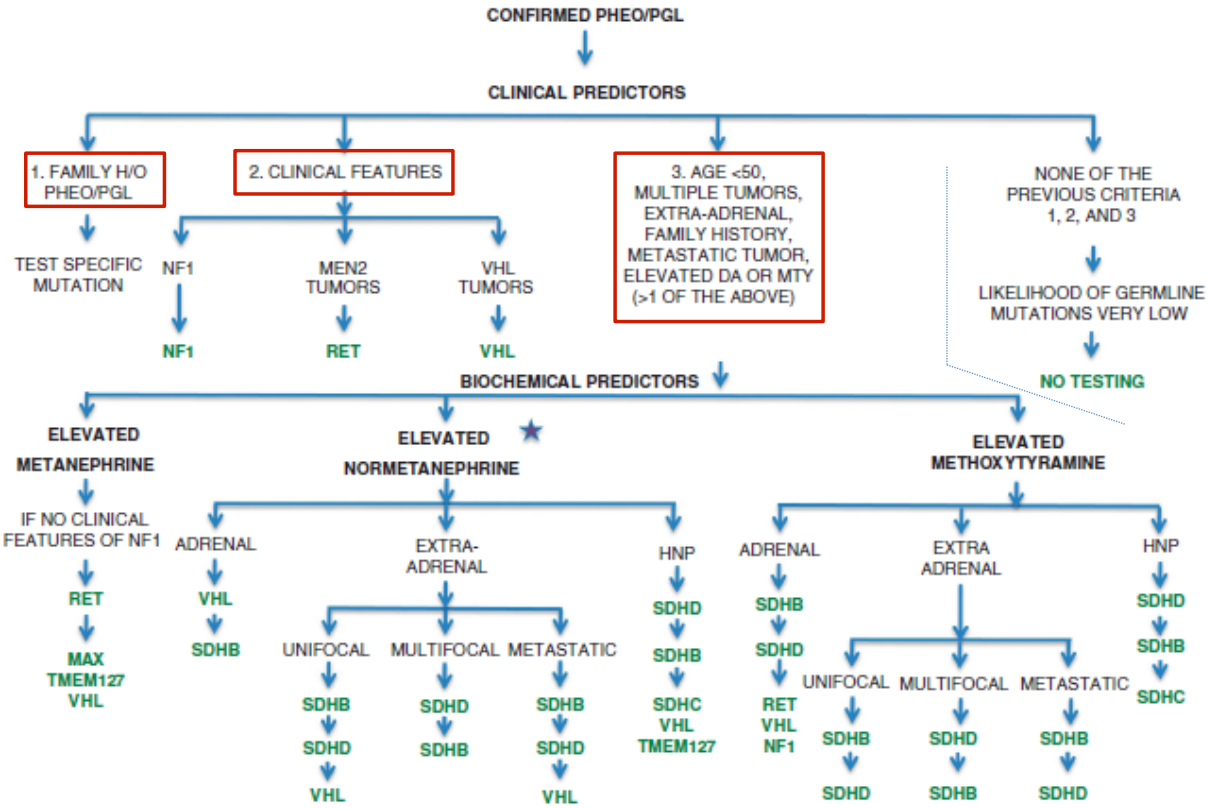



## 4. Phäochromocytom & extraadr. Paragangliome

*"The "great mimic": often sought, rarely found (Prävalenz 5/Mio)…yet, mostly discovered when it is too late… in autopsies*
Becker 01, JCEM 10; 95; NEJM 99; 340: 1872-9, Hypertension 91; 17-733-41; Lancet 05; 366: 665-75, SMF 12: 12: 66-71

**Genotyp-Screening?** (p22, KK-Gutsprache nötig) **RET** (MEN-II, 50% Phäo, typ A>NA), **VHL** (50% Phäo=Typ2, typ NA>A), **SDHD/B** ("maternal imprintin, dh nur Mut v Vater manifest b Kinder, Paragangliome gehäuft maligne, typ. 3-Methoxytyrmin↑), **NF 1** (Neurofibromatosis Typ 1, 2% Phäo)
**Aggressiv:** alle Phäo (25% pos Spontan-Mutation) **vs Kons**:<40j, pos FA, bilat/extraadren. Phäo / MTC / Angiome / CVI (VHL) / Glomustu (SDHD/B)
2x5ml EDTA Blut & informed consent ⇒ Prof. **H. Neumann (neumann@med1.ukl.uni-freiburg.de)** ⇒ **pos** ⇒ **Fam.Screen / Psychol. Beratung**

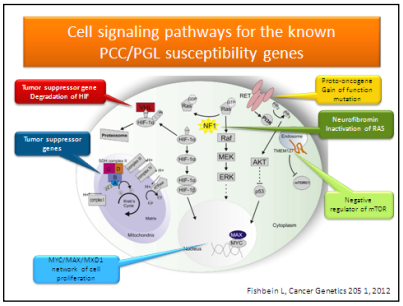
Journal of Human Hypertension (2013) **27,** 141–147

**www.nature.com/jhh**

**REVIEW**

# An update on the genetics of pheochromocytoma

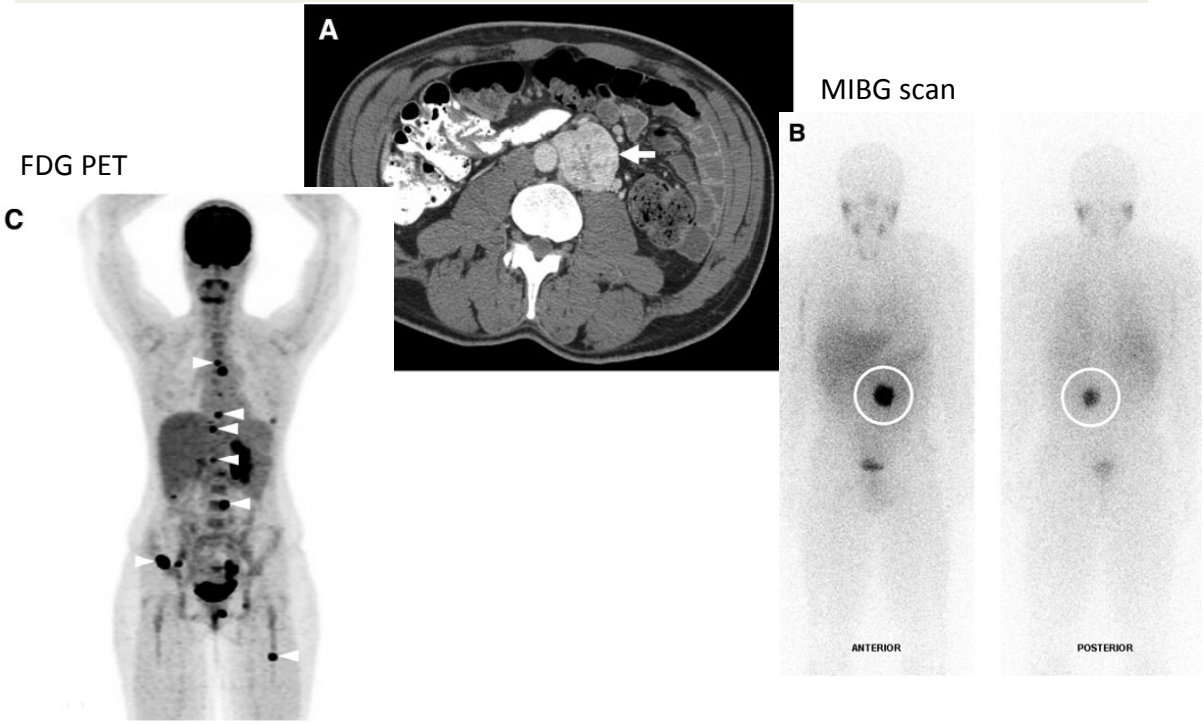
D Karasek[1], U Shah[2], Z Frysak[1], C Stratakis[3] and K Pacak[2]



# Phäochromozytom - Allgemeines

- aus Katecholamin-produzierenden (chromaffinen) Zellen hervorgehender Tumor
  - – adrenal: Nebennieren-Mark = PHEO
  - – extra-adrenal = Paragangliom (PGL)
    - Sympathikus: Thorax-Becken
    - Parasympathikus: Kopf-Hals

# Paragangliom (PGL)



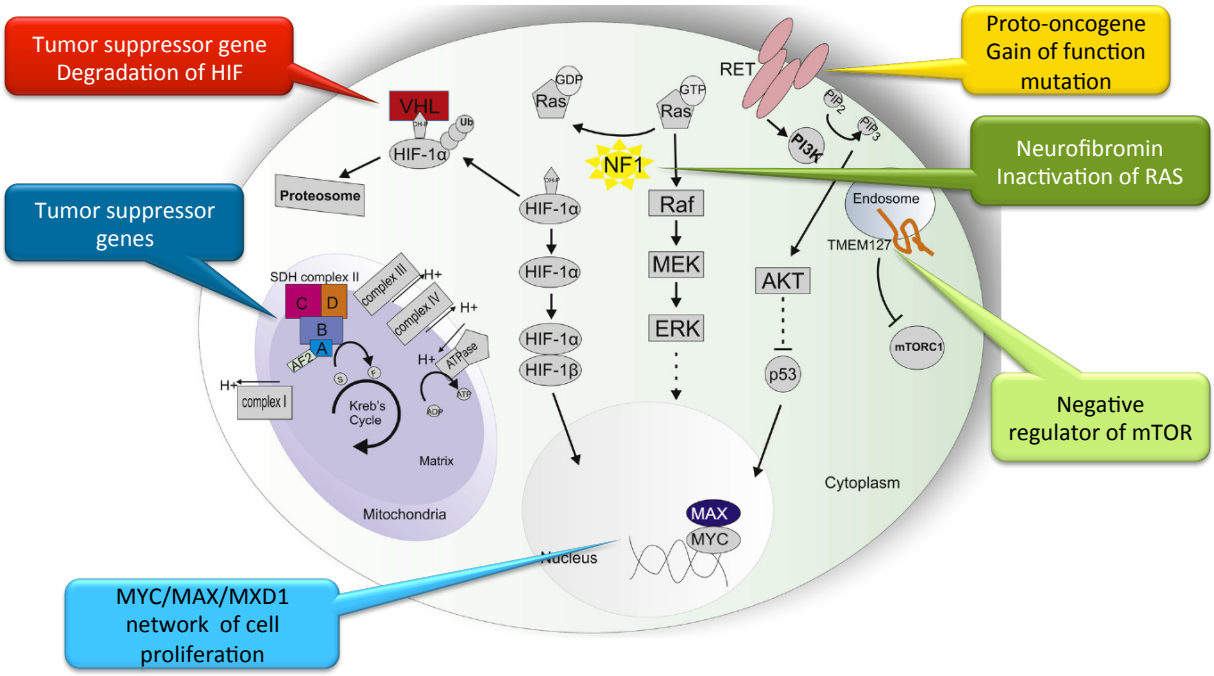
# Phäochromozytom - Genetik

- ~ 1/3 of patients have a germline mutation in one of the known susceptibility genes – Vererbung autosomal dominant
- 54% of patients with head and neck paraganglioma
- Significant portion (~ 25%) of patients with apparently sporadic disease have germline mutations

# Phäochromozytom - Genetik

- PHEO/PGL i.R. eines «genetischen» Syndroms
  - MEN2: RET Proto-Onkogen
  - VHL Syndrom
  - NF Typ1
- isolierte PHEOs/PGLs
  - Familial Paraganglioma: SDH Komplex
  - neu: TMEM127, MAX

# Cell signaling pathways for the known PCC/PGL susceptibility genes




Fishbein L, Cancer Genetics 205 1, 2012

# MEN 2

- aktivierende Mutation im RET Proto-Onkogen

- MTC als Erstmanifestation
- <u>PHEO in 50%, 30-40-j.</u>

- meist adrenal, bilateral >50%, Malignität <5%
  (↑bei Kindern mit MEN 2B)
- A, NA

# NF 1 – M. Von Recklinghausen

- aut. dom., 50% de novo Mutation

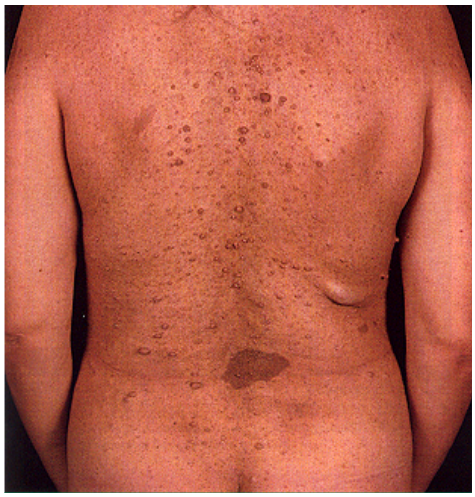
- Dx im Kindesalter
- PHEOs in 0.1-5.7%, ED 40-50-j.

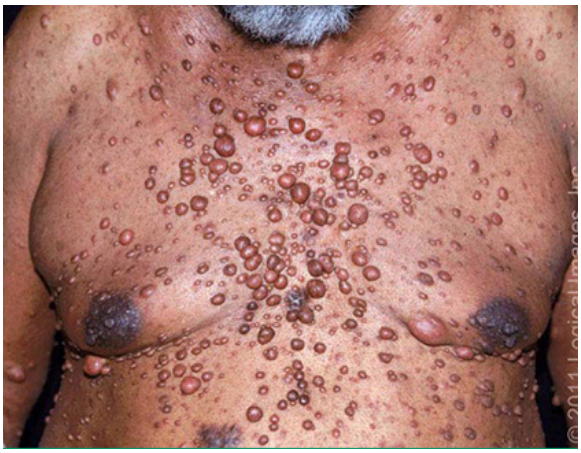
- A > NA

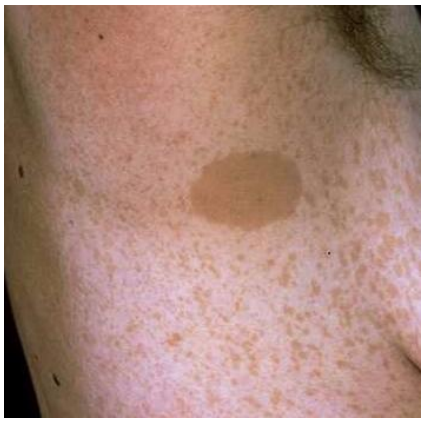
**NIH diagnostic criteria for neurofibromatosis type 1**

| **Two or more of the following clinical features must be present:** |
|---|
| Six or more café au lait macules of more than 5 mm in greatest diameter in prepubertal individuals, and more than 15 mm in greatest diameter in postpubertal individuals. |
| Two or more neurofibromas of any type or one plexiform neurofibroma |
| Freckling in the axillary or inguinal regions |
| Optic glioma |
| Two or more iris hamartoma (Lisch nodules) |
| Distinctive bony lesion such as sphenoid dysplasia, or thinning of the long bone cortex with or without pseudoarthrosis |
| A first-degree relative (parent, sibling, or offspring) with NF 1 based on the above criteria. |

UpToDate









# Von Hippel Lindau (VHL)

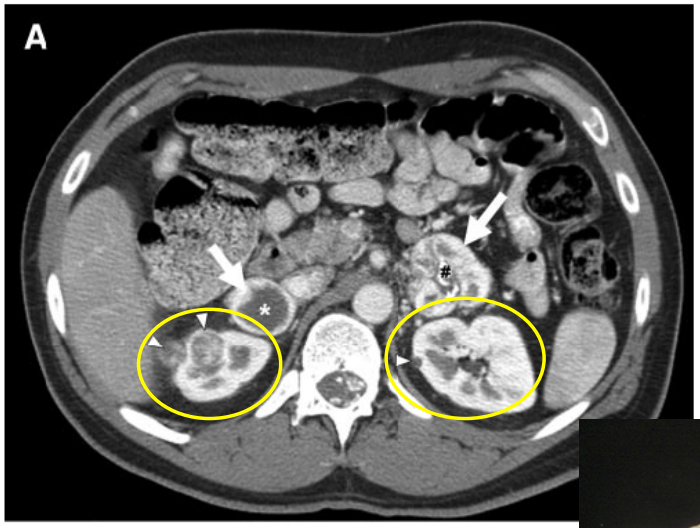
- ↑Tumorinzidenz (benigne + maligne)
- aut. dom., 20% de novo Mutation

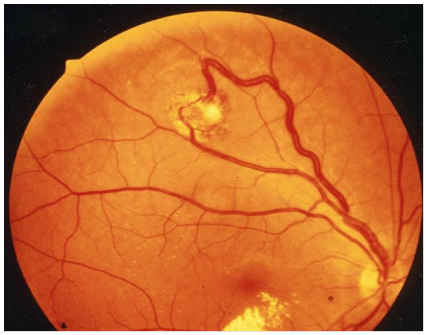
- VHL Typ 1: kein PHEOs/PGLs
- VHL Typ 2: häufig PHEOs/PGLs

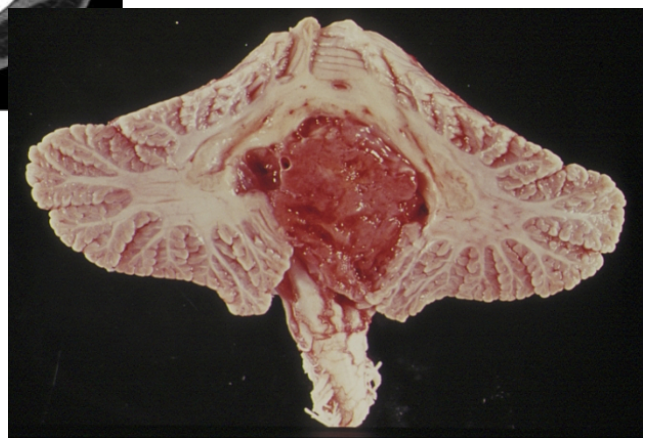
- 30-j., mögliche Erstmanifestation
- meist adrenal, 50% bilateral; Malignität <5%
- nur NA

# VHL - Manifestationen

- Hemangioblastomas of the brain (cerebellum) and spine
- Retinal angiomas
- Endolymphatic sac tumors of the middle ear
- Serous cystadenomas and neuroendocrine tumors of the pancreas
- Pheochromocytomas
- Clear cell renal cell carcinomas (RCCs)
- Papillary cystadenomas of the epididymis and broad ligament





# Familial Paraganglioma Syndrome

- Succinate dehydrogenase enzyme complex (SDH)
- 4 Subunits (SDHx-Gene):
  - SDHA – SDHAF2 (Kofaktor)
  - SDHB
  - SDHC
  - SDHD

- meist PGLs, Lokalisation je nach betroffener Subunit
- oft «maternal imprinting» - Übertragung nur vom Vater
- oft «silent»; oft DA, DA + NA

- SDHB-Positivität in der Immunhistochemie: SDHx 100/84%

# TMEM-127-Gen / MAX-Gen

- TMEM-127:
  - Tumor-Suppressor-Gen
  - 40-50-j.
  - adrenal (1/3 bilateral), Malignität <5%
- MAX:
  - Protein MAX (MYC-associated factor X), Transkriptionsfaktor
  - funktionell Tu-Suppressor-Gen
  - 30-j.
  - bilateral (67%), **maligne** (25%),

# Clinical Features of hereditary PCC/PGL

| | Penetrance of PCC/FPGL | Mean age at presentation | Frequency of PCC/PGL | Metabolites | Frequency of Malignancy | Frequency of bilateral PCC |
|---|---|---|---|---|---|---|
| RET | 50 | 35 | 100/~0 | MN/NMN | 3 | 63 |
| VHL | 10-25 | 29 | 90/19 | NMN | 3 | 44 |
| NF1 | 0.1-5.7 | 42 | 95/6 | MN/NMN | 9 | 14 |
| SDHD | 86 | 35 | 0/100* | NMN/MTX | 4 | |
| SDHB | 77 | 33 | 25/78 | NMN/MTX | 31 | |
| SDHC | U | 43 | 0/100 | -- | 0 | |
| SDHA | U | 40 | 17/83 | NMN | 0-14 | |
| SDHAF2 | 100 | 32 | 0/100* | NMN | 0 | |
| TMEM127 | U | 43 | 95/8 | NMN/MN | 4 | 39 |
| MAX | U | 32 | 100/17 | NMN | 25 | 67 |

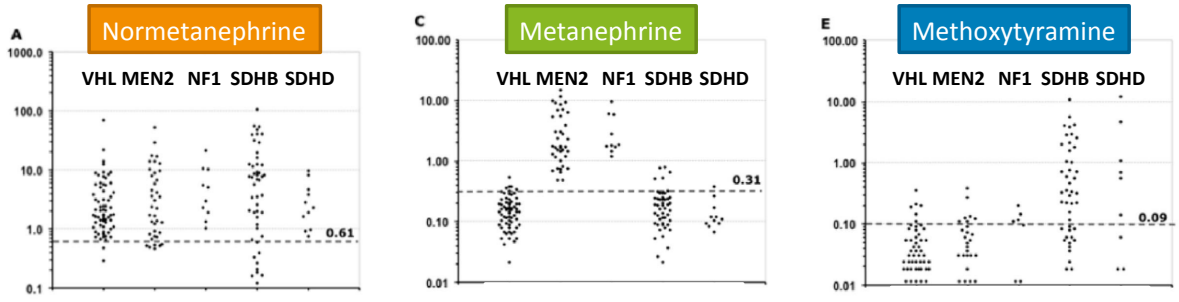
Autosomal-dominant inheritance, * maternal imprinting

Welander J, Endocrine-Related Cancer 18 R253, 2011
Fishbein L, Cancer Genetics 205 1, 2012
Jafri M, EJE 166 151, 2012

# Malignität

- SDHB, MAX:
  **>25-30%**
- NF1, sporadische PHEOs:
  **ca. 12%**
- RET, VHL, SDHD, SDHC, SDHAF2, TMEM-127:
  **<5%**

# Plasma Metanephrines to guide Genetic Testing in hereditary PCC/PGL

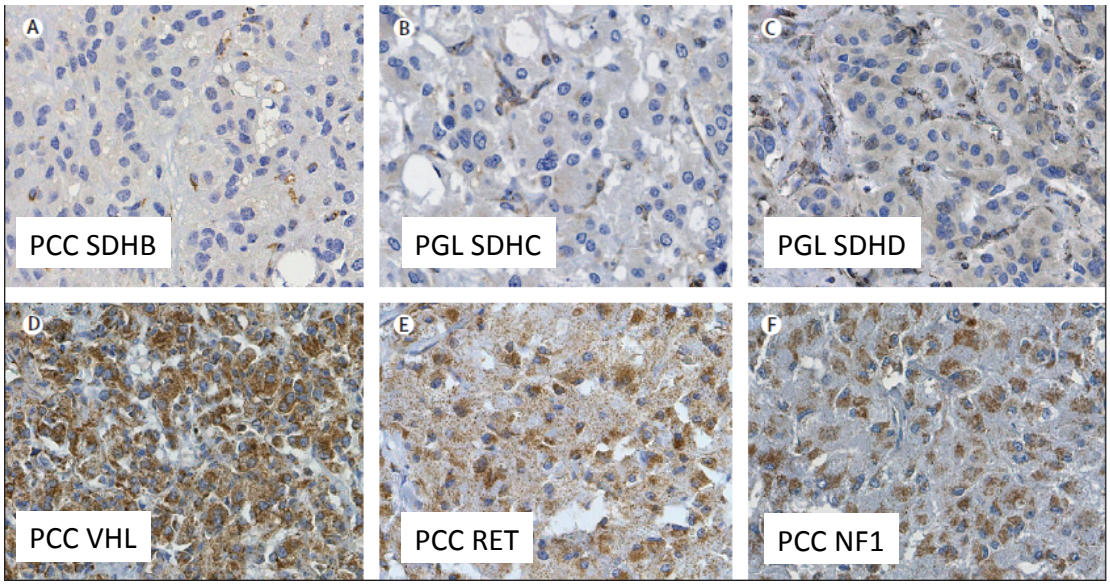



| | | |
|---|---|---|
| Adrenal (bilateral): | NMN↑, MN↑, MTX↔ | ➔ MEN2 (NF1) |
| Adrenal (bilateral): | NMN↑, MN ↔, MTX↔ | ➔ VHL |
| Extraadrenal: | NMN↑, MN ↔, MTX↔ | ➔ SDHD (VHL) |
| Extraadrenal: | NMN↑, MN ↔, MTX ↑ | ➔ SDHB |

Eisenhofer et al, Clin Chem 57: 411, 2011

# SDHB Immunohistochemistry identifies SDHB, -C and D associated tumors

*(Sensitivity 100%, Specificity 84%)*



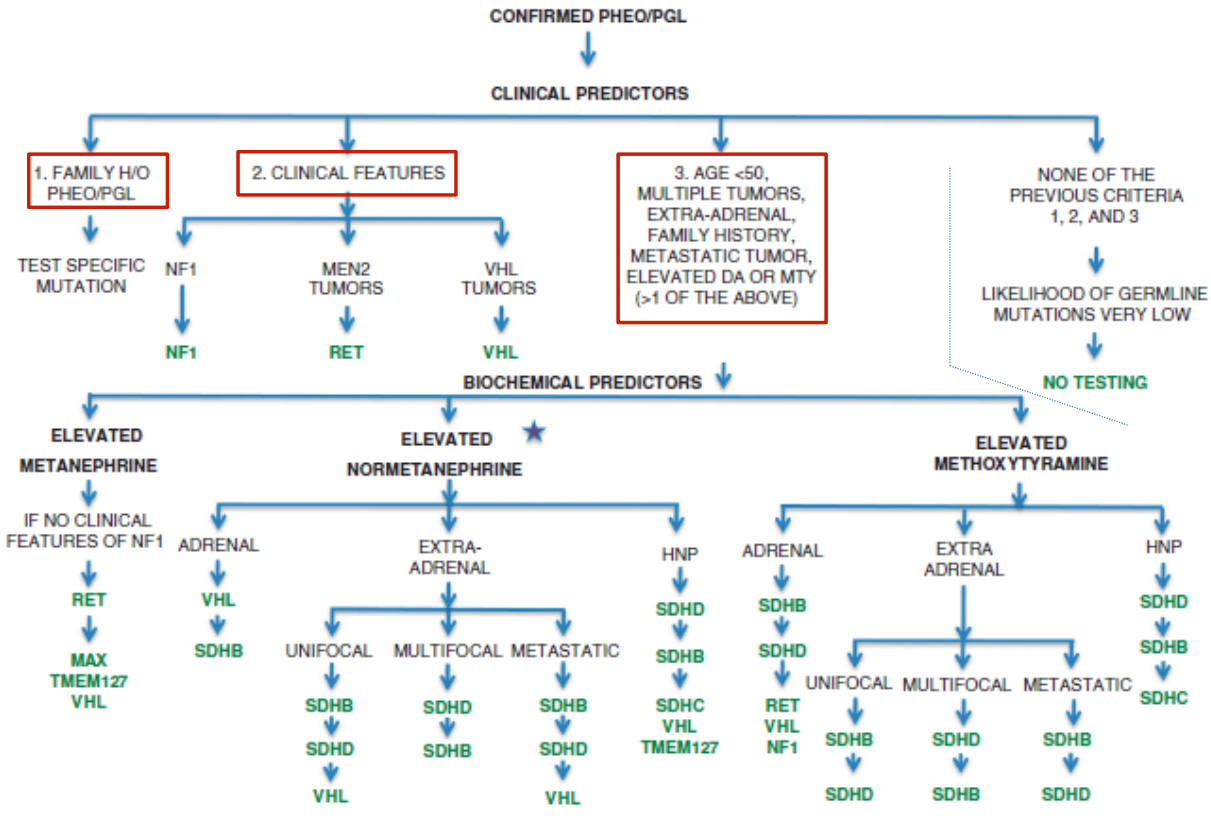

Van Nederveen, Lancet Oncol 10 764, 2009

# Genetische Testung – warum?

1. Assoziation mit anderen (malignen) Tumoren?

2. Planung Follow-up (z.B. vermehrt Bildgebung)

3. Screening von Familienmitgliedern



# Key points

- PHEOs/PGLs mit genetischem Background häufiger als bis anhin angenommen (ca. 30%)
  - mögliche Erstmanifestation eines VHL!

- genetischer Workup bestimmt durch Lokalisation, biochem. Pattern, Immunhistochemie

- In Zukunft spezifische Therapie entsprechend Genotyp(?)