GEMEINSAME JAHRESTAGUNG ÖGES und OSDG
22.-24. MÄRZ 2017, REDOUTENSÄLE, LINZ

Molekulares Profiling von Schilddrüsentumoren

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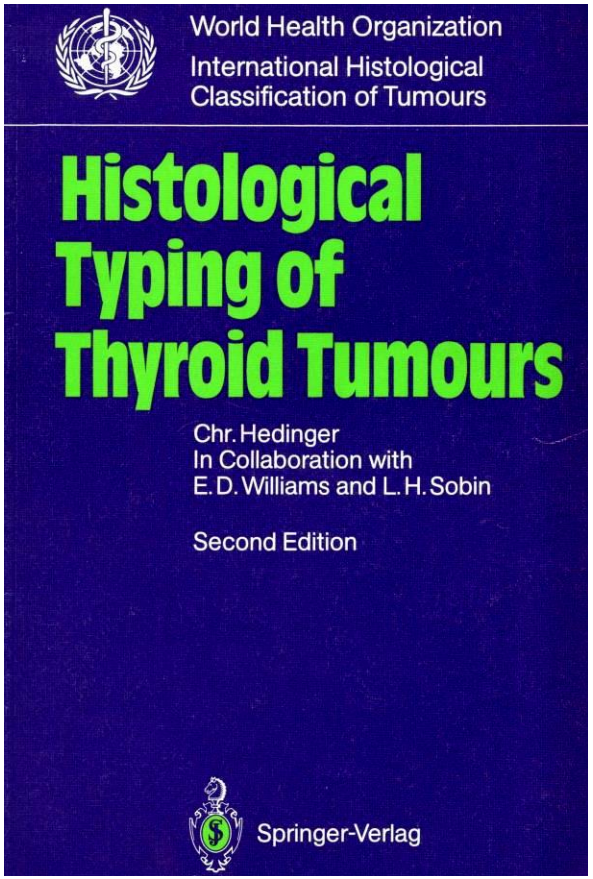
UNIVERSITÄT DUISBURG ESSEN

Universitätsklinikum Essen

Claude L. Pierre Masson
1880 - 1959

“No classification is more difficult to establish than that of thyroid [carcinomas]. Of all cancers, they teach, perhaps, the greatest lessons of humility to histopathologists”.

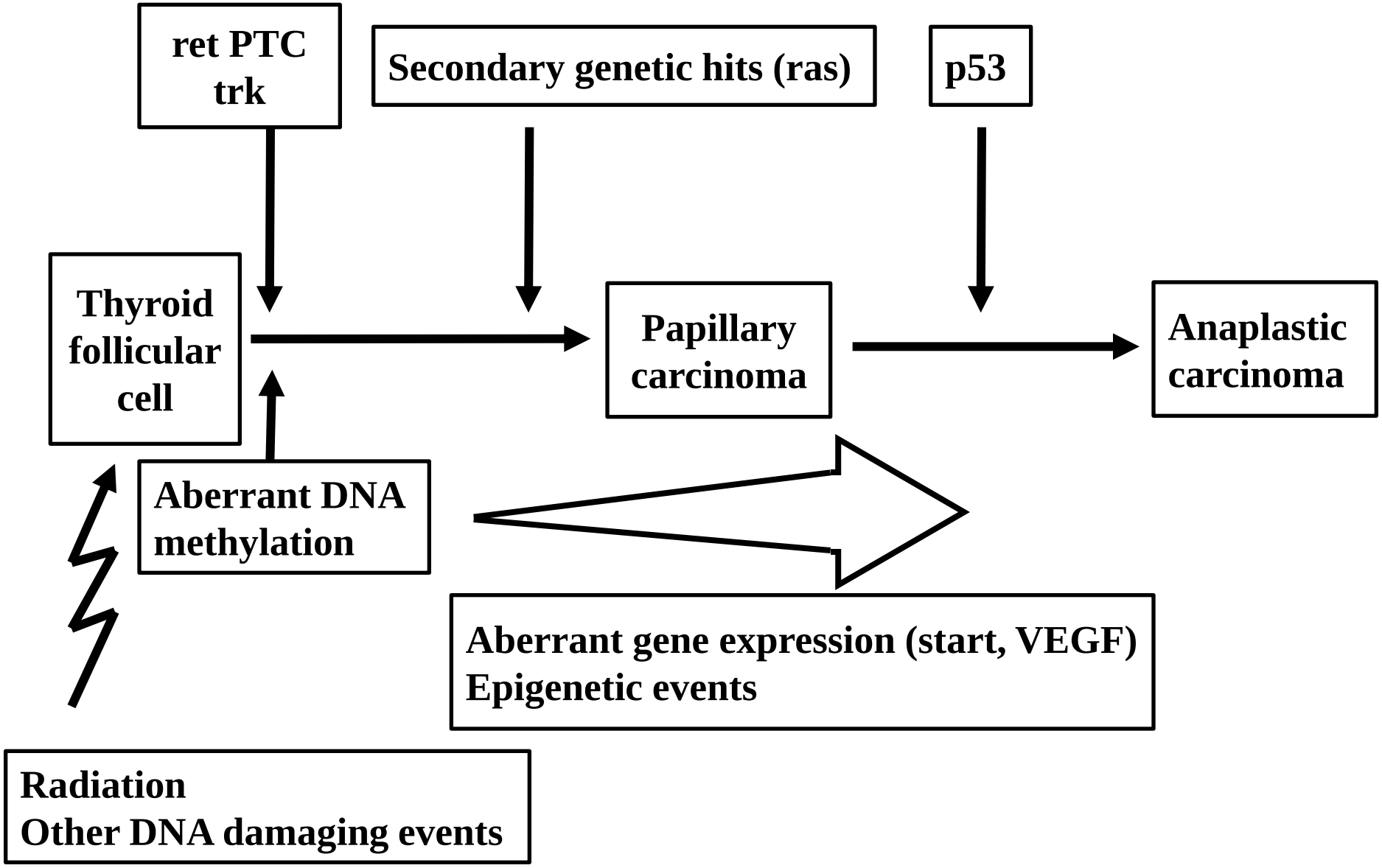
Histological Typing of Thyroid Tumours (WHO 1988)



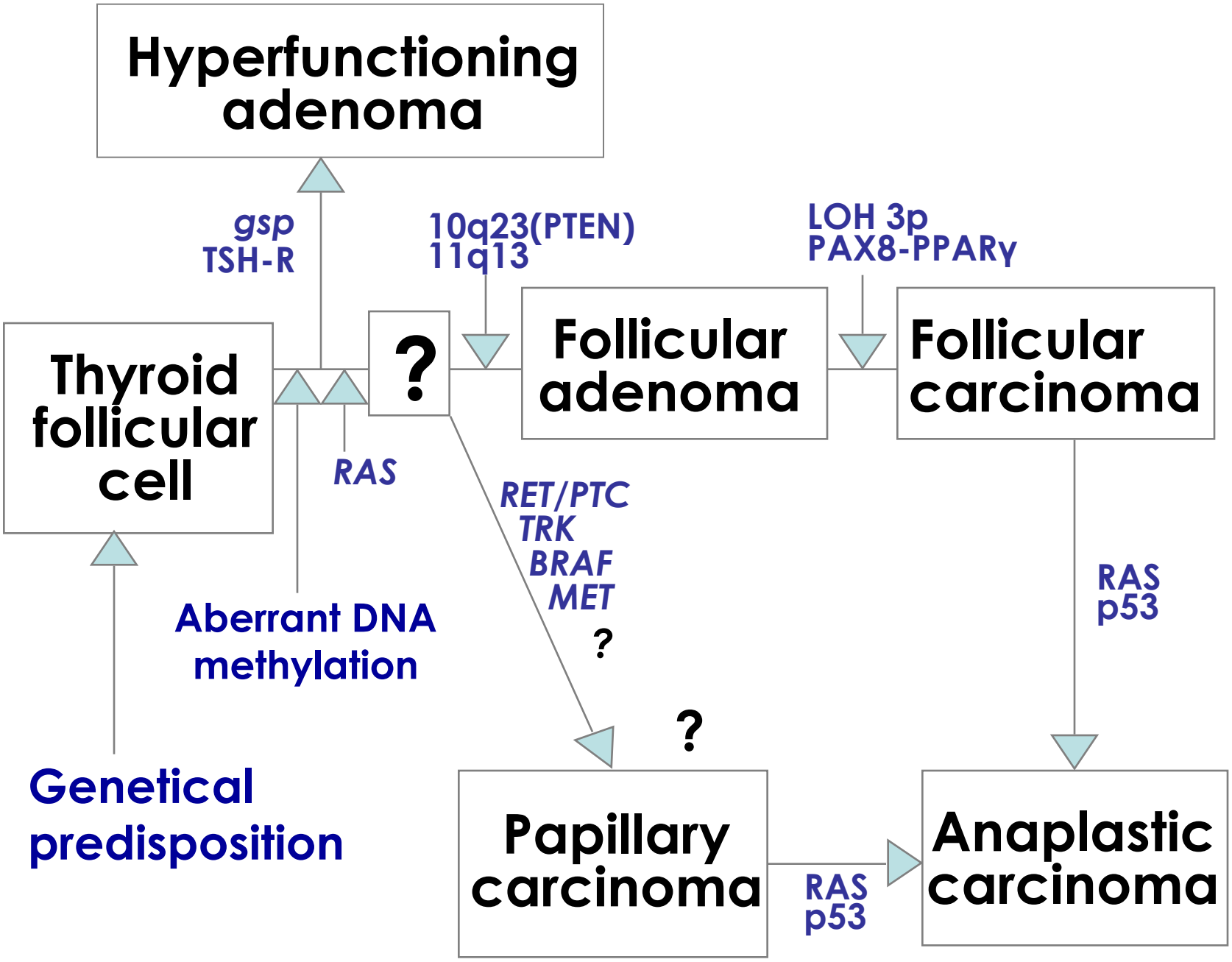
1 Epithelial tumours

1.1 *Benign*
1.1.1 Follicular adenoma
1.1.2 Others
1.2 *Malignant*
1.2.1 Follicular carcinoma
1.2.2 Papillary carcinoma
1.2.3 Medullary carcinoma (C-cell carcinoma)
1.2.4 Undifferentiated (anaplastic) carcinoma
1.2.5 Others

James A. Fagin

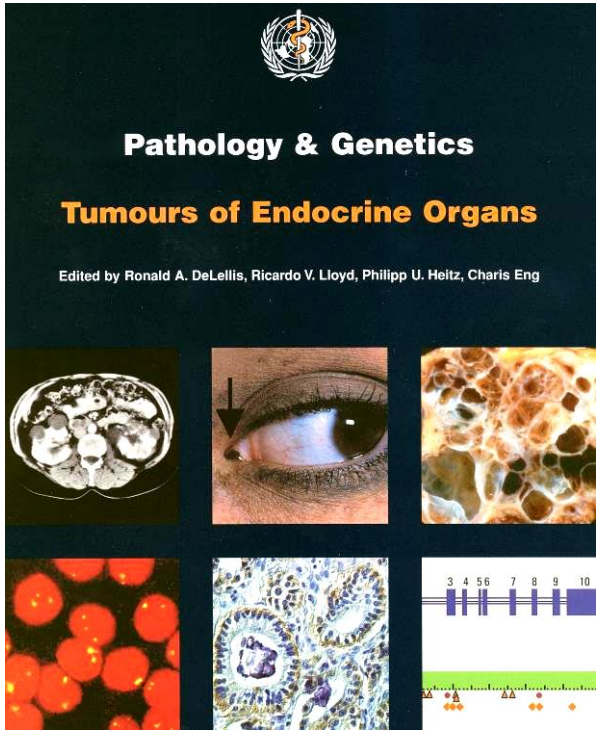


Fagin JA (1998)



Fagin JA 2002

WHO Histological Classification of Thyroid Tumours (2004)



- **Thyroid carcinoma**
  - Papillary carcinoma
  - Follicular carcinoma
  - Poorly differentiated carcinoma
  - Anaplastic carcinoma
  - Squamous cell carcinoma
  - Mucoepidermoid carcinoma
  - Sclerosing mucoepidermoid carcinoma with eosinophilia
  - Mucinous carcinoma
  - Medullary carcinoma
  - Mixed medullary and follicular cell carcinoma
  - Spindle cell tumour with thymus-like differentiation
  - Carcinoma showing thymus-like differentiation
- **Thyroid adenoma and related tumours**
  - Follicular adenoma
  - Hyalinizing trabecular tumour

- **Other thyroid tumours**
  - Teratoma
  - Primary lymphoma and plasmocytoma
  - Ectopic thymoma
  - Angiosarcoma
  - Smooth muscle tumours
  - Peripheral nerve sheath tumours
  - Paraganglioma
  - Solitary fibrous tumour
  - Follicular dentritic cell tumour
  - Langerhans cell histiocytosis
  - Secondary tumours

Classification of thyroid carcinomas

WHO 2004

The traditional separation of thyroid carcinoma into the major groups papillary, follicular, medullary, and anaplastic carcinoma, based on morphology and clinical features, is strongly supported by the involvement of distinct genes in these four groups, with little overlap.

Exceptions

WHO 2004

- **Follicular variant of PTC**
- **FAP-associated thyroid carcinoma**
- **Primary thyroidsquamous carcinoma**
- **Mucoepidermoid carcinoma**

- **Poorly differentiated thyroid carcinoma**

Thyroid Carcinoma

I. *Carcinomas of follicular cell origin*

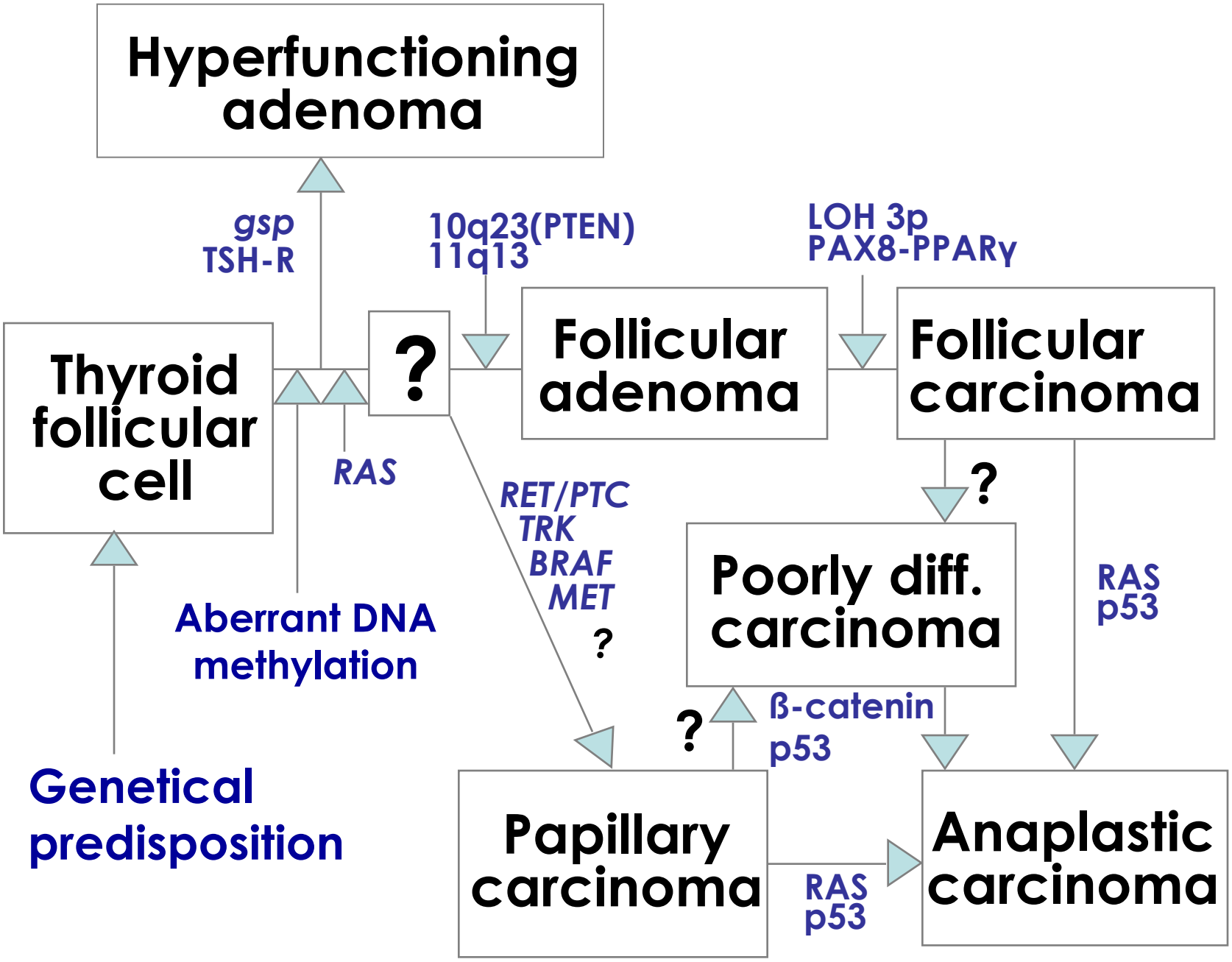
- A. Well differentiated carcinoma
  - 1. Papillary carcinoma
    - a. Conventional type
    - b. Variants (15)
  - 2. Follicular carcinoma
    - a. Minimally invasive carcinoma
    - b. Widely invasive carcinoma
  - 3. NOS (not otherwise specified)
- B. Poorly differentiated carcinoma
- C. Anaplastic (undifferentiated) carcinoma

II. *Carcinomas of C cell origin*

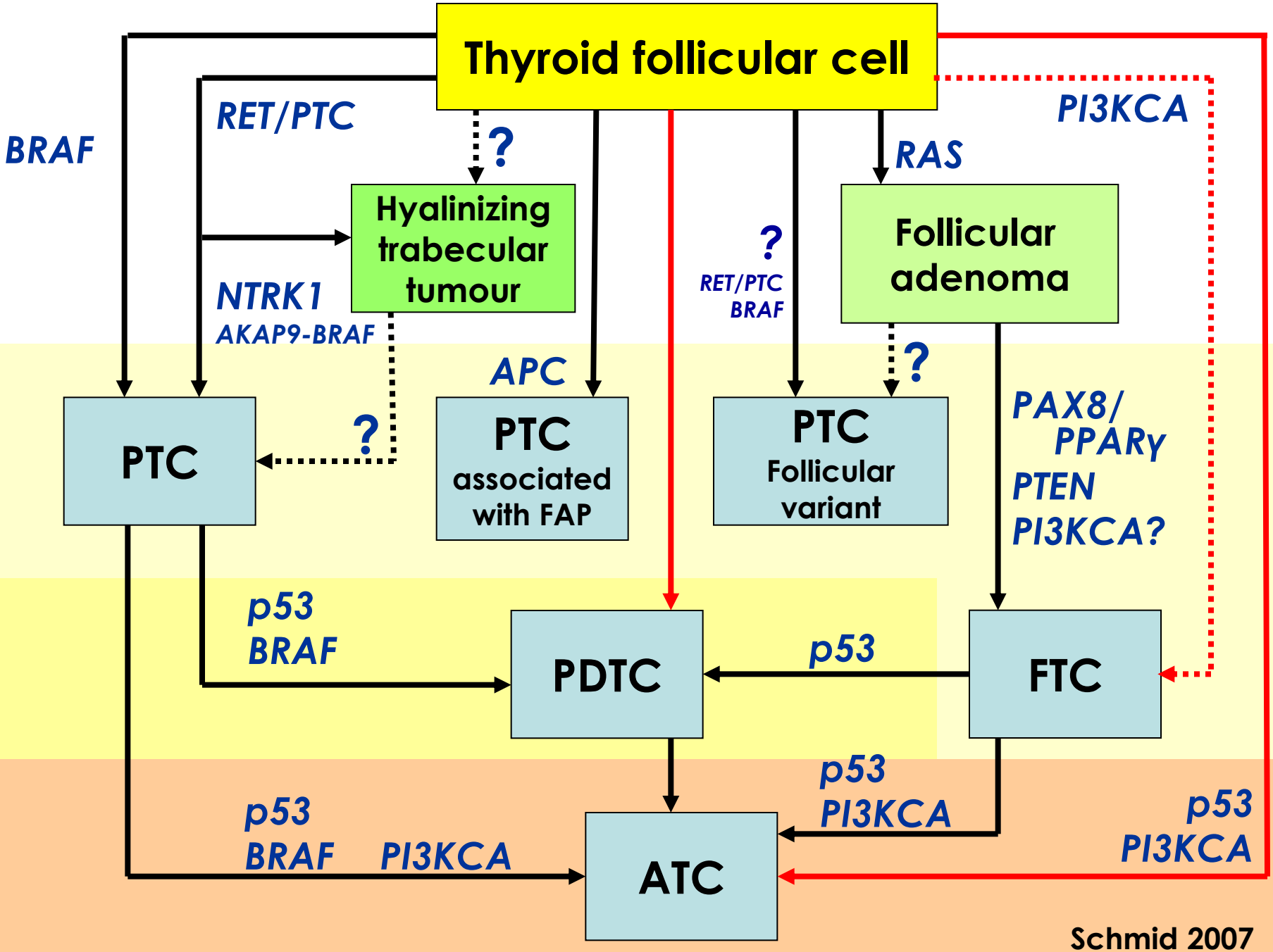
- 1. Medullary carcinoma
  - a. Sporadic
  - b. Hereditary (MEN2, FMTC)
- 2. Mixed C cell - follicular cell origin

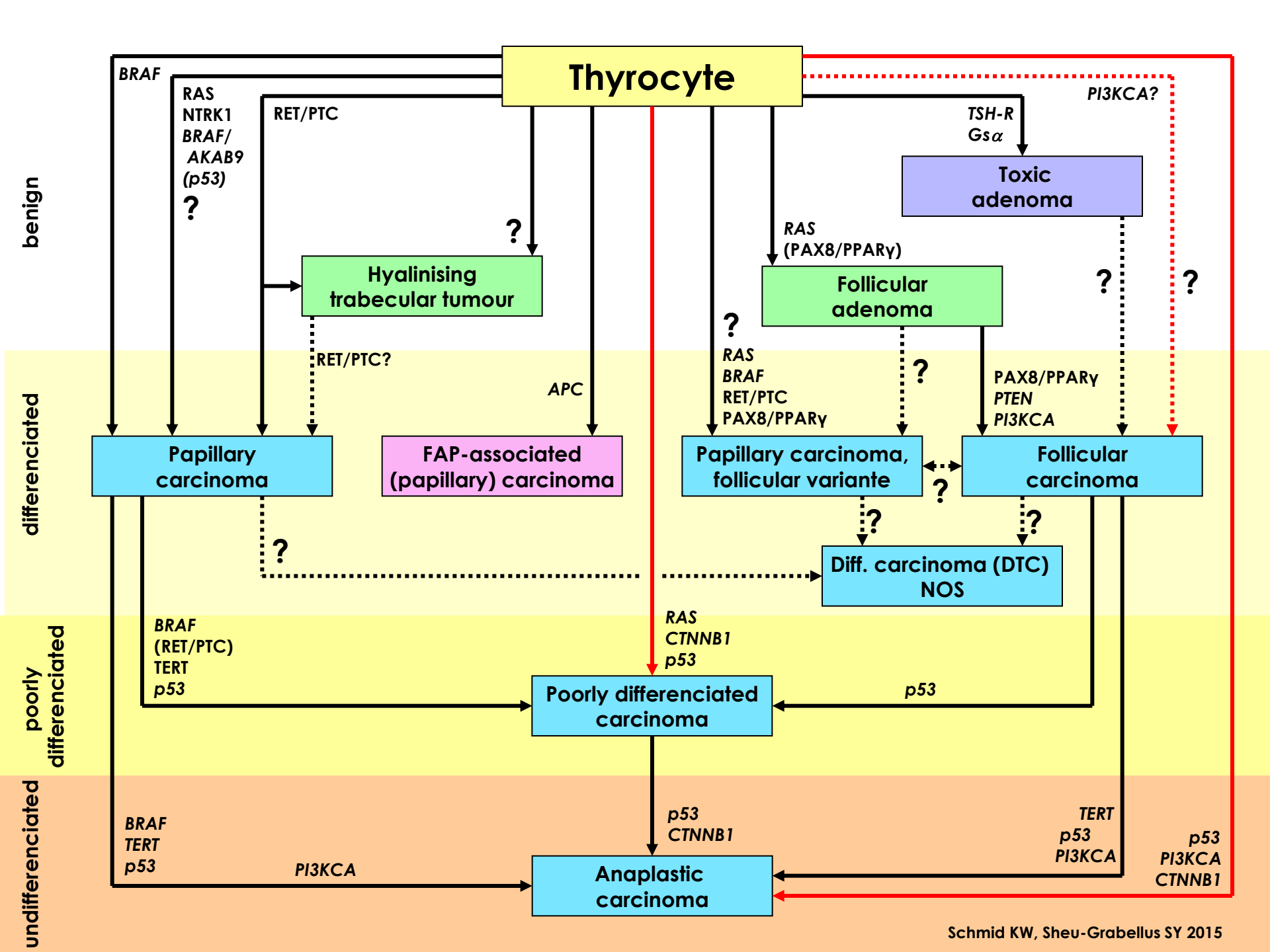
III. *Rare thyroid carcinomas*

Schmid 2005


Hyperfunctioning adenoma
gsp
TSH-R
10q23(PTEN)
11q13
LOH 3p
PAX8-PPARγ
Thyroid follicular cell
?
Follicular adenoma
Follicular carcinoma
RAS
RET/PTC
TRK
BRAF
MET
?
?
Poorly diff. carcinoma
RAS
p53
Aberrant DNA methylation
?
ß-catenin
p53
Genetical predisposition
Papillary carcinoma
RAS
p53
Anaplastic carcinoma

Schmid 2005

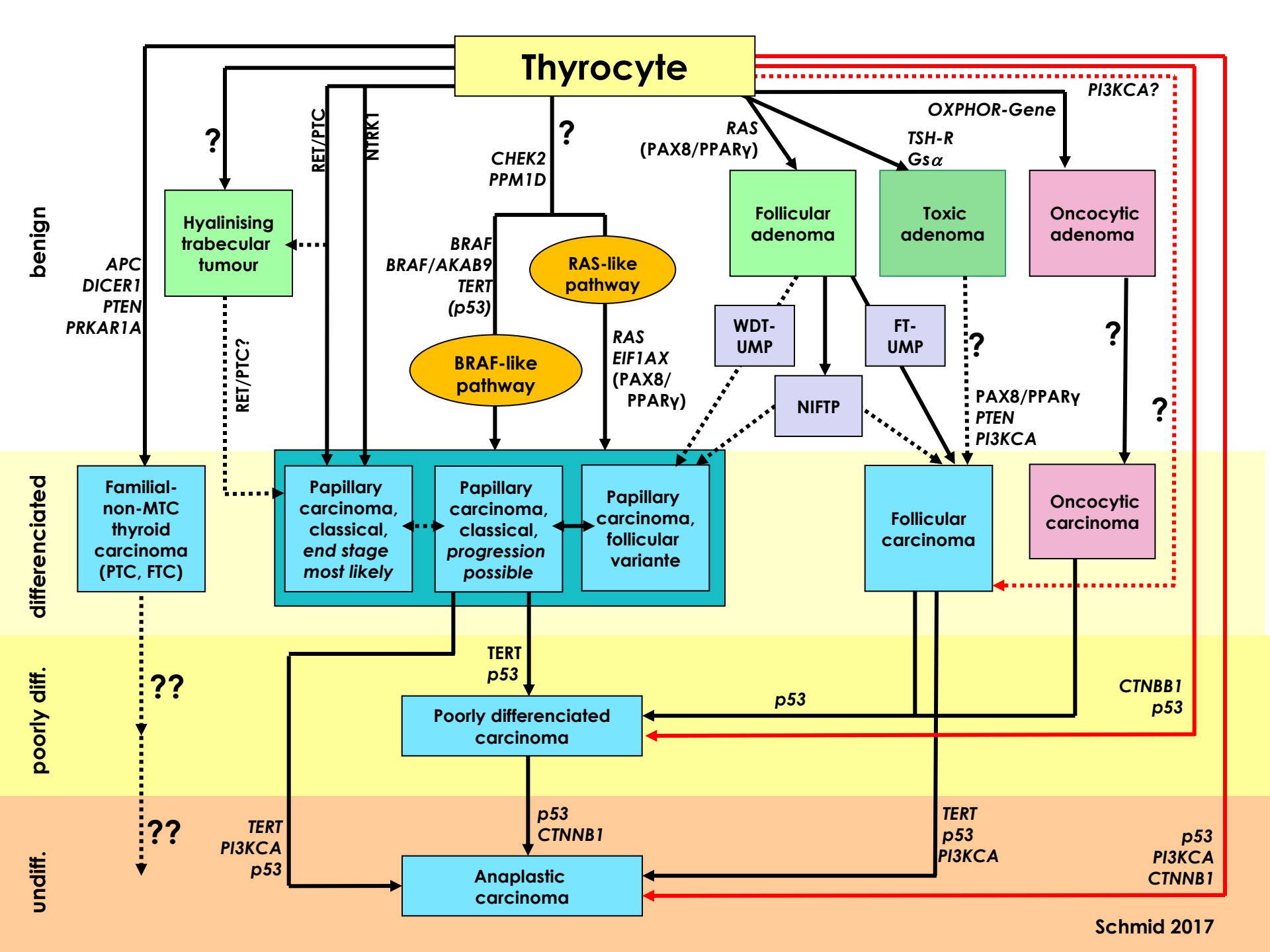

Thyroid follicular cell
BRAF
RET/PTC
?
Hyalinizing trabecular tumour
NTRK1
AKAP9-BRAF
?
PTC
APC
PTC associated with FAP
?
RET/PTC
BRAF
PTC Follicular variant
RAS
Follicular adenoma
?
PAX8/ PPARγ
PTEN
PI3KCA?
PI3KCA
p53
BRAF
PDTC
p53
FTC
p53
PI3KCA
p53
BRAF
PI3KCA
ATC
p53
PI3KCA
Schmid 2007



Schmid KW, Sheu-Grabellus SY 2015

WHO Histological Classification of Thyroid Tumours (2017)

- **Thyroid adenoma and related tumours**
  - Follicular adenoma
  - Hurthle cell adenoma
  - Hyalinizing trabecular tumour
  - Other encapsulated follicular patterned thyroid tumours
- **Thyroid carcinoma**
  - Papillary carcinoma
  - Follicular carcinoma
  - Hurthle cell carcinoma
  - Poorly differentiated carcinoma
  - Anaplastic carcinoma
  - Squamous cell carcinoma
  - Medullary carcinoma
  - Mixed medullary and follicular cell carcinoma
  - Mucoepidermoid carcinoma
  - Sclerosing mucoepidermoid carcinoma with eosinophilia
  - Mucinous carcinoma
- **Other thyroid tumours**
  - Ectopic thymoma
  - Spindle epithelial tumour with thymus-like differentiation
  - Intrathyroidal epithelial thymoma
  - Mesenchymal and stromal tumours
  - Haematologic tumours
  - Germ cell tumours
  - Secondary Tumours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Anaplastic carcinoma
Schmid 2017

# Papillary thyroid carcinoma Genetic alterations	% of PTC
BRAF point mutation V600E • Conventional type (~60%) • Tall cell variant (70 – 80%) • Oncocytic variant (0 – 55%) • Follicular variant (~10%) • Diffuse sclerosing variant (0%)	40 – 45%
BRAF point mutation K601E • Almost exclusively found in follicular variant of PTC	Very rare
RET/PTC Rearrangements • Type 1 (60 – 70%) • Type 3 (20 – 30%) • Other (rare) types (<5%)	10 – 20%
NTRK	5 – 10%
RAS • Almost exclusively found in follicular variant of PTC	15 – 20%

Schmid and Sheu-Grabellus 2015

Original Investigation

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

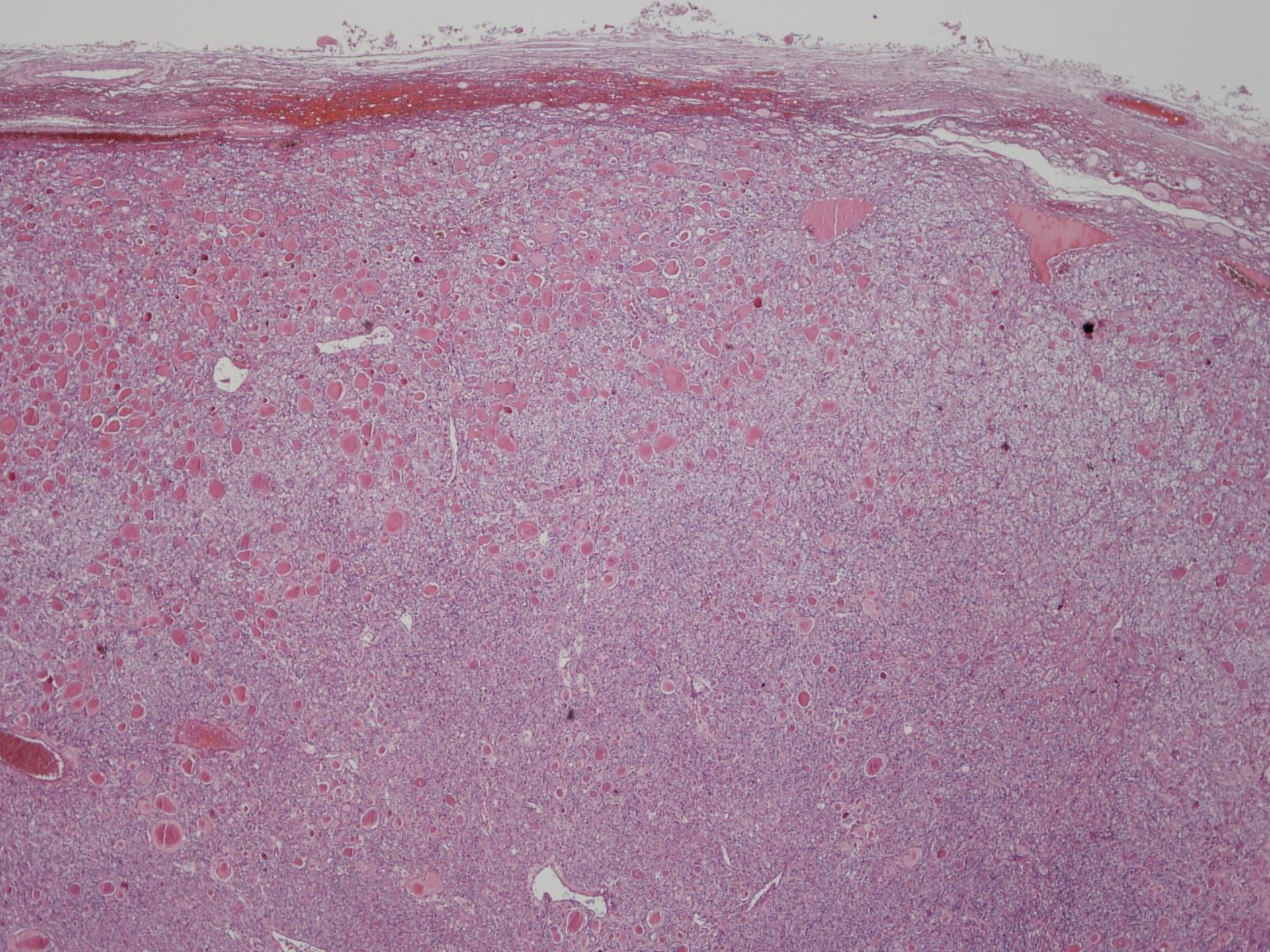
A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

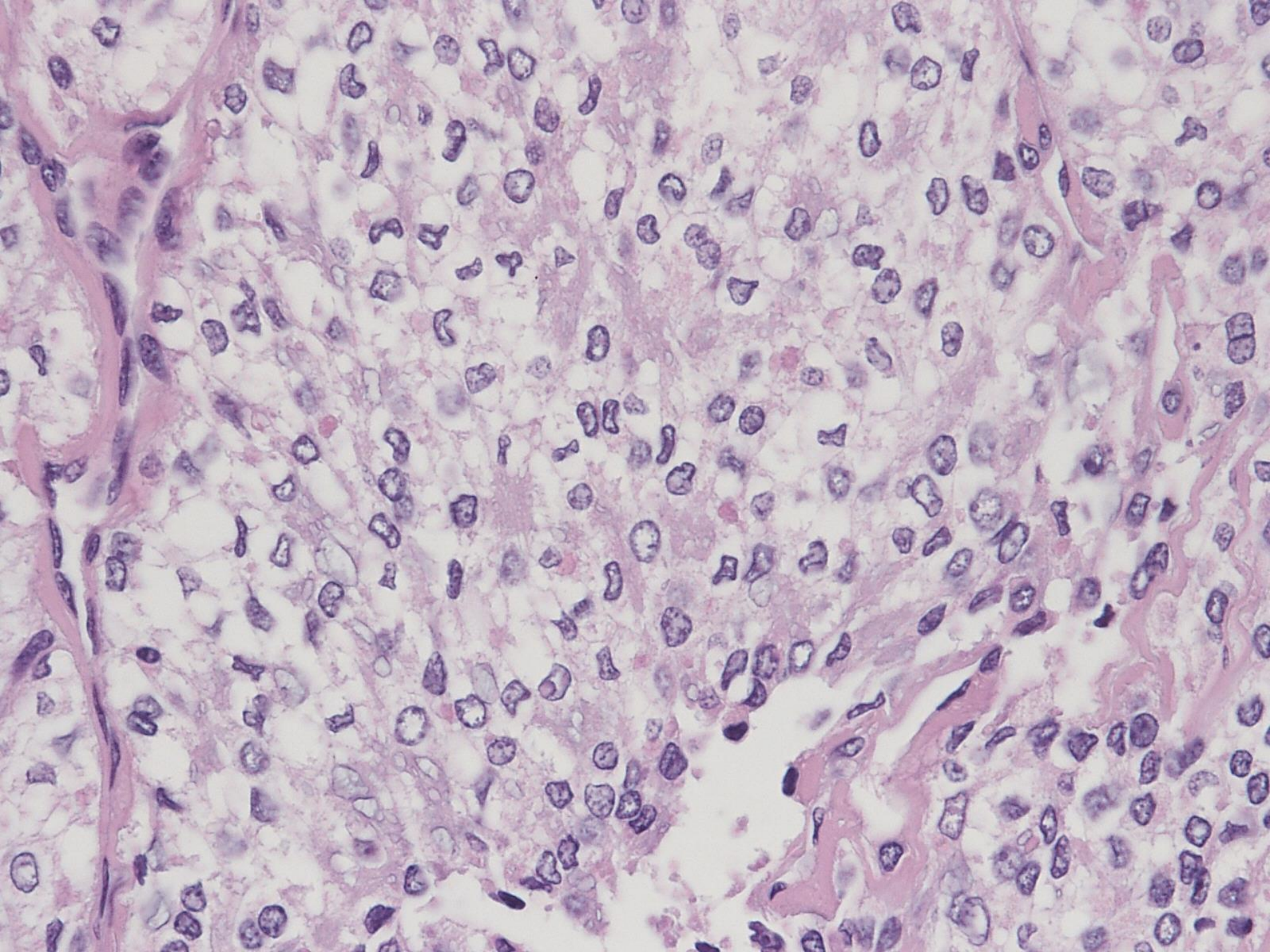
Yuri E. Nikiforov, MD, PhD; Raja R. Seethala, MD; Giovanni Tallini, MD; Zubair W. Baloch, MD, PhD; Fulvio Basolo, MD; Lester D. R. Thompson, MD; Justine A. Barletta, MD; Bruce M. Wenig, MD; Abir Al Ghuzlan, MD; Kennichi Kakudo, MD, PhD; Thomas J. Giordano, MD, PhD; Venancio A. Alves, MD, PhD; Elham Khanafshar, MD, MS; Sylvia L. Asa, MD, PhD; Adel K. El-Naggar, MD; William E. Gooding, MS; Steven P. Hodak, MD; Ricardo V. Lloyd, MD, PhD; Guy Maytal, MD; Ozgur Mete, MD; Marina N. Nikiforova, MD; Vania Nosé, MD, PhD; Mauro Papotti, MD; David N. Poller, MB, ChB, MD, FRCPath; Peter M. Sadow, MD, PhD; Arthur S. Tischler, MD; R. Michael Tuttle, MD; Kathryn B. Wall; Virginia A. LiVolsi, MD; Gregory W. Randolph, MD; Ronald A. Ghossein, MD

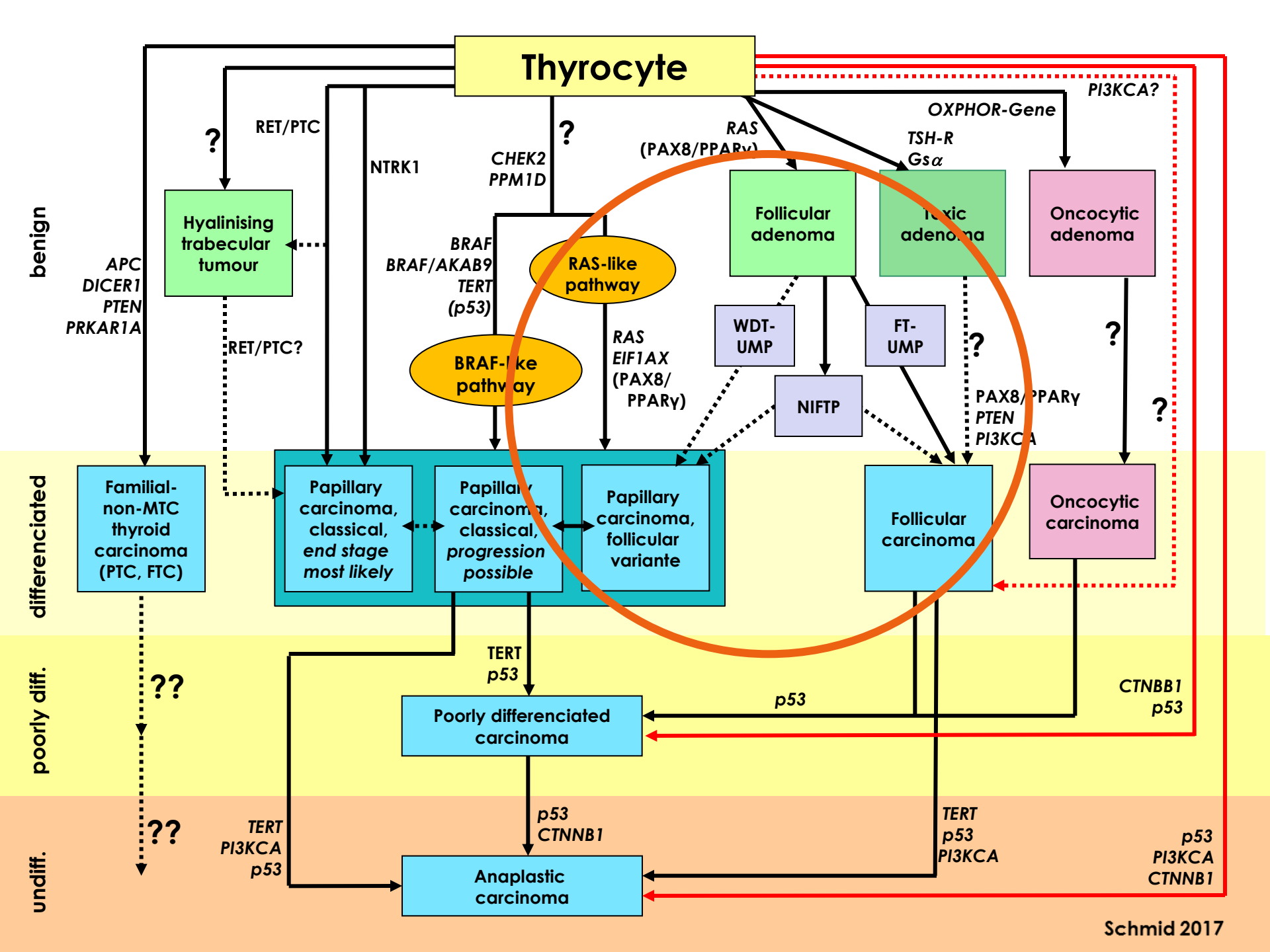
CONCLUSIONS AND RELEVANCE Thyroid tumors currently diagnosed as noninvasive EFVPTC have a very low risk of adverse outcome and should be termed NIFTP. This reclassification will affect a large population of patients worldwide and result in a significant reduction in psychological and clinical consequences associated with the diagnosis of cancer.

NIFTP = non-invasive follicular tumour with PTC-like nuclear features

JAMA Oncol. doi:10.1001/jamaoncol.2016.0386
Published online April 14, 2016.



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Schmid 2017

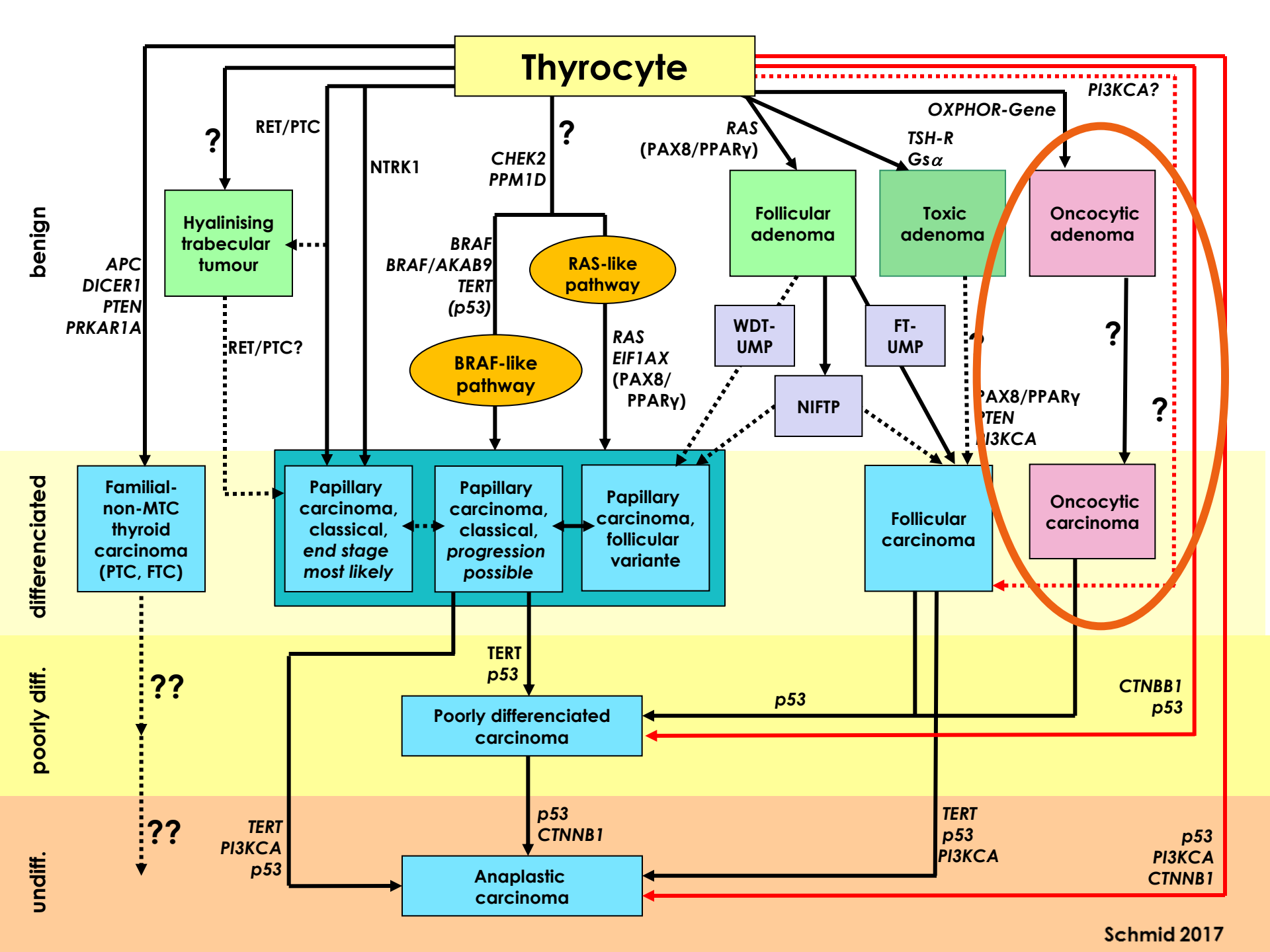
Encapsulated follicular patterned thyroid tumours
WHO 2017

Diagnosis (WHO 2017)	Nuclear features of PTC	Invasive growth	Malignant potential
Follicular adenoma	No or questionable (score 0-1)	no	no
NIFTP	yes (score 2-3)	no	extremely low
FT-UMP	no	questionable	minimally
WDT-UMP	questionable (score 0-1)	questionable	minimally
DTC, NOS	questionable (score 0-1)	yes	very low/ intermediate*
Encapsulated follicular variant PTC	Yes (score 2-3)	yes	very low
Encapsulated FTC	no	yes	very low/ intermediate*

*associated with capsular breakthrough only/vascular invasion into ≤3/≥4 vessels

Encapsulated follicular patterned thyroid tumours
WHO 2017

	RAS	BRAF V600E	BRAF E601K	RET/PTC	PTC assoc. miRNAs	PAX8/ PPARg	THADA gene fusion
Foll. Adenoma	-/+	-	-/+	-	-	-/+	-/+
NIFTP	-/+	-	-/+	-	(-/+)	-/+	-/+
UMP	-/+	-	-/+	-	-	-/+	
WDT-UMP	-/+	-	-/+	-/+ (~ 10%)	(-/+)	-	
FV-PTC	-/+	-/+ (~ 10%)	- (?)	-/+	+	-	
Encap. FTC	-/+	-	-/+	-	-	-/+	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Anaplastic carcinoma
Schmid 2017

Hurthle cell tumours

WHO 2017

Definition

Hurthle cell tumours are neoplasms composed of oncocytic cells which are usually encapsulated. If noninvasive they are termed "adenomas" and if showing capsular and/or vascular invasion, carcinomas.

Karl Hürthle
1860 – 1945

Karl Hürthle hat 1894 in seiner einzigen Arbeit über die Schilddrüse „interfollikuläre Zellen“ beim Hund beschrieben; tatsächlich handelt es sich dabei um eine der ersten Beschreibungen von C-Zellen

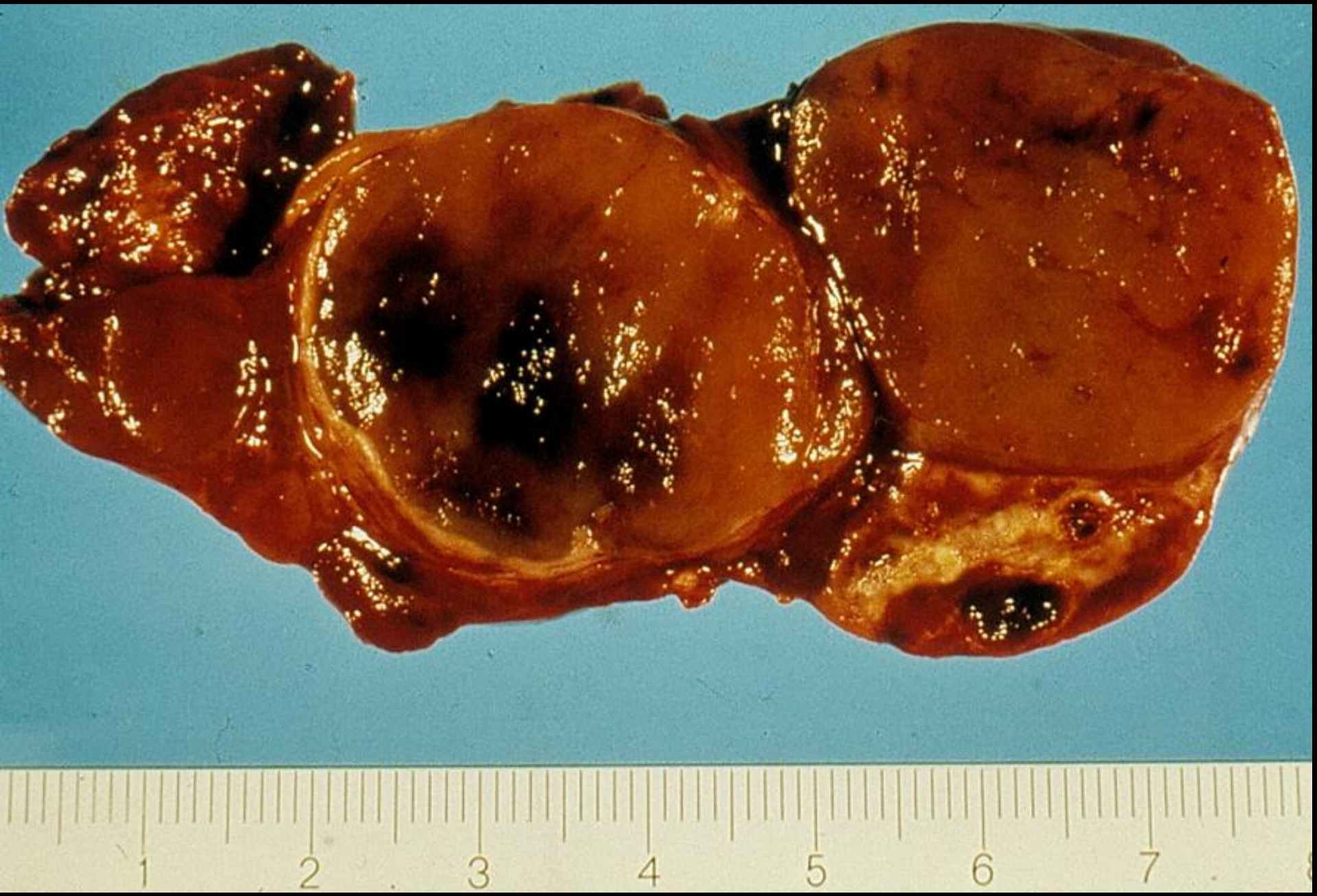
Hürthle K (1894) Beiträge zur Kenntniss des Secretionsvorgangs in der Schilddrüse. Pflugers Arch 56: 1-44

Hürthle-Zellen (onkozytäre Zellen)

Max Askanazy
1865 - 1940

James Ewing
1866 - 1943

- Erstbeschreiber ist Max Askanazy (1898) im M. Basedow
- James Ewing führte 1919 den Begriff „hypertrophic Hürthle cells“ in seiner Tumormonographie ein; seitdem werden onkozytäre Zellen im anglo-amerikanischen Sprachgebrauch irrtümlich als Hürthle-Zellen und die daraus entstehende Tumoren Hürthle-Zell-Adenom/Karzinom benannt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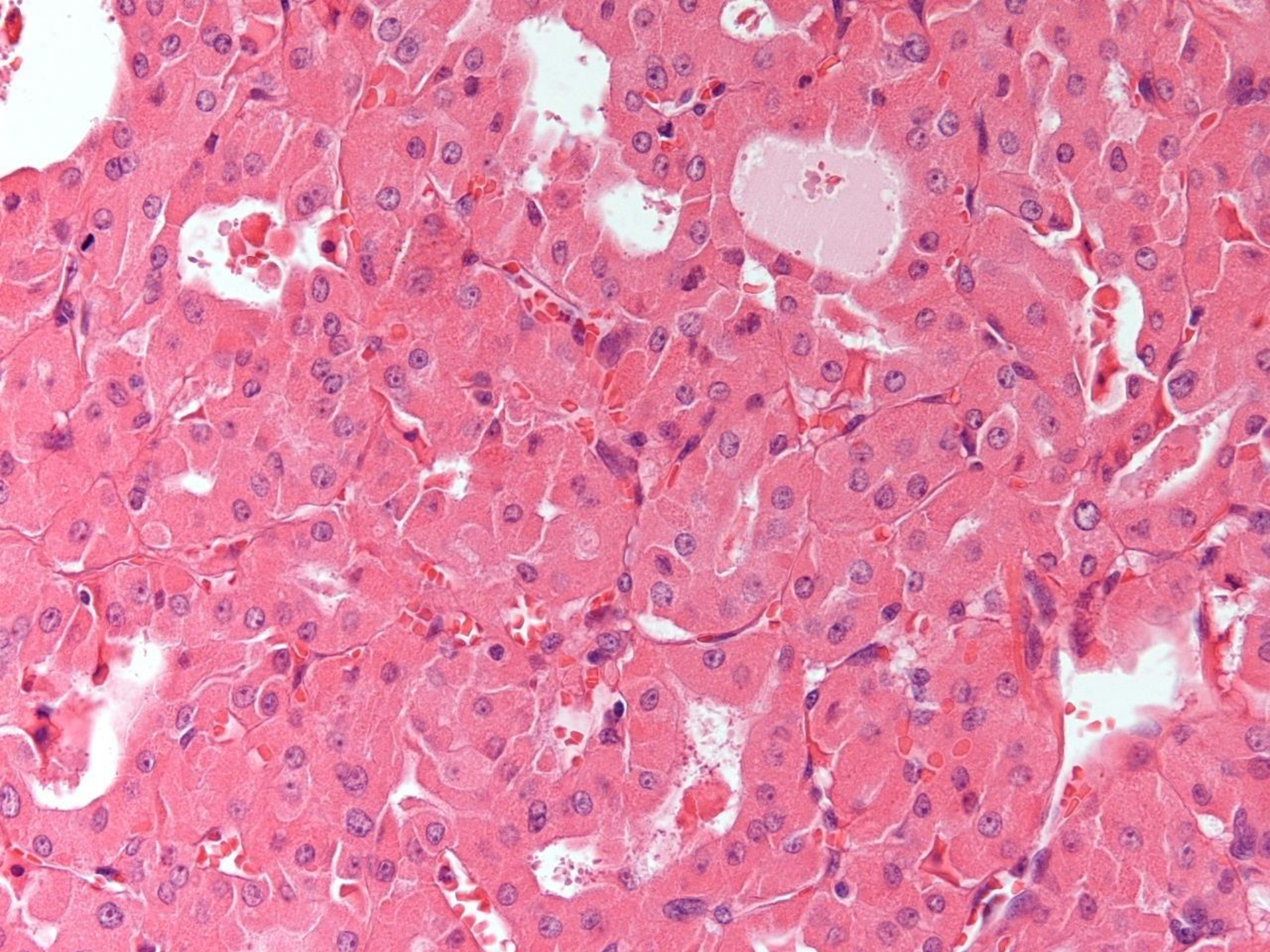
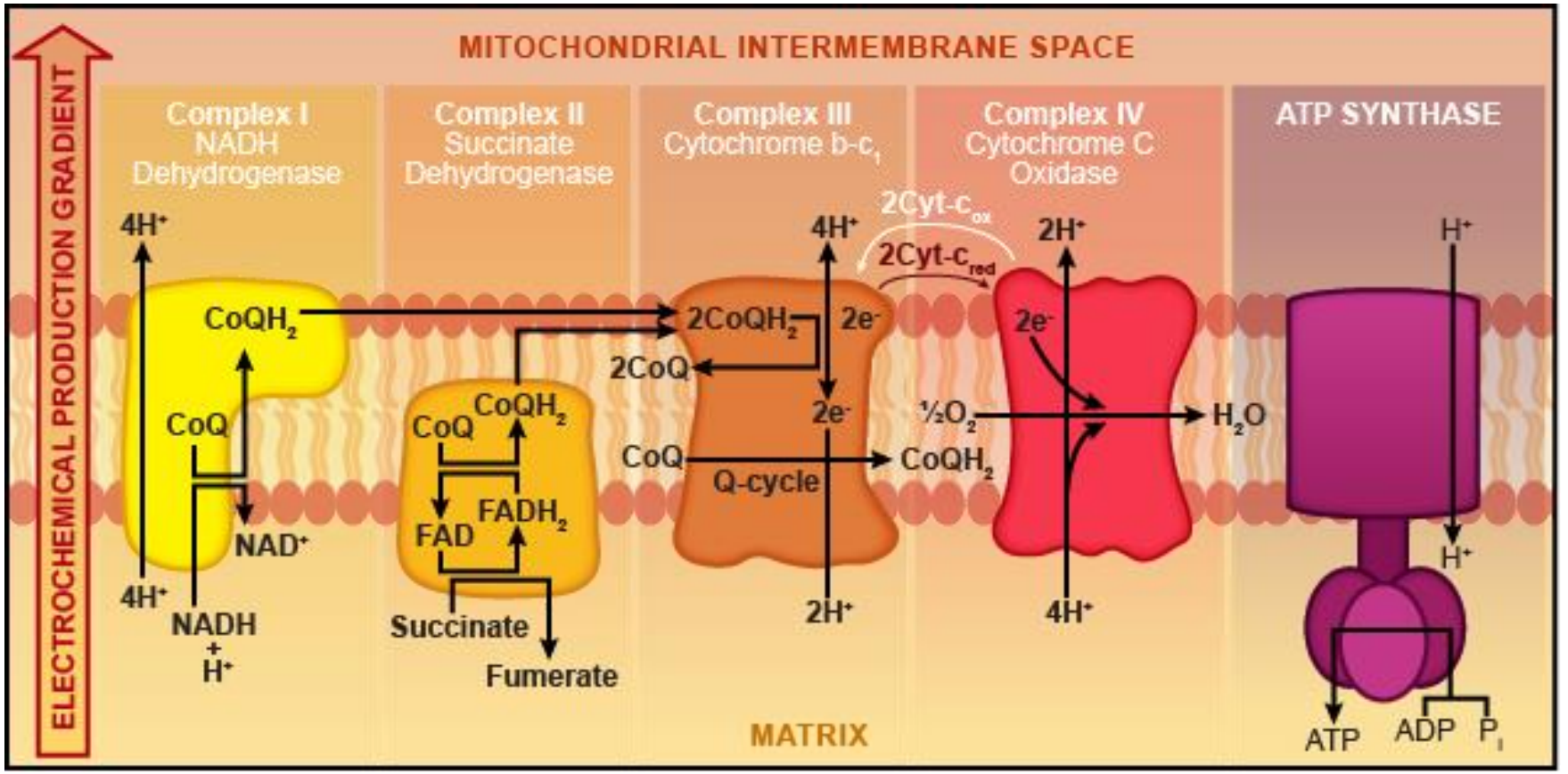


Hurthle cell tumours

OXPHOR-Gene



Hurthle cell tumours

WHO 2017

Genetic Alterations

- Activation of wnt/beta-catenin and PI3K-AKT-mTOR pathways
- RAS and PAX8/PPARg less frequent than in non-Hurthle tumours
- GRIM-19 — mtDNA-Mutationen
- TP53 — 10 – 20%
- PTEN — Cowden-Syndrom

Hurthle cell tumours are the most frequent tumours in familial non-medullary thyroid cancer (FNMTC)

- Chromosomal gains — 5, 7, 12, and 17
- Chromosomal losses — 2q, 9q and 22
- Gains in recurrent tumours — 12q, 19q and 20

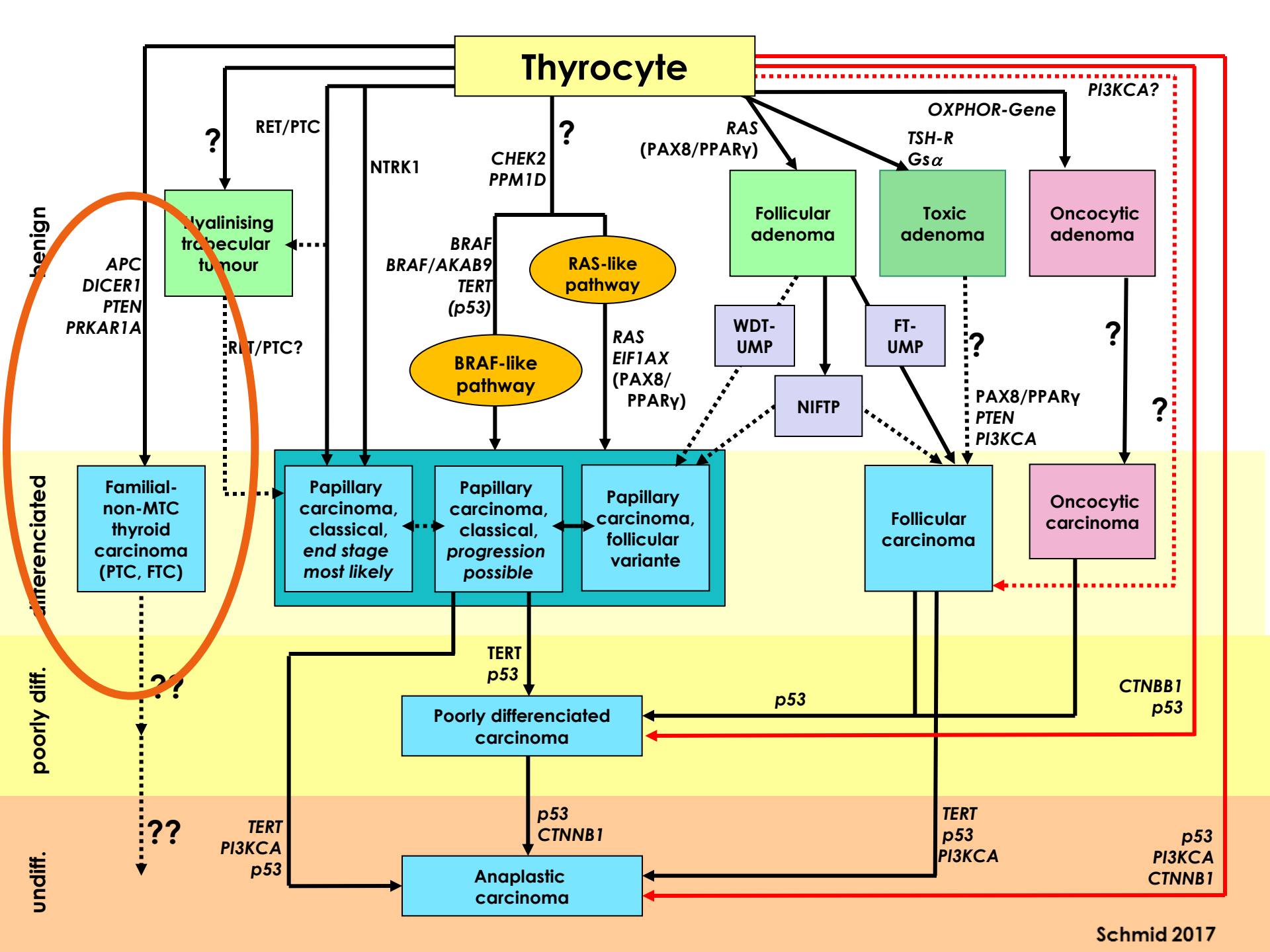
Papillary Thyroid Carcinoma

WHO 2017

a. Conventional/classical type

b. Variants

- Papillary Microcarcinoma
- Encapsulated Variant
- Follicular Variant
- Diffuse Sclerosing Variant
- Tall cell variant
- Columnar cell variant
- Cribriform-morular variant
- Hobnail variant
- PTC with fibromatosis/fascitiis-like stroma
- Solid/ trabecular variant
- Oncocytic variant
- Spindle cell variant
- Clear cell variant
- Warthin like variant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Schmid 2017

Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer

The American Thyroid Association Guidelines Task Force
on Pediatric Thyroid Cancer

TABLE 4. HEREDITARY TUMOR SYNDROMES ASSOCIATED WITH THYROID NODULES/DIFFERENTIATED THYROID CANCER

Hereditary syndrome[a]	*Gene (chromosomal location)*	*Type of thyroid neoplasia*
APC-associated polyposis (familial adenomatous polyposis [FAP], attenuated FAP, Gardner syndrome, and Turcot syndrome)	• *APC* (5q21-q22)	• PTC (cribriform-morular variant)
Carney complex	• *PRKAR1A* (17q24.2) • *"CNC2"* (2p16)	• Multinodular goiter • Follicular adenomas • DTC (PTC and FTC)
DICER1 Syndrome	• *DICER1* (14q32.13)	• Multinodular goiter • DTC (due to second somatic mutation in *DICER1*, possibly related to treatment of pleuropulmonary blastoma)
PTEN hamartoma tumor syndrome (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, *PTEN*-related Proteus syndrome, and Proteus-like syndrome)	• *PTEN* (10q23)	• Multinodular goiter • Follicular adenomas • DTC (FTC overrepresented)
Werner syndrome	• *WRN* (8p12)	• DTC (PTC and FTC)

[a]Although DTC has also been reported to occur in patients with Beckwith–Wiedemann syndrome, the familial paraganglioma syndromes, Li–Fraumeni Syndrome, McCune–Albright syndrome, and Peutz–Jeghers syndrome, it remains unclear if these tumors are a direct result of the underlying genetic defect.

THYROID
Volume 25, Number 7, 2015

DOI: 10.1089/thy.2014.0460

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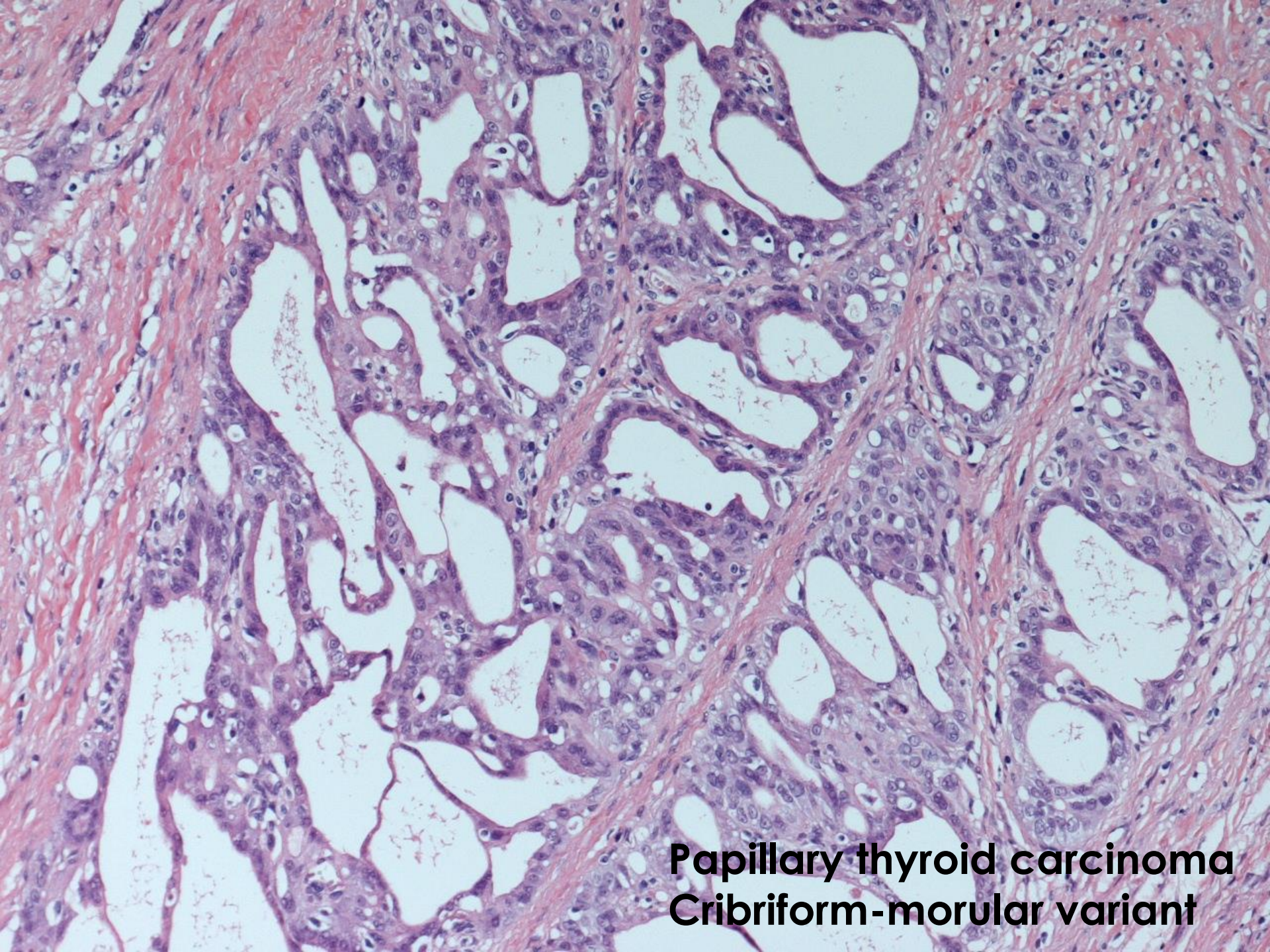
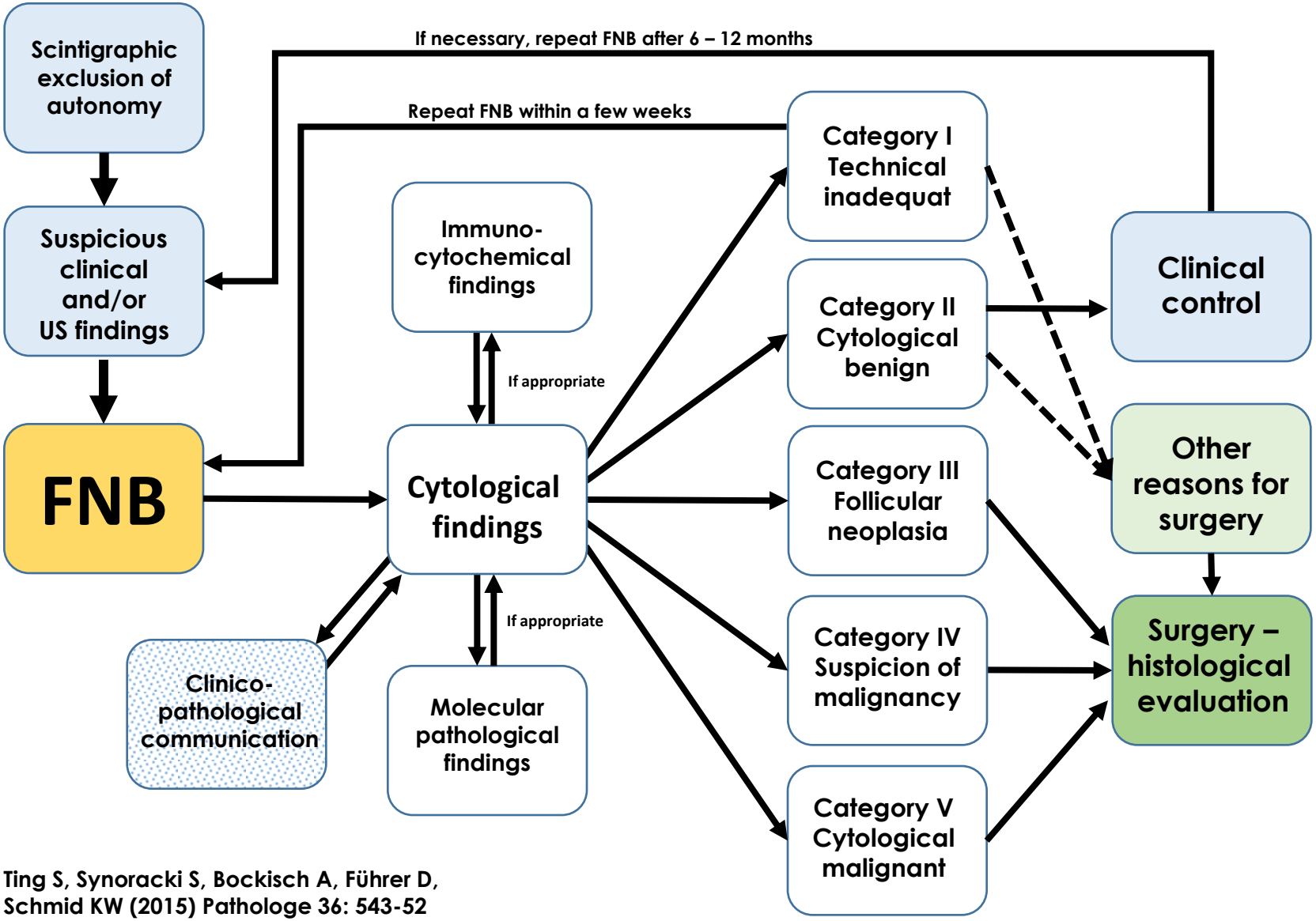

Papillary thyroid carcinoma
Cribriform-morular variant

Selected genetic alterations in thyroid carcinoma

	Adenoma	FTC	PTC	PDTC	ATC	MTC
BRAF mutations (V600E)	0	0	40 – 45%	0 – 13%	10 – 25%	
RET/PTC rearrangements	0	0	10 – 20%	~10%	0	
RET mutations					~7%	98 – 100% 40 – 60%
NTRK1 rearrangements	0	0	5 – 10%	?	?	
RAS mutations	~ 30%	40 – 53%	15 – 20%	18 – 27%	20 – 60%	5 – 10%
PAX8-PPAR rearrangements	~8%	25 – 63%	0 – 38%	~5%	rare	
PI3KCA mutations	~5%	5 - 10%	0	>35%	>40%	
P53 mutations	0	0 – 9%	0 – 5%	17 – 38%	67 – 88%	
CTNNB1 mutations	0	0	0	0 – 25%	66%	
TERT (T228C,T250C)	~3%	~17%	~24%	10 – 30%	35 - 70%	

Modified
Schmid KW, Führer-Sakel D (2015) Onkologe

Indication and diagnostic FNB categorisation of thyroid nodules



Ting S, Synoracki S, Bockisch A, Führer D, Schmid KW (2015) Pathologe 36: 543-52

Molecular evaluation of FNB of the thyroid

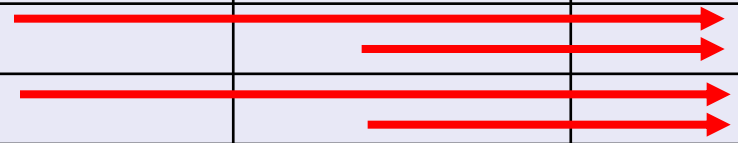
NGS-analysis

Genes	Exons	Diagnostic Category III	Diagnostic Category IV	Diagnostic Category V
BRAF	11,15			
EGFR	18-21			
HRAS	2-4			
KRAS	2-4			
NRAS	2-4			
PIK3CA	3, 5, 10, 16, 21			
CTNNB1				
RET	10, 11, 13-16			
Tp53	4-9			
APC	1-16			
PTEN	1-9			
DICER1	1-28			
PRKAR1A	1-11			

Molecular evaluation of FNB of the thyroid

FISH/CISH analysis of rearrangements

Rearrangement	Diagnostic Category III	Diagnostic Category IV	Diagnostic Category V
RET/PTC rearrangements			
NTRK1 rearrangements			
PAX8-PPAR rearrangements	●		



Molecular evaluation of FNB of the thyroid

NGS-analysis

Genes	Exons	Diagnostic Category III	Diagnostic Category IV	Diagnostic Category V
BRAF	11,15			
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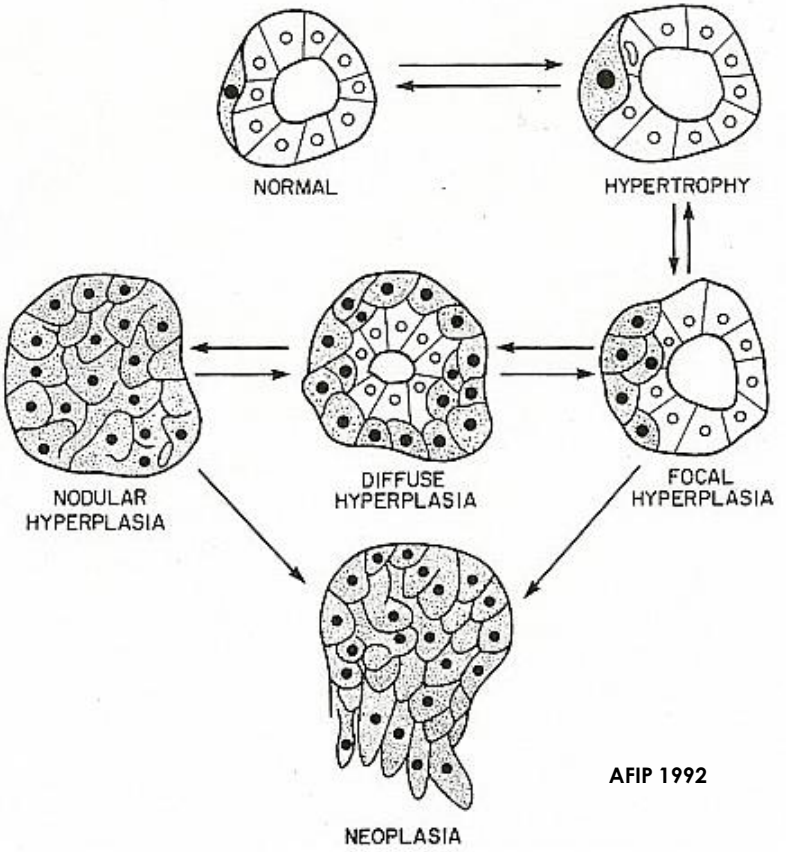
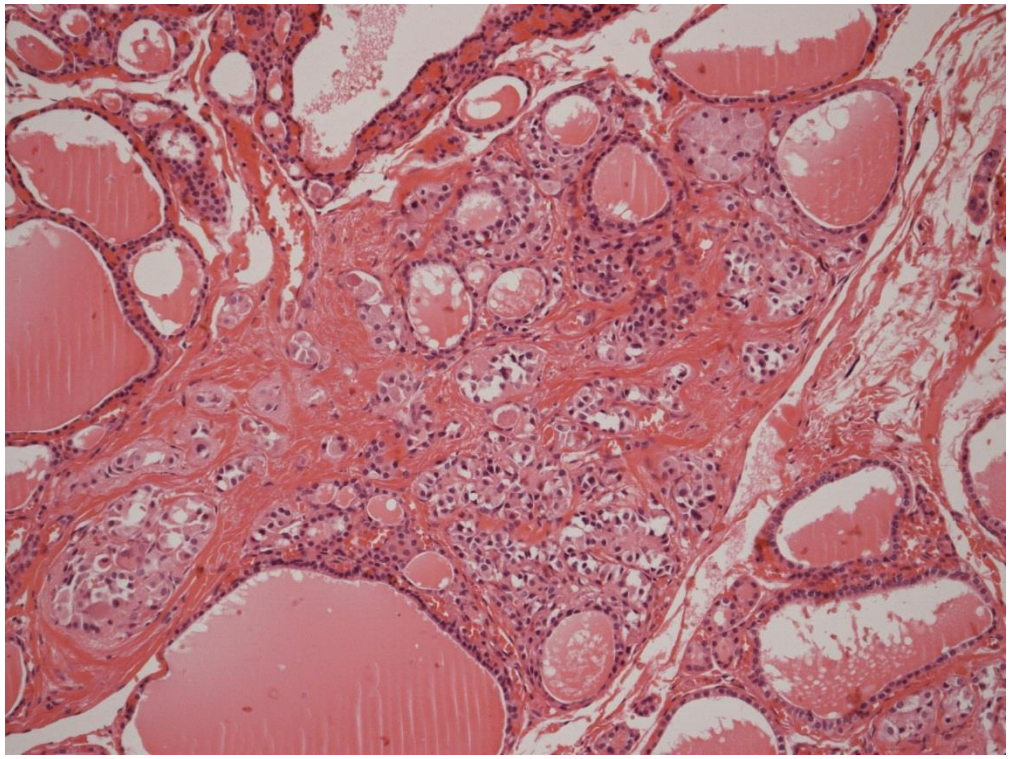
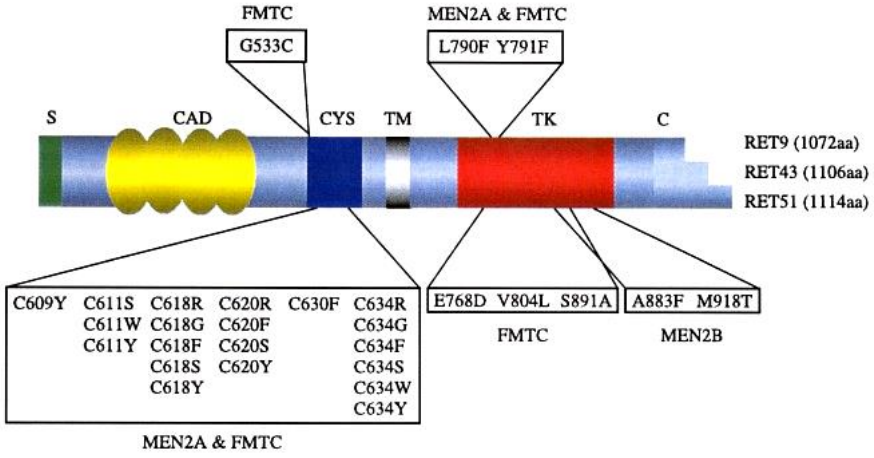
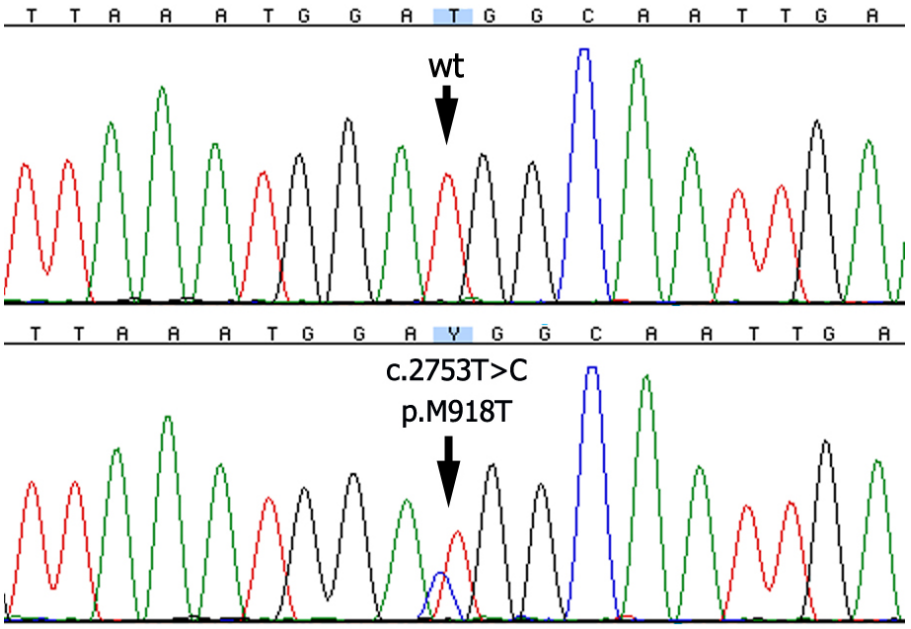
RET	10, 11, 13-16			
Tp53	4-9			
APC	1-16			
PTEN	1-9			
DICER1	1-28			
PRKAR1A	1-11			

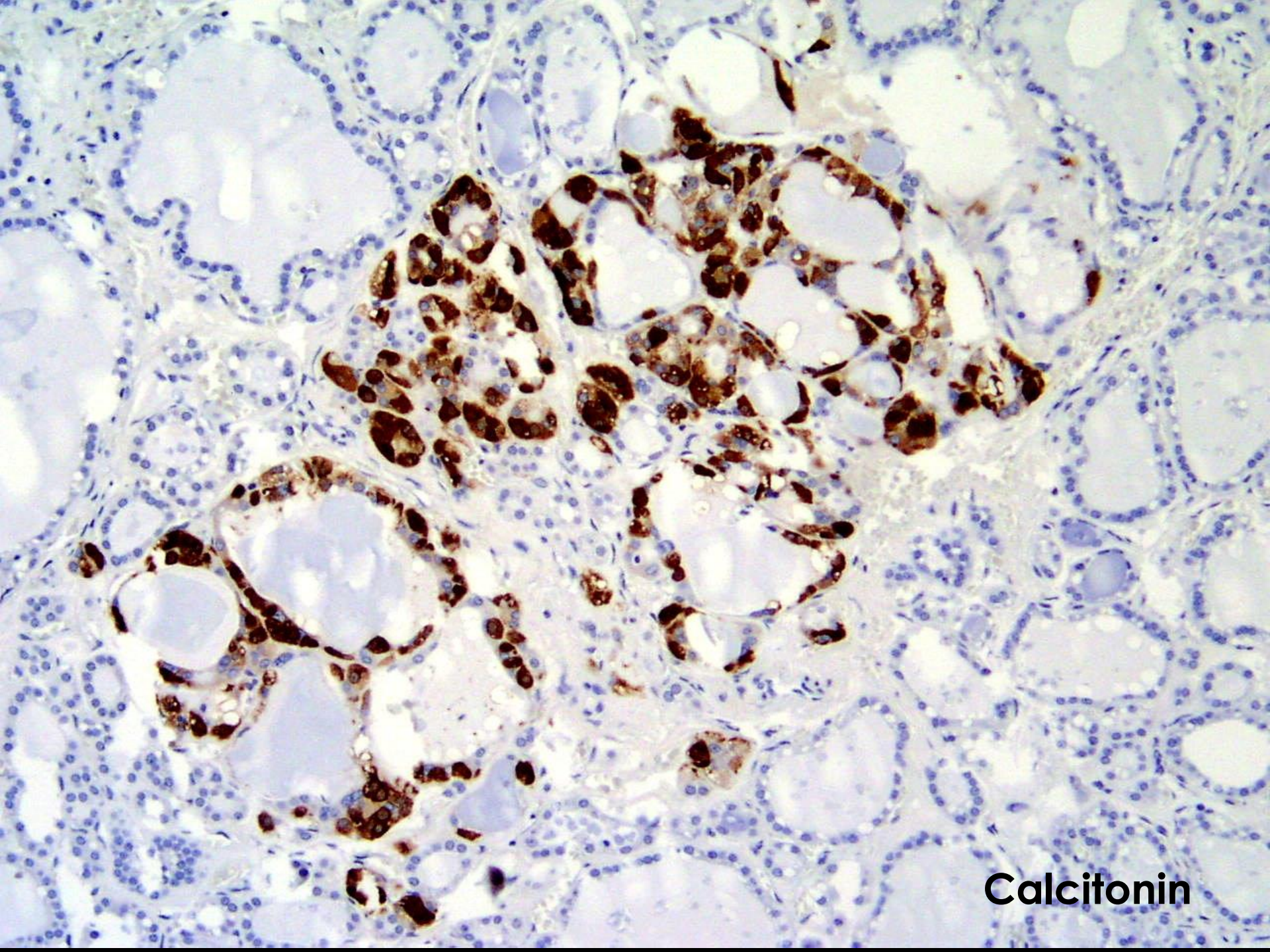

NORMAL
HYPERTROPHY
NODULAR HYPERPLASIA
DIFFUSE HYPERPLASIA
FOCAL HYPERPLASIA
NEOPLASIA

AFIP 1992




FMTC
G533C
MEN2A & FMTC
L790F Y791F
S
CAD
CYS
TM
TK
C
RET9 (1072aa)
RET43 (1106aa)
RET51 (1114aa)
C609Y C611S C611W C611Y C618R C618G C618F C618S C618Y C620R C620F C620S C620Y C630F C634R C634G C634F C634S C634W C634Y
MEN2A & FMTC
E768D V804L S891A
FMTC
A883F M918T
MEN2B


T T A A A T G G A T G G C A A T T G A
wt
T T A A A T G G A Y G G C A A T T G A
c.2753T>C
p.M918T


Calcitonin

Tab. 1 Genophänotypkorrelation als Grundlage der Risikoabschätzung (A–D) beim familiären medullären Schilddrüsenkarzinom. (Mod. nach [25])

ATA-Risikolevel[a]	Exon	Betroffenes Kodon	Frühestes Auftreten des MTC (Alter/Jahre)	MEN2-Phänotyp
A	8	G321R	61	FMTC
		C515S	35	FMTC
		532 Duplikation	19	FMTC
		G533C	21	2A/FMTC
	10	R600Q	46	FMTC
		K603Q	35	FMTC
		Y606C	58	FMTC
	11	635/Insertion	9	FMTC
		ELCR;T636P K666E	35	2A/FMTC
	13	E768D	22	2A/FMTC
		N777S	60	FMTC
		L790F	12	2A/FMTC
	14	V804L	12	2A/FMTC
		V804M	6	2A/FMTC
	15	S891A	13	2A/FMTC
	16	R912P	14	FMTC
B	10	C609R/G/S/Y	27/5/17/14	2A/FMTC
		C611R/G/F/S/W/Y	?/28/41/47/79/7	2A/FMTC
		C618R/G/F/S/Y	8/9/34/9/26	2A/FMTC
		C620R/G/F/S/W/Y	6/44/40/24/37/18	2A/FMTC
		C630R/F/S/Y	1/?/39/22	2A/FMTC
	11	633/9 bp-Duplikation	?	2A/FMTC
		634/12 bp-Duplikation	14	2A
	13/14	V804M/V778I	35	FMTC
C	11	C634R	1,25 (*15 Monate*)	2A
		C634G/F/S/W/Y	25/7/23/3/5	2A/FMTC
D	14	V804M/E805K	50	2B
		V804M/Y806C	23	2B
	14/15	V804M/S904C	34	2B
	15	A883F	10	2B
	16	M918T	0,75 (*9 Monate*)	2B

[a]American-Thyroid-Association(ATA)-Risikolevel: *A* geringes Risiko, *B* intermediäres Risiko, *C* hohes Risiko, *D* höchstes Risiko.
FMTC familiäres medulläres Schilddrüsenkarzinom (MTC-only-Syndrom), heute als spezielle Variante der MEN2A angesehen, *MEN* multiple endokrine Neoplasie.

Ting et al. 2015, Pathologe

Molekulares Profiling bei Schilddrüsentumoren

- **Diagnostisches Instrument**
  - **für einige Tumoren beweisend**
  - **Keimbahn vs. somatische Mutationen**
  - **Instrument zur Präzisierung der FNB**
- **Prognostische Aussagen**
- **Therapie-leitend**

- **Wichtiges Instrument zum Verständnis der Biologie der unterschiedlichen Tumorentitäten**

Thyroid Carcinoma

I. *Carcinomas of follicular cell origin*

- A. Well differentiated carcinoma
  - 1. Papillary carcinoma
    - a. Conventional/classical type
    - b. Variants (14)
  - 2. Follicular carcinoma
    - a. Minimally invasive (capsule invasion only)
    - b. Encapsulated angioinvasive
    - b. Widely invasive
  - 3. Hurthle cell carcinoma
  - 4. Familial non-medullary carcinoma
- B. Poorly differentiated carcinoma
- C. Anaplastic (undifferentiated) carcinoma
- D. Squamous cell carcinoma

II. *Carcinomas of C cell origin*

- 1. Medullary carcinoma
  - a. Sporadic
  - b. Hereditary (MEN2)
- 2. Mixed C cell - follicular cell carcinoma

III. *Rare thyroid carcinomas*

Schmid 2017