in association with UKEPS UK Endocrine Pathology Society

London Endocrine Pathology Update

Monday February 10th and Tuesday February 11th, 2025 - The Gordon Museum of Pathology, Guy's Campus, London, UK

CASE 3

Single 1.8 cm thyroid nodule of the left lobe in a 16 year-old young woman; previous FNA Thy3a (Bethesda III). Left lobectomy

Giovanni Tallini, MD

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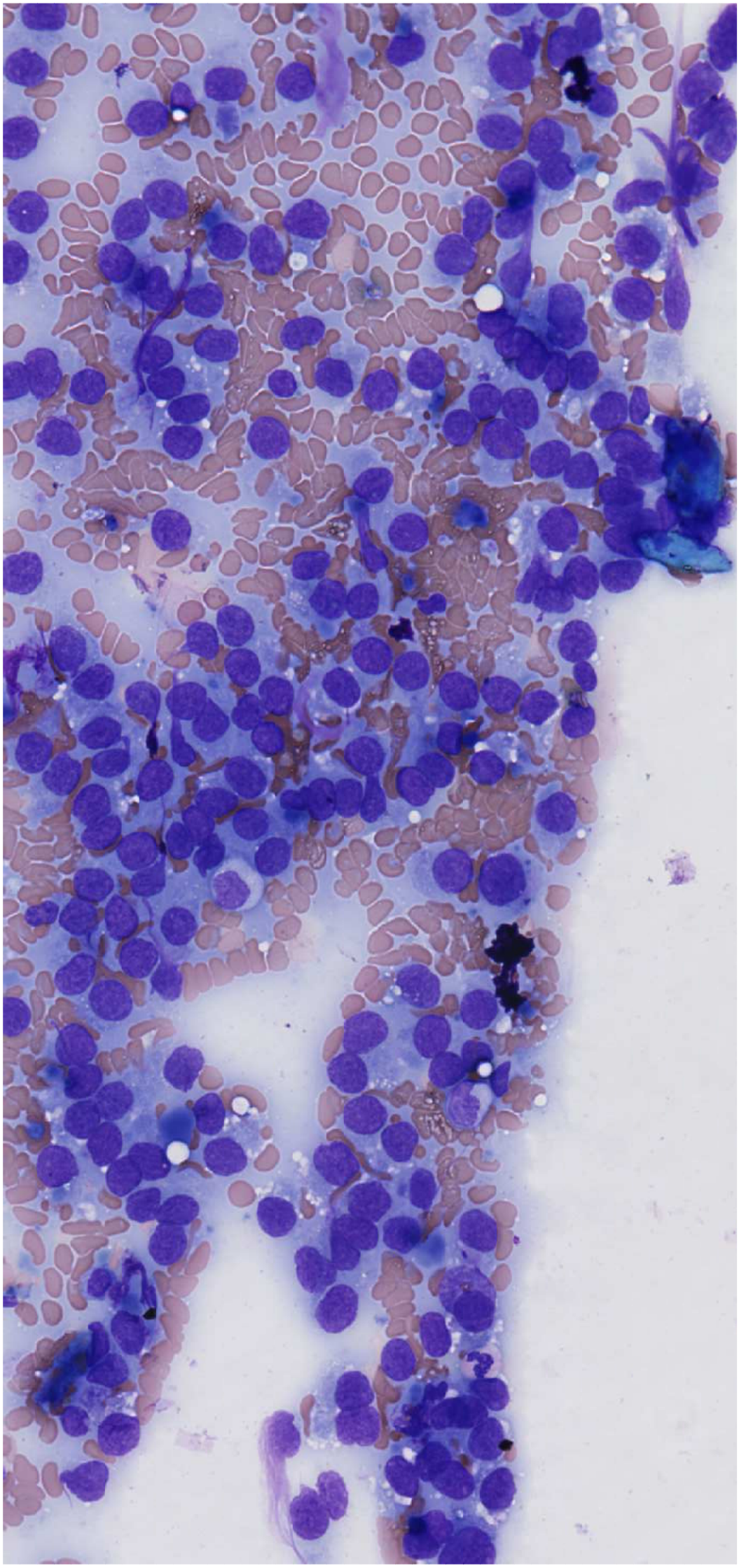
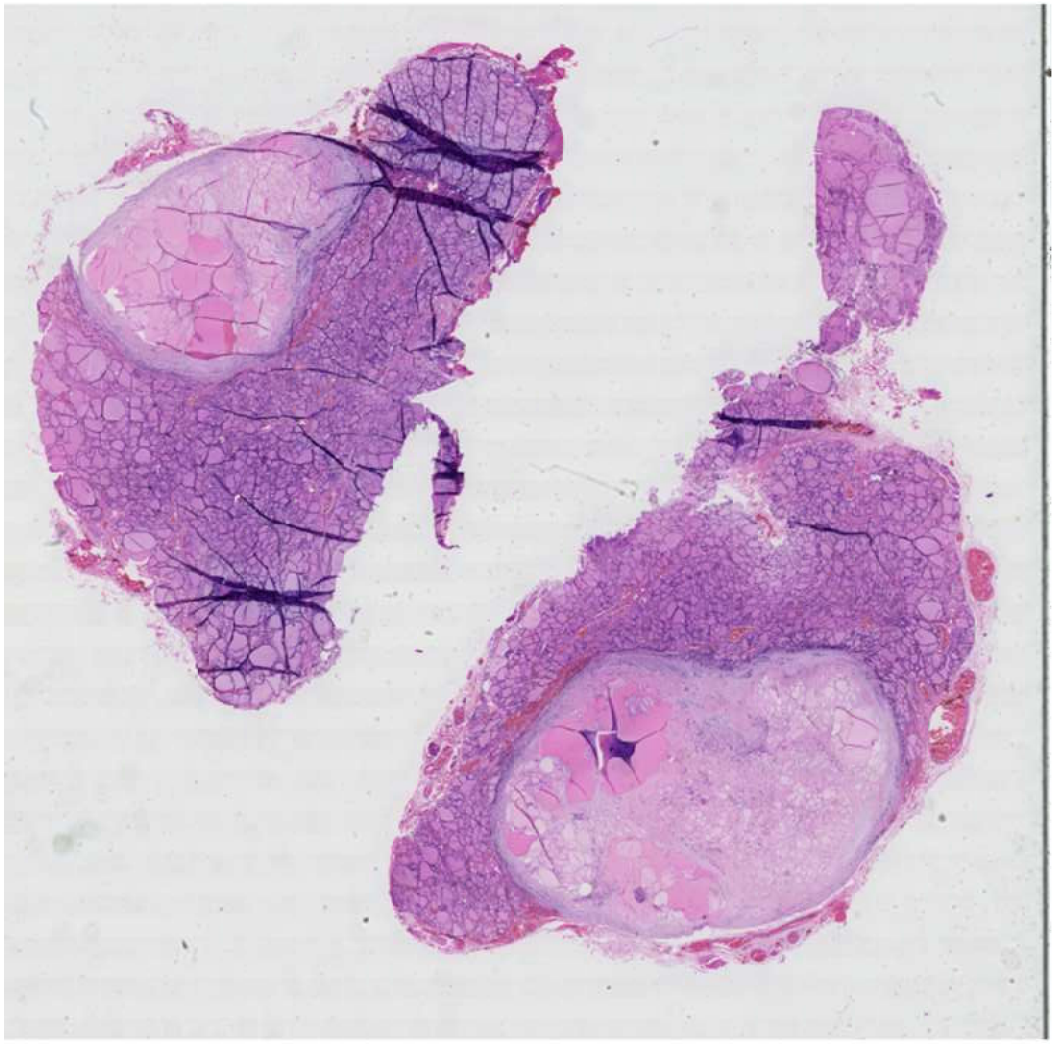
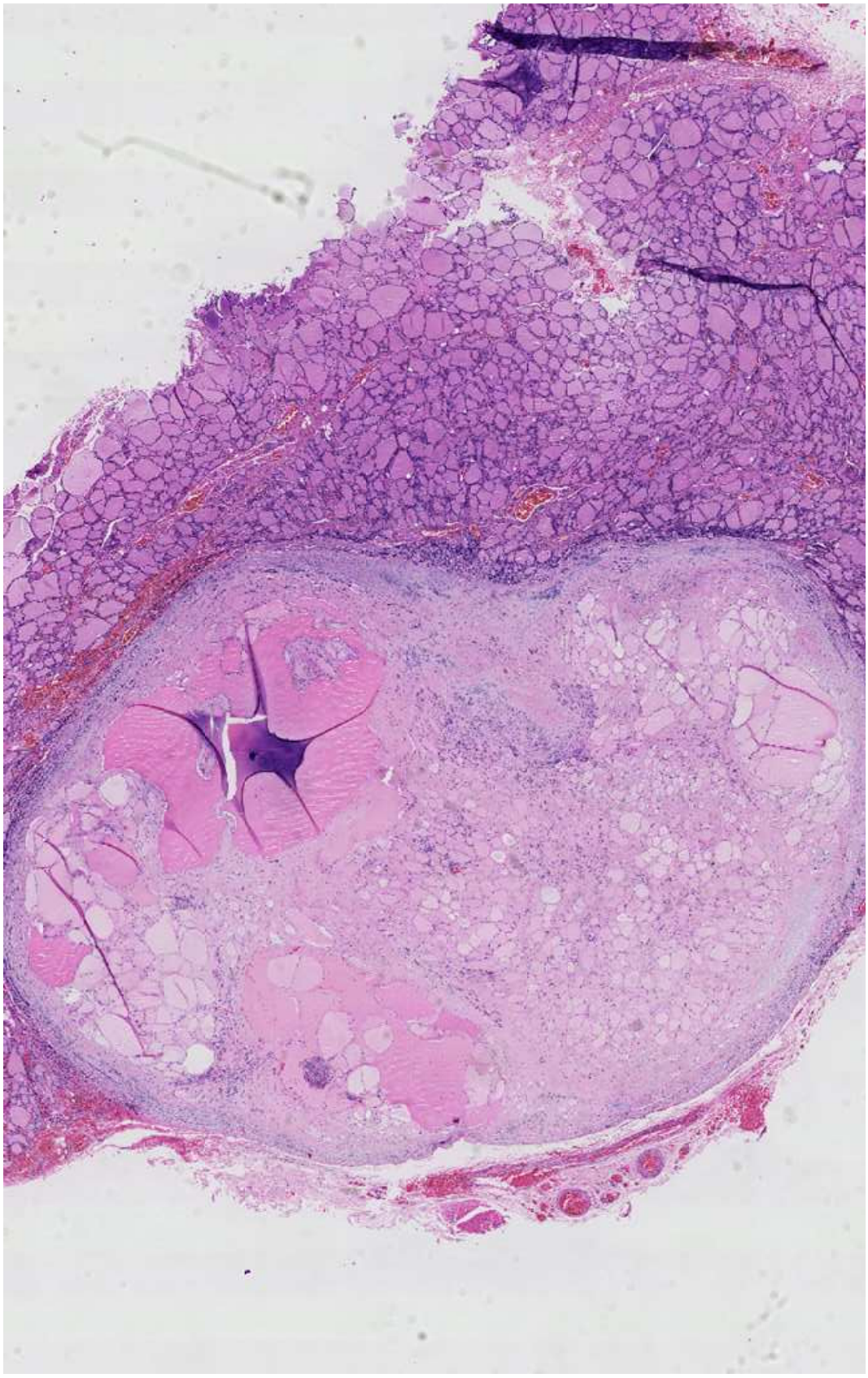
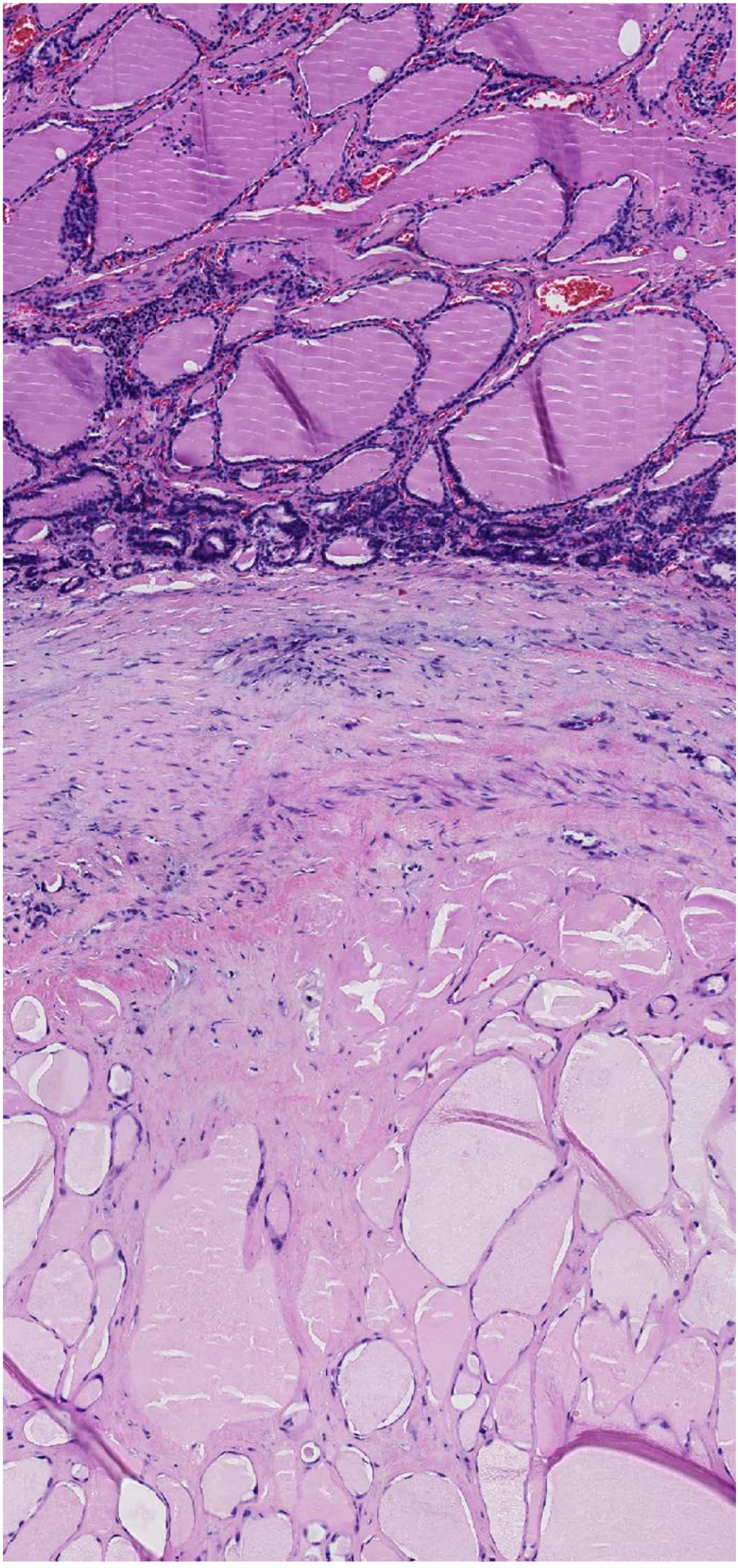
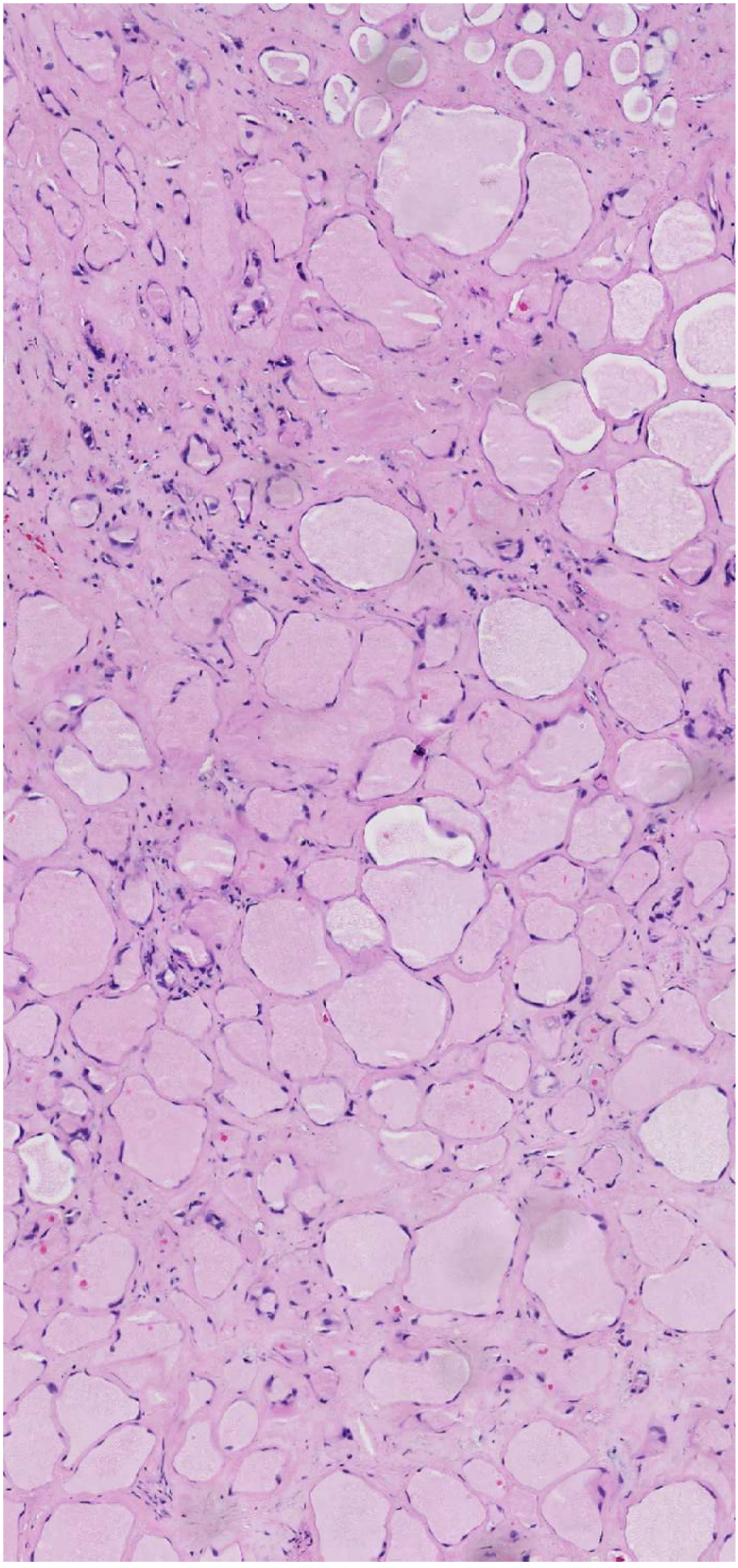
giovanni.tallini@unibo.it

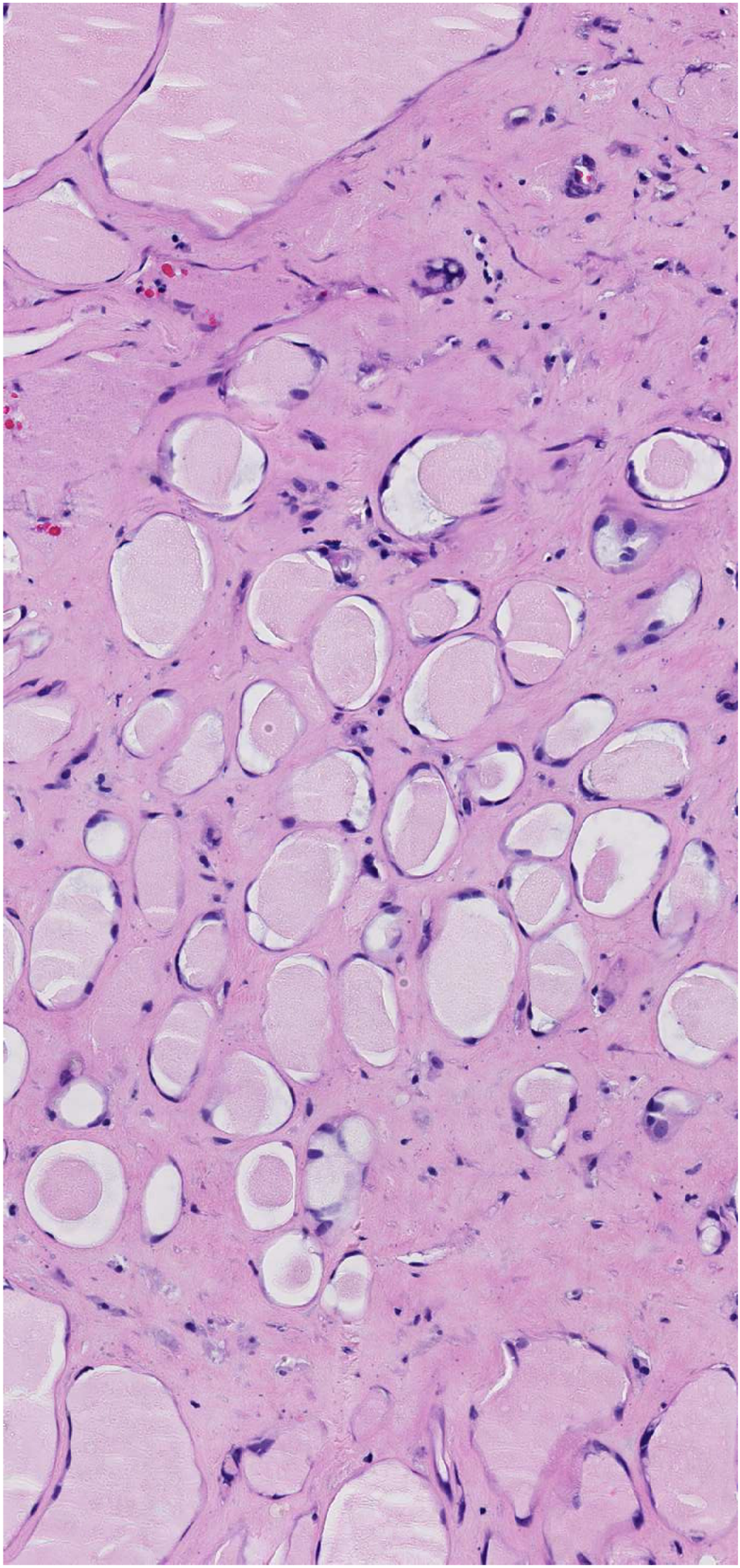


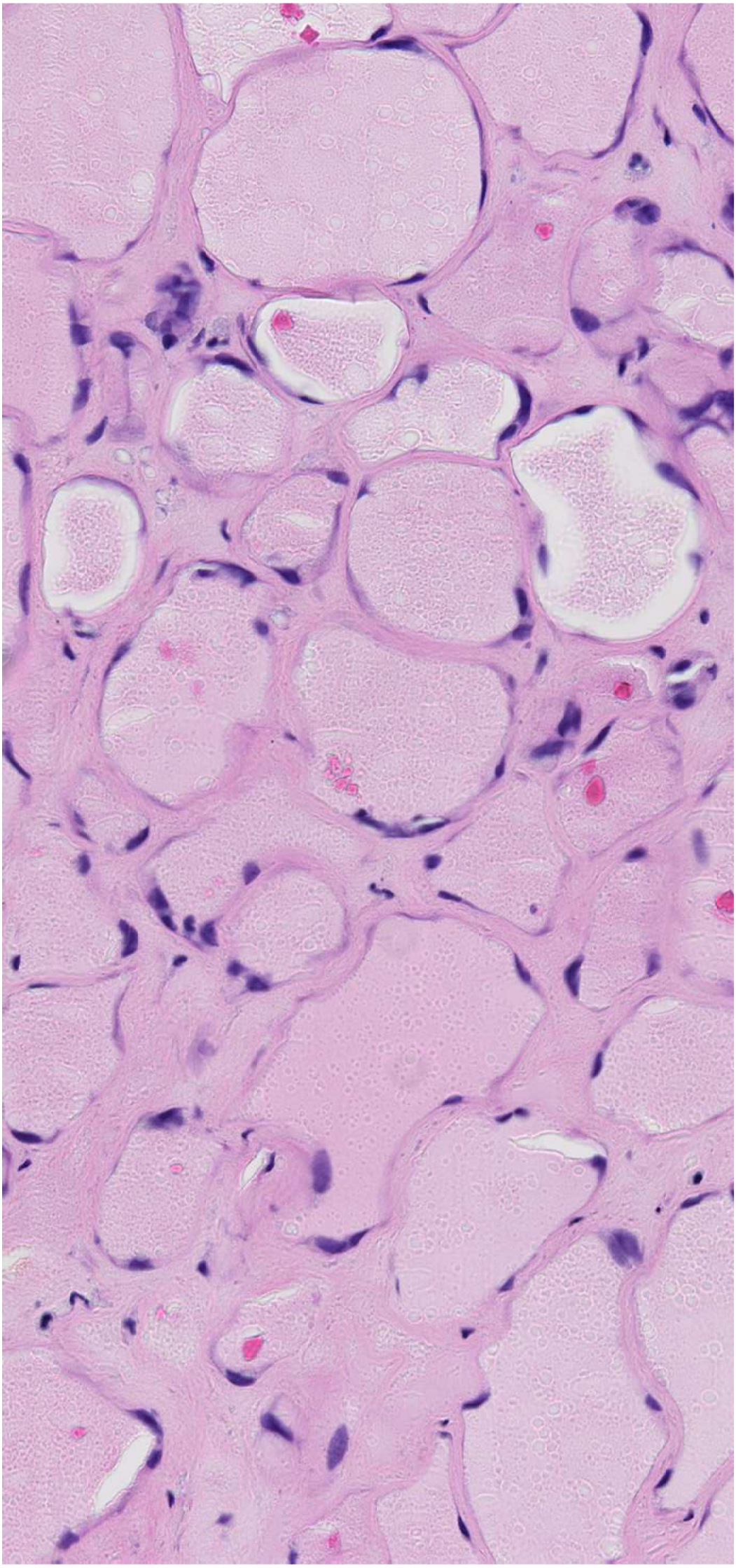












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CASE 3
Follicular adenoma with atrophic follicles ("vanishing follicles")

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CASE 1

Tumor tissue was analyzed by NGS: DICER1 p.Glu1705Lys (c.5113G>A, Esone 24, VAF 39%), Pathogenic ACMG variant (https://varsome.com/), not present in perilesional tissue (i.e. not a germline mutation)

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CASE 1

Points for discussion

- Which type of thyroid nodules are DICER1 mutated?
- Should patients with somatic DICER1 mutation in thyroid nodules be tested for DICER1 syndrome?

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DICER1-mutated tumors/nodules

Macrofollicular Variant of Follicular Thyroid Carcinoma: A Rare Underappreciated Pitfall in the Diagnosis of Thyroid Carcinoma
Bongiovanni M, Sykiotis GP, La Rosa S, Bisig B, Trimech M, Missiaglia E, Gremaud M, Salvatori Chappuis V, De Vito C, Sciarra A, Foulkes WD, Pusztaszeri M
Thyroid. 2020 Jan;30(1):72-80

Poorly differentiated thyroid carcinoma of childhood and adolescence: a distinct entity characterized by DICER1 mutations
Chernock RD, Rivera B, Borrelli N, Hill DA, Fahiminiya S, Shah T, Chong AS, Aqil B, Mehrad M, Giordano TJ, Sheridan R, Rutter MM, Dehner LP, Foulkes WD, Nikiforov YE
Mod Pathol. 2020 Jul;33(7):1264-1274

Prevalence and Spectrum of DICER1 Mutations in Adult-onset Thyroid Nodules with Indeterminate Cytology
Chong AS, Nikiforov YE, Condello V, Wald AI, Nikiforova MN, Foulkes WD, Rivera B
J Clin Endocrinol Metab. 2021 Mar 25;106(4):968-977.

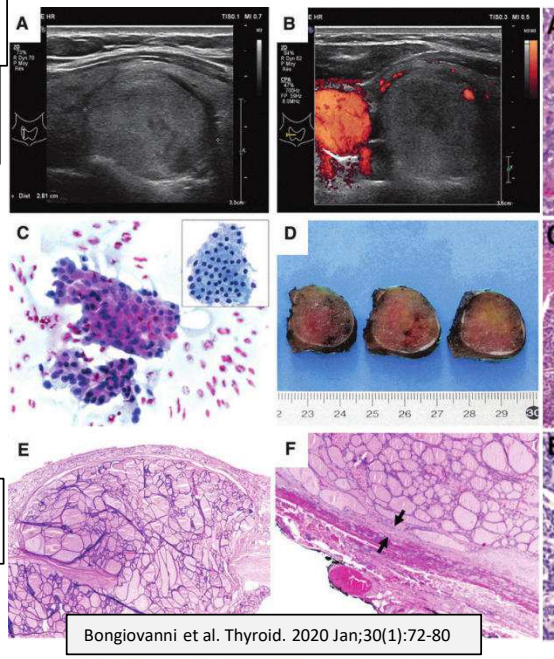
Macrofollicular variant follicular thyroid tumors are DICER1 mutated and exhibit distinct histological features
Juhlin CC, Stenman A, Zedenius J
Histopathology. 2021 Oct;79(4):661-666

Expanding the spectrum of thyroid carcinoma with somatic DICER1 mutation: a survey of 829 thyroid carcinomas using MSK-IMPACT next-generation sequencing platform
Ghossein CA, Dogan S, Farhat N, Landa I, Xu B
Virchows Arch. 2022 Feb;480(2):293-302

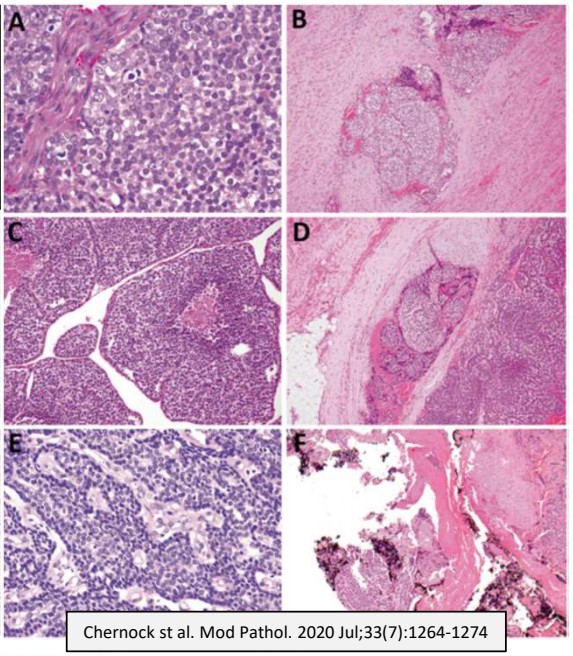
Evaluation of the Molecular Landscape of Pediatric Thyroid Nodules and Use of a Multigene Genomic Classifier in Children
Gallant JN, Chen SC, Ortega CA, Rohde SL, Belcher RH, Netterville JL, Baregamian N, Wang H, Liang J, Ye F, Nikiforov YE, Nikiforova MN, Weiss VL
JAMA Oncol. 2022 Sep 1;8(9):1323-1327

Prevalence, Molecular Landscape and Clinical Impact of DICER1 and DGCR8 Mutated Follicular-Patterned Thyroid Nodules
Condello V, Poma AM, Macerola E, Vignali P, Paulsson JO, Zedenius J, Basolo F, Juhlin CC
J Clin Endocrinol Metab. 2024 Jan 22:dgae034. doi: 10.1210/clinem/dgae034

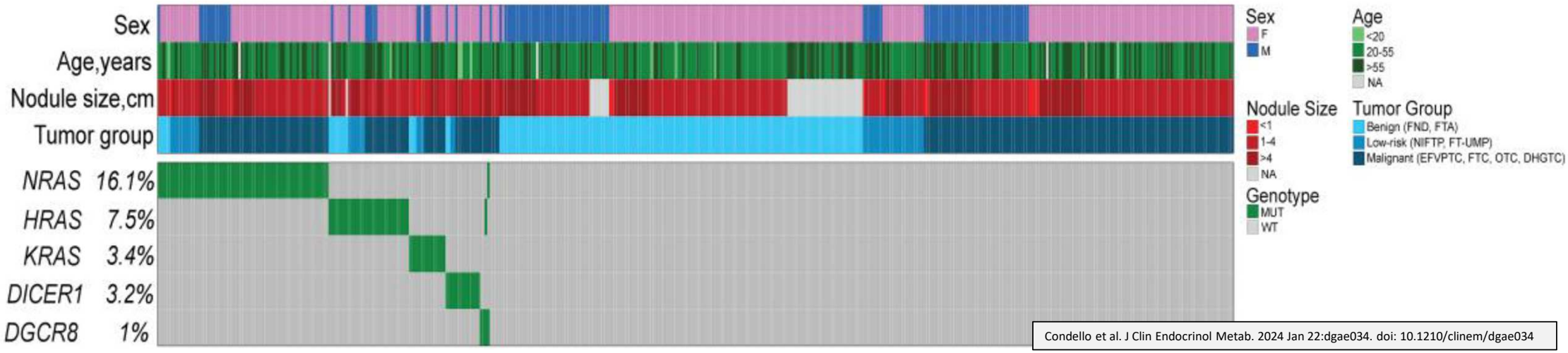
Histological clues of DICER1 mutations in thyroid nodules
Jung CK, Liu Z, Hirokawa M, Bychkov A
Virchows Arch. 2024 Oct;485(4):755-757



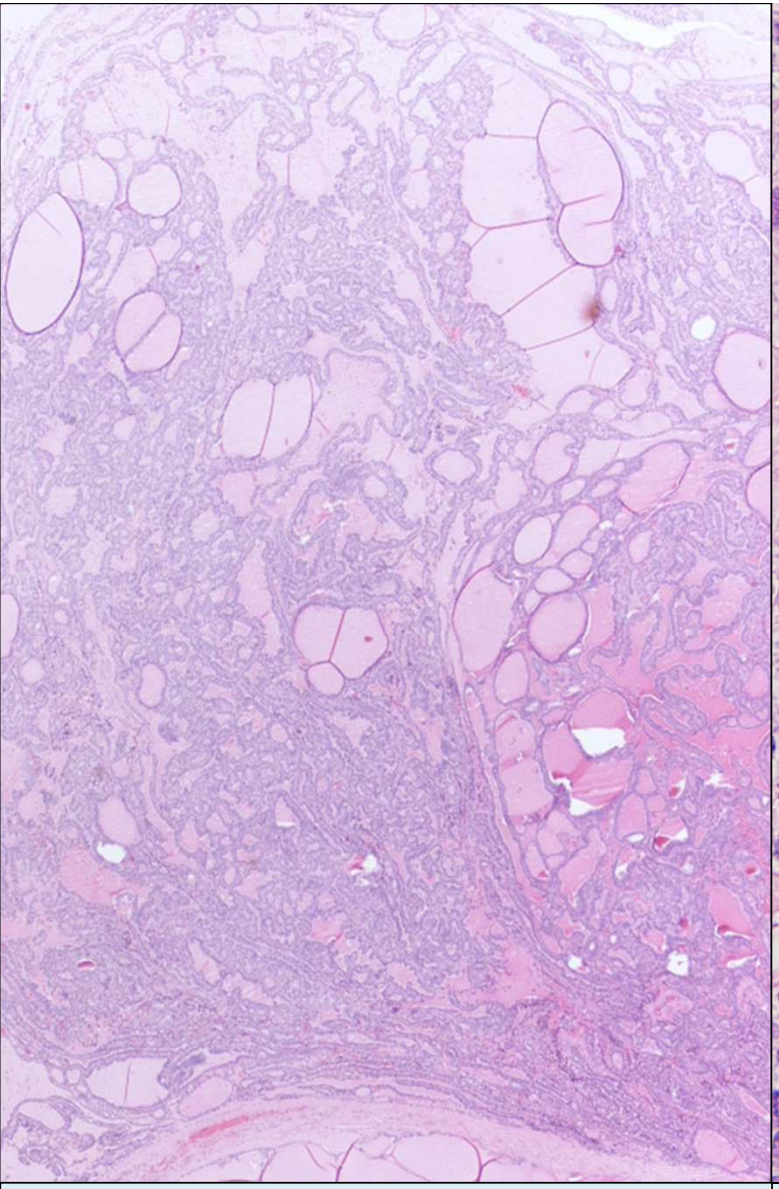
Bongiovanni et al. Thyroid. 2020 Jan;30(1):72-80



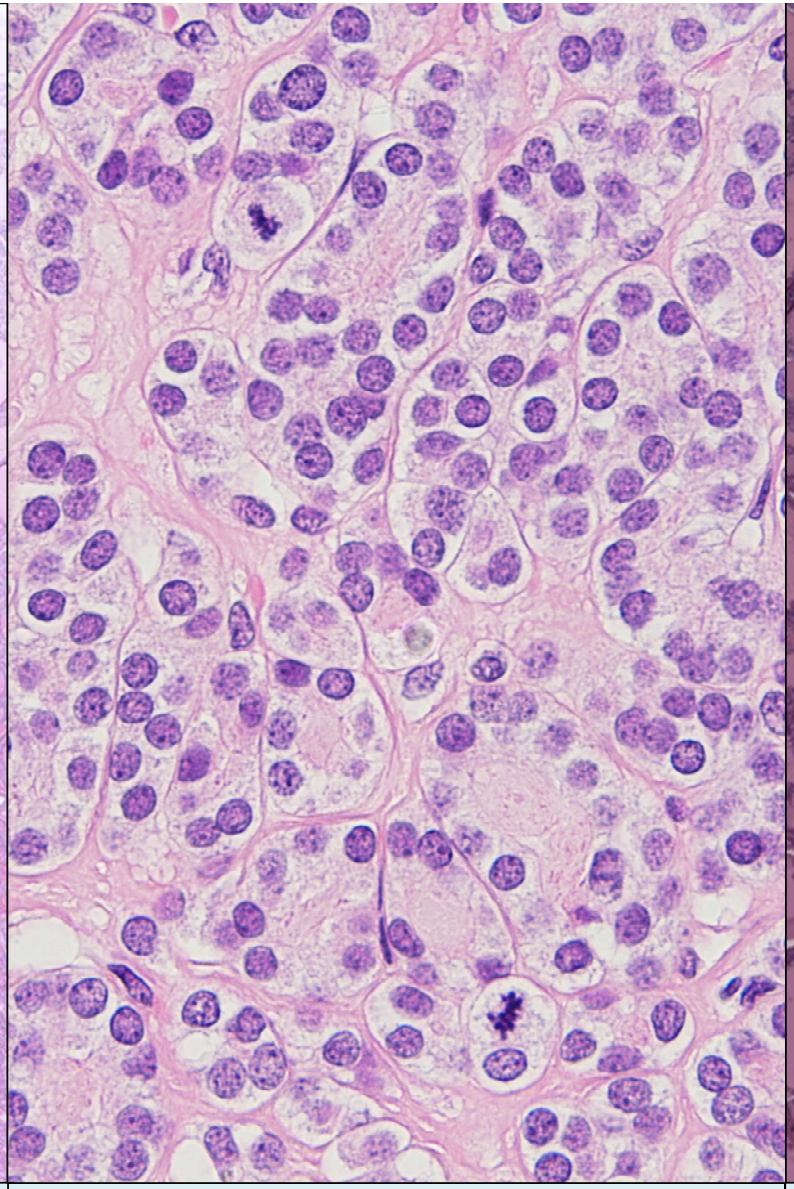
Chernock st al. Mod Pathol. 2020 Jul;33(7):1264-1274



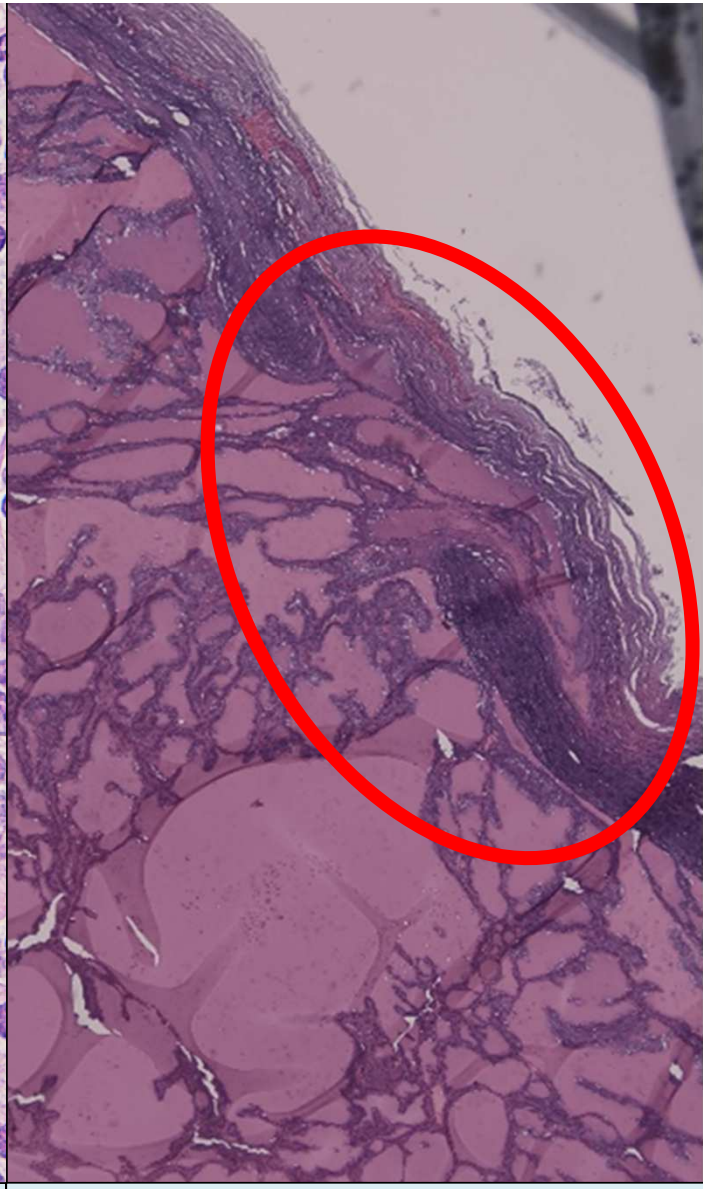
Condello et al. J Clin Endocrinol Metab. 2024 Jan 22:dgae034. doi: 10.1210/clinem/dgae034



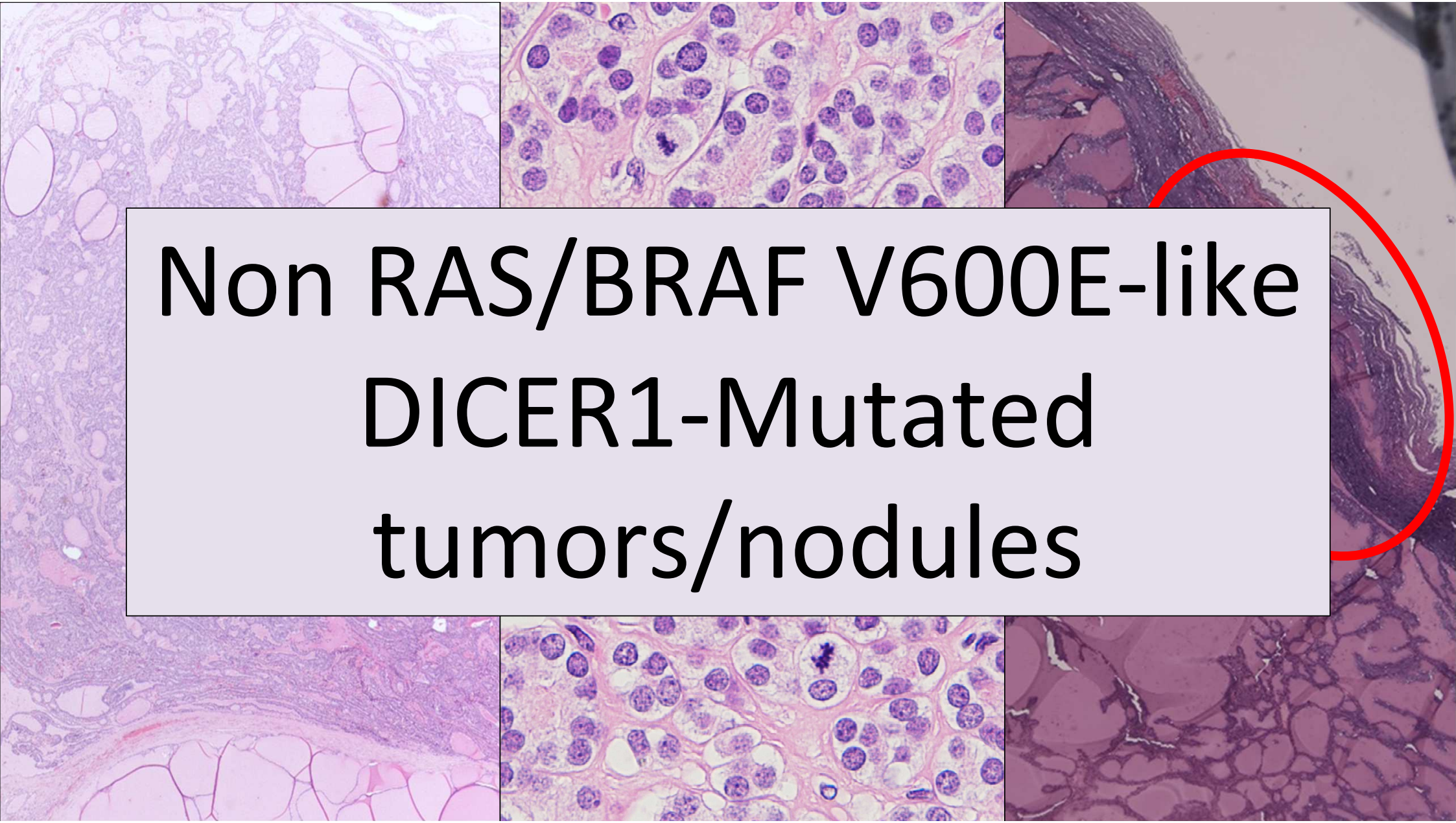
Follicular Nod. Disease



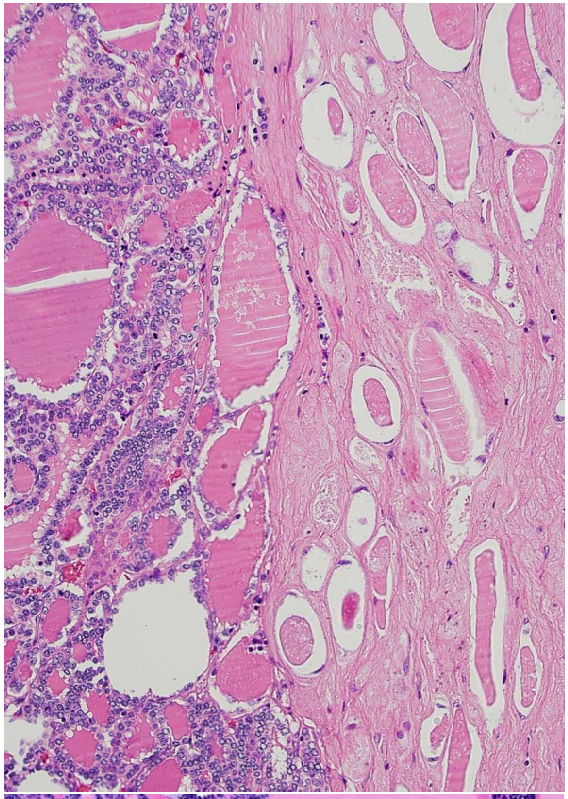
Follicular Adenoma

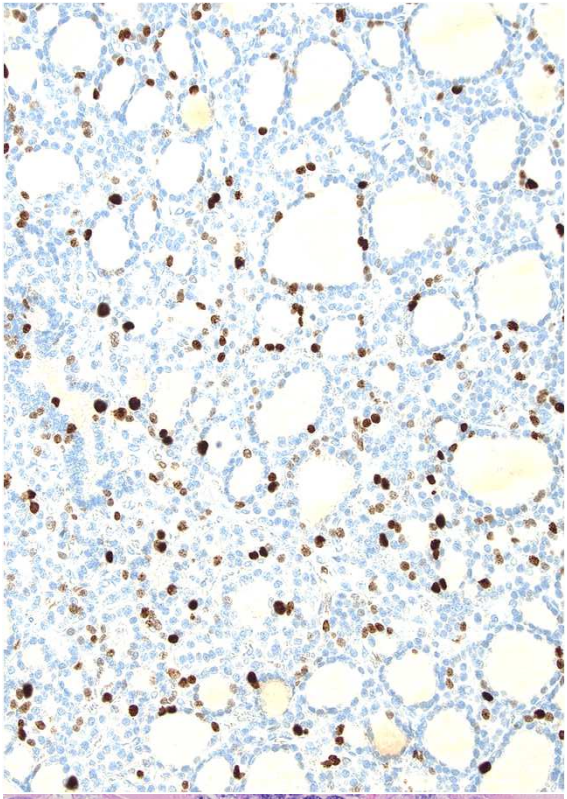


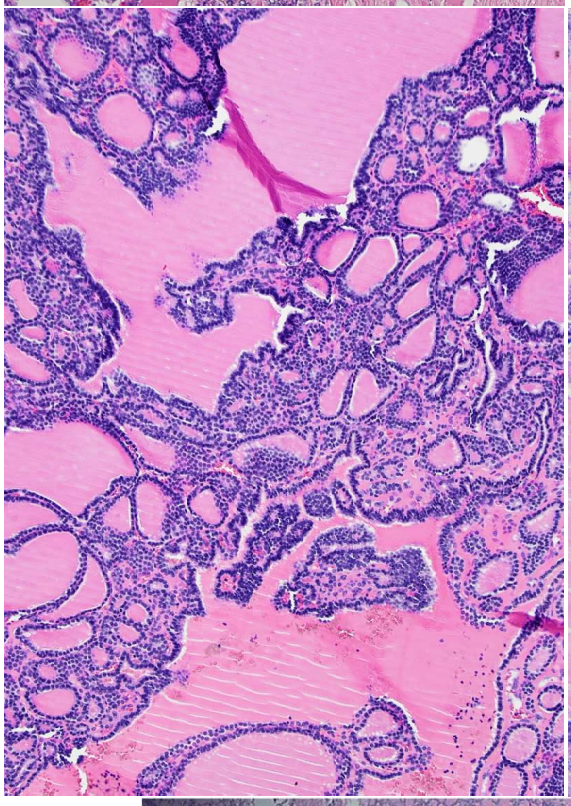
Foll. Ca. (Pap. architecture)

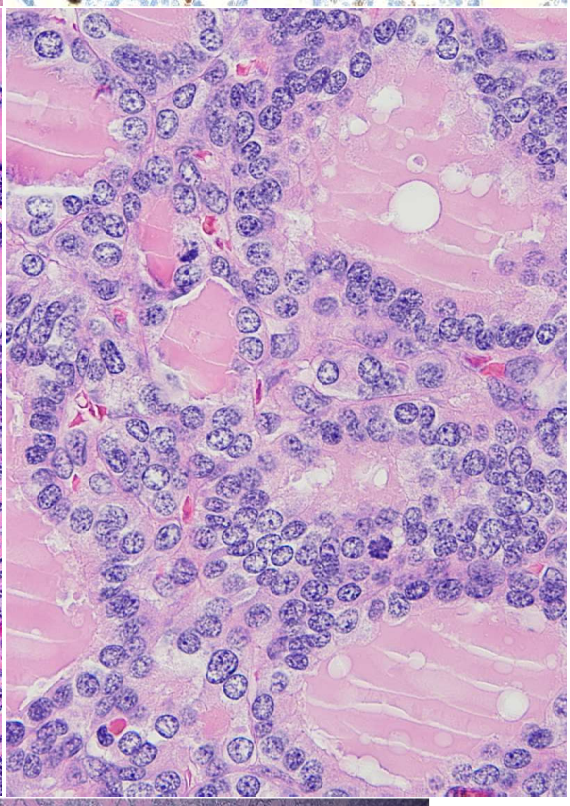


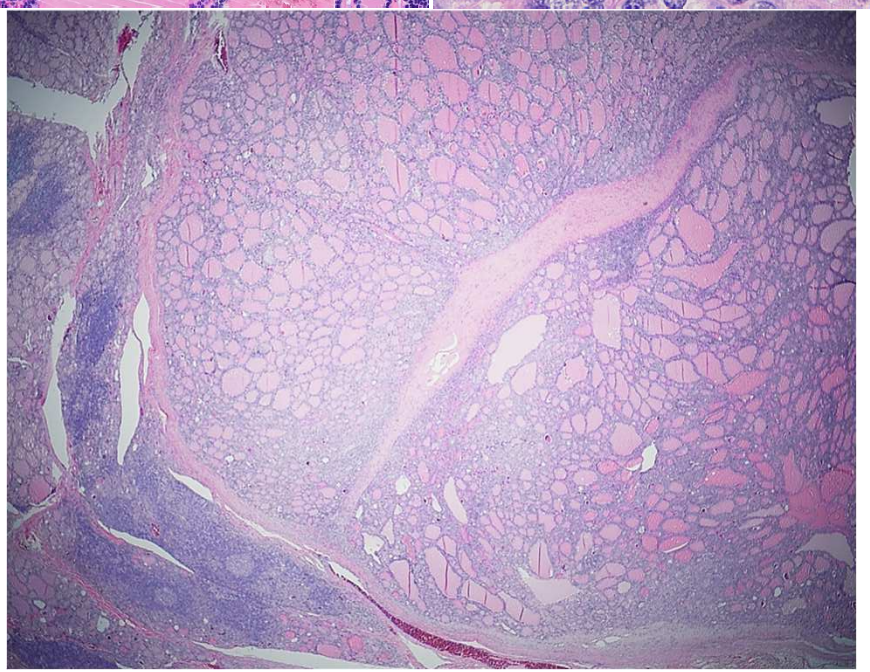
Non RAS/BRAF V600E-like DICER1-Mutated tumors/nodules

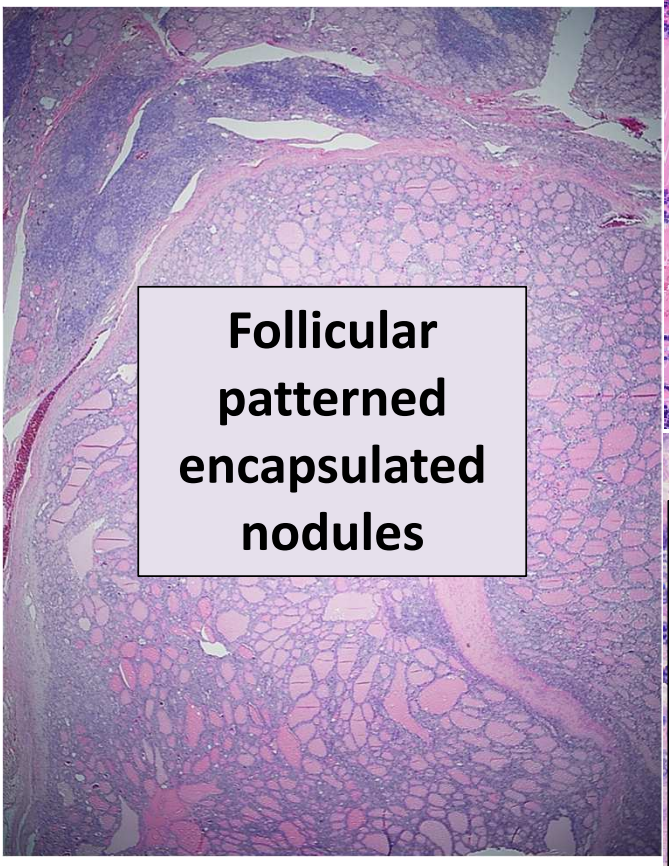




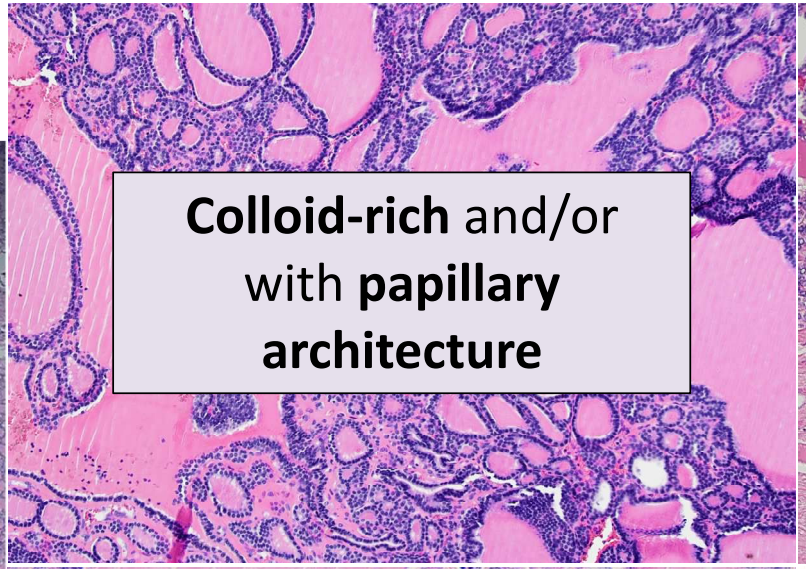




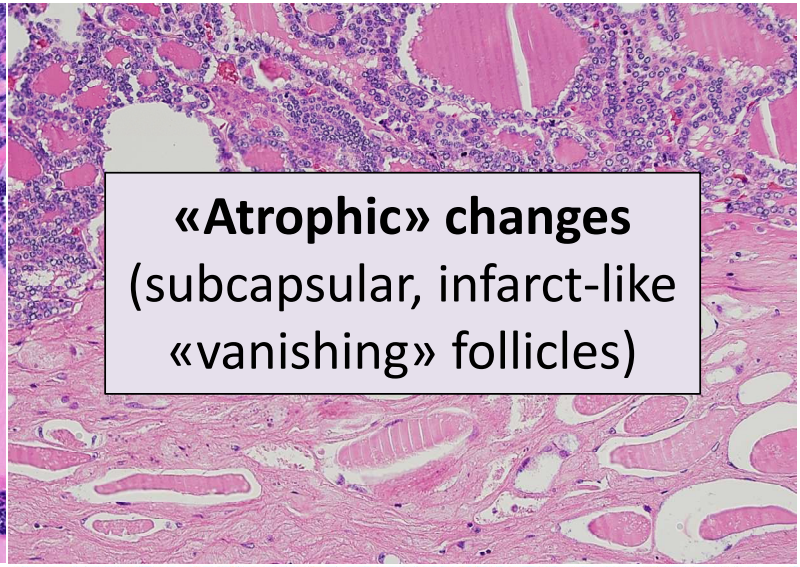




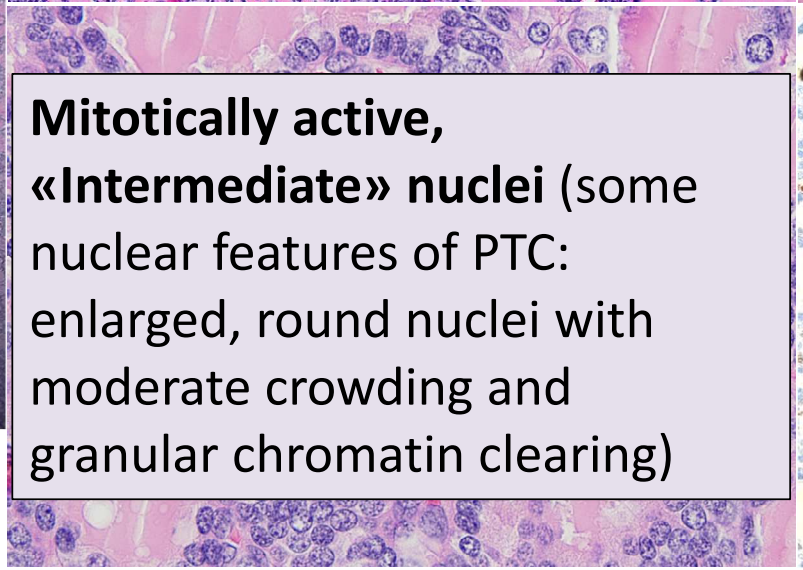
Follicular patterned encapsulated nodules



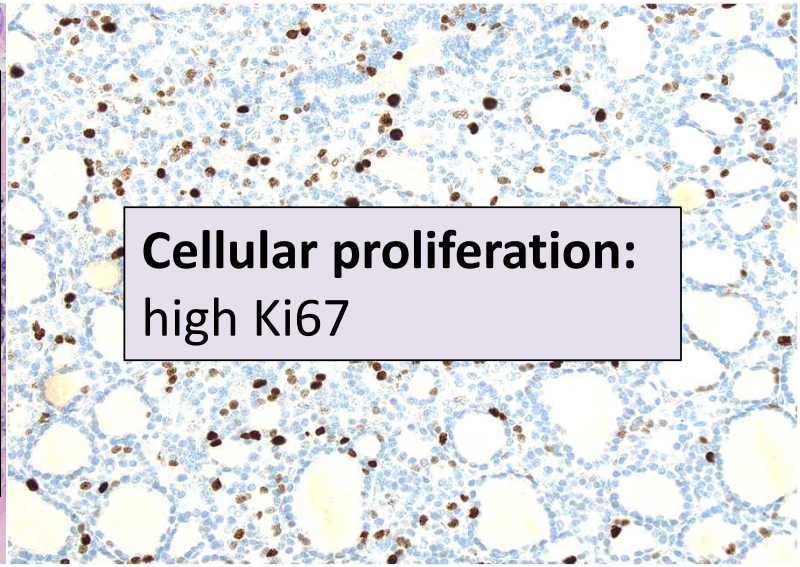
Colloid-rich and/or with **papillary architecture**



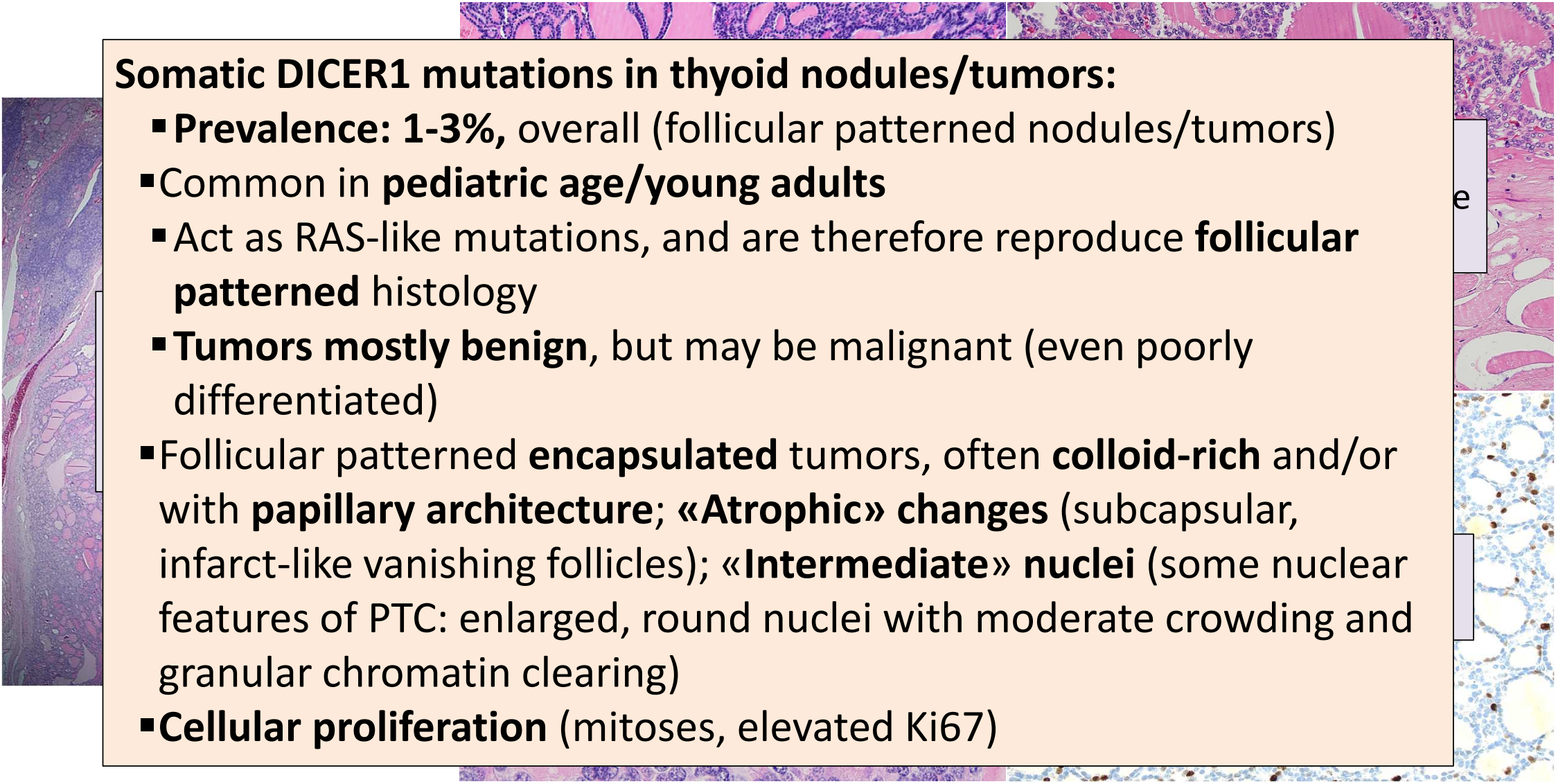
«Atrophic» changes (subcapsular, infarct-like «vanishing» follicles)



Mitotically active, «Intermediate» nuclei (some nuclear features of PTC: enlarged, round nuclei with moderate crowding and granular chromatin clearing)



Cellular proliferation: high Ki67



Somatic DICER1 mutations in thyoid nodules/tumors:

- **Prevalence: 1-3%,** overall (follicular patterned nodules/tumors)
- Common in **pediatric age/young adults**
  - Act as RAS-like mutations, and are therefore reproduce **follicular patterned** histology
  - **Tumors mostly benign**, but may be malignant (even poorly differentiated)
- Follicular patterned **encapsulated** tumors, often **colloid-rich** and/or with **papillary architecture**; **«Atrophic» changes** (subcapsular, infarct-like vanishing follicles); «**Intermediate**» **nuclei** (some nuclear features of PTC: enlarged, round nuclei with moderate crowding and granular chromatin clearing)
- **Cellular proliferation** (mitoses, elevated Ki67)

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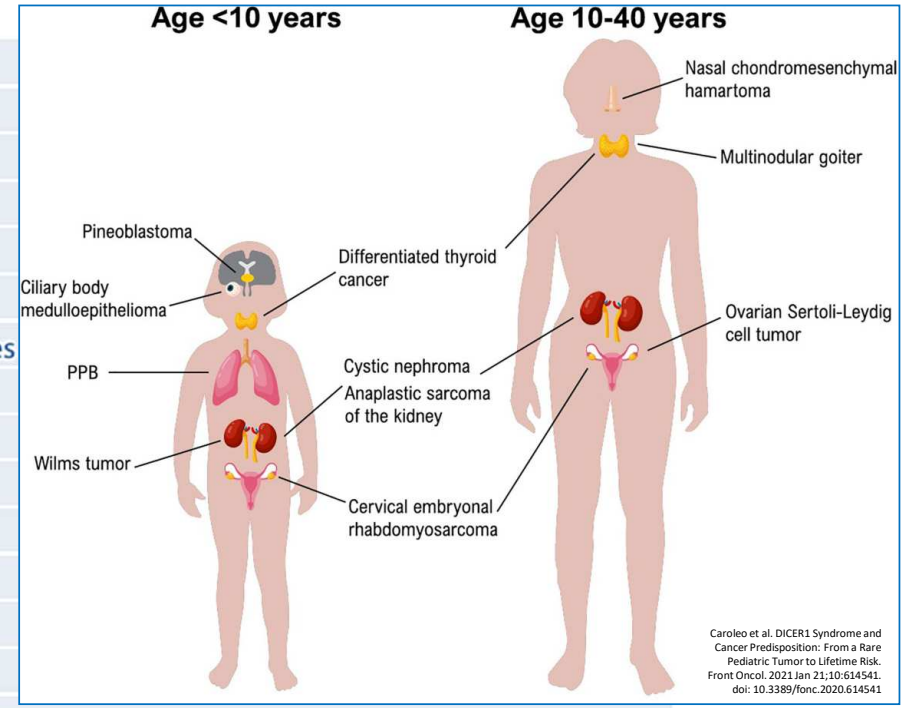
DICER1 Syndrome

Table 1. *DICER1*-associated neoplasms.

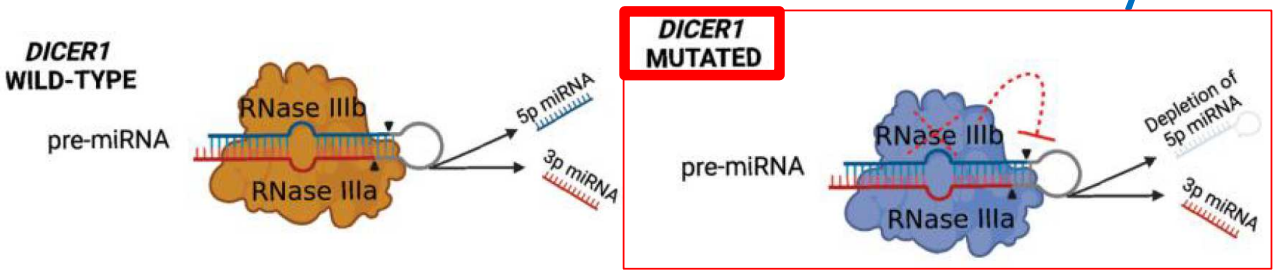
Pleuropulmonary blastoma (PPB) and PPB-like neoplasms
Pleuropulmonary blastoma, type I, IR, II, III
PPB-like Sertoli-Leydig cell tumor of lung
Pediatric cystic neoplasms and *DICER1*-sarcoma (anaplastic sarcoma of kidney)
Nasal chondromesenchymal hamartoma
Central nervous system sarcoma with rhabdomyosarcoma/PPB III-like features
Sertoli-Leydig cell tumor with and without heterologous features and type I PPB-like features
Peritoneal, ovarian and fallopian tube sarcoma with PPB-like features
DICER1-associated cystic hepatic neoplasm with type I PPB-like features
Cervical embryonal rhabdomyosarcoma
Teratoid and primitive neuroepithelial neoplasms
Cervical-thyroid teratoma
Malignant teratoid neoplasm of sacrococcygeal region
Ciliary body medulloepithelioma
Pituitary blastoma
Pineoblastoma
Embryonal tumor with multilayered rosettes
Thyroid
Multinodular hyperplasia (goiter)
Papillary thyroid carcinoma, invasive follicular variant
Follicular carcinoma, pediatric type
Poorly differentiated thyroid carcinoma, pediatric type
Intestine
Hamartomatous polyp with juvenile polyp-like features



- DICER1 syndrome (OMIM 606241, 601200) is an autosomal dominant familial tumor predisposition disorder with heterozygous DICER1 germline mutation
- *DICER1* on chromosome 14q32.13 encodes an RNA endonuclease (Dicer) involved in the post-transcriptional gene expression of over 30% of protein-coding genes by modulating microRNAs
- Reduced penetrance, which likely decreases the rate of familial cases; in cases with pleuropulmonary blastoma, ~80% of *DICER1* germline pathogenic variants are inherited by a parent, ~ 20% are *de novo*

González IA, Stewart DR, Schultz KAP, Field AP, Hill DA, Dehner LP. DICER1 tumor predisposition syndrome: an evolving story initiated with the pleuropulmonary blastoma. Mod Pathol. 2022 Jan;35(1):4-22

DICER1 Syndrome



Disabling mutations in RNase III domains of *DICER1* lead to 5p miRNA depletion. Schematic representation of the mechanism by which DICER1 cleaves pre-miRNA in wild-type and mutated conditions; hotspot mutations in the RNase IIIb domain lead to a significant reduction of 5p strand miRNAs in *DICER1* mutants compared with wild-type cases [Condello et al. J Clin Endocrinol Metab. 2024 Jan 22:dgae034. doi: 10.1210/clinem/dgae034] Disabling mutations in RNase III domains of DICER1 lead to 5p miRNA depletion. Schematic representation of the mechanism by which DICER1 cleaves pre-miRNA in wild-type and mutated conditions; hotspot mutations in the RNase IIIb domain lead to a significant reduction of 5p strand miRNAs in DICER1 mutants compared with wild-type cases [Condello et al. J Clin Endocrinol Metab. 2024 Jan 22:dgae034. doi: 10.1210/clinem/dgae034]

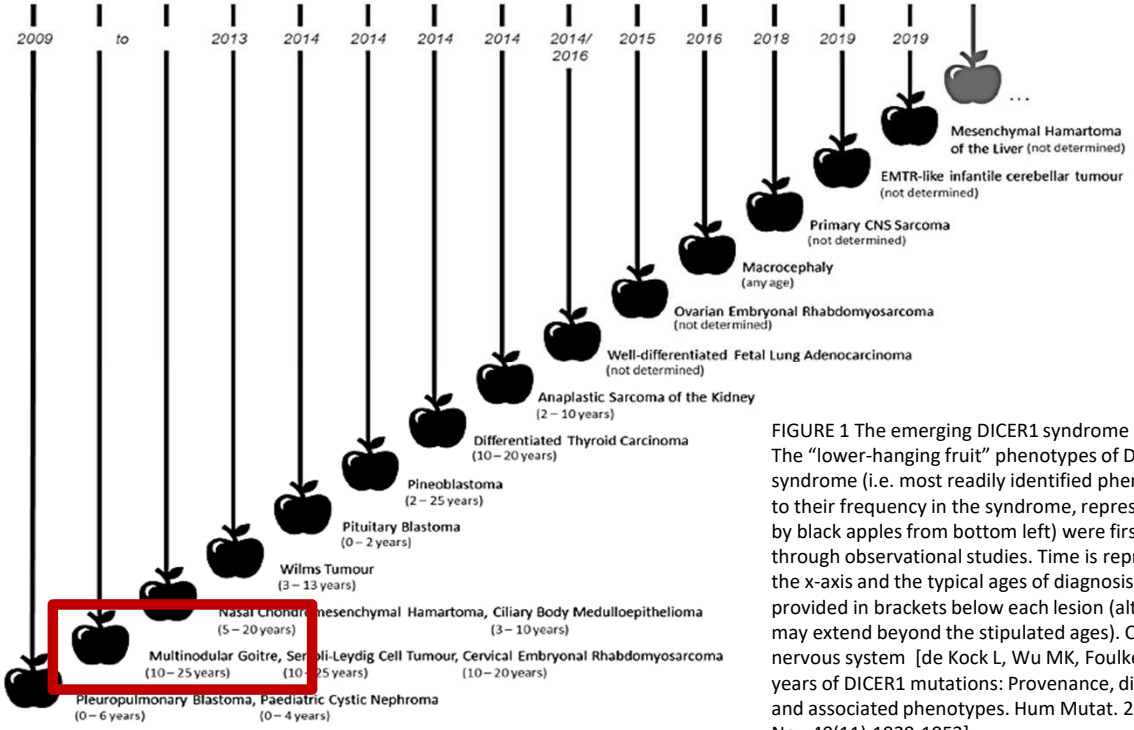
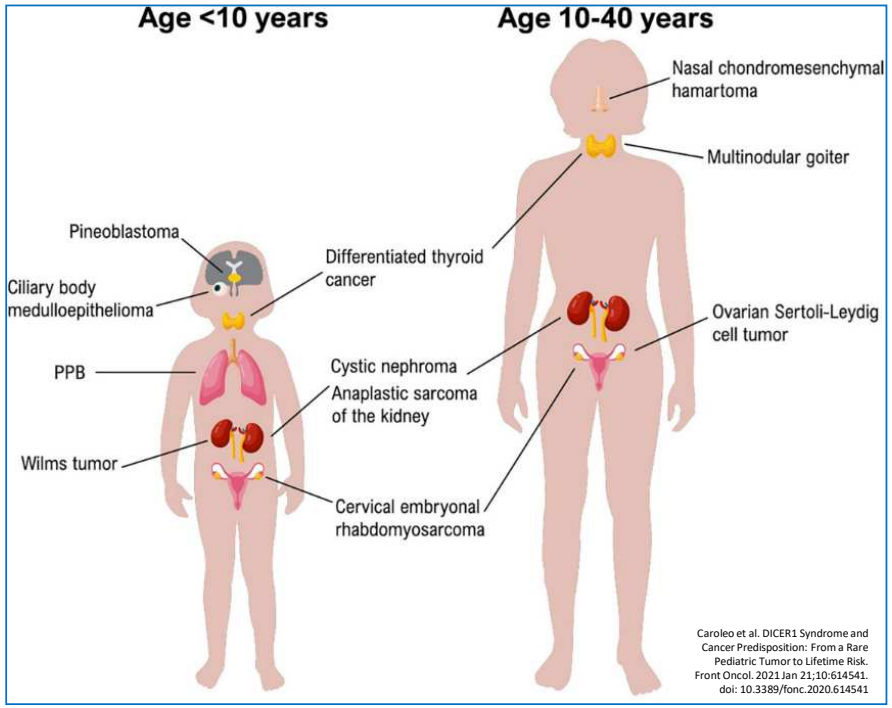


FIGURE 1 The emerging DICER1 syndrome phenotype. The "lower-hanging fruit" phenotypes of DICER1 syndrome (i.e. most readily identified phenotypes due to their frequency in the syndrome, represented here by black apples from bottom left) were first noted through observational studies. Time is represented on the x-axis and the typical ages of diagnosis are provided in brackets below each lesion (although risk may extend beyond the stipulated ages). CNS, central nervous system [de Kock L, Wu MK, Foulkes WD. Ten years of DICER1 mutations: Provenance, distribution, and associated phenotypes. Hum Mutat. 2019 Nov;40(11):1939-1953]



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DICER1 Syndrome

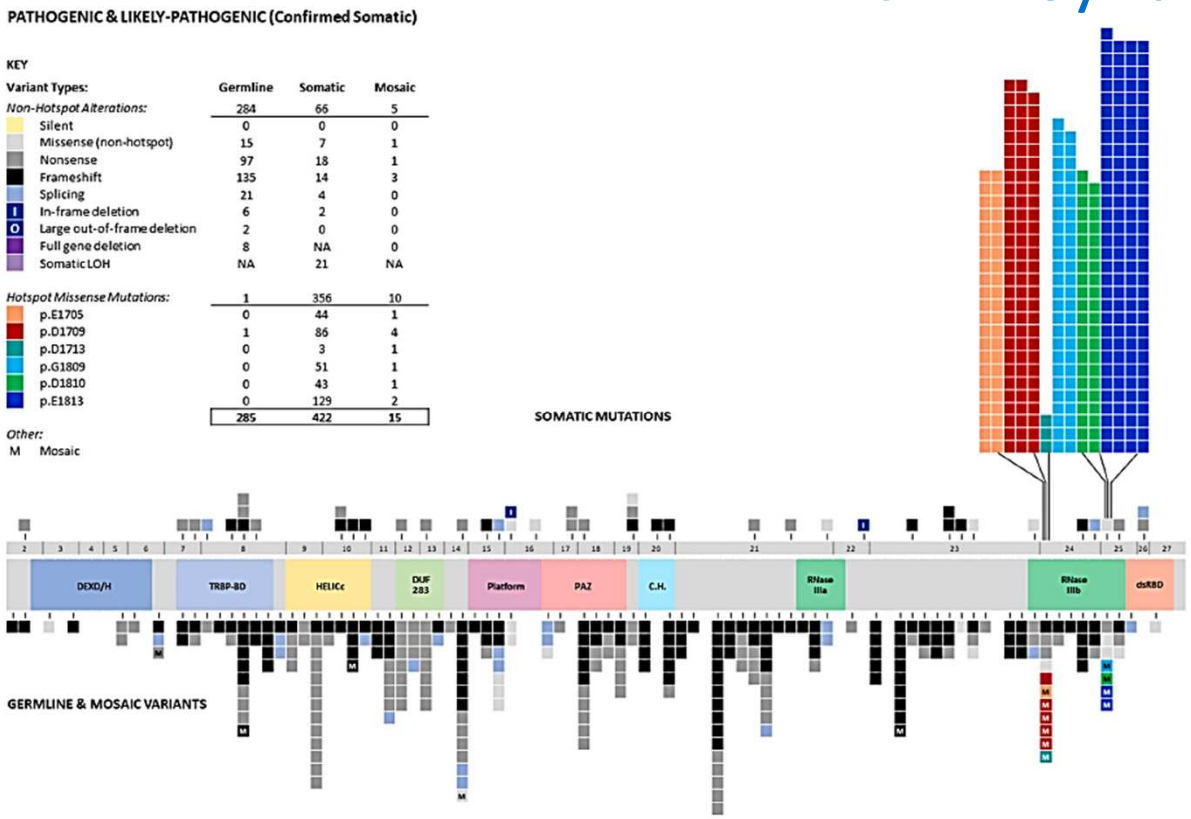
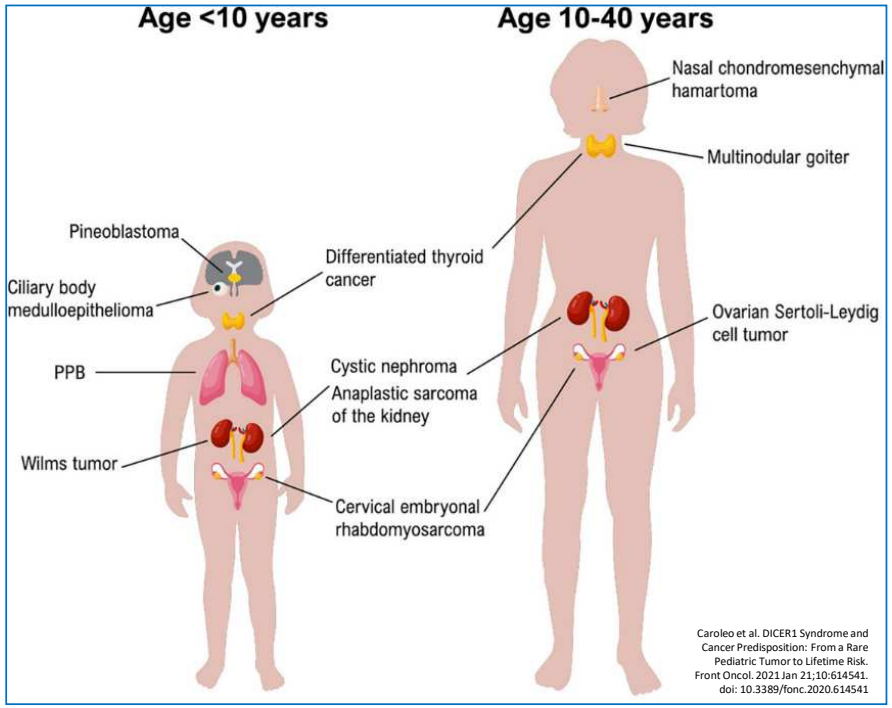


FIGURE 4 Pathogenic and likely pathogenic DICER1 alterations published before January 31st, 2019. Only unique-per-family (UPF) germline variants and confirmed-somatic mutations considered pathogenic or likely pathogenic have been plotted along the length of the unfolded DICER1 protein (n = 722). The 422 confirmed somatic events are plotted above the protein, except for the 21 confirmed-somatic LOH events that are shown at the bottom of the figure. LOH, loss of heterozygosity; NA, not applicable [de Kock L, Wu MK, Foulkes WD. Ten years of DICER1 mutations: Provenance, distribution, and associated phenotypes. Hum Mutat. 2019 Nov;40(11):1939-1953]



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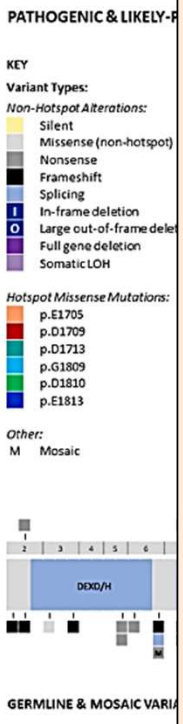
DICER1 Syndrome



- **DICER1 Putative tumor suppressor** (in most cases biallelic inactivation)
- **Dysregulation of miRNA biogenesis** with reduced expression of 5p miRNAs and increased levels of 3p miRNAs compared with wild-type cases
- **Mutations:**
  - **Hot spot** mutations (in the functionally important RNAse III (A and B) region: exons 24-25) are typically somatic, but may represent second hit in patients with germline DICER1 mutation (need to evaluate DICER1 germline: entire gene)
  - **Non-Hot spot** mutations (throughout the gene, usually truncating) can be germline or somatic
  - **Mutually exclusive** with alterations in other thyroid cancer-related genes
- Many patients with DICER1 syndrome have follicular nodular disease and sometimes follicular patterned tumors, **but germine DICER1 mutations are rare in adult patients with incidentally discovered DICER1 hot spot mutated nodules**

✓ Should patients with DICER1 mutated thyroid nodules discovered incidentally, undergo clinical genetics evaluation to rule out DICER1 syndrome?

➢ **Ideally yes** (germline mutations can be trasmited to progeny!), although germline mutations are uncommon in patients with unremarkable medical history

FIGURE 4 Path
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et al. DICER1 Syndrome and
Predisposition: From a Rare
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ncol. 2021 Jan 21;10:614541.
: 10.3389/fonc.2020.614541

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DICER1-Mutated tumors and DICER1 Syndrome

Congenital nodular goitre: *TG, TPO, NIS, PDS, IYD, DOUX2, DUOXA2*

Nodular goitre debuting at >10 years of age: *DICER1, NKX2-1, KEAP1*

Nodular goitre debuting during the first decade: *DICER1, RGS12, GRPEL1, CLIC6, WFS1*

Altaraihi M et al. Prevalence of Pathogenic Germline DICER1 Variants in Young Individuals Thyroidectomised Due to Goitre - A National Danish Cohort. Front Endocrinol (Lausanne). 2021 Sep 6;12:727970. doi: 10.3389/fendo.2021.727970

Mutation in 6/46 children/young adults aged ≤ 25 years with thyroidectomy for goiter with germline DICER1 testing (13%)

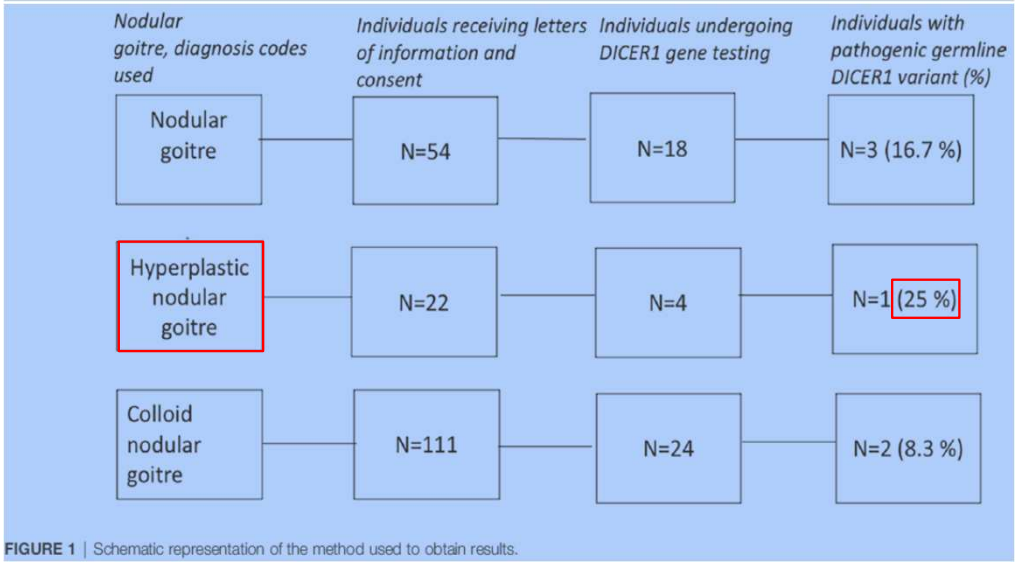


FIGURE 1 | Schematic representation of the method used to obtain results.

Table 2 Clinical and genetic characteristics of all *DICER1*-mutated cases

Case ID	Diagnosis	Sex	Age, years	Nodule size, cm	Architectural pattern	Papillary formations	Atrophic changes	*DICER1* hotspot mutation in thyroid lesions (AF%)	Constitutional *DICER1* mutation (AF%)	Other mutations apart from *DICER1* in thyroid lesions (AF%)
EC 1	FTA	F	19	5.5	Macrofollicular	YES	NO	c.5126 A>G p.D1709G (32%)	NP	None
EC 2	NIFTP	F	22	7.8	Macrofollicular	YES*	NO	c.5126 A>G p.D1709G (30%)	NP	None
EC 3	MIFTC	F	36	2.5	Macrofollicular	YES	YES	c.5439 G>T p.E1813D (63%)	NP	None
EC 4[§]	PDTC	F	15	2.5	Microfollicular	NO	YES	c.5127 T>G p.D1709E (27%)	c.5464 G>A p.D1822N (VUS)	None
EC 5[§]	FTA	F	15	1.2	Macrofollicular and solid	NO	YES	c.5437 G>A p.E1813K (15%)	c.5464 G>A p.D1822N (VUS)	None
EC 6	FTA	F	49	1.5	Microfollicular	NO	YES	c.5126 A>G p.D1709G (37%)	NP	None
EC 7	FTA	F	55	2	Macrofollicular	NO	YES	c.5126 A>G p.D1709G (43%)	NP	None
EC 8	DHGTC	M	25	2.8	Macrofollicular	YES	YES	c.5429 A>T p.E1810V (60%)	NP	None
EC 9	MIFTC	F	17	2	Macrofollicular	YES	YES	c.5126 A>G p.D1709G (41%)	WT	None
EC 10	MIFTC	F	22	3.2	Microfollicular	YES	YES	c.5429 A>T p.E1810V (51%)	NP	None
KI 1	TFND	F	15	12	Macrofollicular	YES	YES	NO	c.4154_4155ins p.Y13* (48%)	None
KI 2	MIFTC	F	13	1.2	Macrofollicular	YES	YES	c.5126 A>G p.D1709G (20%)	c.2830 C>T p.R944* (50%)	*FGFR4* p.T179A (51%)
KI 3	MIFTC	F	29	5	Macrofollicular	YES	YES	c.5437 G>C p.E1813Q (39%)	c.2908 G>T p.E790* (40%)	None
KI 4	MIFTC	F	33	1.5	Macrofollicular	YES	YES	c.5439 G>T p.E1813D (39%)	WT	None
KI 5	MIFTC	F	44	2.8	Macrofollicular	YES	YES	c.5428 G>T p.E1810Y (40%)	WT	None
KI 6	DHGTC	F	20	6.5	Microfollicular	NO	NO	c.5437 G>A p.E1813K (27%)	WT	None
KI 7	MIFTC	F	27	2.5	Macrofollicular	YES	YES	c.5126 A>G p.D1709G (11%)	WT	None
KI 8	FTA	F	31	4	Macrofollicular	YES	YES	c.5428 G>T p.E1810Y (42%)	WT	None
KI 9	FTA	F	51	4.2	Macrofollicular	NO	YES	c.5437 G>C p.E1813Q (34%)	WT	None
KI 10	DHGTC	F	17	2.5	Microfollicular	NO	YES	c.5437 G>A p.E1813K (57%)	NP	None
KI 11	FTA	F	30	3.5	Macrofollicular	NO	YES	c.5437 G>A p.E1813K (43%)	WT	None
KI 12	PDTC	M	47	2.5	Trabecular, solid	NO	NO	c.5126 A>T p.D1709V (69%)	WT	None
KI 13	MIFTC	F	27	4.5	Macrofollicular	YES	YES	c.5437 G>C p.E1813Q (25%)	WT	*SMARCB1* p.F25L (46%)
KI 14	TFND	F	41	4.5	Macrofollicular	YES	NO	c.5126 A>G p.D1709G (39%)	NP	None
KI 15	MIFTC	F	38	2.8	Macrofollicular	YES	YES	c.5126 A>G p.D1709G (17%)	NP	*PTPN11* p.A72T (11%)
KI 16	TFND	F	23	3.2	Macrofollicular	YES	NO	c.5126 A>G p.D1709G (37%)	NP	*KRAS* p.Q61L (24%)

Condello V et al. Atrophic changes in thyroid tumors are strong indicators of underlying DICER1 mutations: a bi-institutional genotype-phenotype correlation study. Virchows Arch. 2024 Jul;485(1):105-114

Mutation in 3/15 cases with germline DICER1 testing (20%): 2 minimally invasive follicular carcinoma, 1 follicular nodular disease

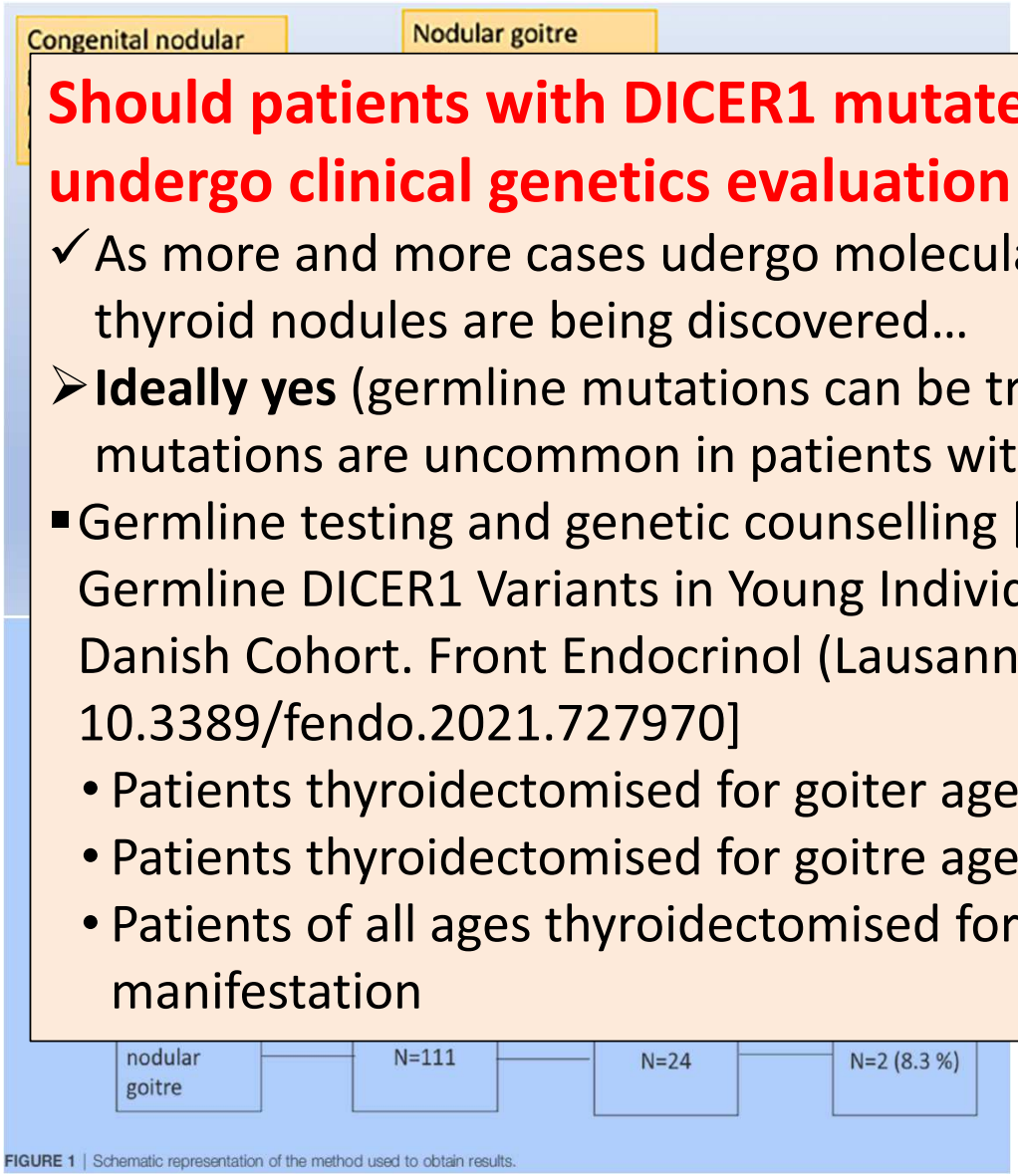
Specificity	Phenotypes
High-specificity (much more likely than not to have germline P/LP DICER1)	Pleuropulmonary blastoma (PPB) (including type 1r)
	Pituitary blastoma
	Anaplastic renal sarcoma
	Ciliary body medulloepithelioma
	Cystic nephroma (<18 yrs)
	Embryonal rhabdomyosarcoma (ovarian)
	Embryonal rhabdomyosarcoma (cervix)
Moderate-specificity (more likely than not to have germline P/LP DICER1)	Differentiated thyroid cancer and/or multinodular goiter (<18 years)
	Nasal chondromesenchymal hamartoma
	Ovarian Sertoli-Leydig cell tumors
	Ovarian sex-cord stromal tumor of mixed type (specifically, gynandroblastoma)
Low-specificity (less likely to have DICER1)	Nonparasitic liver cysts (childhood)
	Wilms tumor
	Pineoblastoma
	Cerebral sarcoma
	Lung cysts (<18 yrs)

Hatton JN et al. Specifications of the ACMG/AMP Variant Classification Guidelines for Germline DICER1 Variant Curation. Hum Mutat. 2023;2023:9537832

DICER1-Mutated tumors and DICER1 Syndrome

Should patients with DICER1 mutated thyroid nodules discovered incidentally, undergo clinical genetics evaluation to rule out DICER1 syndrome?

- ✓ As more and more cases udergo molecular profiling, more and more DICER1 mutated thyroid nodules are being discovered…
- ➢ **Ideally yes** (germline mutations can be trasmited to progeny!), although germline mutations are uncommon in patients with unremarkable medical history
- ▪ Germline testing and genetic counselling [Altaraihi M et al. Prevalence of Pathogenic Germline DICER1 Variants in Young Individuals Thyroidectomised Due to Goitre - A National Danish Cohort. Front Endocrinol (Lausanne). 2021;12:727970. doi: 10.3389/fendo.2021.727970]
  - Patients thyroidectomised for goiter aged <21 years
  - Patients thyroidectomised for goitre aged <25 years + family history of goiter
  - Patients of all ages thyroidectomised for goitre, who are affected by another DICER1 manifestation



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Low-specificity (less likely to have DICER1)

Wilms tumor
Pineoblastoma
Cerebral sarcoma
Lung cysts (<18 yrs)

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