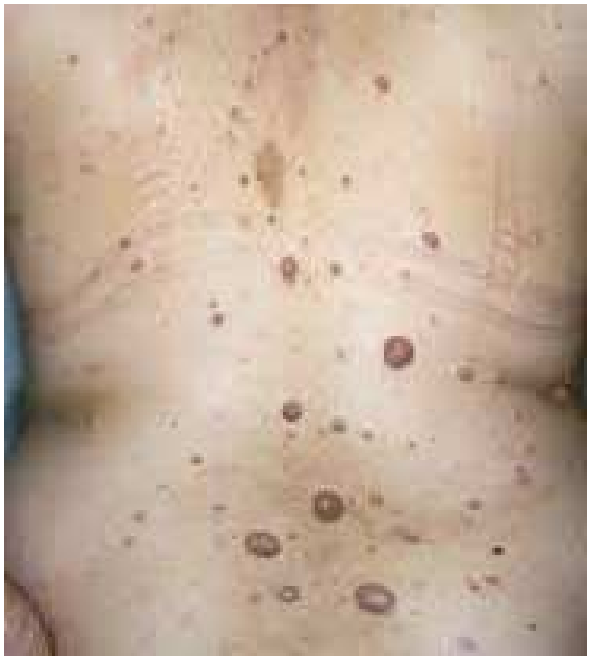
Les prédispositions aux TNE

- NF1
  - 1/3 000
  - Signes cutanés au 1er plan +++

• Sarcoma	
– Malignant Peripheral Nerve Sheath Tumor (MPNST)	10% lifetime risk
– Rhabdomyosarcoma	rare
– Angiosarcoma	rare
• Plexiform neurofibroma (benign)	common – 20-25%
• Gastrointestinal stromal tumor (WT GIST)	rare
• Pheochromocytoma	rare
• Astrocytoma	
– High-grade Astrocytoma (glioblastoma)	rare
– Optic nerve pathway tumor (low-grade)	common - ~15%
• JMML (jeuvenile myelomonocytic leukemia)	rare

  - Gène *NF1*
  - Autosomique dominant
  - Mutation *de novo* 50%

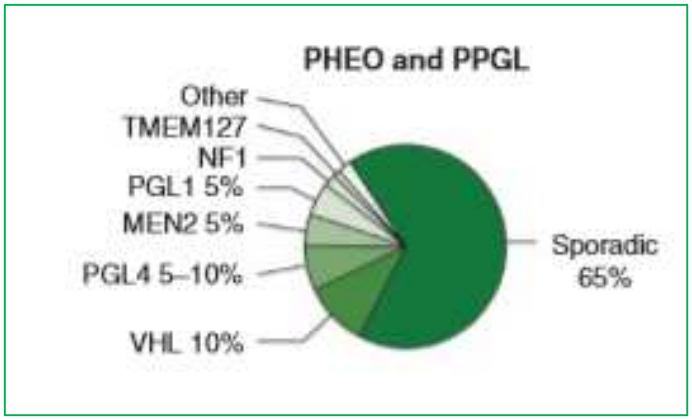




Les indications d'analyses génétiques

1) TOUT Phéochromocytome et Paragangliome même isolé

- 40 % de forme héréditaire
- Analyse en panel de gènes



GEP- NETS UPDATE
Genetics of neuroendocrine tumors
Joakim Crona and Britt Skogseid

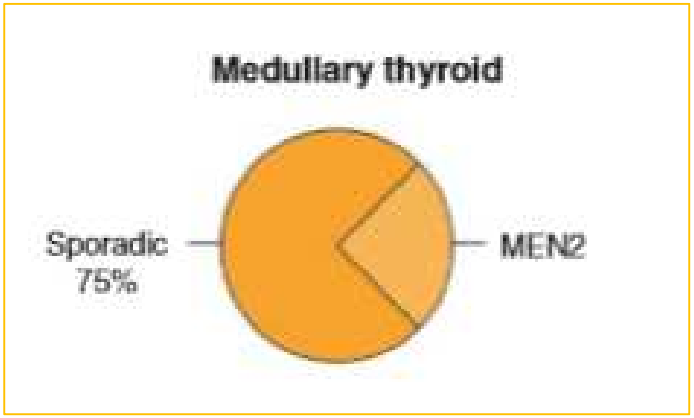
MAX
RET
SDHA
SDHAF2
SDHB
SDHC
SDHD
TMEM127
VHL

NF1 pas analysé systématiquement, importance de l'examen clinique

Les indications d'analyses génétiques

2) TOUT Carcinome Médullaire de la Thyroïde même isolé

- 35 % de forme héréditaire
- Analyse gène *RET*



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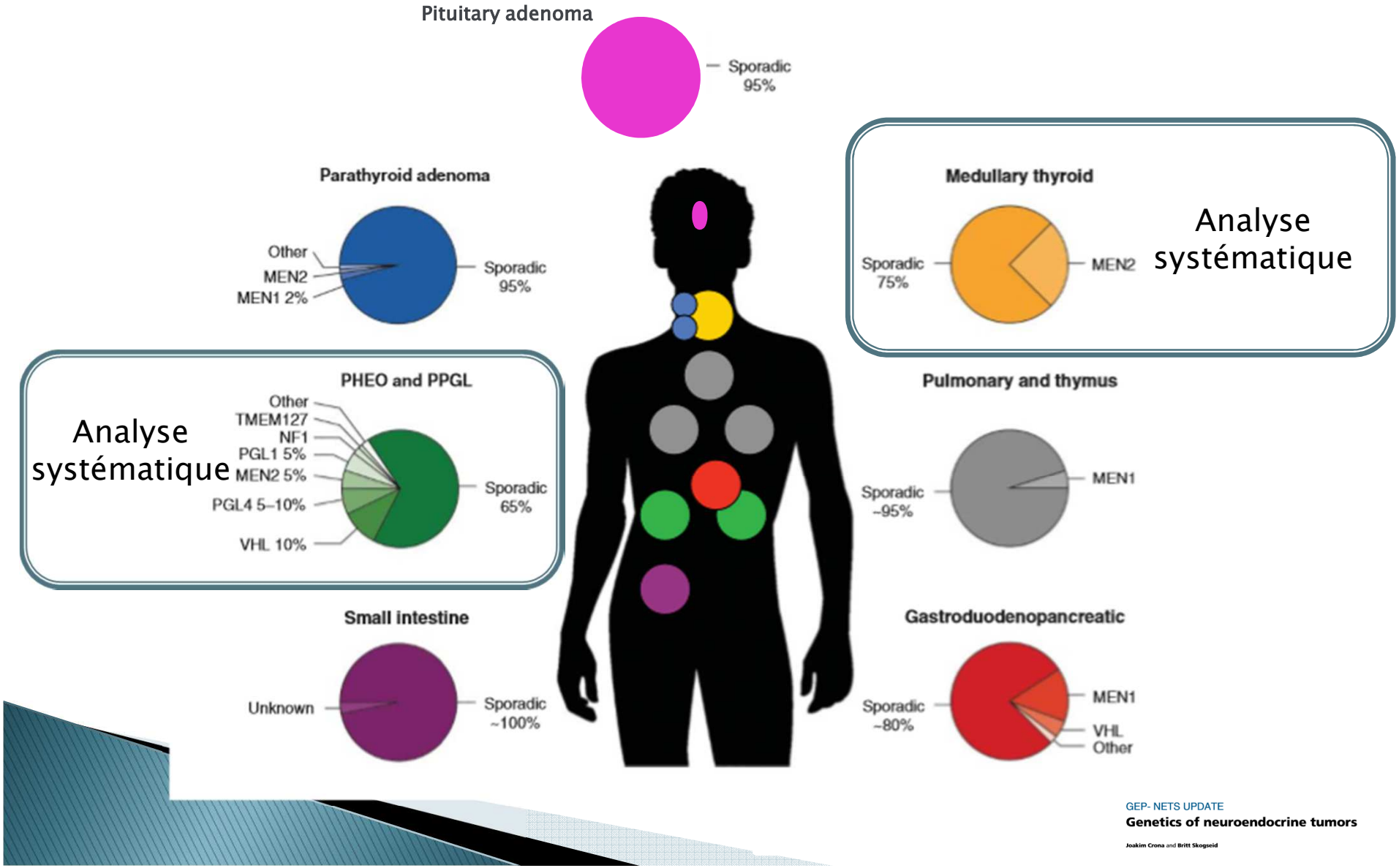
Les indications d'analyses génétiques



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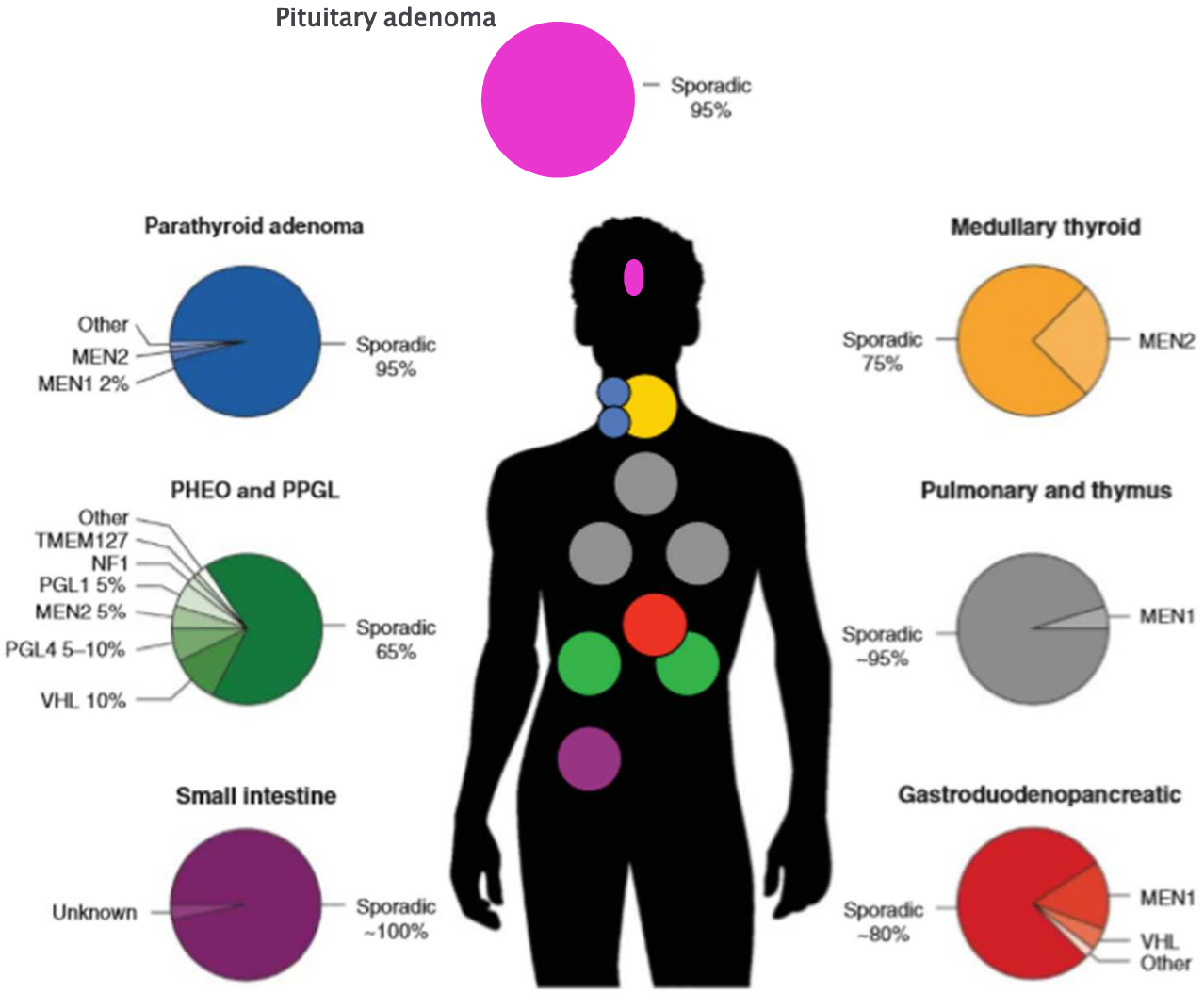
Les indications d'analyses génétiques

3) **Atteintes multiples**

- **Familiales**
- **Individuelles :**
  - TNE primaires multiples
  - TNE multifocale ou bilatérale

  - Atteintes autres : hémangioblastome, cancer du rein, signes cutanés, autres tumeurs, …

Les indications d'analyses génétiques



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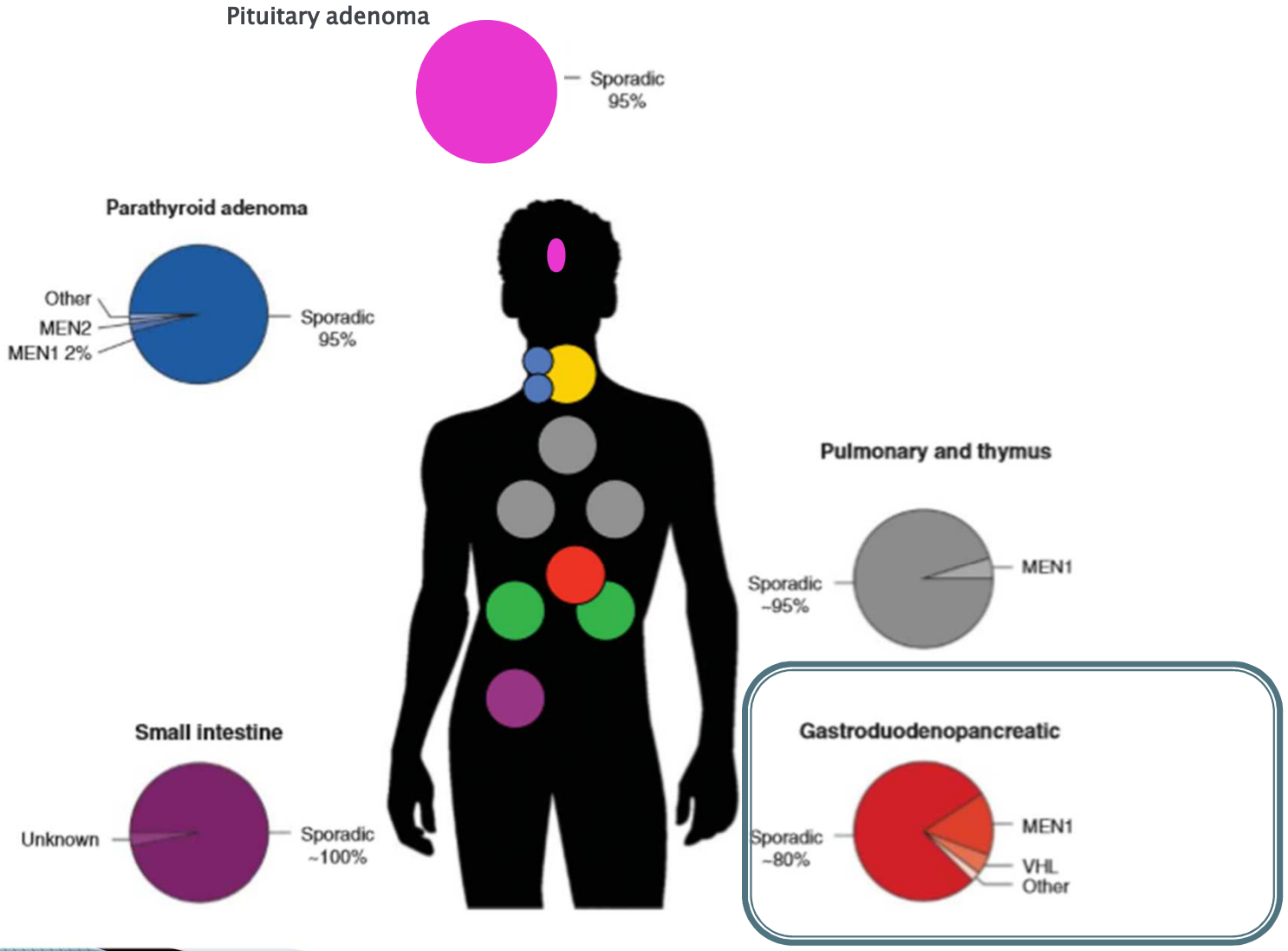
Les indications d'analyses génétiques

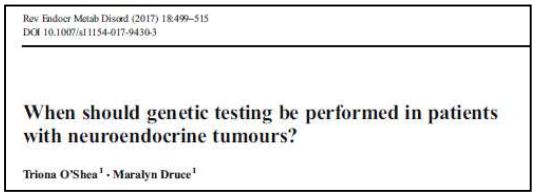


GEP- NETS UPDATE
Genetics of neuroendocrine tumors
Joakim Crona and Britt Skogseid

Les indications d'analyses génétiques

4) Tumeurs endocrines duodéno-pancréatiques

- Rechercher éléments personnels et familiaux évoquant NEM1, VHL, NF1
- Discussion analyse systématique :
  - TNE duodéno-pancréatiques multiples,
  - TNE < 40 ans (ou < 50 ans),
  - Gastrinome, notamment duodénal +++ pour NEM1


Rev Endocr Metab Disord (2017) 18:499–515
DOI 10.1007/s11154-017-9430-3

When should genetic testing be performed in patients with neuroendocrine tumours?

Triona O'Shea[1] · Maralyn Druce[1]


Oncologie (2013) 15: 515–519
© Springer-Verlag France 2013
DOI 10.1007/s10269-013-2330-6

Aspects génétiques des tumeurs neuroendocrines

Genetics of neuroendocrine tumors

V. Rohmer[1,2]

Les indications d'analyses génétiques

5) Adénome pituitaire

	MEN4
Pituitary adenoma	+
Parathyroid adenoma	+

Gène CDKN1B

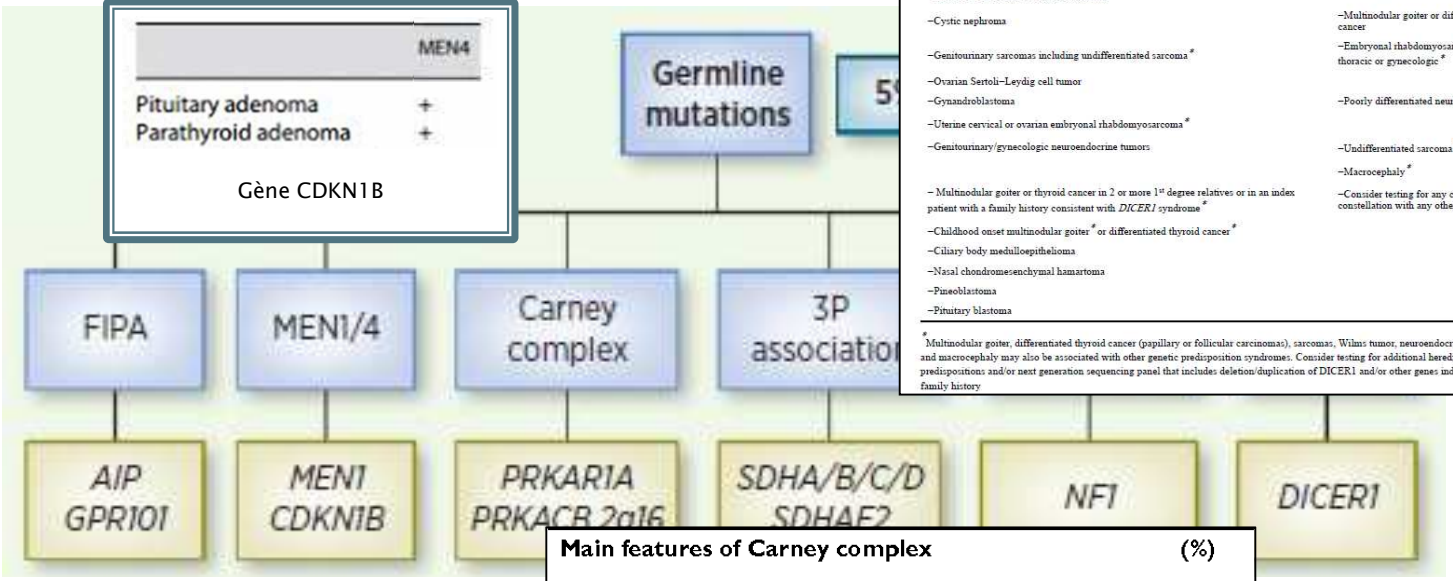


Table 1.

Indications for *DICER1* testing. Consider germline *DICER1* genetic testing in an individual with one major or two minor indications.

Major:	Minor:
–Individuals with PPB (all types)	–Lung cyst(s) in adults
–Lung cyst(s) in childhood, especially if multi–septated, multiple or bilateral	–Renal cyst(s) *
–Thoracic embryonal rhabdomyosarcoma *	–Wilms tumor
–Cystic nephroma	–Multinodular goiter or differentiated thyroid cancer
–Genitourinary sarcomas including undifferentiated sarcoma *	–Embryonal rhabdomyosarcoma other than thoracic or gynecologic *
–Ovarian Sertoli–Leydig cell tumor	
–Gynandroblastoma	–Poorly differentiated neuroendocrine tumor
–Uterine cervical or ovarian embryonal rhabdomyosarcoma *	
–Genitourinary/gynecologic neuroendocrine tumors	–Undifferentiated sarcoma *
	–Macrocephaly *
– Multinodular goiter or thyroid cancer in 2 or more 1st degree relatives or in an index patient with a family history consistent with *DICER1* syndrome *	–Consider testing for any childhood cancer in constellation with any other minor criteria
–Childhood onset multinodular goiter * or differentiated thyroid cancer *	
–Ciliary body medulloepithelioma	
–Nasal chondromesenchymal hamartoma	
–Pineoblastoma	
–Pituitary blastoma	

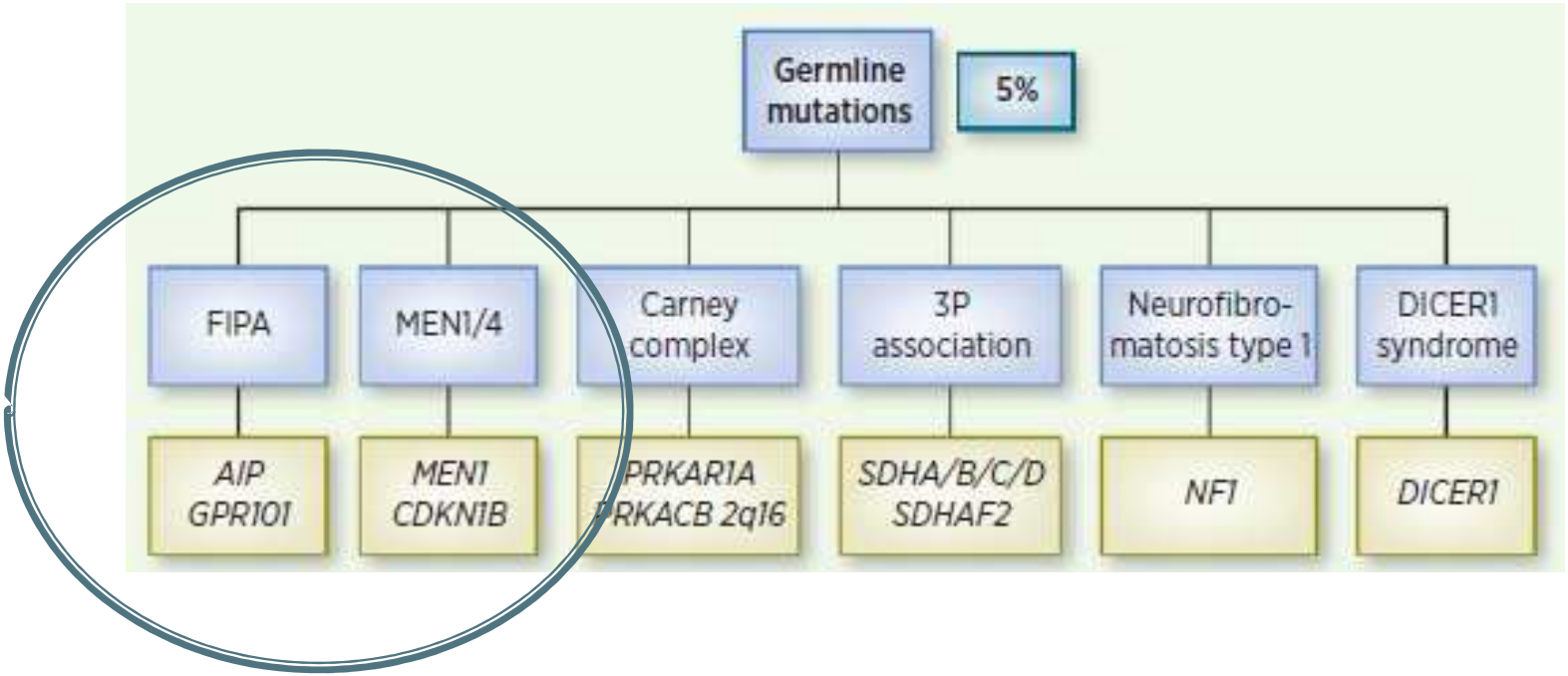
* Multinodular goiter, differentiated thyroid cancer (papillary or follicular carcinomas), sarcomas, Wilms tumor, neuroendocrine tumors, renal cysts and macrocephaly may also be associated with other genetic predisposition syndromes. Consider testing for additional hereditary cancer predispositions and/or next generation sequencing panel that includes deletion/duplication of DICER1 and/or other genes indicated by clinical and family history

Main features of Carney complex	(%)
Primary Pigmented Nodular Adrenocortical Disease (PPNAD)	25–60
Cardiac myxoma	30–60
Skin myxoma	20–63
Lentiginosis	60–70
Multiple blue nevus	
Breast ductal adenoma	25
Testicular tumors (LCCSCT: Large-Cell Calcifying Sertoli Cell Tumor) (in male)	33–56
Ovarian cyst (in female)	20–67
Acromegaly	10
Thyroid tumor	10–25
Melanotic schwannoma	8–18
Osteochondromyxoma	<10

Les indications d'analyses génétiques

5) Adénome pituitaire

Novel Genetic Causes of Pituitary Adenomas
Francisca Caimari and Márta Korbonits
Clin Cancer Res; 22(20) October 15, 2016

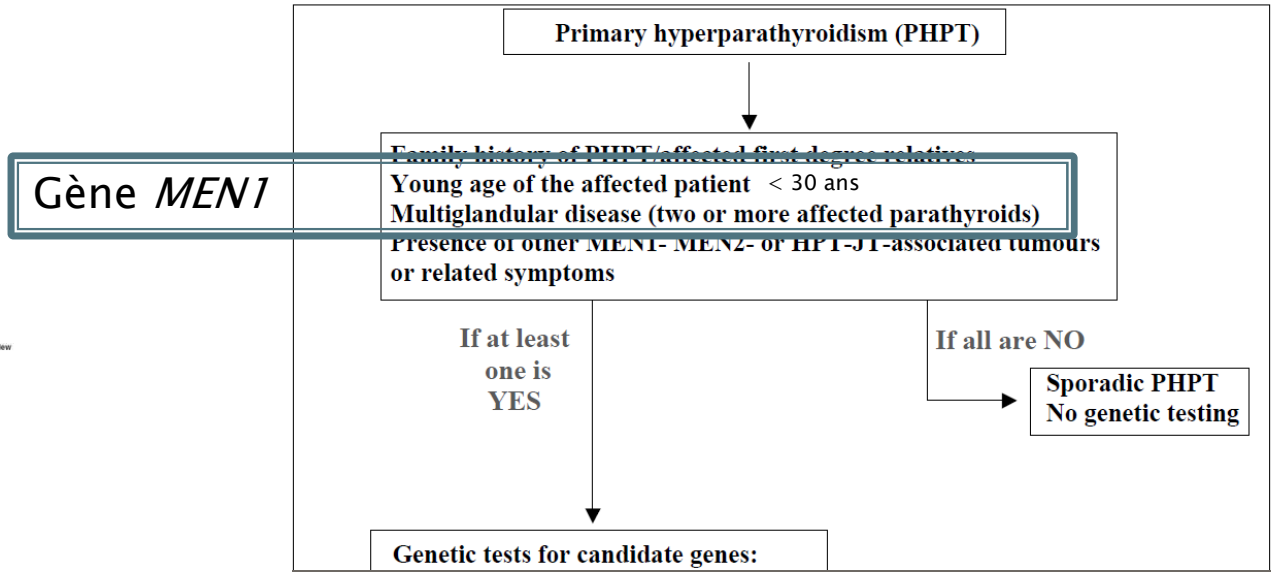


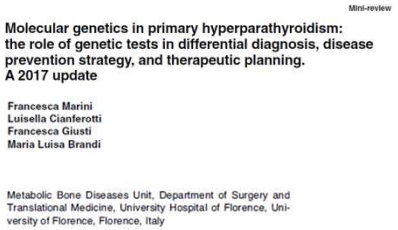
- Pourrait être inaugural
- Analyse AIP ou NEM1 à discuter sur adénome pituitaire isolé < 30 ans

Les indications d'analyses génétiques

6) Hyperparathyroïdie

- Rechercher éléments personnels et familiaux évoquant NEM1, NEM2, HRPT2 (hyperparathyroïdie familiale)




Mini-review

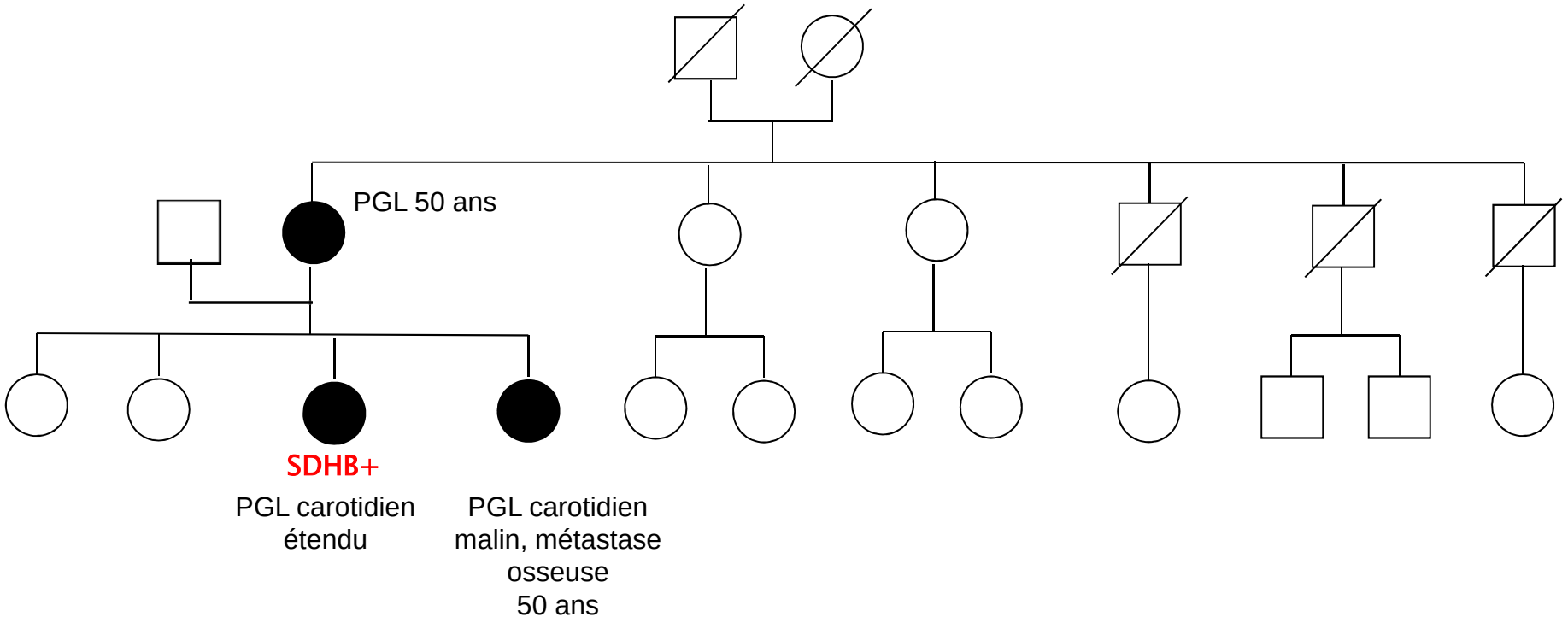
Molecular genetics in primary hyperparathyroidism: the role of genetic tests in differential diagnosis, disease prevention strategy, and therapeutic planning. A 2017 update

Francesca Marini
Luisella Cianferotti
Francesca Giusti
Maria Luisa Brandi

Metabolic Bone Diseases Unit, Department of Surgery and Translational Medicine, University Hospital of Florence, University of Florence, Florence, Italy

Les indications d'analyses génétiques

7) Mutation connue dans la famille



La réalisation des tests génétiques

- Consultation médicale individuelle dédiée
- Information détaillée
- Consentement signé

- Information de la parentèle : quasi-obligation de diffuser l'information
(si refus, responsabilité civile engagée)

La réalisation des tests génétiques

Test diagnostic	Test prédictif
Individu symptomatique Majeur ou mineur	Individu asymptomatique Majeur (ou mineur si intérêt directe dans le suivi)
Peut être prescrit par tout médecin ds le cadre d'une consultation médicale dédiée	Prescrit par un médecin ds le cadre d'une équipe pluridisciplinaire Cs psychologue +++ Délai de réflexion

Au total

- Indications classiques bien connues
- Importance de l'examen clinique et de l'histoire personnelle et familiale, de bilan paraclinique éventuel
- Emergence de panel de gène facilitant les explorations
- Consultation d'oncogénétique :
  - Pour les situations inhabituelles à explorer,
  - Pour les tests ciblés (prédictifs)