DICER1 Syndrome

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Learning Objectives

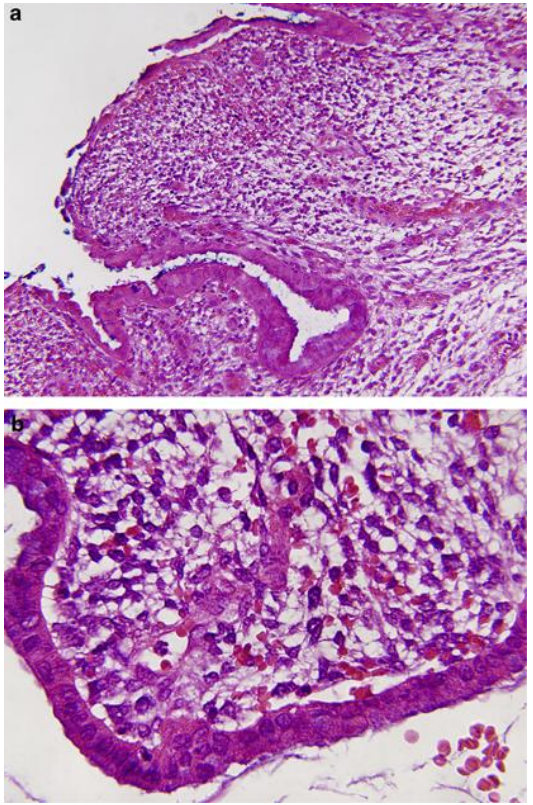
- Describe *DICER1* syndrome.
- Predict risk for *DICER1* syndrome for a patient with a rare tumor.
- Evaluate association of *DICER1* mosaicism and GLOW syndrome.
- Discuss cancer risks and management for individuals with *DICER1* mutations.

Patient Background

- 32 year old female developed heavy bleeding and went to a gynecologist.
- Gyn did a pap smear revealing a 3 cm embryonal rhabdomyosarcoma of the cervix.
- Currently in chemotherapy after excision of the polyp.
- Additionally, the patient was recently found to have a lung cyst.
- Family history: Cervical cancer in grandmother, prostate cancer in maternal grandfather, lung cancer in maternal grandmother.

Embryonic Rhabdomyosarcoma

- Can occur at any age, most common peaks are 1-5 yrs (90%), 15-19 yrs and 50-70 y.
- Very rare tumor. University of Tehran study found 6/1,528 cases of RMS among patients with genital tract malignancies (.39%).
- Uterine sarcomas comprise 2-6% of all malignant tumors of the uterus, fewer than 60 cases of rhabdomyosarcomas reported.
- Unique association in individuals with *DICER1* syndrome is ERMS of uterine cervix in older children and young adults.
- ERMS of the uterine cervix is highly characteristic of *DICER1* mutation.

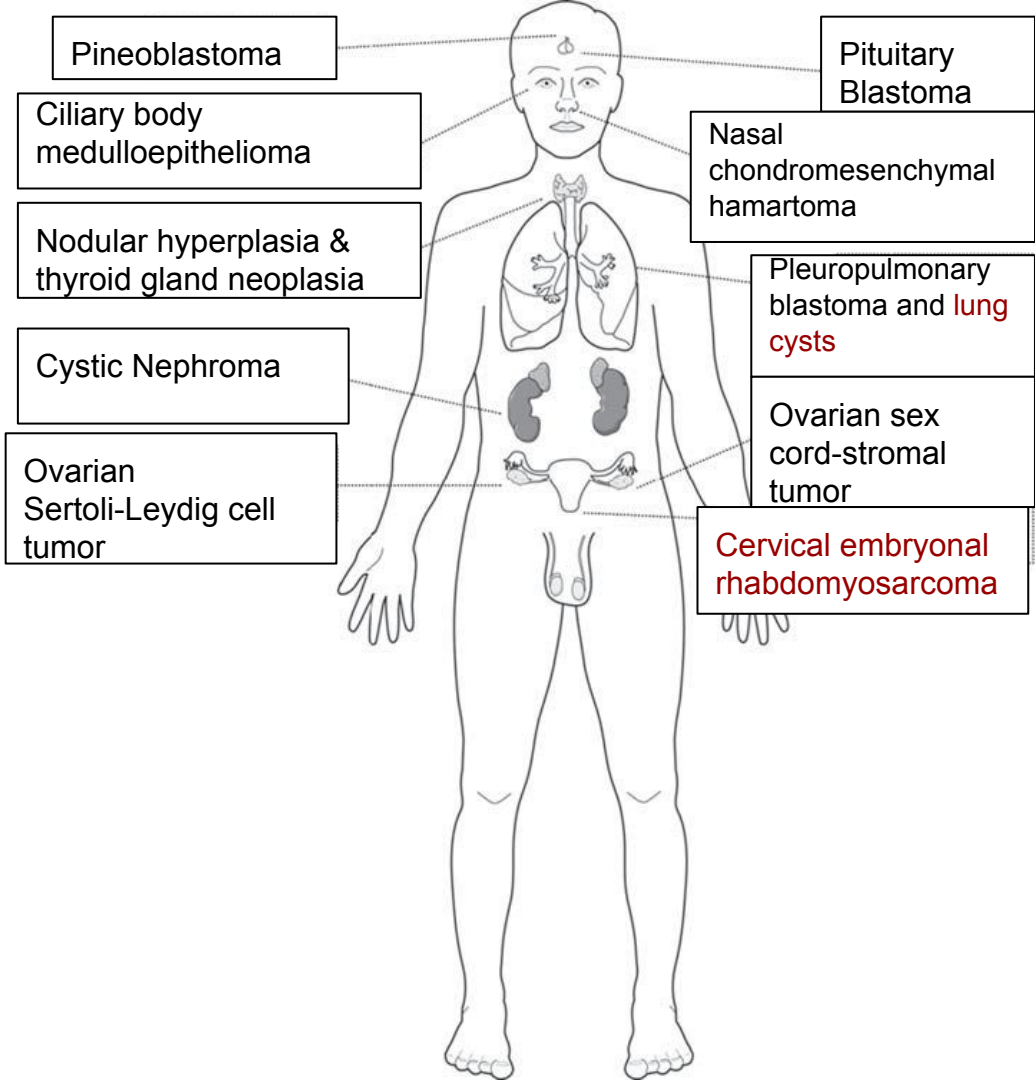


Differential Diagnosis

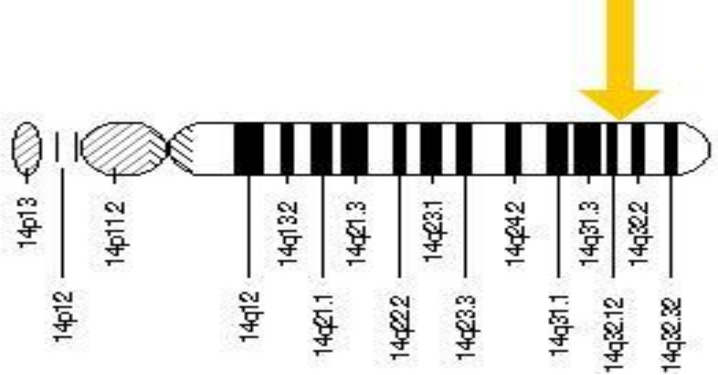
- 5-9% of childhood rhabdomyosarcomas associated with Li-Fraumeni Syndrome.
- 1% of childhood rhabdomyosarcomas associated with NF1.
- Occurs in cases of biallelic germline mutations in mismatch repair genes *MLH1, MSH2, MSH6* or *PMS2*.
    - Constitutional mismatch repair-deficiency.
    - Tumor spectrum: hematological neoplasias, brain tumors and Lynch syndrome-associated tumors.

DICER1 Syndrome

- Also known as *DICER1*-pleuropulmonary blastoma familial tumor predisposition syndrome.
- Autosomal dominant inheritance
- In individuals with pleuropulmonary blastoma, 80% were inherited and 20% were *de novo*.
- Decreased penetrance seen.
- *DICER1* located on chromosome 14q32.
- Prevalence: rare.

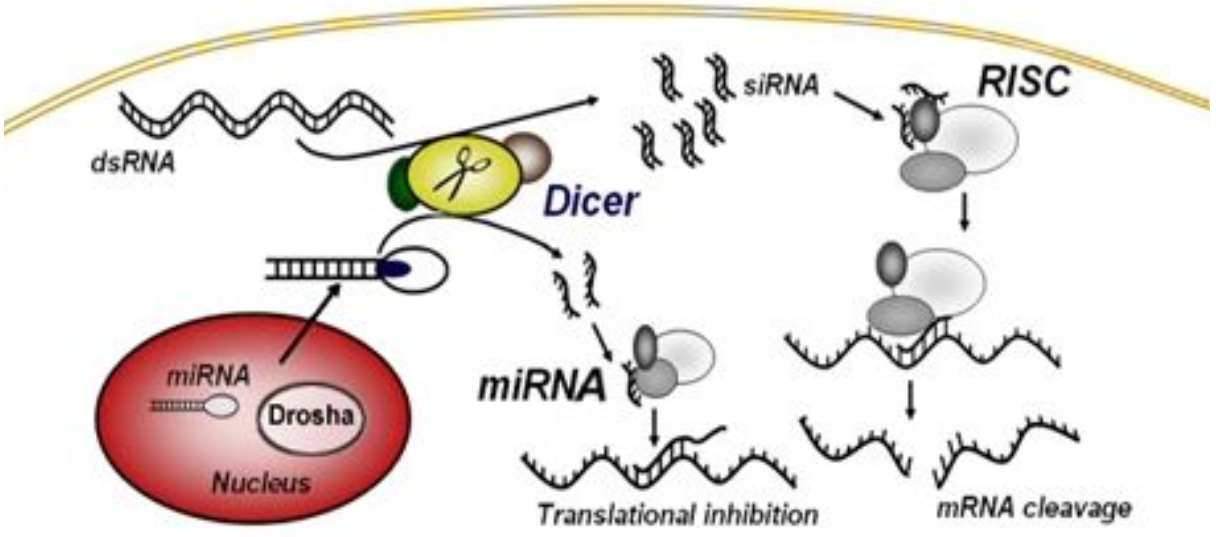


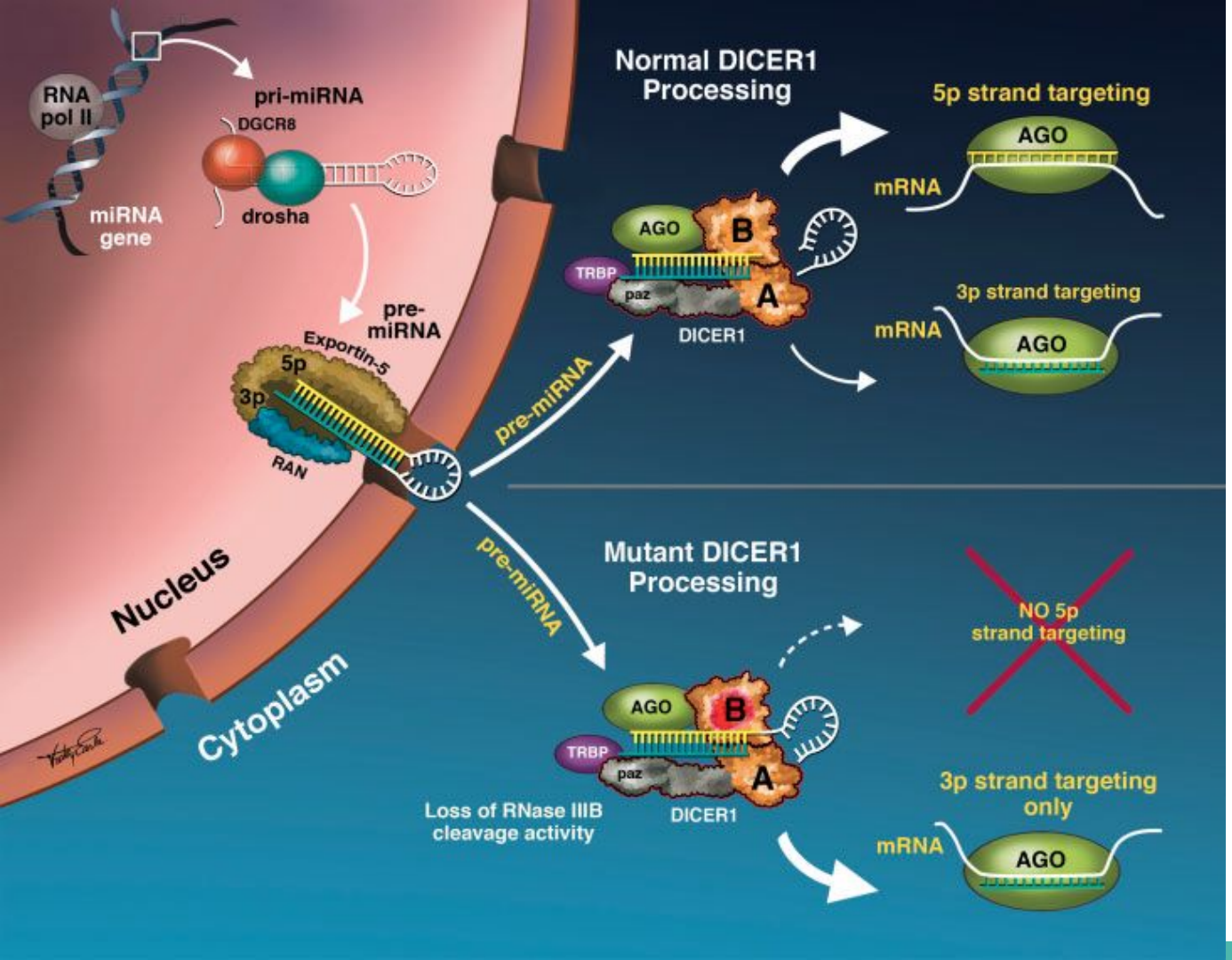
DICER1 Gene



- *DICER1* gene contains 1,922 codons.
- Mutations in germline are loss of function.
- Encodes DICER, an enzyme part of the RNase III family.
- Cleaves dsRNA resulting in siRNA, binds with RISC and guides to specific gene. SiRNA binds to the gene, resulting in cleavage of mRNA and turns off that gene.
- Cleaves miRNA, inhibits protein formation through translational inhibition.
- Tumor suppressor gene.

DICER1 Gene

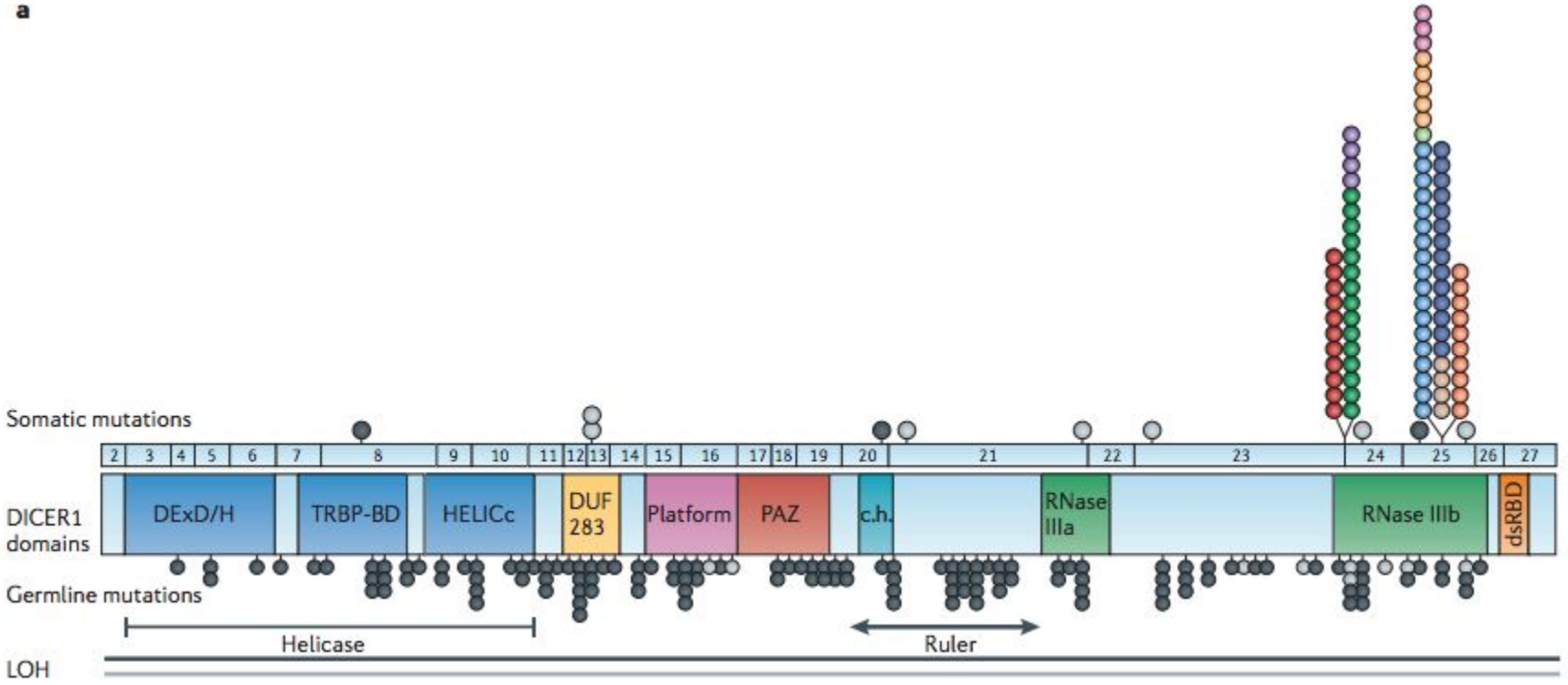

dsRNA
Dicer
siRNA
RISC
miRNA
Drosha
Nucleus
miRNA
Translational inhibition
mRNA cleavage


RNA pol II
pri-miRNA
DGCR8
miRNA gene
drosha
pre-miRNA
Exportin-5
5p
3p
RAN
Nucleus
Cytoplasm
Normal DICER1 Processing
5p strand targeting
AGO
mRNA
AGO
B
TRBP
paz
A
DICER1
3p strand targeting
mRNA
AGO
pre-miRNA
pre-miRNA
Mutant DICER1 Processing
NO 5p strand targeting
AGO
B
TRBP
paz
A
DICER1
Loss of RNase IIIB cleavage activity
3p strand targeting only
mRNA
AGO

DICER1 Mosaicism

- Hotspot domain for somatic second hits in RNase IIIb (5 codons).
  - When germline (or mosaic) *DICER1* LOF mutation, second hits almost always LOF-> cell death or limited proliferation.
  - In second hit RNase IIIb mutation, allows for continuing cell viability and growth, at the cost of skewed miRNA processing-> promote tumorigenesis. Probability = .26%
- Those with mutations in RNase IIIb domain much more severe symptoms.
- They are often mosaic due to fully expressed germline mutations not being well tolerated during embryogenesis.
- Associated with GLOW syndrome (Global developmental delay, Lung cysts Overgrowth and Wilms tumor).
- Affects miRNAs that target MTOR, MAPK, and TGF-B signaling pathways.

DICER1 Mosaicism



Tumor Descriptions

Pleuropulmonary Blastoma

- Presents as shortness of breath, weight loss and fever.
- Can be purely cystic, cystic and solid, or purely solid.
- Most arise in the lung parenchyma
- Age of onset: children < 6 y

Ovarian Sex Cord-Stromal Tumors

- May present as a lump of tissue in the uterus, sometimes with excess hormone production.
- Typically unilateral and solid.
- Age of onset not well defined.

Cystic Nephroma

- Presents in children < 4 y.
- Symptoms include an enlarging abdominal mass, usually painless.
- When bilateral, highly suggestive of germline *DICER1* variant.

Ciliary Body Medulloepithelioma

- Arises in anterior chamber of the eye
- Presents as poor vision, pain, leukocoria (abnormal white reflection in eye).
- Exam may show cyst or mass in iris, anterior chamber or ciliary body.

Tumor Descriptions, cont.

Thyroid Gland Neoplasia

- Includes multinodal goiter, adenomas or differentiated thyroid cancer.
- MNG is multifocal and cystic, can be mixed solid/cystic.
- Adenomas and thyroid ca usually unifocal and solid.

Nasal Chondromesenchymal Hamartoma

- Usually presents as unilateral polyp/mass in nasal cavity/sinuses.
- Symptoms include persistent nasal drainage, nasal obstruction, and respiratory or feeding difficulties as an infant.

Pituitary Blastoma

- Presents at <2 y.
- Symptoms include ophthalmoplegia (paralysis of eye muscles), proptosis (eye bulging), visual disturbance and Cushing disease.

Pineoblastoma

- Presents with intracranial pressure due to obstructive hydrocephalus. Occurs due to compression of cerebral aqueduct by tumor.
- Symptoms may include upgaze paralysis and nystagmus.

Embryonic Rhabdomyosarcoma

TABLE 1. Summary of cERMS Cases Associated With Germ-Line and/or Somatic *DICER1* Mutations

Case	Diagnosis (age at Dx)	Germ-line *DICER1* status	Somatic *DICER1* status	Other DICER1-associated conditions	Family history	Reference
1	cERMS (13 y)	c.3907_3908delCT	c.5113G>A	MNG	MNG, lung cysts, E-polyp, thyroid nodule	Foulkes et al.[5] (2011), Heravi-Moussavi et al.[6] (2012)
2	cERMS (15 y)	c.3611_3616delACTACAinsT	Unknown	Lung cysts, MNG	cERMS, SLCT, MNG, PLMS, MNG, lung cysts	Foulkes et al.[5] (2011)
3	cERMS (14 y)	c.3611_3616delACTACAinsT	c.5438A>G[a]	MNG	(Same as above, daughter of case 2)	Foulkes et al.[5] (2011)
4	cERMS (17 y)	c.2117-1G>A	Unknown	MNG	WT (child), MNG (female paternal cousins)	Foulkes et al.[5] (2011)
5	cERMS (9 y)	c.5104C>T	Unknown	Type 1r PPB	Unknown	Dehner et al.[7] (2012), Doros et al.[8] (2012)
6	cERMS (8 y)	c.4309_4312delGACT	Unknown	Bladder ERMS, type 2 PPB	Unknown	Doros et al.[8] (2012)
7	cERMS (13 y)	c.3535_3538delTCTT	c.5437G>A	Lung cysts (likely type 1r PPB)	Thyroidectomies (mother and maternal uncle)	Tomiak et al.[9] (2014)
8	cERMS (44 y)	Negative	c.2062C>T and c.5438A>G	None	Unremarkable	Case 1 (this report)
9	cERMS (53 y)	c.2457C>G	c.5439G>T	MNG	MNG (son and daughter), SLCT (daughter)	Case 2 (this report), Rio Frio et al.[4] (2011)

DICER1 Testing by Phenotype

Table 1 | **Key clinical phenotypes associated with germline *DICER1* mutations**

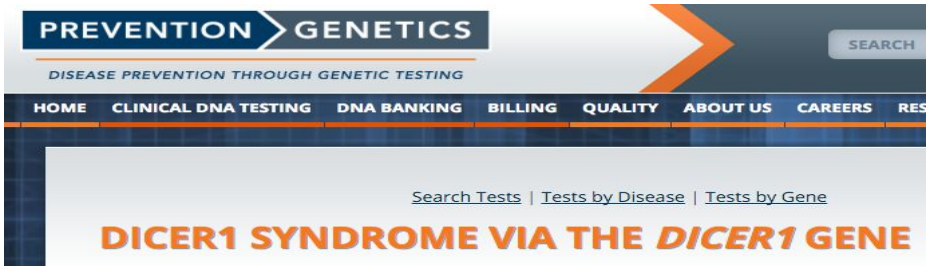
Phenotype and relative frequency*	Is *DICER1* mutation testing indicated following a diagnosis?‡	Approximate range for age of susceptibility (peak)	Malignant (M) or benign (B)	Deaths associated?
Most frequent phenotypes§				
Type I (cystic) PPB	Yes	0–24 months (8 months)	M	Yes, if it progresses to type II or III
Type II (cystic/solid) PPB	Yes	12–60 months (31 months)	M	Yes, ~40%
Type III (solid) PPB	Yes	18–72 months (44 months)	M	Yes, ~60%
Type Ir (cystic) PPB	Yes	Any age	B or M**	None observed**
MNG	No	5–40 years (10–20 years)	B	No
Cystic nephroma	Yes	0–48 months (undetermined)	B	No (see ASK, below)
SLCT of ovary	Yes	2–45 years (10–25 years)	M	Yes, <5% of cases
Moderate frequency phenotypes‖				
cERMS	Yes	4–45 years (10–20 years)	M	None observed
Rare frequency phenotypes¶				
DTC	No	5–40 years (10–20 years)	M	None observed
Wilms' tumour	No	3–8 years (undetermined)	M	None observed
Juvenile hamartomatous intestinal polyps	No	0–4 years (undetermined)	B	No
CBME	Yes	3–10 years (undetermined)	B or M[‡‡]	None observed
NCMH	Yes	6–18 years (undetermined)	B	No
Pituitary blastoma (PitB)	Yes	0–24 months (undetermined)	Undetermined[§§]	Yes, ~50%[§§]
Pineoblastoma (PinB)	Yes	2–25 years (undetermined)	M	Yes
Very rare phenotypes#				
ASK	Yes	Estimated 2–20 years	M	Yes
Medulloblastoma	No	Undetermined	M	Unknown
ERMS of the bladder	No	Estimated <5 years	M	None observed
oERMS	Yes	Undetermined	M	None observed
Neuroblastoma	No	Estimated <5 years	M	Yes
Congenital phthisis bulbi	No	Birth	B	No
OSCST juvenile granulosa cell tumour	Undetermined	Undetermined	M	None observed
OSCST gynandroblastoma	Undetermined	Undetermined	M	None observed
Cervix primitive neuroectodermal tumour	Undetermined	Undetermined	M	None observed

DICER1 Testing

Table 1.

- Summary of Molecular Genetic Testing Used in *DICER1*-Related Disorders

Gene [1]	Test Method	Proportion of Probands with a Pathogenic Variant Detectable by This Method
DICER1	Sequence analysis [2]	~65% [3]
	Deletion/duplication analysis [4]	See footnote 5 (Only seen in one individual)



Invitae DICER1 Syndrome Test

Management

No guidelines have been established.

Based on data from International PPB Registry (includes 500+ individuals with *DICER1*) recommendations include:

- Annual physical exam and targeted ROS
- Imaging study type and frequency based on tumor type, patient age, and suspicious clinical finding.

Management

- PPB
  - Baseline CT to eval for lung cysts/tumors at any age (critical <3 y)
- NC
  - Baseline kidney CT or US exam in pt dx with PPB
  - Annual abdominal exam
- Thyroid
  - Thyroid physical exam, us if nodes detected.
  - Thyroid function testing
- Ovarian stromal tumors
  - Examine all females for masses in abdomen or pelvis.
  - Abdominal-pelvic US, MRI or CT
  - Education regarding possible signs and symptoms
- Pituitary blastoma:
  - Brain MRI for people with signs of cortisol excess.
- CBME
  - Eval of young children including measurement of visual acuity, visual inspection of eye and orbit.
- ERMS
  - Education of signs and symptoms (hematuria, abnormal bleeding)
  - Endoscopic eval of bladder or direct visualization of the cervix.
- NCMH: in infants, children and young adults
  - ROS including respiratory and feeding difficulties, rhinorrhea, epistaxis, visual disturbances and otitis media.
  - Nasal endoscopy if ophthalmologic symptoms occur.
- Pineoblastoma:
  - Brain MRI for those with signs of increased intracranial pressure.

Review Questions

Who is more likely to have a *DICER1* mutation?

A. 5 yo boy diagnosed with Wilm's tumor.
B. 4 yo girl diagnosed with pleuropulmonary blastoma.
C. 38 yo woman with multinodal goiter.
D. 16 yo girl diagnosed with embryonic rhabdomyosarcoma of the cervix.

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Who is more likely to have severe symptoms?

A. Someone with a germline loss of function *DICER1* mutation.
B. Someone with a somatic *DICER1* mutation found in their tumor.
C. Someone mosaic for a *DICER1* mutation in RNase IIIb domain.

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