“Neuroendocrine Tumor (NET) Genetics”

Robert L. Nussbaum, MD

Cancer Risk Program

Helen Diller Family Comprehensive Cancer Center at UCSF

Hereditary Tumors

- There are multiple affected family members because they share **an inherited gene mutation** that causes a greatly increased risk for cancer, generally 5-fold or more (sometimes MUCH more), over the risk for that tumor in the general population.
- Hereditary tumors make up a varying percentage of all tumors, depending on the particular type.

Sporadic Tumors

- The tumor results from a gene change in one tissue in a one individual and is not present in the germline, the cells that go to make eggs or sperm. It cannot be passed on.

Familial Tumors

- Even when there is no clear hereditary pattern, there may still be a ***familial tendency*** to develop a tumor. There just seems to be “too many” tumors in family members but without a clear inheritance pattern.
- The increase in risk is moderate, usually about 2-fold over the general population.

NETs are Caused by Alterations in Genes

What does this mean?

All NETs result from changes (mutations) or other alterations in genes that disrupt the control of cell growth and migration

These changes are usually present just in the tumor cells themselves and not the rest of the body.

NETs are Caused by Alterations in Genes

This does NOT mean all NETs are hereditary

In fact, 75-95% NETs (depending on the particular NET) are NOT hereditary

but still involve changes in genes

Germline and Somatic Mutations

- **Germline:** Already present at the time of conception and therefore present in every cell of the individual, including sperm and eggs. They can therefore be passed on to the next generation.
- **Somatic:** Occur after conception and are present in only some cells or some tissues. If not in the germline, they are not passed on to the next generation.

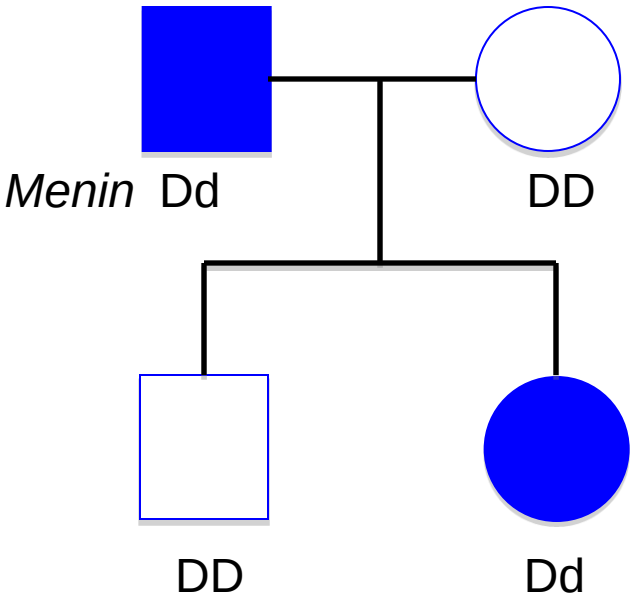
Germline and Somatic Mutation

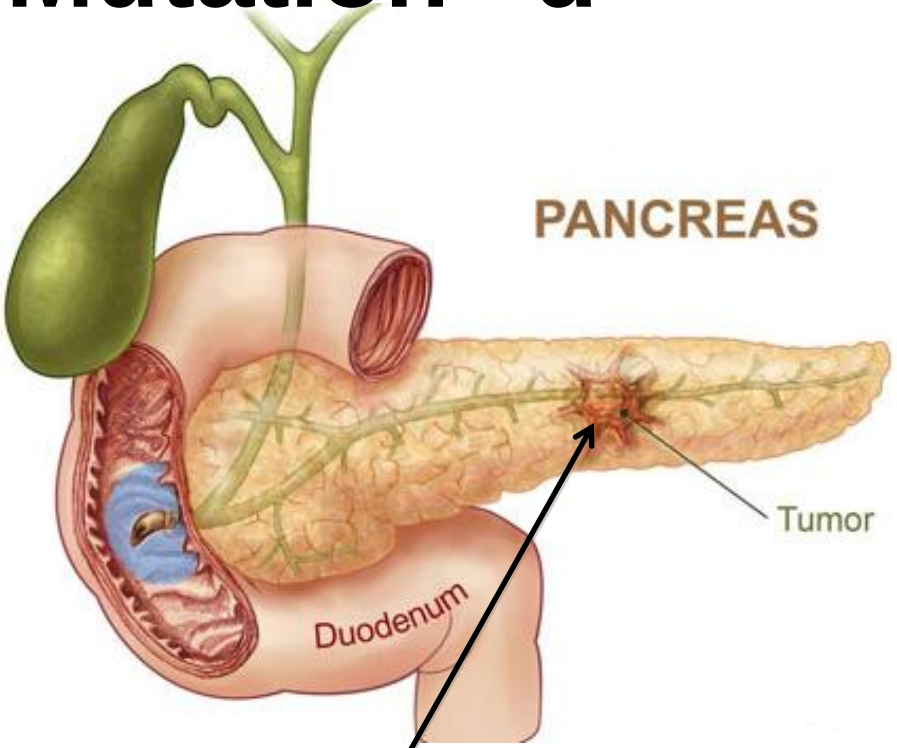
- Hereditary Cancers result from germline mutations present in every cell that can be passed to the next generation.
- Sporadic cancers begin because of an altered gene in one cell.

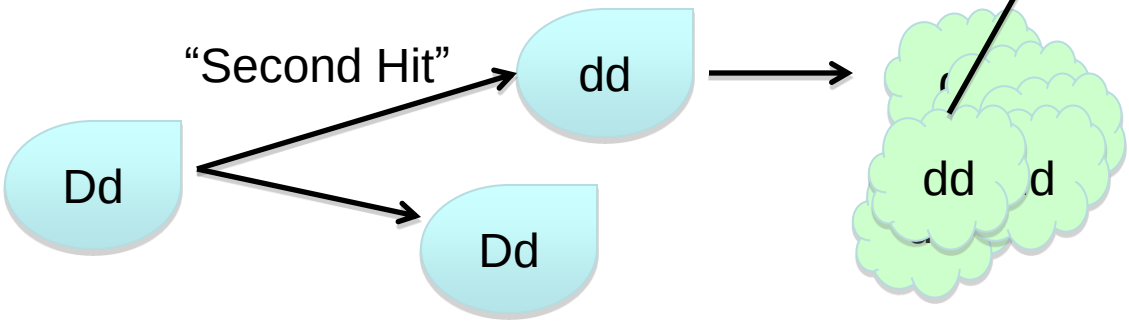
Red Flags for Hereditary or Familial Cancer Syndrome

- Family History
- Early Age at Onset
- Two or more tumors of the same type in an individual (not a recurrence, but a second independent primary)
- Multiple Tumors in the same person

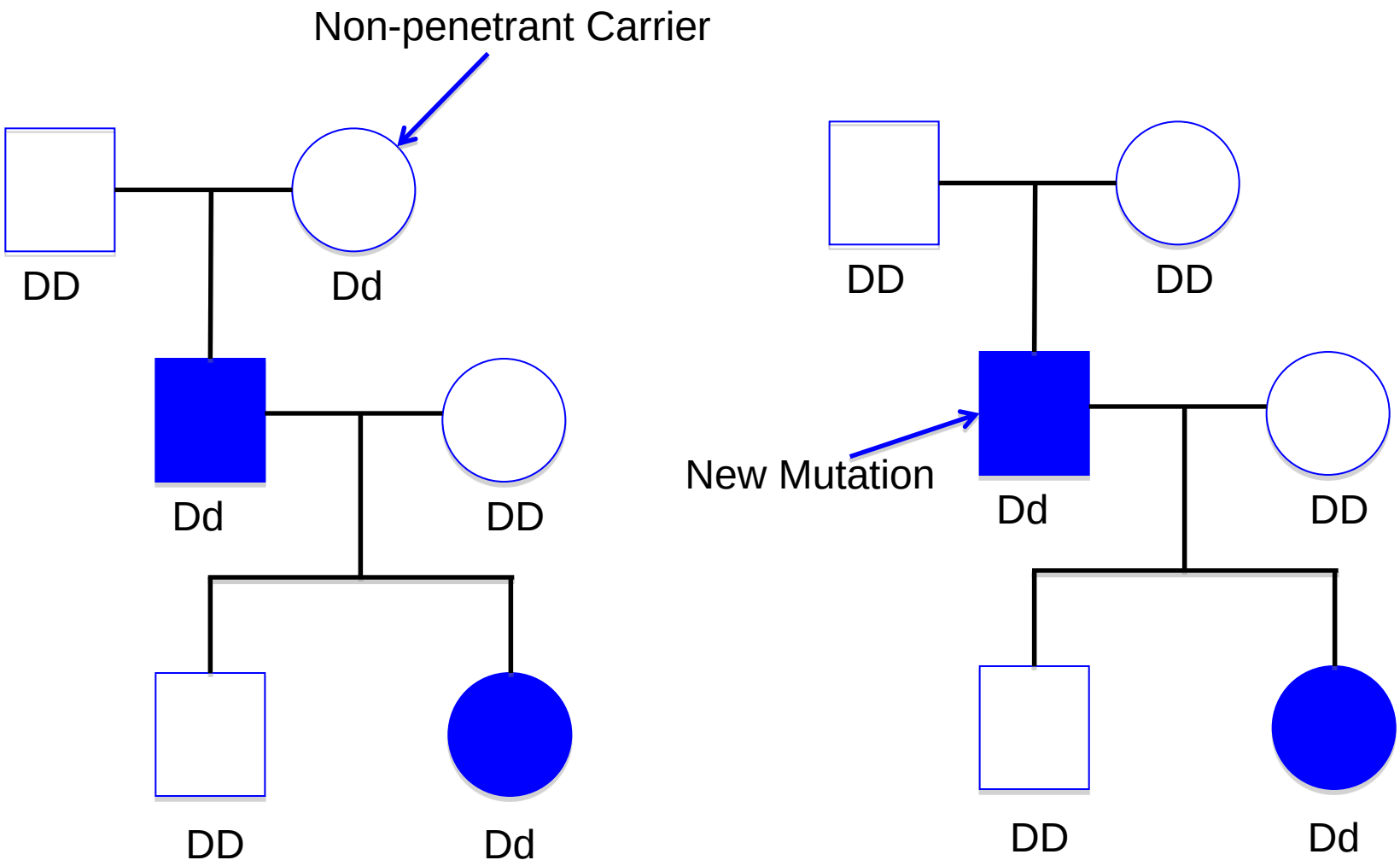
Autosomal Dominant Inheritance of a Menin Mutation “d”







Inheritance of MEN1: Pattern and Special Features



Multiple Endocrine Neoplasia Type I (MEN1)

- Parathyroid tumors – 90% by age 50
- Pancreatic/Gastric Neuroendocrine 30-70%
  - Gastrinoma 40%
  - Insulinoma 10%
  - Non-functioning 20-25%
  - Glucagonoma, VIPoma rare
- Adrenal cortical tumor – 40%
- Bronchopulmonary carcinoid 2%
- Thymic carcinoid – 2%

Multiple Endocrine Neoplasia Type I (MEN1) (cont.)

- Lipomas 30%
- Skin tumors 70-85%
- Meningiomas 8%

MEN1 - Genetics

- Gene: Menin
- Autosomal dominant
- 10% de novo mutations
- Hyperparathryoid disease only
- Differential diagnosis (PHPT)
  - CASR, HRPT2

MENIN Testing in MEN1

	Familial	Isolated
Sequence variants	80%-90%	65%
Deletion /Dup	Exonic and whole-gene deletions	
	1%-4%	

A few other genes have been associated with MEN1

When to suspect MEN1

- Two or more same or different MEN1 associated tumors
- One MEN1 tumor and a close relative with MEN1
- Carrier of a mutation in the MEN1 gene

PRACTICAL APPLICATIONS OF CLINICAL GENETICS IN HEREDITARY CANCER SYNDROMES

Clinical Cancer Genetics in the care of families with hereditary cancer syndromes like MEN1

Benefits to the patient and family:

- Calculate Risks
- Provide Tailored Surveillance guidelines
- Gene Testing and Family Counseling clarify risk and either demonstrate or eliminate high risk status
- (Risk reduction strategies)

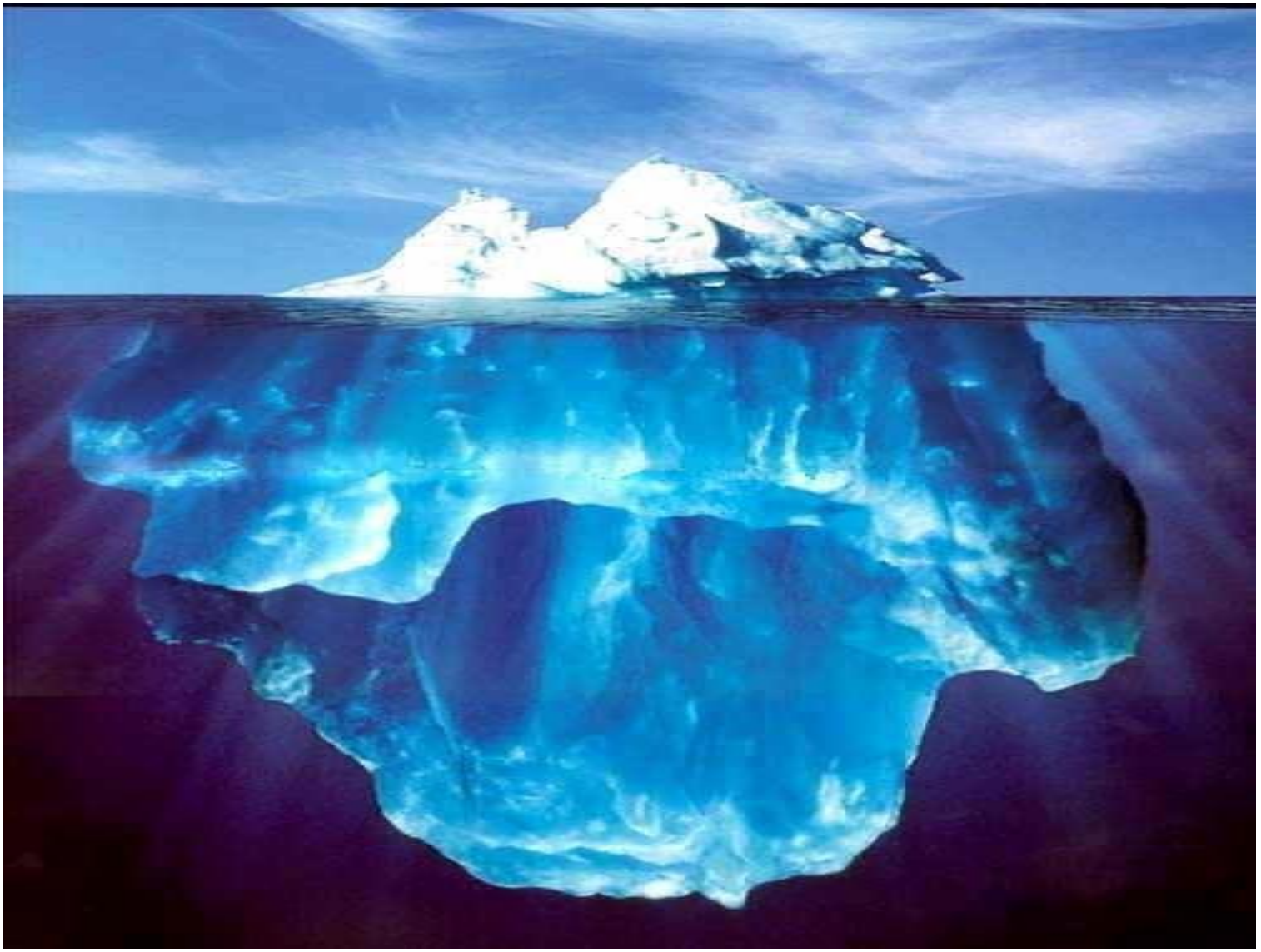
RISK

- Absolute Risk: “What is the chance I could develop a certain cancer?”

- Relative Risk: “How does my risk for developing a cancer compare to the risk in the general population?”

Find one person with a gene mutation

Now it is possible to alert other family members who may be at risk



Genetic Information Non-Discrimination Act (GINA)

- Federal Law
- Unaffected, disease-free carriers of a hereditary cancer-associated gene mutation do not have that disease Prohibits using genetic testing results in accepting or denying health insurance
- Prohibits using genetic testing results in employment
- Does not affect use of genetic testing results for life or long-term disability insurance


Thank you