Updates on the Genetics of Neuroendocrine Tumors

NET Patient Conference

March 8, 2019

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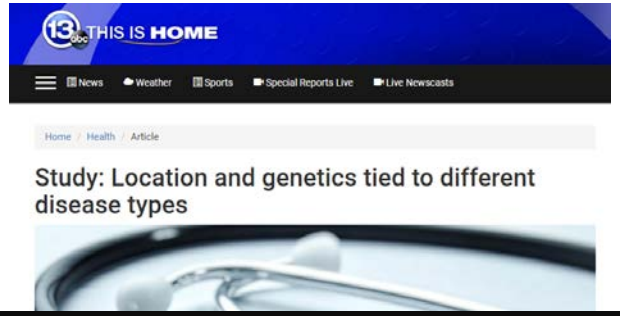
Division of Translational Medicine and Human Genetics

Penn Medicine

- **No disclosures**



HEALTH & FITNESS

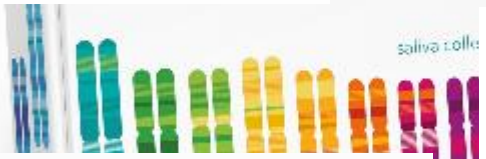
Doctors voice concerns over popular at-home genetic testing

Friday, March 23rd, 2018

CNN Health » Food | Fitness | Wellness | Parenting | Live Longer Live TV U.S. Editic

New recommendations say not all women need genetic testing for cancer. Critics say it could cost lives

By **Susan Scutti**, CNN
Updated 12:11 PM ET, Tue February 19, 2019



Forbes

19,481 views | Dec 3, 2018, 09:32am

GSK Buys Tesaro For $5 Billion In Dramatic Bet On Cancer Genetics

All of Us project seeks to analyze health, genetic data from 1 million Americans by 2024

Updated 9:39 AM; Posted 9:25 AM

cleveland.com
COVERING NORTHEAST OHIO

Overview

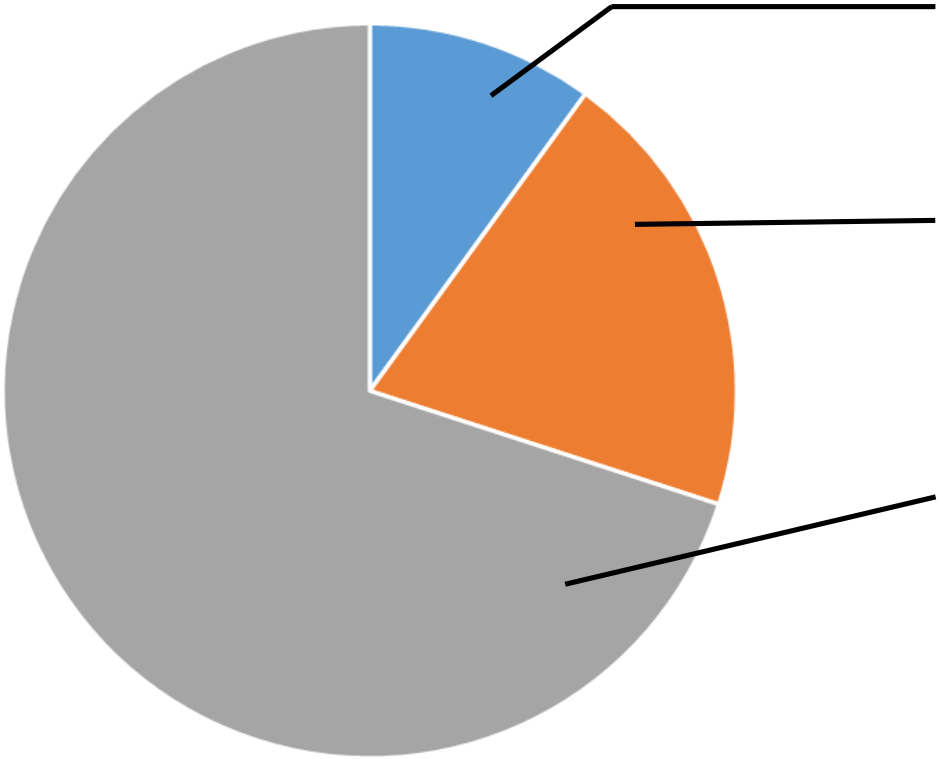
1. Cancer/tumor genetics
2. Genetics of neuroendocrine tumors

sciencemag.org

The Genetics of Cancers and Tumors

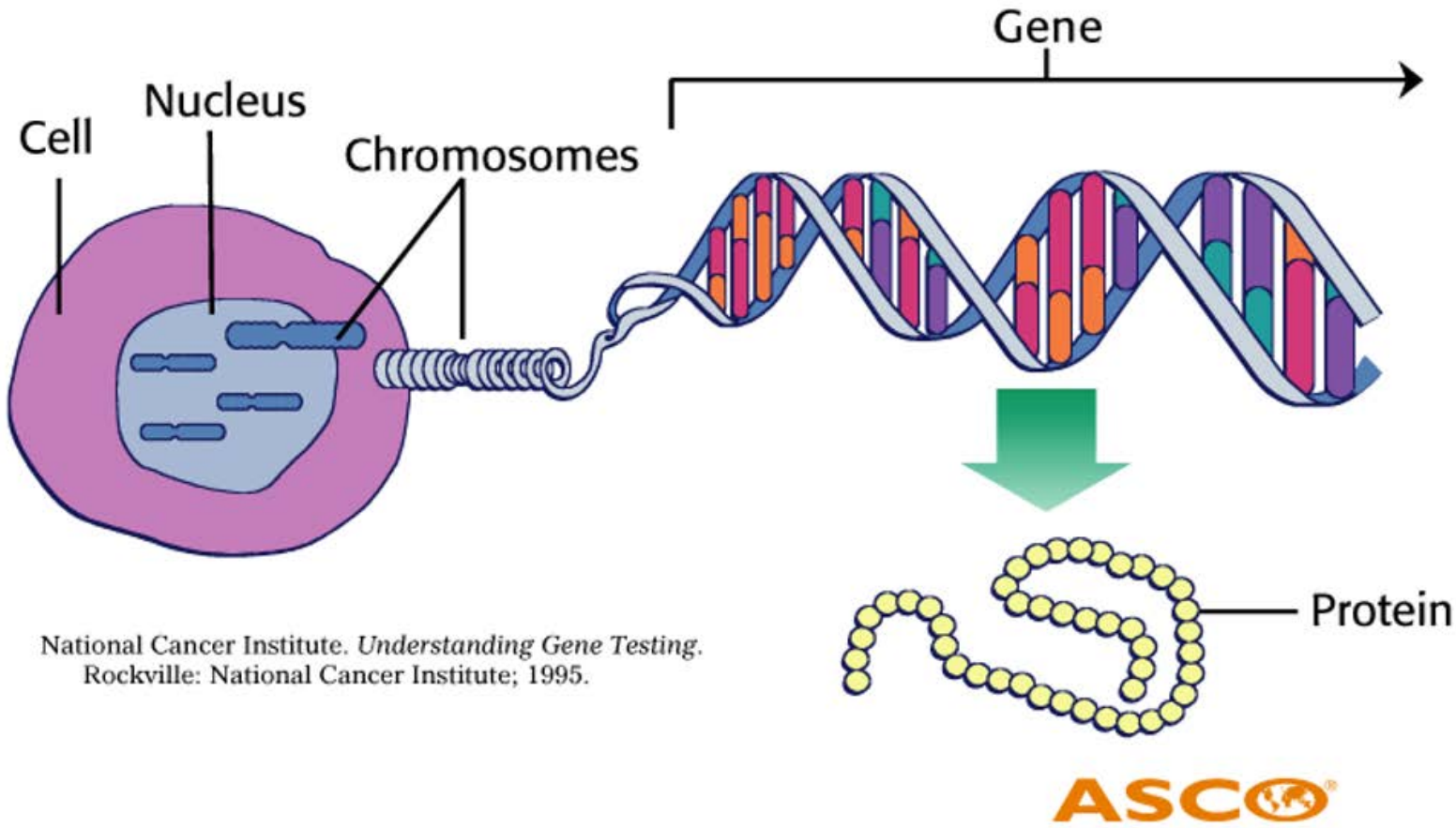
- Hereditary v. Familial v. Sporadic
- Germline v. somatic genetics
- Risk
- When to suspect hereditary susceptibility

Cancer Distribution - General



- **Hereditary (5-10%)**
  - Specific gene variant is inherited in family
  - Associated with increased tumor/cancer risk
- **Familial (10-20%)**
  - Multiple genes and environmental factors may be involved
  - Some increased tumor/cancer risk
- **Sporadic**
  - Occurs by chance, or related to environmental factors
  - General population tumor/cancer risk

What are genes again?

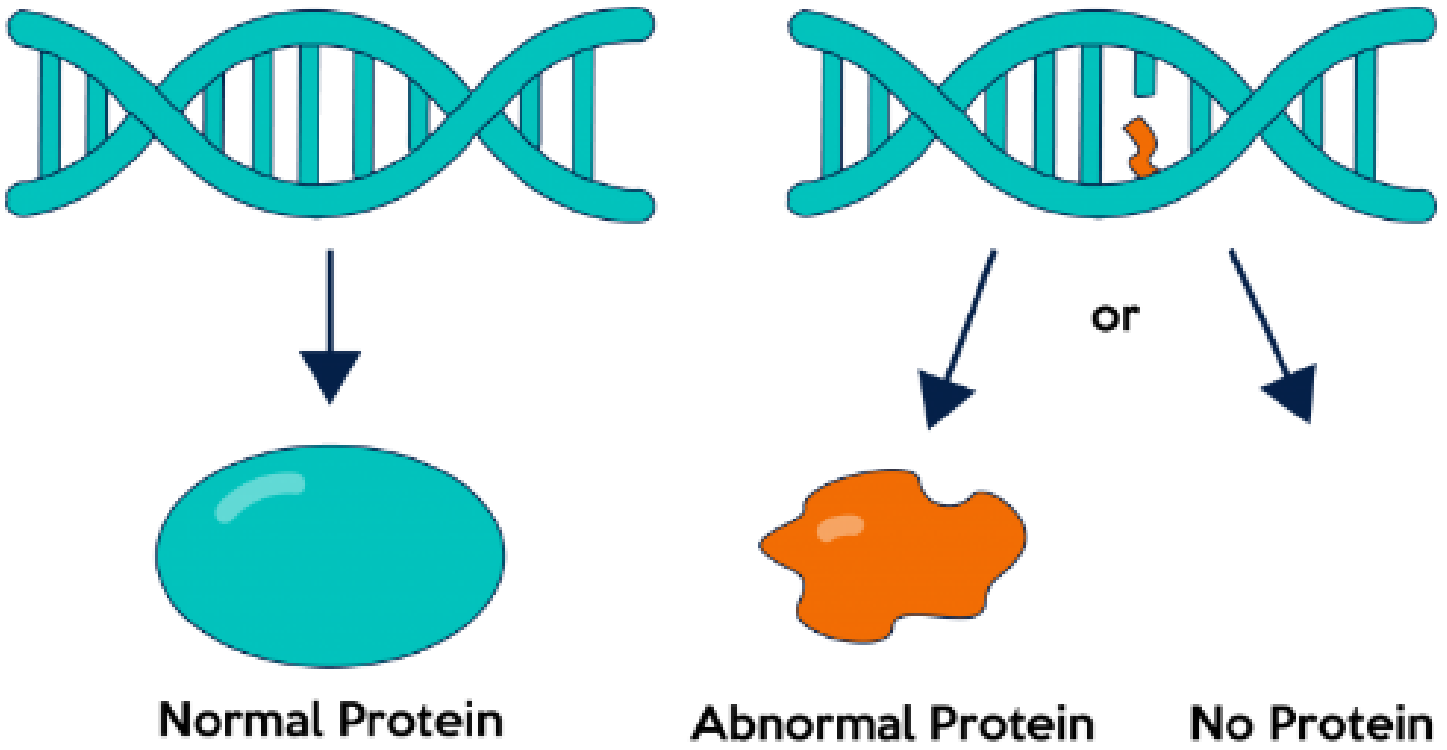


National Cancer Institute. *Understanding Gene Testing.* Rockville: National Cancer Institute; 1995.

ASCO

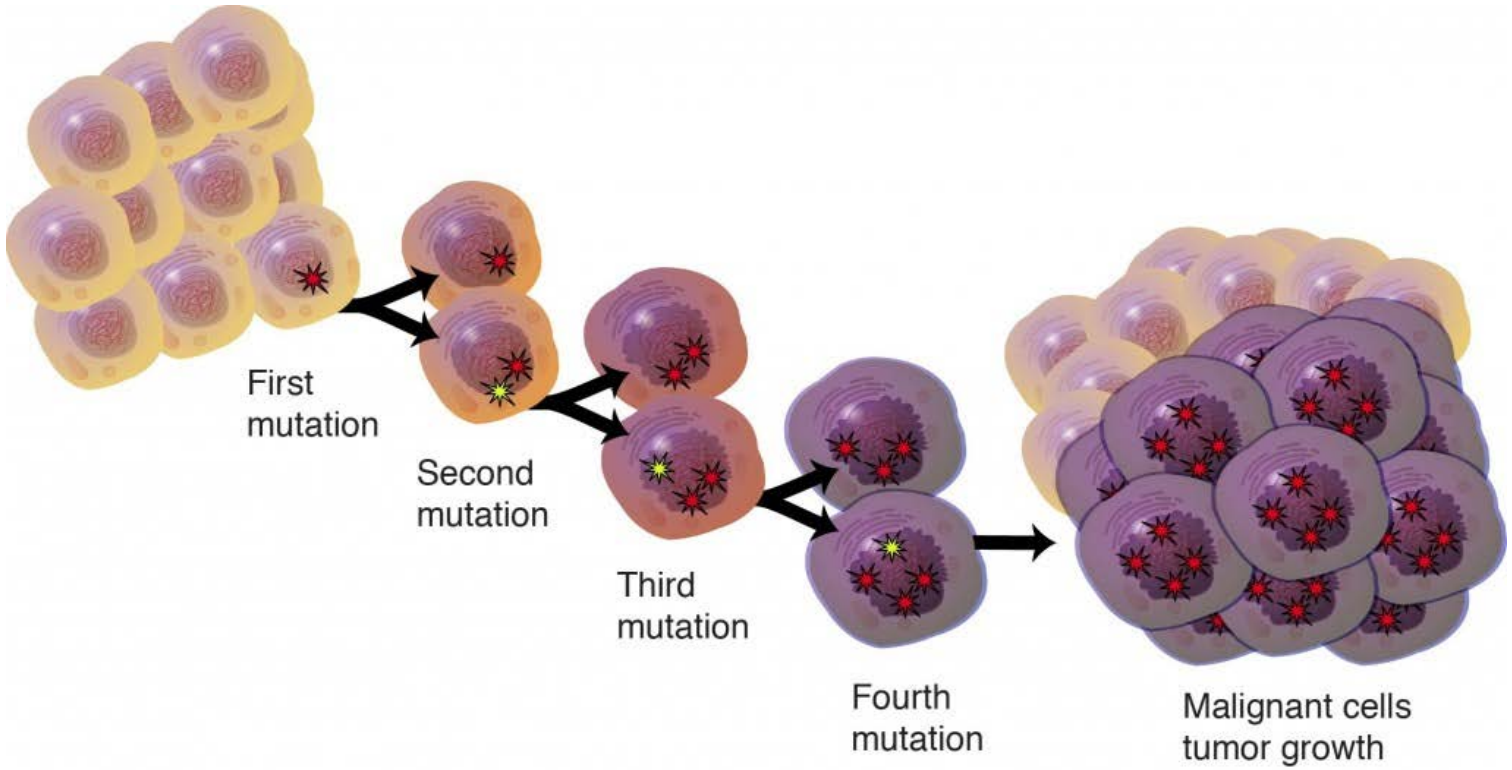
Normal gene

Pathogenic gene variant ("mutation")



kintalk.org

Cancer is a genetic disease



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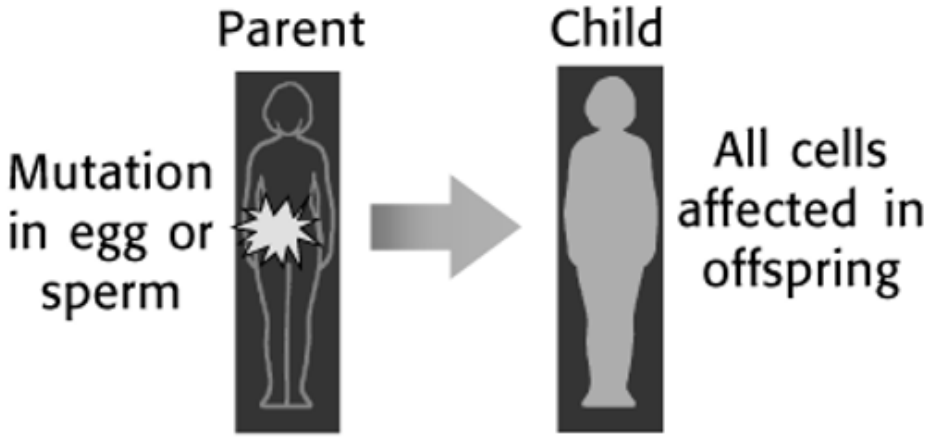
Germline v. Somatic gene mutations

Germline mutations



- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

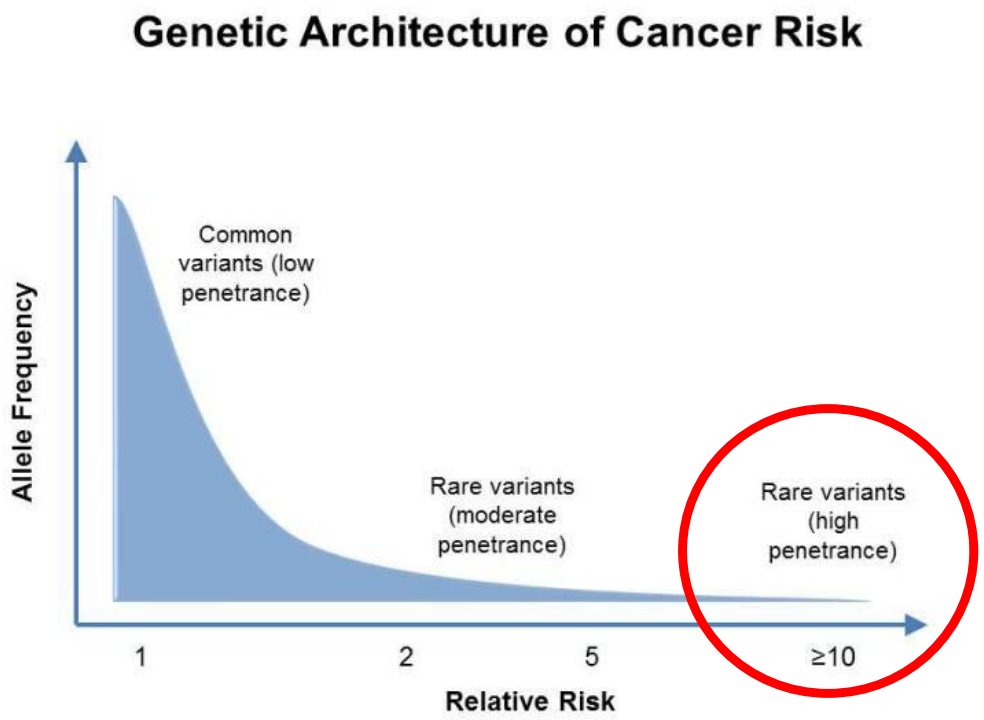
Somatic mutations

- Occur in nongermline tissues
- Are nonheritable
- Acquired alterations common for all cancers

ASCO

Hereditary susceptibility to cancer

- **Germline mutations**
- **Depending on the gene, increased risk for certain tumor/cancer types**
- **Does not mean an individual WILL develop cancer, but could change screening and management recommendations**



National Cancer Institute

Features that raise suspicion for hereditary condition

- **Specific tumor types**
- **Early ages of diagnosis compared to the general population**
- **Multiple or bilateral (affecting both sides) tumors**
- **Family history**
  - Clustering of certain tumor types
  - Multiple generations affected
  - Multiple siblings affected

When is genetic testing offered?

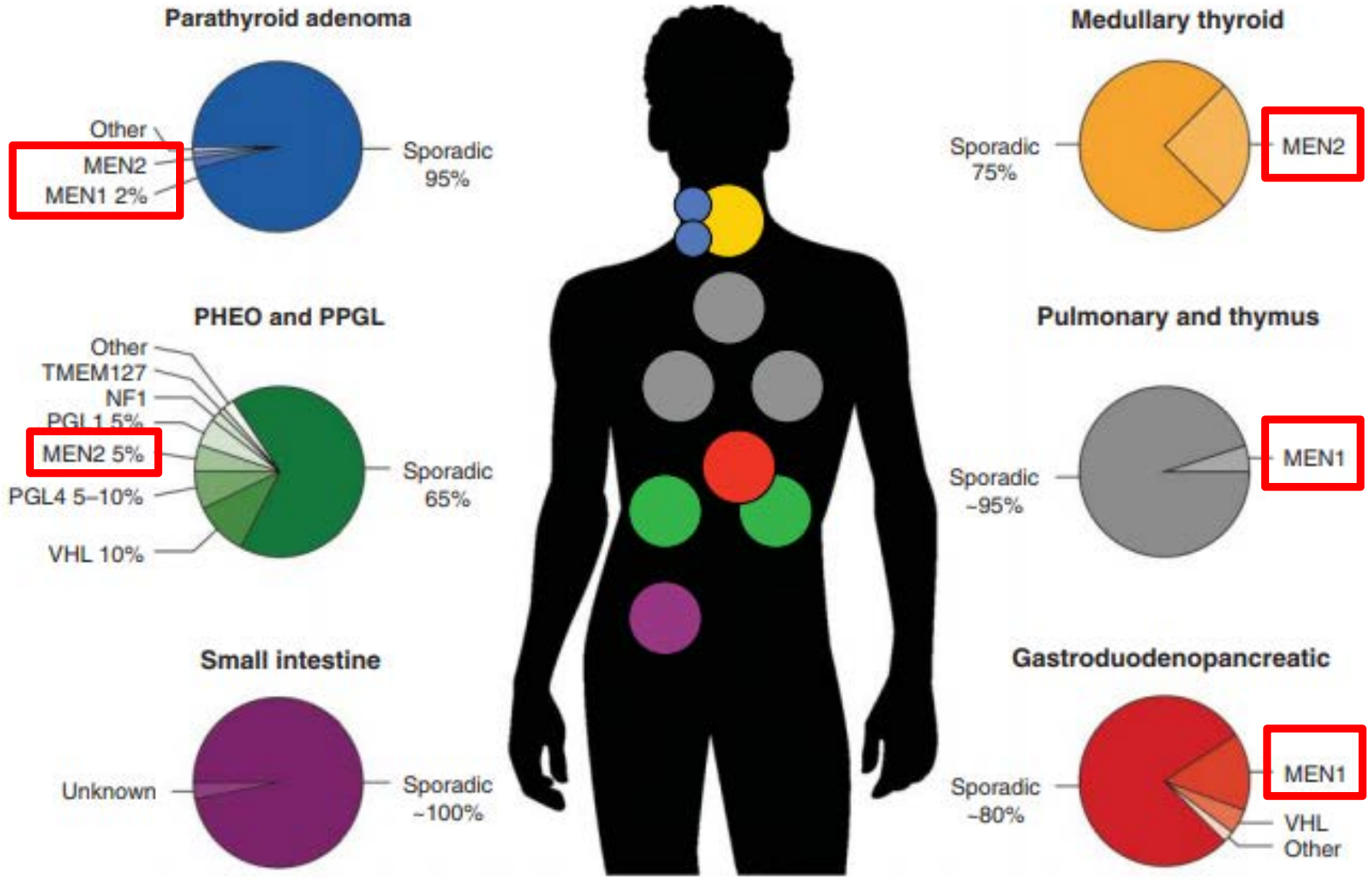
- A hereditary condition has been identified in the family
- An individual's personal history and/or family history are suspicious for a hereditary predisposition to tumor development
- There is available genetic testing with sufficient sensitivity and specificity to be interpreted
- The test will impact the individual's diagnosis, management, and/or help to clarify risk in family members

Neuroendocrine tumor predisposition

- How often are neuroendocrine tumors associated with a hereditary susceptibility?
- Known NET predisposition syndromes
- Who should be referred

Likelihood of finding a hereditary predisposition - NETs

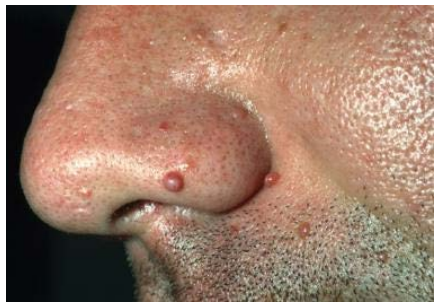
- **Dependent on tumor type**
- **Tumor types:**
  - Pheochromocytomas and paragangliomas
  - Parathyroid adenomas
  - Thyroid cancer – medullary specifically
  - Small intestine NETs
  - Pulmonary and thymus NETs
  - Gastroduodenopancreatic NETs

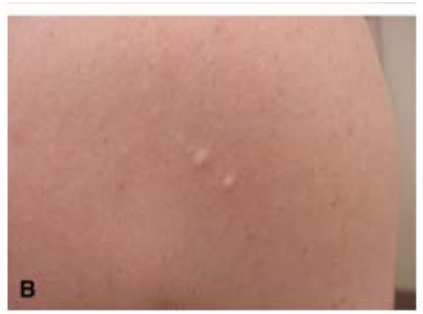


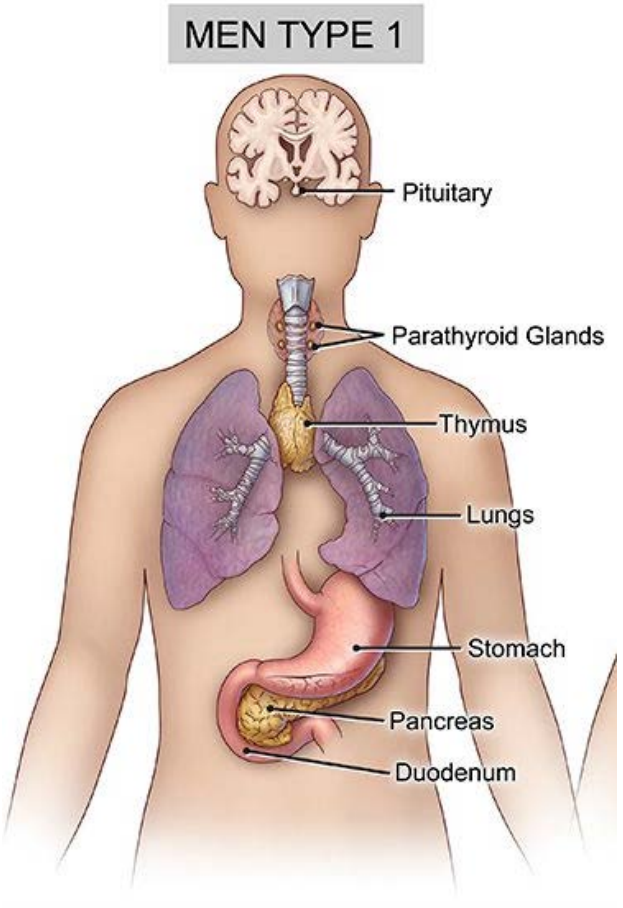
Crona and Skogseid, 2016

Multiple Endocrine Neoplasia Type 1

- **Caused by pathogenic variants in the *MEN1* gene**
- **Characterized by:**
  - Hyperparathyroidism
    - >95% of patients with MEN1
    - Typically diagnosed under the age of 50
  - Pituitary adenomas
  - GEP neuroendocrine tumors
    - Gastrinomas, ZES
    - Insulinomas, VIPoma, somatostatinoma, glucagonoma
    - Non-functional
  - Skin findings
    - Angiofibromas
    - Collagenomas
    - Lipomas





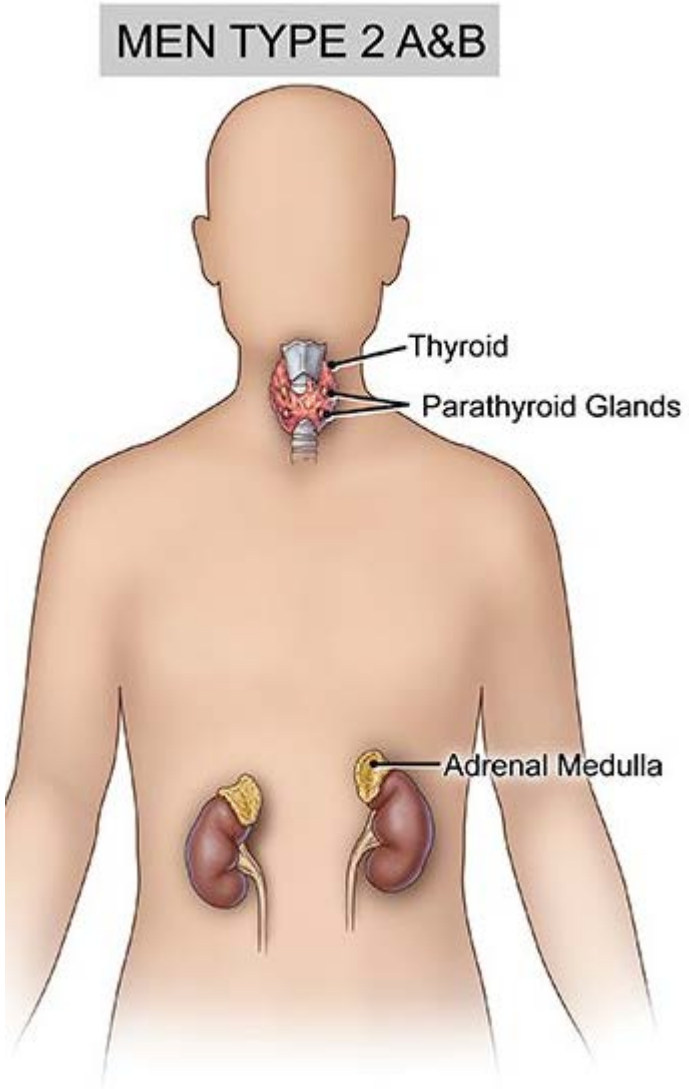


Xia and Darling, 2006
Medscape
mdanderson.org

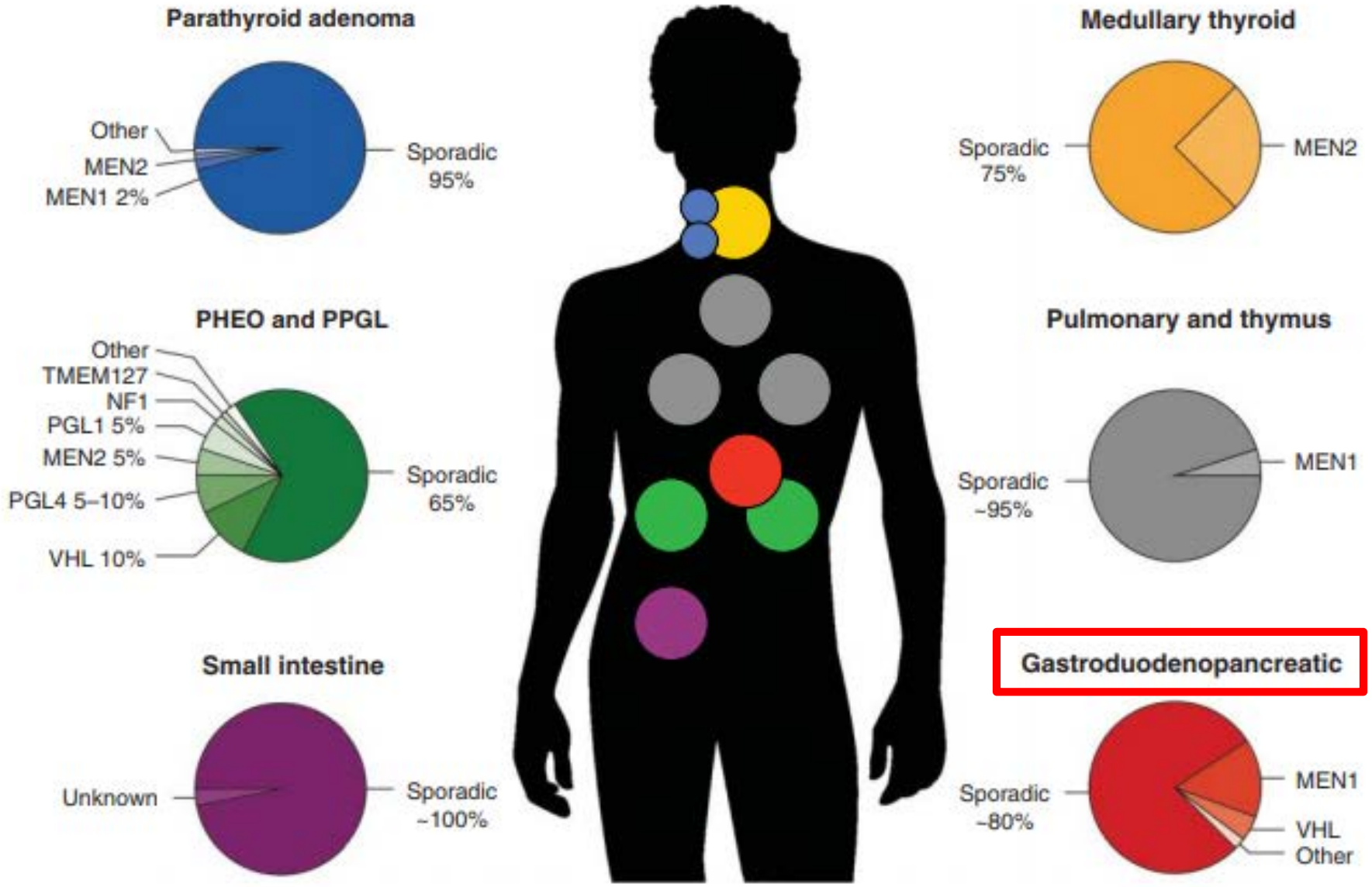
Multiple Endocrine Neoplasia Type 2

- **Hallmark feature is medullary thyroid carcinoma (MTC)**
  - Typically younger age than in general population
  - More likely bilateral (both sides), multifocal (multiple lesions)
  - Associated with c-cell hyperplasia

- **Caused by pathogenic variants in the *RET* gene**
  - Type 2A
    - Characterized by: MTC (95%), pheochromocytoma (50%) or parathyroid adenoma/hyperplasia (20-30%)
  - Type 2B
    - Characterized by: very early MTC (100%), pheo (50%), specific physical exam findings and facial features
  - Familial medullary thyroid carcinoma
    - Families with more than one individual diagnosed with medullary thyroid carcinoma in absence of pheochromocytoma or parathyroid disease



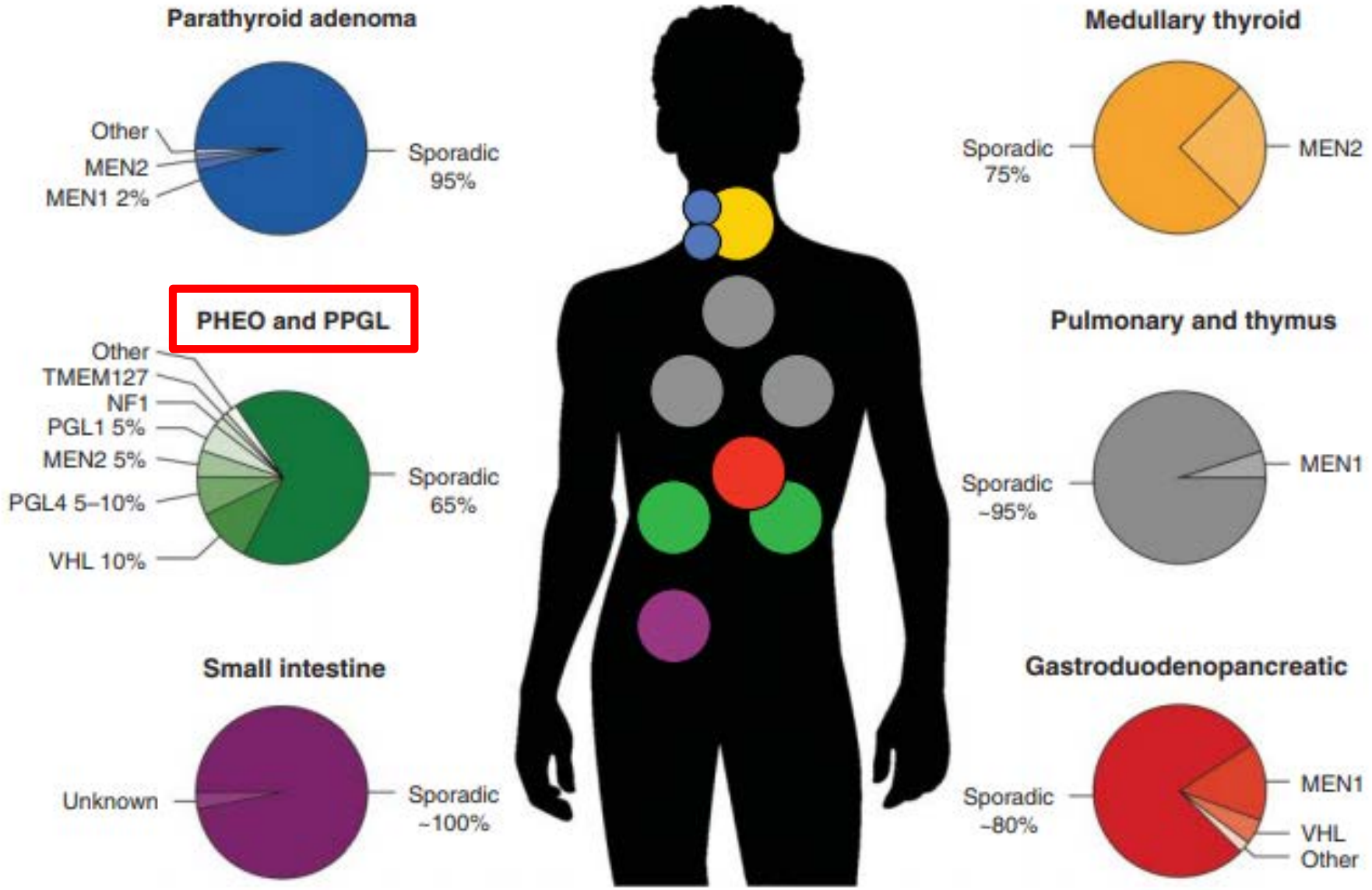
mdanderson.org



Crona and Skogseid, 2016

Von Hippel Lindau Syndrome

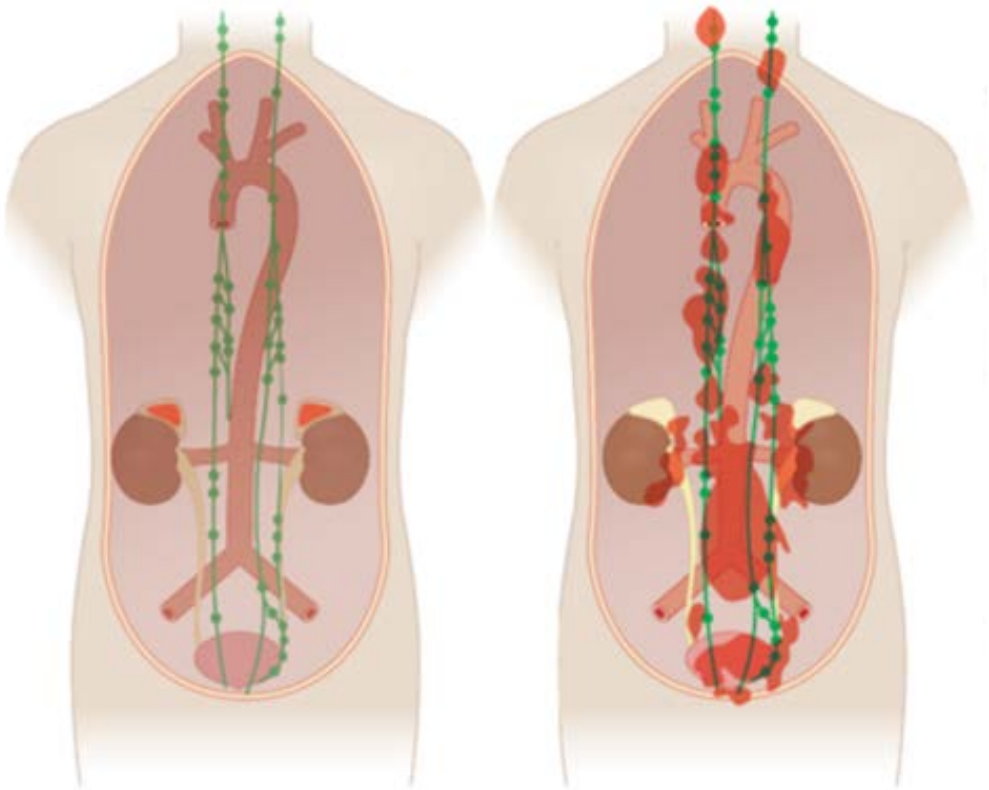
- **Caused by pathogenic variants in the *VHL* gene**
- **Characterized by:**
  - Hemangioblastomas – benign, vascular tumors; prototypic lesion
    - Brain
    - Spinal cord
    - Retina (70% of individuals with VHL, mean age of detection 25 years)
  - Renal cysts and clear cell renal cell carcinoma
  - Pheochromocytoma
  - Endolymphatic sac tumors
  - Epididymal and broad ligament cysts
  - Pancreatic cysts
  - **Pancreatic neuroendocrine tumors (5-17%)**



Crona and Skogseid, 2016

Pheochromocytomas and paragangliomas

Tumors of the autonomic nervous system

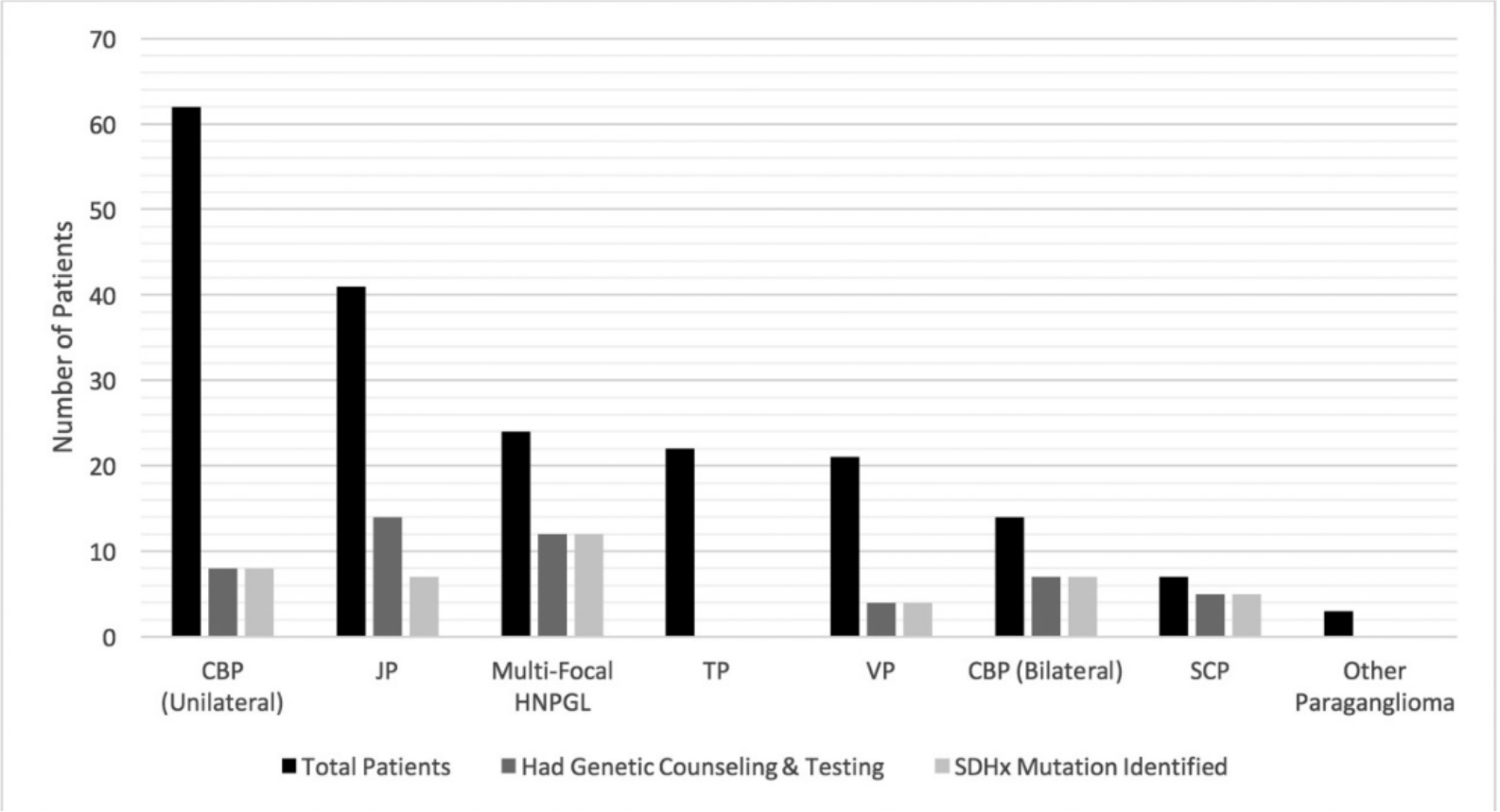


Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

- **Pheochromocytomas (PCC)**
  - Tumors that originate in the chromaffin cells in the adrenal medulla
- **Paragangliomas (PGL)**
  - Sympathetic: usually located retroperitoneal, but can be found in abdomen or thorax, usually secrete catecholamines
    - Also called "extra-adrenal pheochromocytoma"
  - Parasympathetic: usually in the head and neck region, generally biochemically silent (non-secreting)
- **Up to 40% are associated with a hereditary cause**

Head and Neck Paragangliomas (HNPGLs)

- **Most cases of multiple HNPGL tumors have a genetic cause**
- **Solitary tumors have underlying genetic cause in 15 to 35%**
- **Highest likelihood in bilateral carotid body tumors**



Laryngoscope Investig Otolaryngol. 2017 Dec; 2(6): 380–389

Ann Surg Oncol (2013) 20:1444–1450
DOI 10.1245/s10434-013-2942-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Inherited Mutations in Pheochromocytoma and Paraganglioma: Why All Patients Should Be Offered Genetic Testing

Lauren Fishbein, MD, PhD[1], Shana Merrill, MS[2], Douglas L. Fraker, MD[3,4], Debbie L. Cohen, MD[5], and Katherine L. Nathanson, MD[2,4]

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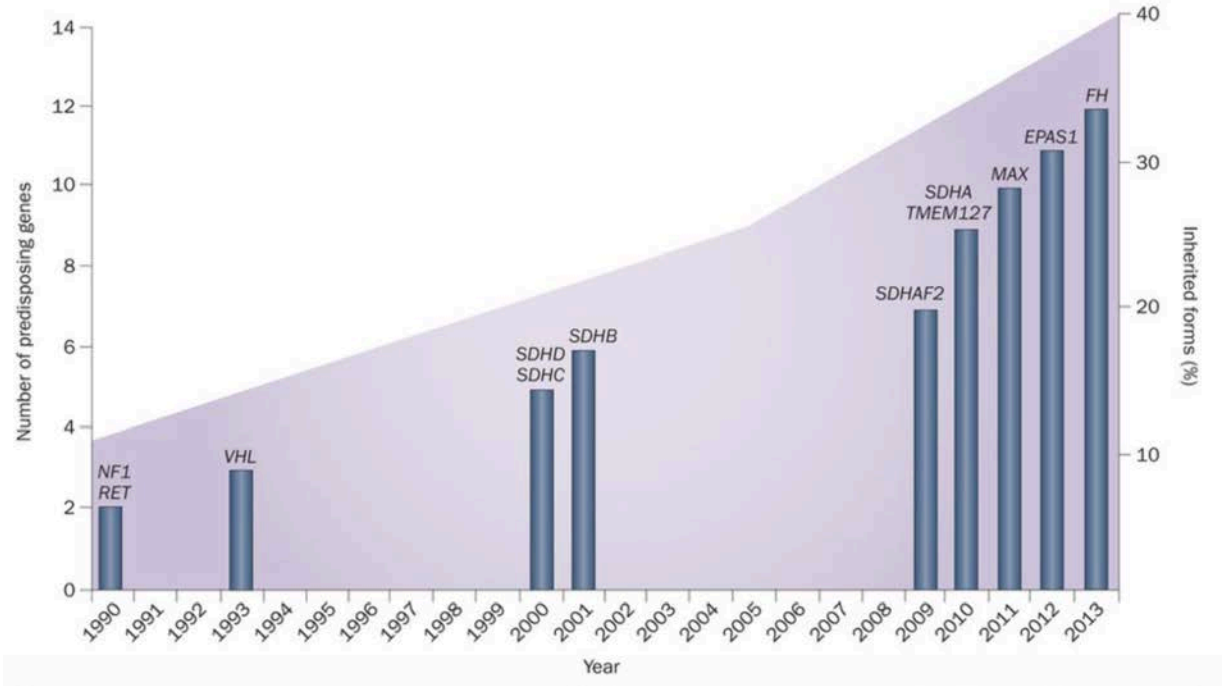
Genes associated with Hereditary PGL/PCC

- **Syndromic conditions (15-20% PGL/PCC)**
  - Majority: MEN2, VHL, Neurofibromatosis type 1
  - 1% - Polycythemia-paraganglioma-somatostatinoma syndrome (*EPAS1* gene)
  - 1% - Hereditary Leiomyomatosis and Renal cell carcinoma (*FH* gene)
- **Hereditary PGL/PCC**
  - Succinate dehydrogenase genes (*SDHA, SDHB, SDHC, SDHD, SDHAF2*)
  - *TMEM127*
  - *MAX*



Favier et al, 2015

Hereditary PGL/PCC, continued

Gene	NET Characteristics	Mutation Frequency	Other Associations
SDHA	HNPGL, extra-adrenal PGL	<1%	GIST, RCC
SDHB	HNPGL, solitary PCC; extra-adrenal PGL, **higher risk for metastatic disease**	10%	RCC
SDHC	Primarily HNPGL; 10% in the thoracic cavity	1%	RCC
SDHD	Primarily HNPGL, extra-adrenal PGL, PCC; **more likely to have multiple tumors**	9%	RCC
SDHAF2	HNPGL	<0.1%	
TMEM127	PCC, rare PGL	1%	
MAX	PCC	1%	

Emerging gene associations

Gene	NET Characteristics
EGLN1	PCC
KIF1B	PCC
*MDH2	PGL/PCC
*DNMT3A	PGL/PCC

Genetics inMedicine

Article | Published: 08 May 2018

Gain-of-function mutations in *DNMT3A* in patients with paraganglioma

Laura Remacha BS, Maria Currás-Freixes MD, PhD, [...] Alberto Cas

Genetics in Medicine **20**, 1644–1651 (2018) | Download Citation

Genetics inMedicine | **INVITED COMMENT**

Discovery of new susceptibility genes: proceed cautiously

Tobias Else, MD[1] and Lauren Fishbein, MD, PhD[2]

Genetics in Medicine (2018) 20:1512–1514; https://doi.org/10.1038/s41436-018-0139-9

Genetics inMedicine

Article | Published: 16 July 2018

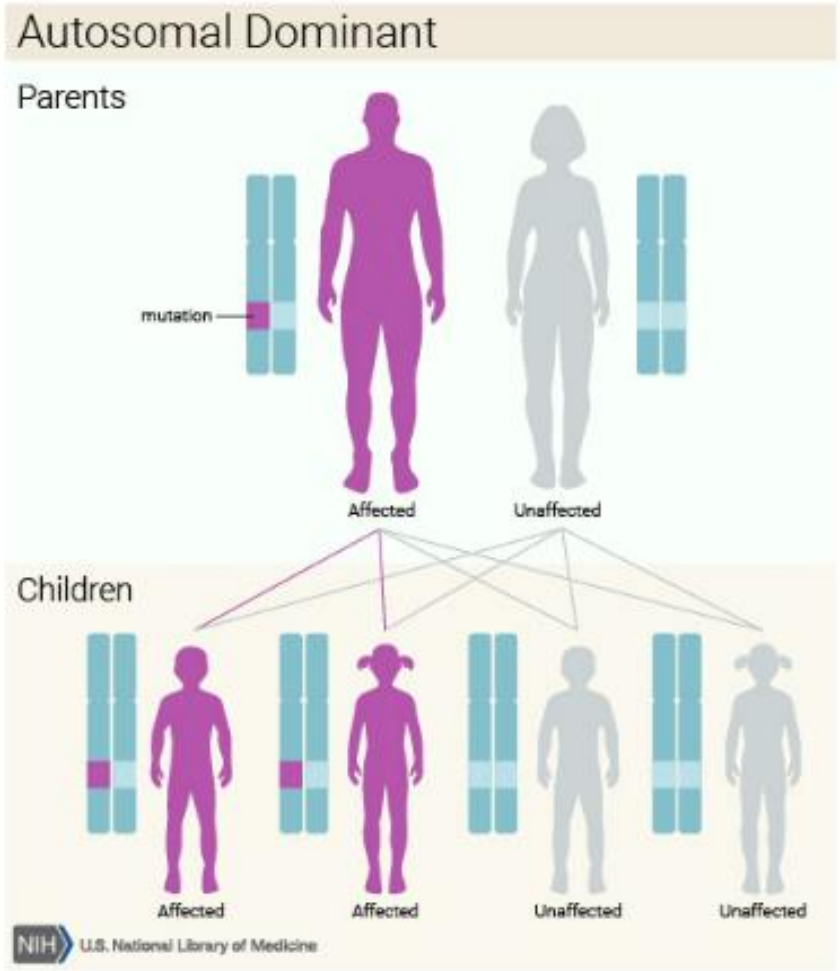
Role of *MDH2* pathogenic variant in pheochromocytoma and paraganglioma

a Currás-Freixes MD, PhD, [...] Mercedes Robledo PhD

1652–1662 (2018) | Download Citation

Inheritance

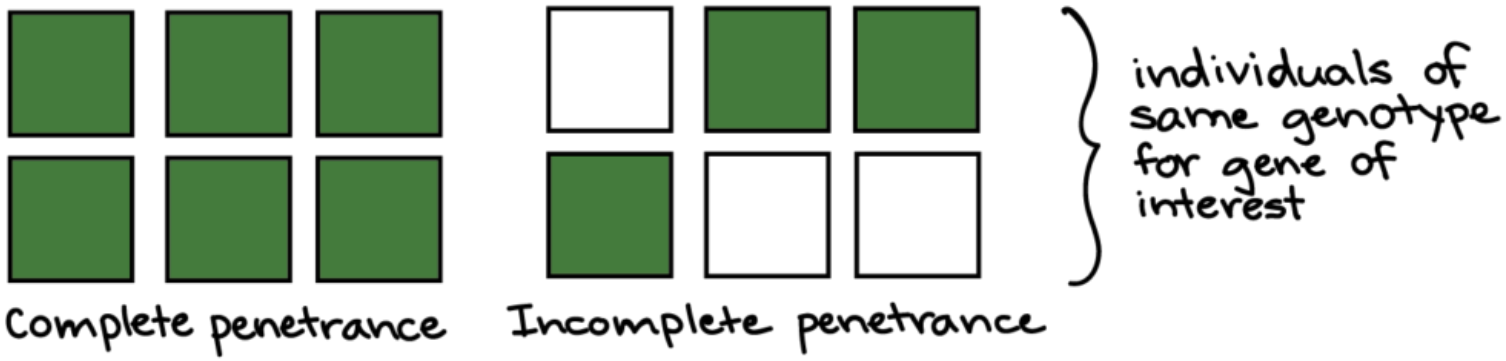
- **Most conditions discussed inherited in Autosomal Dominant pattern**
- **Some conditions there is risk for disease if inherited paternally**
  - e.g. *SDHD, SDHAF2*
- **Testing of relatives recommended**
  - Consider screening guidelines



Screening Guidelines

- **Identifying susceptibility allows for targeted surveillance recommendations**
  - Consider cost, time, risk/benefit, anxiety
- **Well-established for certain conditions: VHL, MEN1, MEN2**
  - Updated periodically, reviewed at follow-up appointments
- **Evolving for hereditary PGL/PCC**
  - New penetrance data

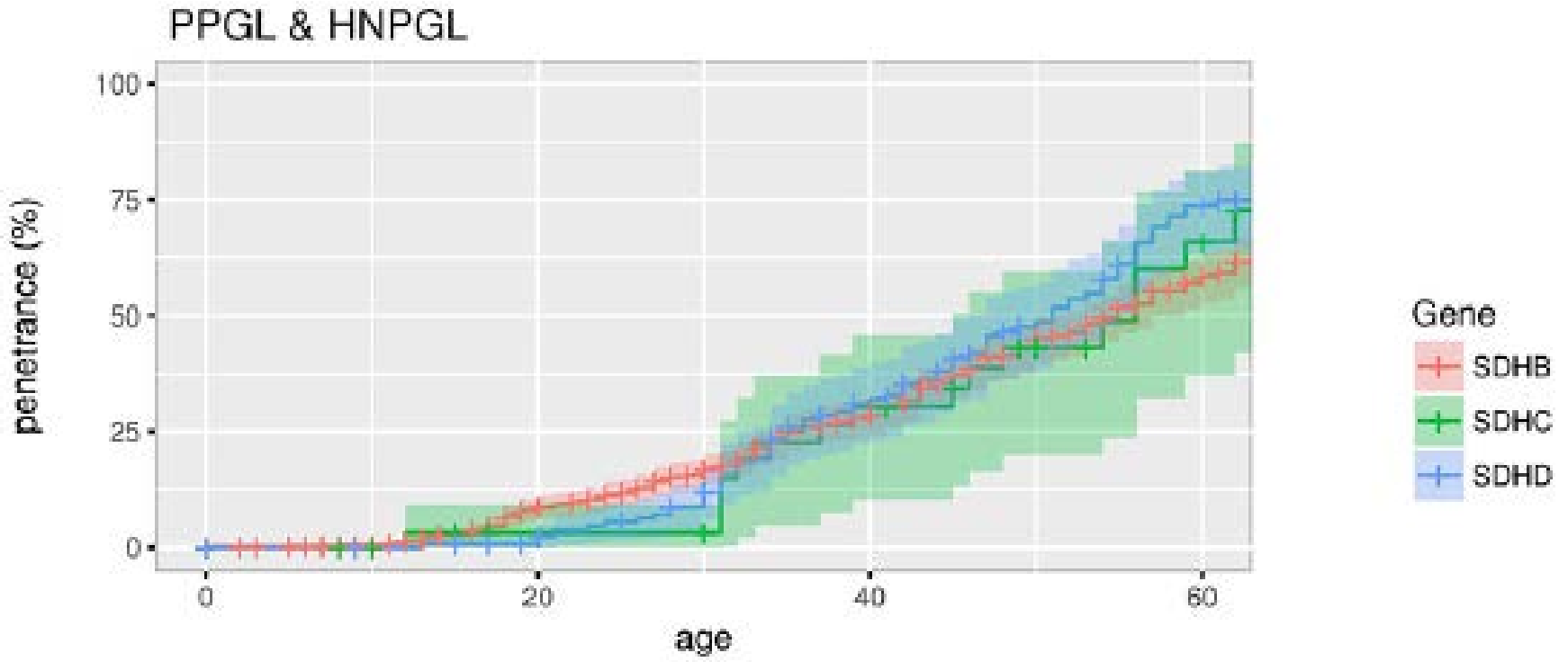
- **Penetrance = the proportion of individuals carrying a particular variant of a gene that express the associated trait**



Lumenlearning.com

Penetrance of SDHx Pathogenic variants

- **Previous risk estimates based on affected individuals (probands)**
- **Now collecting more data from family members**



Andrews et al, 2018

Penetrance of SDHx Pathogenic Variants

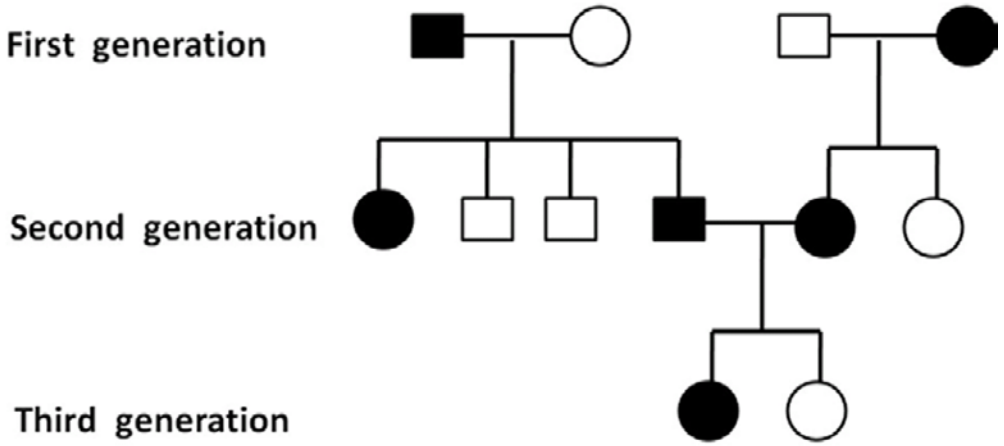
Risk estimates are evolving

Gene	Age	Penetrance of PGL/PCC – family members	Penetrance of PGL/PCC – proband and family members
SDHA	70	10%	50%
SDHB	60	22.5%	60.2%
SDHC	60	25%	75%
SDHD	60	50%	79%

Van der Tuin et al, 2018
Andrews et al, 2018

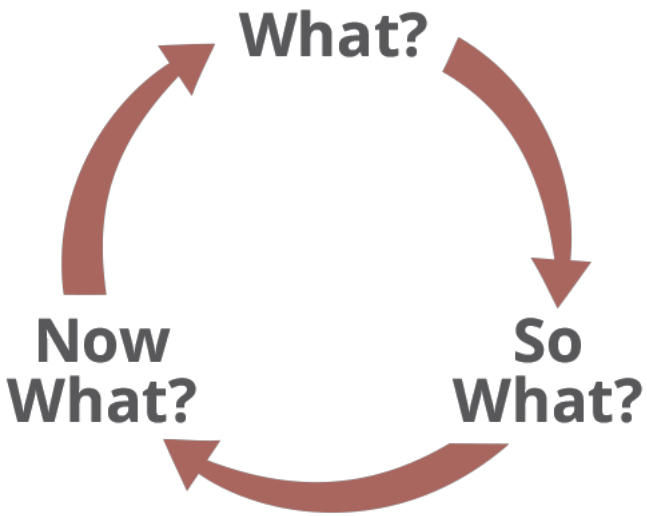
I’ve been referred to genetics, what now?

- **Evaluation with a geneticist and/or genetic counselor**
  - Review of medical history
  - Family history
  - Physical exam
  - Discussion of testing
- **Sometimes a clinical diagnosis can be made**
- **Genetic testing via blood or saliva sample**
  - Testing recommended based on personal and family history



Something has been identified, what now?

- **Screening and management discussion**
  - Follow-up periodically to review updates to recommendations
- **Familial testing**
  - Targeted for the same variant detected
  - Depending on the gene, determines the age at which testing would be recommended
- **Review inheritance and reproductive options**
  - Prenatal testing
  - Preimplantation genetic diagnosis with IVF
  - Egg/sperm donation
  - Adoption



Testing was recommended and was uninformative…

- **Uninformative testing: Variants of unknown significance, normal test results**
- **Continue management with available clinical information**
- **Check back in with genetics every 2-3 years**
  - Update personal and family history
  - Improvements in technology
  - New genes could be discovered
  - Variants can be re-classified

For sporadic cases, or no hereditary cause identified…

- **For neuroendocrine tumors, no evidence that clinical screening family members is indicated**

Summary

- **Most cases of NETs are sporadic**
- **Consider genetics evaluation:**
  - Anyone with a paraganglioma or pheochromocytoma (up to 40% have an identifiable hereditary cause)
  - If there is suspicion for a syndrome (e.g. MEN1, MEN2, VHL)
  - Multiple primary tumors
  - Family history
    - Known genetic predisposition syndrome
      - Most are autosomal dominant
      - Best to send genetic testing first for a known, affected individual
    - Early ages at diagnosis
    - Multiple generations affected
    - Multiple members of a generation affected
- **Gene mutations are associated with prognostic implications and management decisions**
- **Research is ongoing**

Penn Medical Genetics Neuroendocrine Team

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