UCSF Helen Diller Family Comprehensive Cancer Center

Genetics of Neuroendocrine Tumors: When to think of it

World NEN Lives 2020 Patient Virtual Conference

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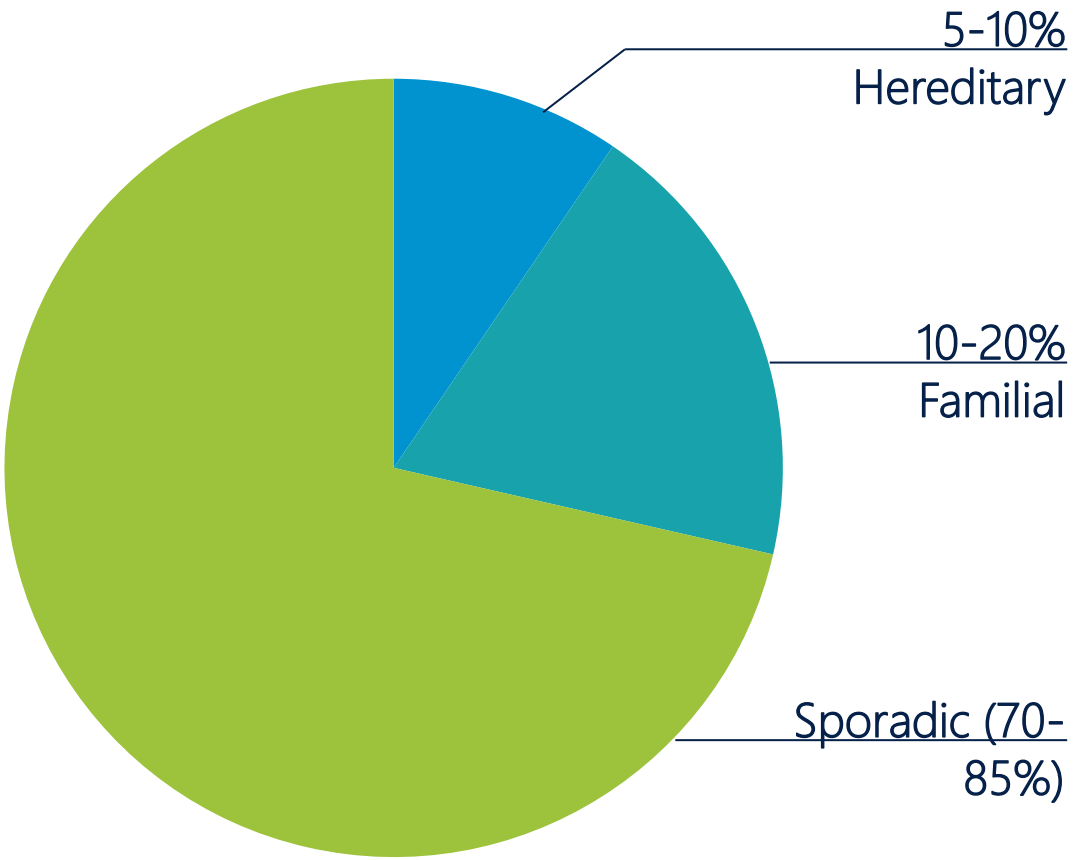
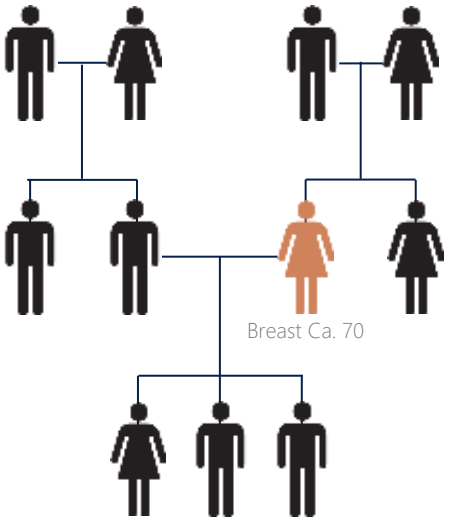
- How much cancer is hereditary?
- What is a mutation?
- How do you test for germline alterations?
- Neuroendocrine tumor genetics and syndromes

Most cancer is sporadic, i.e. not inherited



Sporadic

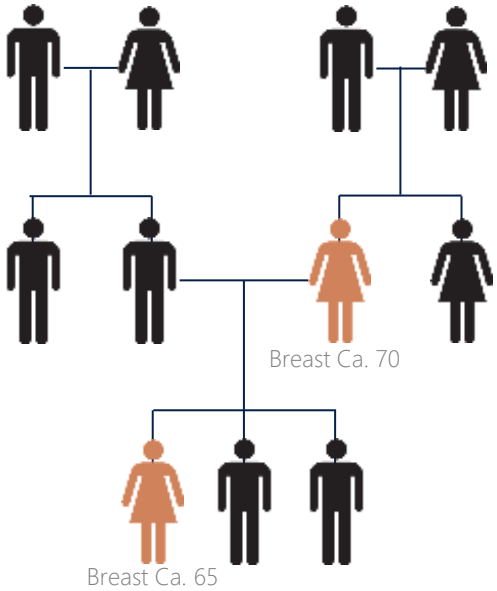


- ★ Single affected individual
- ★ Average or older for that type of cancer
- ★ Relatives usually at no increased risk

Direct Exposures
(smoking, chemicals, radiation, etc)

Unknown factors

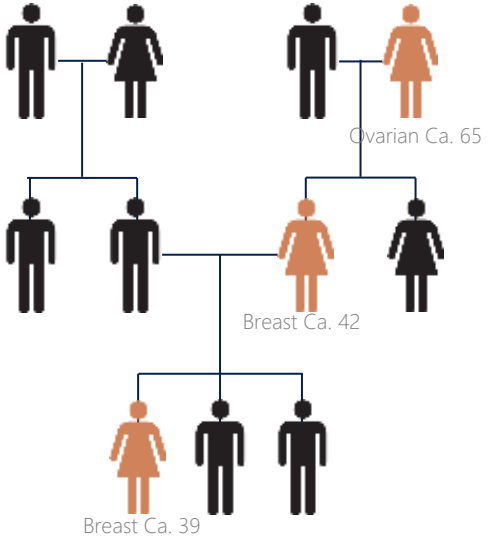
Familial



- ★ Clustering of cancers
- ★ Average or older for that type of cancer
- ★ Relatives at moderately increased risk

Genes + Environment
(same diet, lifestyle, environment, + shared genetic background)

Hereditary

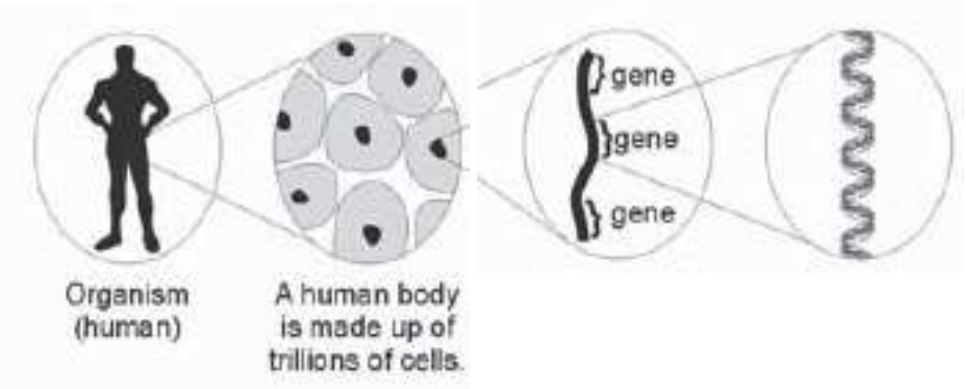


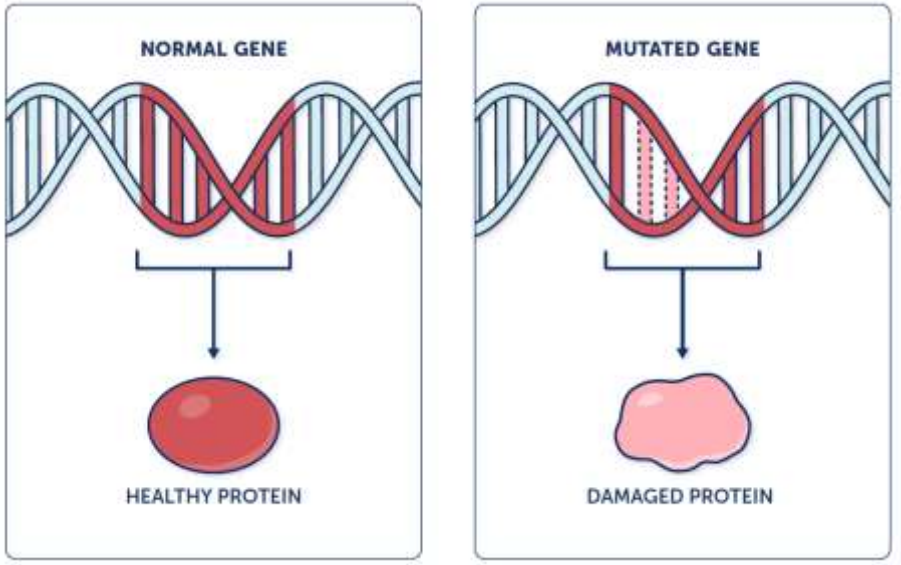
- ★ Multiple affected individuals
- ★ Younger than average age of onset for that cancer type
- ★ Multiple generations
- ★ Can test for single gene mutation

Caused by a single gene mutation

What is a mutation?

In every cell we have ~20,000 different genes





- A gene =functional unit of heredity. Genes are made up of DNA.
- Some genes act as instructions to make molecules called proteins.
- Mutation = permanent alteration in the DNA sequence of a gene, such that it differs from what is found in most people
- Sometimes, gene mutations cause proteins to malfunction or to be missing entirely.
- When a mutation alters a protein that plays a critical role in the body, it can disrupt normal development or cause a medical condition (like cancer).

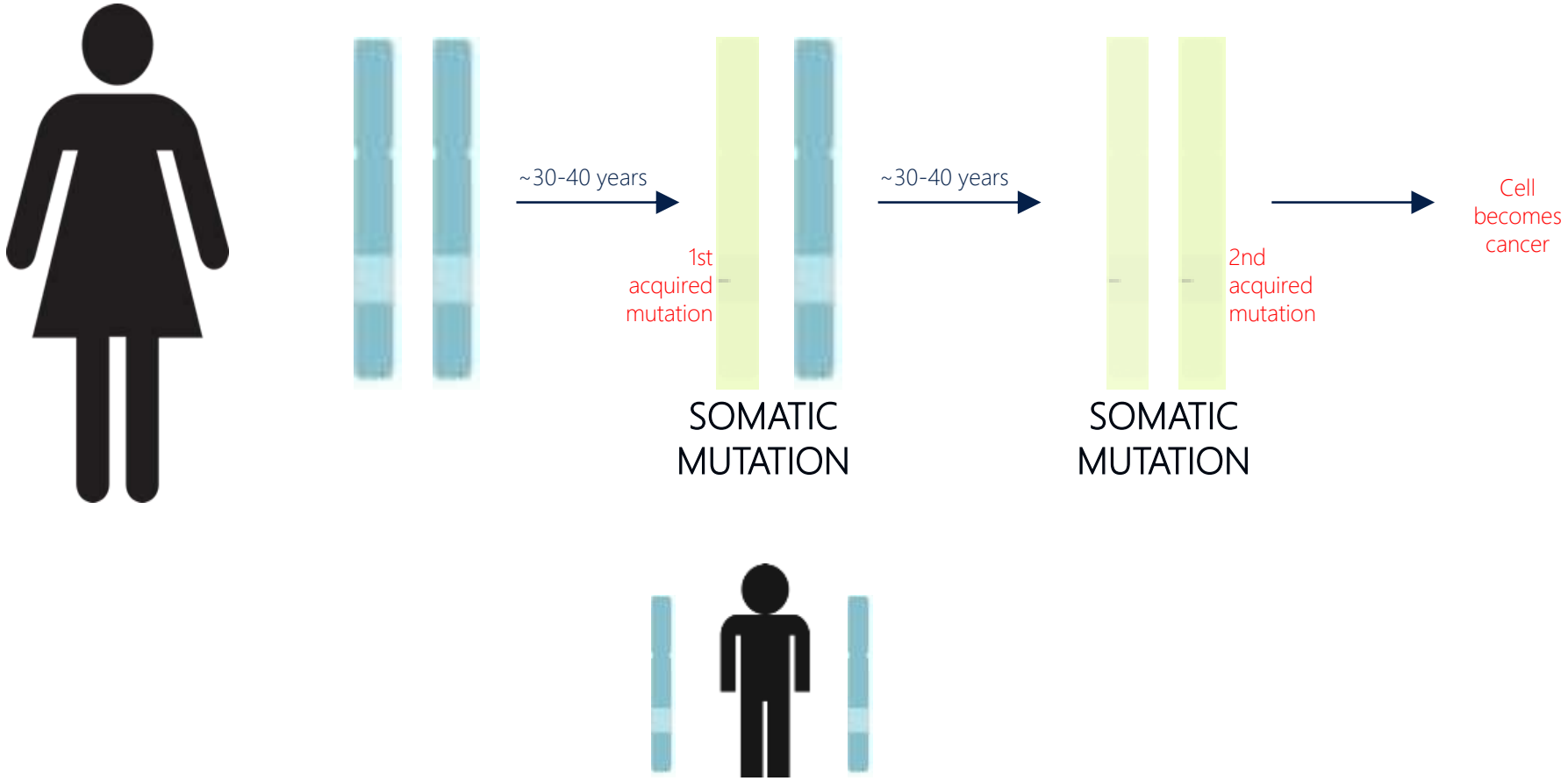
Mutations: 2 kinds

- Hereditary
  - inherited from a parent and are present throughout a person's life in virtually every cell in the body
  - also called germline mutations because they are present in the parent's egg or sperm cells, which are also called germ cells.

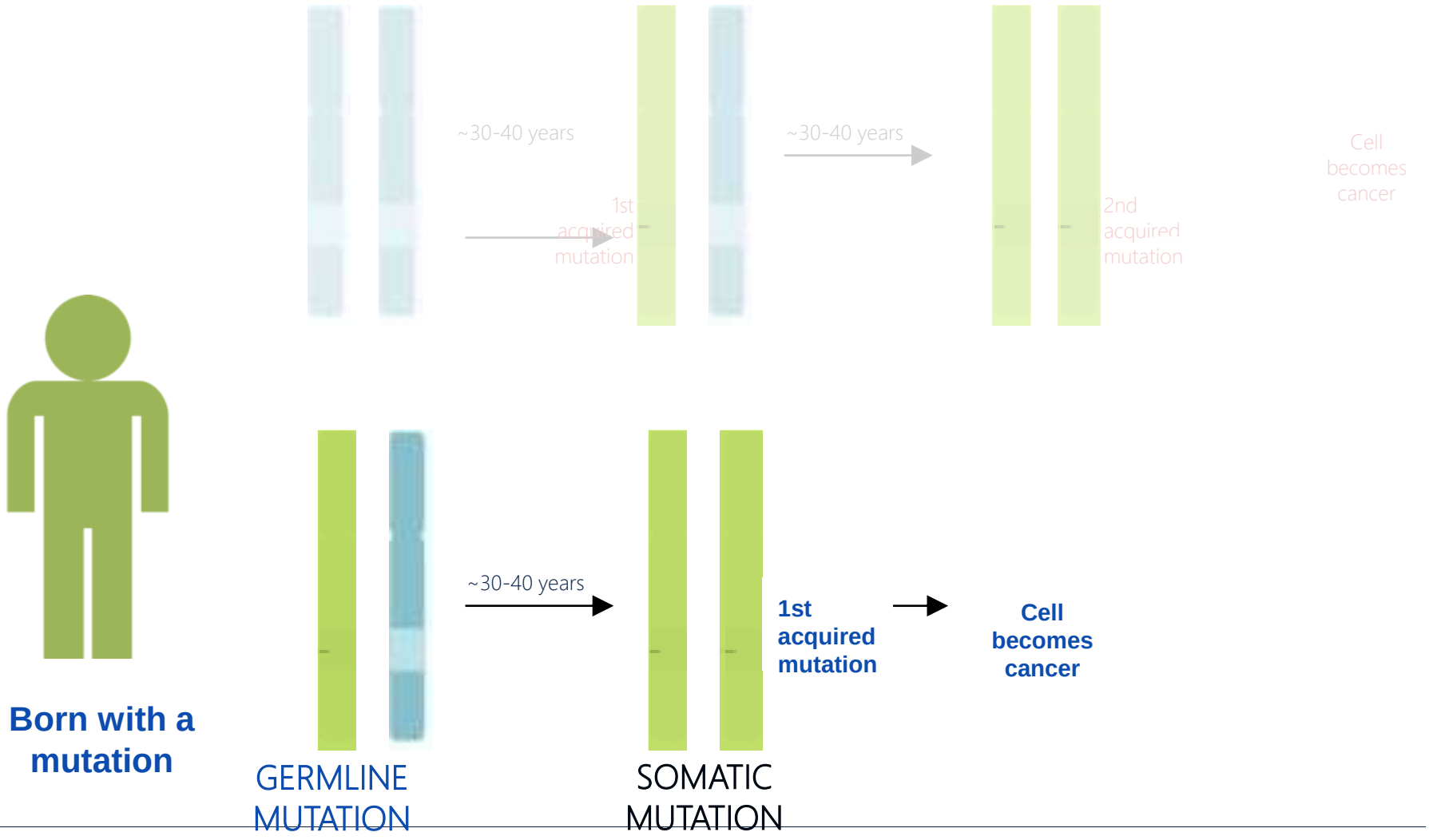
- Acquired (or somatic)
  - mutations occur at some time during a person's life and are present only in certain cells, not in every cell in the body.
  - can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if an error is made as DNA copies itself during cell division.
  - Can't be passed to the next generation

https://ghr.nlm.nih.gov/primer/mutationsanddisorders/genemutation

Sporadic (most common) cancer formation:

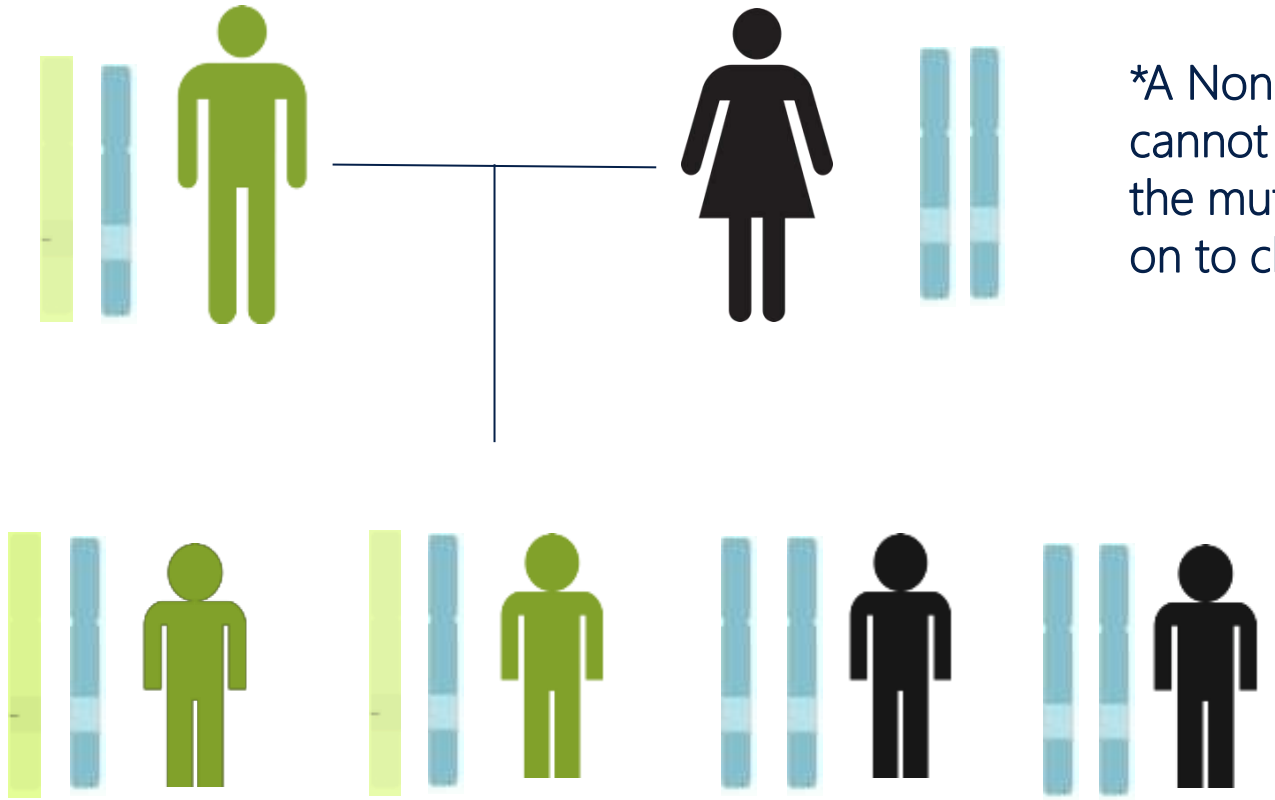


Hereditary cancer formation:



Dominant Inheritance

One Parent has the genetic mutation



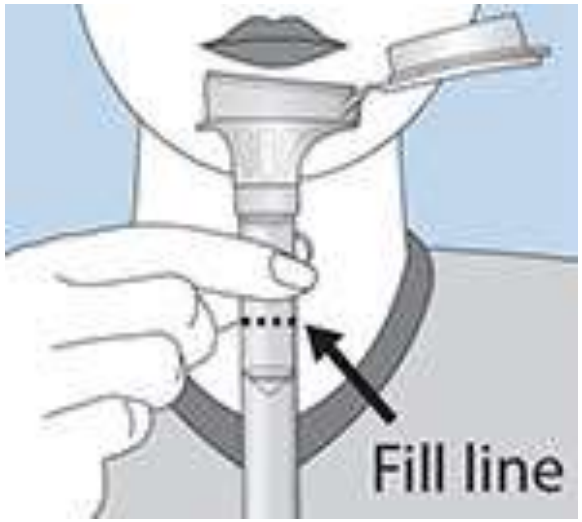
*A Non-Carrier cannot pass the mutation on to children.

50% Carry Cancer Risk Mutation

50% Non-Carriers

How do you test for germline mutations?

We can test with saliva or blood



Single gene or multigene panel

There are 3 possible results

NEGATIVE

Negative for the genes tested. Important to consider if there is a known mutation in your family

VUS *Variant of Uncertain Significance*

Unknown at this time if change identified is harmful

POSITIVE

Positive for a gene that increases the risk of cancer

Medical management based on personal and family history of cancer

Deleterious/suspected pathogenic: Medical management based on cancer risk specific to gene mutation

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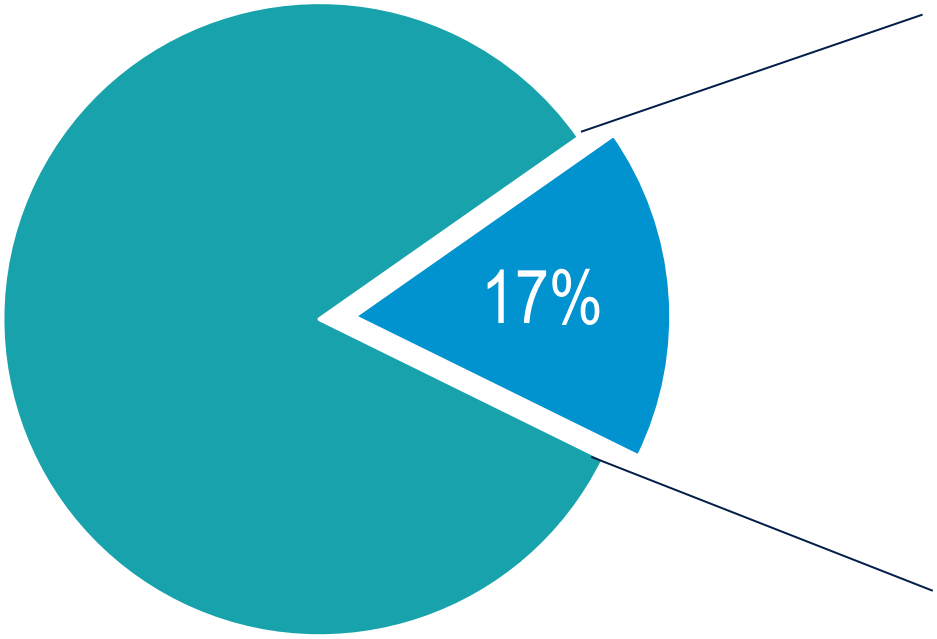
Benefits, Risks and Limitations of Testing

Benefits	Risks	Limitations
• provides explanation for cancer • results may inform medical management (screening, treatment) • may provide information for family members	• psychological impact (pathogenic mutation, VUS) • normal result could give false reassurance • Potential for insurance/employment discrimination	• Negative result most helpful when a familial mutation is known • Testing may not pick up all known alterations • Significance of VUS unclear

Genetic syndromes and NETs

Pancreatic Neuroendocrine Tumors (pNETs)



Germline (inherited) mutations in 17% of patients, e.g.

- **MUTYH**
- **CHEK2**
- **BRCA2**
- **MEN1**
- **VHL**

GERMLINE TESTING: if multiple panNET or feature of another syndrome is present

Scarpa, et al. Nature, 2017; Hampel et al. Genetics in Medicine, 2015

Paraganglioma/pheochromocytoma

Pheochromocytoma/Paragangliomas (PPGL)

- Autosomal dominant
  - Prevalence 1:36,000
- Paragangliomas- NET of the head, neck, chest, or abdomen
- Pheochromocytomas- arise in adrenal gland (medulla)
- Some tumors associated with catecholamine excess (sweating, rapid heart rate, high blood pressure)

Pheochromocytoma/Paragangliomas (PPGL)

- >40% attributed to germline alteration
  - Of these, 80% from alteration in *SDHx* or *VHL*
  - Many other genes implicated
- Syndromes vary- mutation, site of origin, hormone production and other features
- Germline testing indicated in all patients

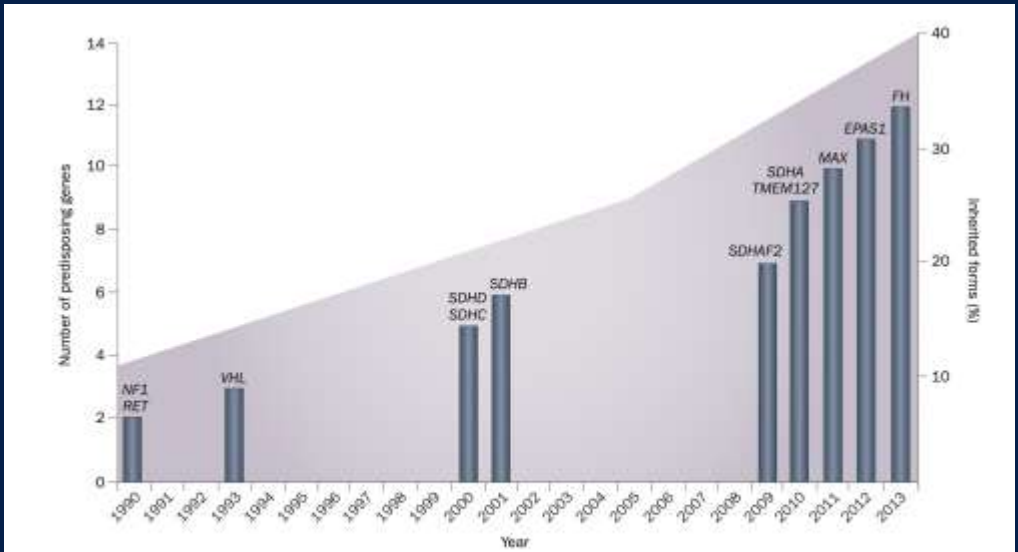


Figure 1 | Timescale of the discovery of PPGL susceptibility genes. The cumulative number of susceptibility genes and the year of identification for each of them are illustrated by the histograms. The curve highlights the increase in the percentage of known inherited forms of PPGL through time. Abbreviation: PPGL, phaeochromocytoma and/or paraganglioma.

Favier, et al. Nat Reviews Endocrinology, 2015

Pheochromocytoma/Paragangliomas (PPGL)

Table 1 | Genes and diseases

Disease (phenotype MIM numbers)	Genes	Mutation rate (%)*	Main features
Neurofibromatosis type 1 (162200)	*NF1*	3	Café-au-lait spots, neurofibromas, axillary and inguinal freckling, Lisch nodules, osseous lesions, optic gliomas, mainly phaeochromocytomas
Multiple endocrine neoplasia type 2 (171400; 162300)	*RET*	6	2A: Medullary thyroid cancer, primary hyperparathyroidism, PPGL 2B: Medullary thyroid cancer, PPGL, Marfanoid habitus, mucocutaneous neuromas, gastrointestinal ganglioneuromatosis
von Hippel–Lindau disease (193300)	*VHL*	7	Central nervous system or retinal haemangioblastomas, renal cell carcinoma, PPGL, pancreatic neuroendocrine tumours and cysts, endolymphatic sac tumours, papillary cystadenoma of the epididymis and broad ligament
Hereditary paragangliomas (168000; 605373; 115310; 601650; 614165)	SDHx genes: *SDHB* *SDHD* *SDHC* *SDHA* *SDHAF2*	 10 9 1 <1 <0.1	 PPGL, rare renal cancers, GIST PPGL, rare renal cancers, GIST PPGL, rare renal cancers, GIST PPGL, GIST Head and neck paraganglioma
Familial phaeochromocytomas (173300; 613403; 154950)	*TMEM127* *MAX*	1 1	Mainly phaeochromocytomas, rare renal cancers Mainly PPGL
Polycythemia paraganglioma syndrome (603349)	*EPAS1*	1	Polycythemia, PPGL, somatostatinoma
Leiomyomatosis and renal cell cancer (150800)	*FH*	1	Cutaneous and uterine leiomyomas, type 2 papillary renal carcinoma, rare PPGL

*The mutation rate is the percentage of patients with PPGL with mutations in the gene concerned. Abbreviations: GIST, gastric stromal tumours; MIM, Mendelian Inheritance in Man; PPGL, paraganglioma and/or phaeochromocytoma.

Favier, et al. Nat Reviews Endocrinology, 2015

Screening considerations: Familial and SDX-related PPGL

- Physical examination with blood pressure monitoring every year
- Metanephrine level determination every year
- Whole-body MRI every 2 or 3 years
- Begin 5 years before youngest age of onset in family?
- Begin 5 y/o (SDHB), 10 y/o (for other mutations)?

Favier, et al. Nat Reviews, 2015
Muth, et al JIM, 2018
Wong, et al. Clinical endocrinology, 2019

MEN1

Multiple Endocrine Neoplasia-Type 1 (MEN1)

- Autosomal dominant
- Prevalence 1-10/100,000
- Mutation in *MEN1* gene in 95%
- Must have at least 2 classic (25% + germline):
  - Parathyroid adenoma -Typically benign
  - GI/pancreas NET
    - Well differentiated PanNET (gastrinoma, insulinoma)-20% gastrinoma germline
  - bronchial/thymic NET (carcinoids)
  - Pituitary tumor (seen in 90%, usually by 25 y/o)-prolactinoma most common

- OR 1st degree relative w MEN1, PTH adenoma before age 30 (or more than one), 2+ MEN1 tumors but not from classic triad

- Also-skin findings (angiofibromas, collagenomas, ffibromas)

Screening considerations for MEN1

- Screening begins between age 5-20

- parathyroid adenomas -blood tests (age 8)
- pituitary tumors -pituitary MRI every 3-5 yr (age 5)
- GI/panc neuroendocrine tumors and adrenal cancers (age 5-10)
  - blood tests
  - imaging with MRI/CT of the abdomen
- thoracic tumors - chest (CT/MRI) imaging every 1-2 yr (age 15)

- Screening depends on local resources, clinical judgment and patient preferences

Thakker, et al. JCEM, 2012

MEN2

Multiple Endocrine Neoplasia Type 2 (MEN2)

- Autosomal Dominant
- Prevalence is 1:35,000
- Caused by mutations in the *RET* gene
- Medullary Thyroid Cancer (MTC)

3 subtypes:

1. *MEN2A*
2. *MEN2B*
3. *Familial medullary thyroid carcinoma (FMTC)*

MEN2 Subtypes

MEN2A (70-80%)	MEN2B (5%)	FMTC (10-20%) Familial Medullary Thyroid Cancer
Hyperparathyroidism (20-30%)		
Pheochromocytoma (50%)		
Medullary thyroid cancer (MTC)		
MTC in young adults	MTC in childhood	MTC in middle age
+/- cutaneous lichen amyloidosis (CLA); pruritic CLA	• "marfanoid" body habitus • Neuromas =lips, tongue, eyelid; • Distinctive facial features/enlarged lips • Diffuse ganglioneuromatosis of GI tract (84%)	

MEN2 Testing & Screening recs: Depend on mutation

American Thyroid Association (ATA) Risk per RET Mutation

RET *mutation*[a]	*Exon*	*MTC risk level*[b]	*Incidence of PHEO*[c]	*Incidence of HPTH*[c]
G533C	8	MOD	+	–
C609F/G/R/S/Y	10	MOD	+/++	+
C611F/G/S/Y/W	10	MOD	+/++	+
C618F/R/S	10	MOD	+/++	+
C620F/R/S	10	MOD	+/++	+
C630R/Y	11	MOD	+/++	+
D631Y	11	MOD	+++	–
C634F/G/R/S/W/Y	11	H	+++	++
K666E	11	MOD	+	–
E768D	13	MOD	–	–
L790F	13	MOD	+	–
V804L	14	MOD	+	+
V804M	14	MOD	+	+
A883F	15	H	+++	–
S891A	15	MOD	+	+
R912P	16	MOD	–	–
M918T	16	HST	+++	–

Screening– usually begins < age 5: ultrasound, RET testing, calcitonin (age of thyroidectomy also varies)

Wells, et al. (ATA Guidelines Task Force) Thyroid, 2015

MEN4

Multiple Endocrine Neoplasia Type 4 (MEN-4)

- Mimics MEN1
- Germline alteration of CDKN1B

- Parathyroid tumors
- Pituitary tumors
- Other endocrine gland tumors

Von Hippel Lindau (VHL)

Von Hippel-Lindau Syndrome *(VHL)*

- Autosomal Dominant
- Prevalence is 1:36,000
- Caused by mutations in the *VHL* gene

- Suspect if
  - Retinal (eye) angioma, especially in a young individual (benign)
  - Spinal or cerebellar hemangioblastoma (benign)

  - Pheochromocytoma
  - Kidney cancer (early onset or family history)
  - Neuroendocrine tumors of the pancreas (pNETS)

  - Multiple renal and pancreatic cysts
  - Endolymphatic sac tumors
  - Less commonly, multiple papillary cystadenomas of the epididymis or broad ligament

Screening considerations for VHL

- Ages 1-4: annual eye exam
- Starting at 5 years old: blood pressure measurements, dilated eye exams, annual plasma or 24 hr urine for metanephrines
- Starting at age 16: annual US of abdomen; MRI of brain/abdomen every 2 years

Other syndromes associated with NETs

- Neuroendocrine Tumors can by found in several other syndromes as well
  - Neurofibromatosis (NF1 or NF2)
  - Tuberous Sclerosis (TSC1 or TSC2)
  - Lynch syndrome (MLH1, MSH2, MSH6, MS2, EPCAM)
  - and others
- Overlap between syndromes

Genetic syndromes and NETS

NET	Syndrome	Test
Pancreas NETs (about 15% germline)	• MEN1 • MEN4 • Von Hippel Lindau (VHL) • Neurofibromatosis type 1 (NF1) • Tuberous sclerosis complex (TSC) • CHEK2, BRAC2, MUTYH	• **If multiple or another feature of a syndrome** • **Gastrinoma**
GI NETs (rare)	• VHL • MEN1 (MEN4) • NF1 (duodenal somatostatinoma)	• **If another feature of syndrome**
Lung/thymic NETs (rare)	• MEN1 (MEN4)	
Pheochromocytoma/ Paraganglioma (PPGL) (about 35-40% germline)	• Von Hippel Lindau • MEN2 • Other hereditary PPGL syndromes (e.g. succinate dehydrogenase syndromes, SDHx- and others)	• **Every patient**
Medullary thyroid cancer (MTC) (25%+ inherited)	• MEN2	• **Every patient**

Key points:

- Most NENs are not hereditary- Most people who undergo testing will not have a germline mutation
  - EXCEPTIONS: 40% PPGL or 25% MTC (hereditary)
- Having a germline mutation doesn't mean you have cancer; it just means you have a higher risk for developing it
  - Allows us to implement a screening plan with the goal of identifying growths early, so they don't turn into something more dangerous.
- Not all patients with a germline alteration have a positive family history
- Not all tumors associated with genetic syndromes are malignant (some are benign)
- Genetic counselors can help guide you through germline testing, and review of results and screening recommendations

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