2025 City of Hope Multidisciplinary Thyroid Cancer Symposium

Hereditary Thyroid Cancer Syndromes

Joanne Jeter, MD, MS, FASCO

Clinical Professor, Department of Medical Oncology

Interim Director, Division of Clinical Cancer Genomics

City of Hope National Cancer Center

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Use of interpreters for genetic counseling.*
- *Increased prevalence of consanguinity/founder mutations in certain ethnic populations.*
- *Routine evaluation for Ashkenazi Jewish ancestry and other race/ethnicity.*

Prevalence of Germline Pathogenic Variants in Thyroid Cancer

- Medullary: 25% germline
- Nonmedullary: 5-15% estimated as germline

Moses W et al. 2011;21(4):367–371
Jeter J et al. ASCO SEP 2023.

Table 6-9 **Prevalence of Germline Cancer Susceptibility Pathogenic Variants for Unselected Patients**

Cancer Type	Patients with germline variants, N/ Total patients, N	GPV Prevalence
Breast	83/959[158] 494/4581[159]	8.65%-10.8%
Triple-negative breast	267/1824[160]	14.6%
Lung (Advanced cancer only)	222/5118[161] 448/7668[159]	4.3%-5.8%
Colon	305/5303[162] 105/1058[159]	5.8%-9.9%
Prostate	247/2887[162] 620/3607[163]	8.6%-17.3%
Osteosarcoma	281/1044[164]	28.0%
Renal	85/1336[159]	6.4%
Pancreatic (adenocarcinoma)	273/3535[165] 25/177[159]	7.7%-14.1%
Bladder/ Urothelial (Advanced cancer only)	79/1188[166] 80/586[167]	6.6%-14%
Ovarian	60/515 (BRCA1 /BRCA2 only)[159] 380/2756[159]	11.7%-13.8%
Endometrial	76/1542[168] 35/381[159]	4.9%-9.2%
Head/neck	51/1218[159]	4.2%
Cholangiocarcinoma	36/840[159]	4.3%
Esophageal	36/747[159]	4.8%

Abbreviation: GPV, germline pathogenic variant.

Genetics Referral Guidelines -- Thyroid

Thyroid cancer	• Medullary thyroid cancer	MEN2, OMIM 171400, 155240, 162300
	• Nonmedullary thyroid cancer and one additional Carney complex criterion (Table 3) in the same person	Carney, OMIM 160980
	• Nonmedullary thyroid cancer and 2 additional Cowden syndrome criteria (Table 4) in the same person	Cowden, OMIM 158350
	• Papillary thyroid cancer (cribriform-morular variant)	FAP, OMIM 175100

Table 3 Carney complex criteria[21]

- Spotty skin pigmentation on lips, conjunctiva and inner or outer canthi, and/or vaginal or penile mucosa
- Myxoma (cutaneous and mucosal)
- Cardiac myxoma
- Breast myxomatosis or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis
- Acromegaly due to growth hormone–producing adenoma
- Large cell calcifying Sertoli cell tumor or characteristic calcification on testicular ultrasonography
- Primary pigmented nodular adrenocortical dysplasia
- Thyroid carcinoma (nonmedullary) or multiple hypoechoic nodules on thyroid ultrasonography in a young patient
- Psammomatous melanotic schwannoma
- Blue nevus, epithelioid blue nevus (multiple)
- Breast ductal adenoma (multiple)
- Osteochondromyxoma

DIAGNOSTIC CRITERIA FOR COWDEN SYNDROME (CS)/*PTEN* HAMARTOMA TUMOR SYNDROME (PHTS)[a,*]

Major criteria:
- **Breast cancer**
- **Endometrial cancer (epithelial)**
- **Follicular thyroid cancer**
- **≥3 GI hamartomas or ganglioneuromas[ss]**
- **Lhermitte-Duclos disease (adult)**
- **Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult female, 60 cm in adult male)[tt]**
- **Macular pigmentation of glans penis**
- **Mucocutaneous lesions[uu]**
  - **Trichilemmoma (≥3, at least 1 biopsy-proven)**
  - **≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)**
  - **≥3 mucocutaneous neuromas**
  - **Oral papillomas (particularly on tongue and gingiva) (≥3 or 1 biopsy-proven or dermatologist diagnosed)**

Minor criteria:[vv]
- **Autism spectrum disorder**
- **Colon cancer**
- **≥3 esophageal glycogenic acanthoses**
- **≥3 lipomas**
- **Intellectual disability (ie, IQ ≤75)**
- **Renal cell carcinoma**
- **Testicular lipomatosis**
- **Papillary or follicular variant of papillary thyroid cancer**
- **Thyroid structural lesions (eg, adenoma, nodule[s], goiter)**
- **Single GI hamartoma or ganglioneuroma**
- **Vascular anomalies (including multiple intracranial developmental venous anomalies)**

Hampel H, et al. Genet Med 2015
NCCN Genetic/High Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate. Version 3.2025

Considerations for Genetic Evaluations

- Use of patient's preferred language via interpreter services (telemedicine or in person)
- Review of personal history with focus on
    - Symptoms
    - Cancers/precancers and treatment
    - Cancer screening frequency/results
    - Relevant somatic testing results
- Three-generation pedigree focusing on cancer diagnoses, subtypes, and age at diagnosis
- Routine assessment for
    - Ashkenazi Jewish ancestry (BRCA1, BRCA2, APC, others)
    - Consanguinity (for consideration of autosomal recessive syndromes, more common in some populations)

Syndromes including Thyroid Cancer

- Multiple Endocrine Neoplasia, Type 2 (RET)
- Familial Adenomatous Polyposis (APC)
- Cowden Syndrome (PTEN)
- DICER1-associated cancer predisposition
- Carney complex (PRKAR1A)
- ? CHEK2- associated cancer syndrome
- ? Multiple Endocrine Neoplasia, Type 4 (CDKN1B)

Multiple Endocrine Neoplasia, Type 2

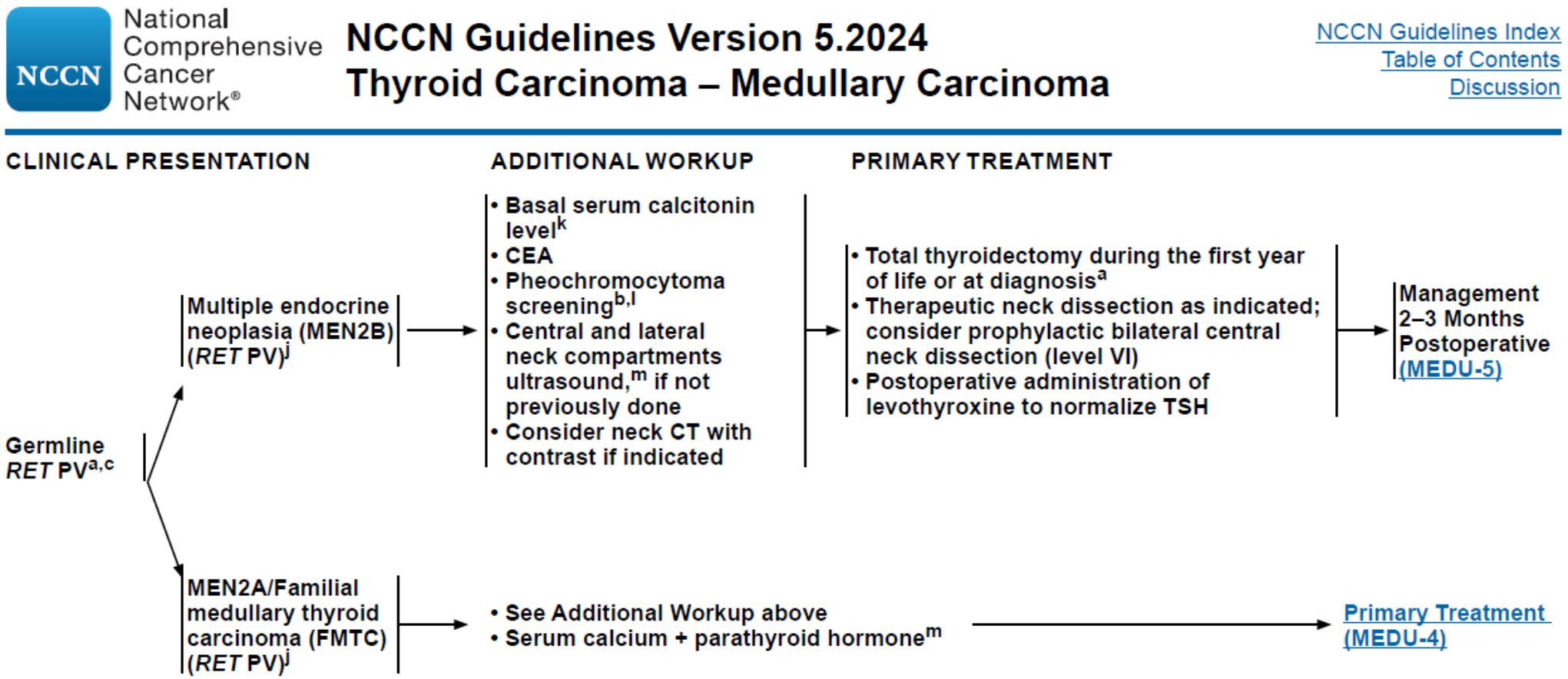
- RET proto-oncogene mutations in exons 10, 11, 13-16
- Timing of prophylactic thyroidectomy depends on the aggressiveness of the inherited RET mutation.
  - Highest risk: Codon M918T
  - High risk: Codon 634 and A883F
  - Moderate risk: Other RET mutations associated with MEN2A or FMTC
- Also need annual screening for pheo and hyperparathyroidism (type 2A)

PRINCIPLES OF HEREDITARY CANCER RISK ASSESSMENT AND GENETIC COUNSELING

Tumor Associations of Hereditary Endocrine Neoplasia Syndromes[b]

Syndrome (Gene)[c]	Endocrine Neoplasia Manifestations	Other Manifestations	Surveillance
Hereditary PCC/PGL syndrome (*MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127*)	PCC[c] PGL[c]	GI stromal tumor (GIST) (*SDHx*) Renal cell cancer (*SDHx*)	NE-G (7 of 8) NCCN Guidelines for Kidney Cancer (HERED-RCC-B)
Multiple endocrine neoplasia type 1 (*MEN1*)[1]	Parathyroid adenoma/hyperplasia (>95%) PanNETs (functioning) or duodenal NETs (20%–80%) ▸ Gastrinoma (20%–61%) ▸ Insulinoma (7%–31%) ▸ Glucagonoma (1%–5%) ▸ VIPoma/somatostatinoma (<2%) Pituitary adenomas (30%–40%) Gastric carcinoids (7%–35%) Lung/thymic carcinoids (<8%) Adrenal adenomas (27%–36%)	Angiofibromas Collagenomas Lipomas Meningiomas	MEN1-2[1] and MEN1-A[1]
Multiple endocrine neoplasia type 2 (*RET*)	Medullary thyroid carcinoma (≤98%) PCC (≤50%) Parathyroid adenoma/hyperplasia (≤25% MEN2A, rare in MEN2B)	MEN2A: • Cutaneous lichens amyloidosis • Hirschsprung disease MEN2B: • Intestinal ganglioneuromas • Mucosal neuromas • Marfanoid habitus	MEN2-1 and NE-G (7 of 8)[2] NCCN Guidelines for Thyroid Carcinoma (MEDU-4 and MEDU-5)

Multiple Endocrine Neoplasia, Type 2

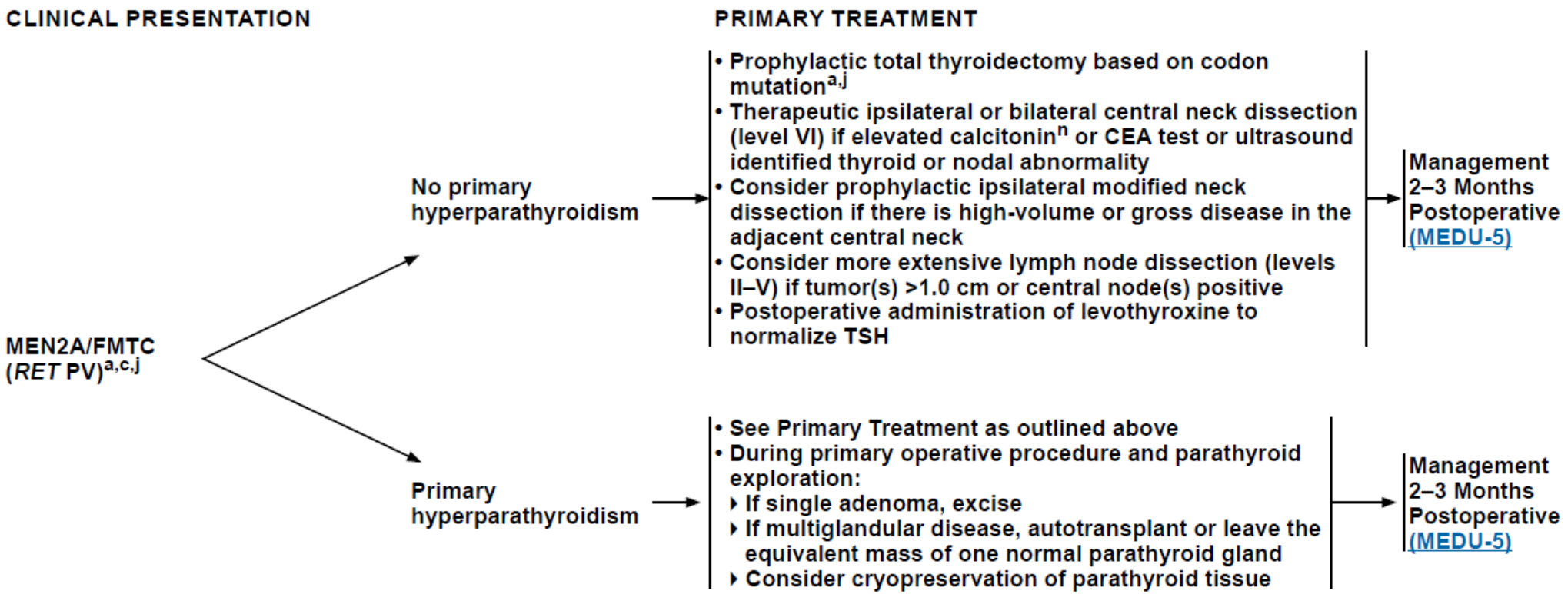


Multiple Endocrine Neoplasia, Type IIA

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2024
Thyroid Carcinoma – Medullary Carcinoma

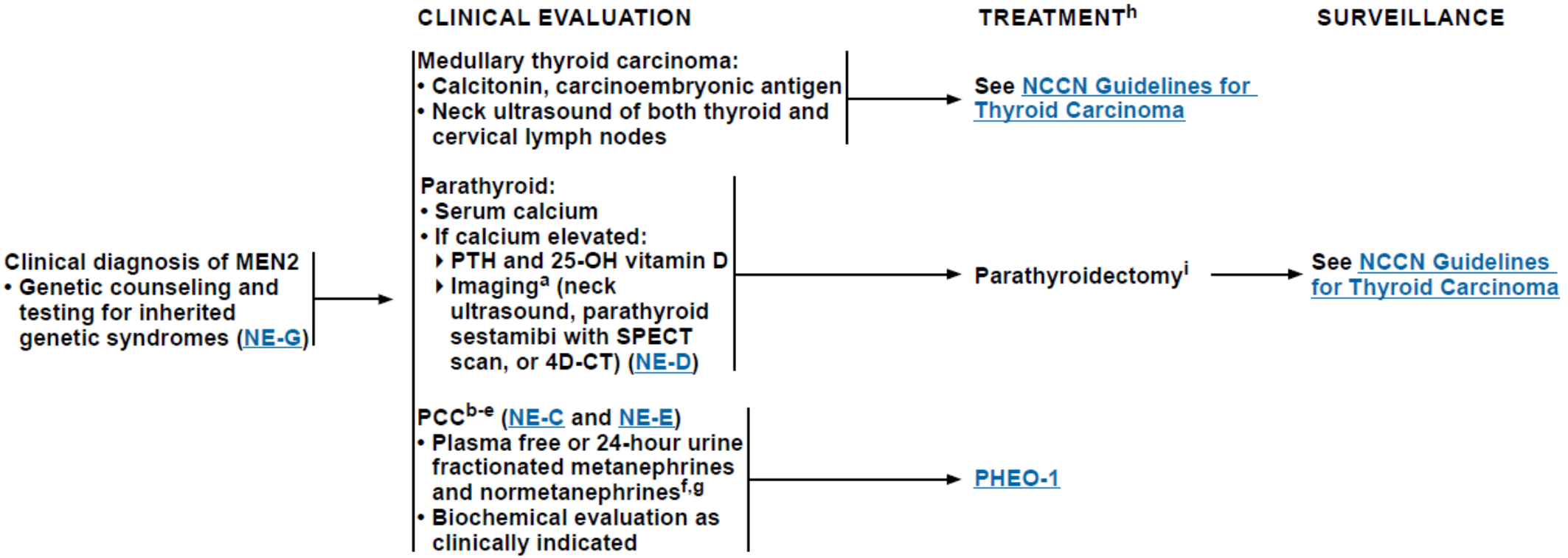
NCCN Guidelines Index
Table of Contents
Discussion



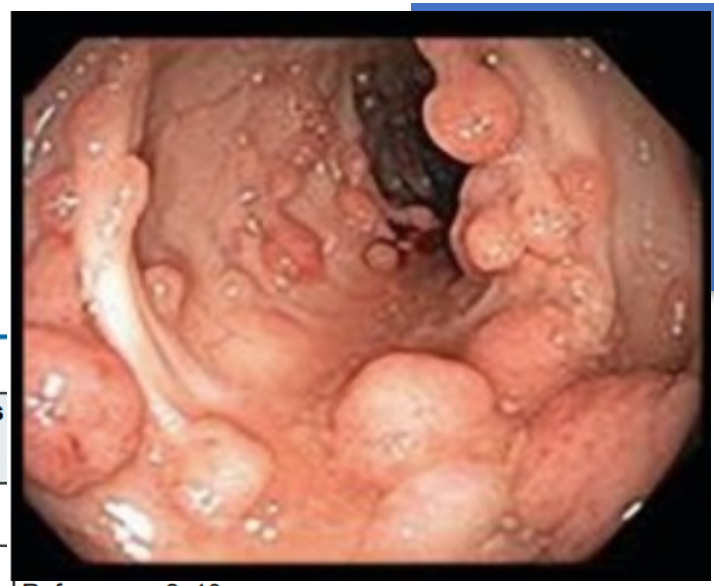
National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2024
Multiple Endocrine Neoplasia, Type 2

NCCN Guidelines Index
Table of Contents
Discussion



Familial Adenomatous Polyposis



National Comprehensive Cancer Network®

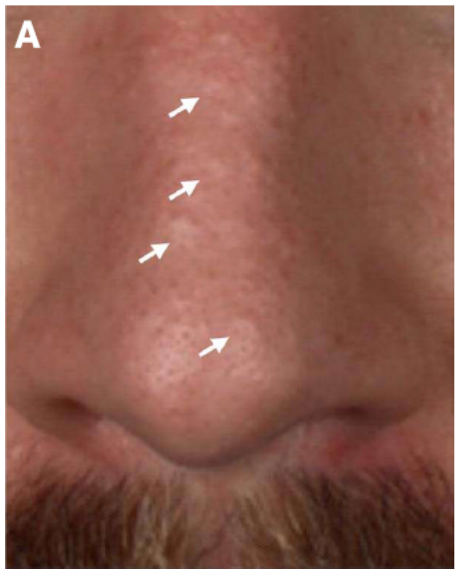
NCCN Guidelines Version 1.2023
Familial Adenomatous Polyposis

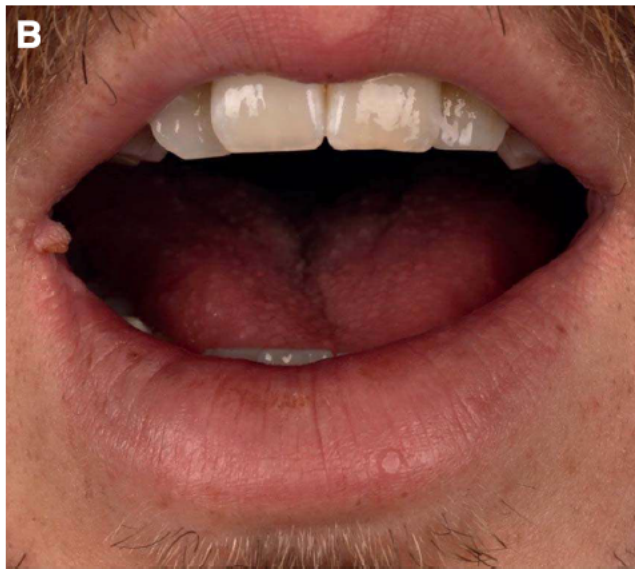
FAP: CANCER RISKS

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y[a]	Cumulative Risk for Diagnosis Through Lifetime for General Population[f]	
Colon cancer (without colectomy)	39 years (median)	Approaches 100%	4.1%	References: 2–10
Colon cancer (post-colectomy)	Rectal (s/p IRA): 46–48 years Pouch and ATZ/rectal cuff (s/p IPAA): Not available	Rectal (s/p IRA): 10%–30%[b] Pouch and ATZ/rectal cuff (s/p IPAA): <1%–3%	4.1%	
Duodenal or periampullary cancer	50–52 years	<1%–10%	—[g]	References: 11–19
Gastric cancer	52–57 years	0.1%–7.1%[c]	0.8%	References: 19–27
Small bowel cancer (distal to duodenum)	43 years	<1%	0.3%	Reference: 19
Intra-abdominal desmoid tumors	31–33 years	10%–24%[d] Mutations in the 3' end of the *APC* gene have a higher risk	—[g]	References: 28–33
Thyroid cancer (predominantly papillary thyroid carcinoma)	26–44 years	1.2%–12%	1.2%	References: 34–43
Hepatoblastoma	18–32 months	0.4%–2.5%	—[g]	References: 44–48
CNS cancer (predominantly medulloblastoma)	18 years	1%	0.6%	References: 49–50

Cowden Syndrome

- Major clinical criterion: Follicular thyroid cancer
- Minor clinical criteria:
  - Papillary or follicular variant of papillary thyroid cancer
  - Thyroid adenoma, nodule, goiter
- Associated Cancers:
  - Major: breast, endometrial
  - Minor: renal, colorectal
- Physical examination:
  - Tricholemmoma
  - Gingival/oral papules
- Lifetime risk of thyroid cancer 3-38%





Horton A et al. JCO Oncol Pract. 2024 Sep;20(9):1182-1197.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Cowden Syndrome/PTEN Hamartoma Tumor Syndrome Management

NCCN Guidelines Index
Table of Contents
Discussion

COWDEN SYNDROME (CS)/*PTEN* HAMARTOMA TUMOR SYNDROME (PHTS) MANAGEMENT

Site	Screening/Surveillance Procedure and Interval
Endometrial cancer	• For endometrial cancer screening,[d] consider starting by age 35 years. ▸ Encourage patient education and prompt response to symptoms (eg, abnormal bleeding). Patients are encouraged to keep a calendar in order to identify irregularities in their menstrual cycle. ▸ Because endometrial cancer can often be detected early based on symptoms, individuals should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding. The evaluation of these symptoms should include endometrial biopsy. ▸ Endometrial cancer screening does not have proven benefit in individuals with CS/PHTS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1 to 2 years can be considered. ▸ Transvaginal ultrasound to screen for endometrial cancer in postmenopausal individuals has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Transvaginal ultrasound is not recommended as a screening tool in premenopausal individuals due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle. • Discuss option of hysterectomy[e] upon completion of childbearing and counsel regarding degree of protection, extent of cancer risk, and reproductive desires. Risk of ovarian cancer is not elevated; therefore, ovaries can be left in situ. • Address psychosocial and quality-of-life aspects of undergoing risk-reducing hysterectomy.
Kidney cancer	• Consider renal ultrasound starting at age 40 y, then every 1–2 y.
Colorectal cancer	• Colonoscopy, starting at age 35 y unless symptomatic or if close relative with CRC before age 40 y, then start 5–10 y before the earliest known CRC in the family. Colonoscopy should be done every 5 y or more frequently if patient is symptomatic or polyps are found.
Neurologic	• Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.
Skin	• There may be an increased risk of melanoma, and the prevalence of other skin characteristics with CS/PTHS may independently make routine dermatology evaluations of value. Annual dermatology exams are recommended.
Thyroid	• Annual thyroid ultrasound starting at age 7 y. This may also be considered for children at 50% risk of inheriting a known P/LP variant whose parents wish to delay genetic testing until age 18 y.

DICER1

May have increased risk of anaplastic cancer

Select Features of *DICER1* Tumor Predisposition

Feature	% of Persons w/*DICER1* Germline Pathogenic Variant w/Feature	Comment
Macrocephaly	~42%	
Pleuropulmonary blastoma	Lung cysts / type Ir PPB in 25%-40%; PPB types I, II, & III in <10%	65% of children w/PPB had a *DICER1* germline pathogenic variant.
Multinodular goiter	32% of women; 13% of men	By age 20 yrs
	75% of women; 17% of men	By age 40 yrs
Ovarian sex cord-stromal tumors	<10%	~50% of persons w/SLCT & gynandroblastoma had a *DICER1* germline pathogenic variant. [1]
Cystic nephroma	≤10%	
Ciliary body medulloepithelioma	~5%	
Differentiated thyroid carcinoma	Rare	16- to 24-fold ↑ risk
Nasal chondromesenchymal hamartoma	Rare	~1% of persons ascertained by family history (non-probands)
Other tumors	Rare	Embryonal rhabdomyosarcoma, pituitary blastoma, pineoblastoma, CNS sarcomas, presacral malignant teratoid tumor, & other CNS embryonal tumors/ETMR-like
Multicystic hepatic lesions	Very rare [2]	

GeneReviews, Schultz et al, 2020

DICER1

Multinodular goiter / thyroid gland neoplasia	Thyroid physical exam for thyroid gland asymmetry &/or nodules	• At diagnosis (any age) • Annually
	Thyroid US	• Consider US by age 8 yrs. [1] If normal, consider repeat US every 3-5 yrs. • Earlier for thyroid gland asymmetry &/or nodules • Post-chemotherapy: By age 10 yrs or w/in 3-5 yrs of treatment
	Thyroid function testing	If clinical signs/symptoms of hypo- or hyperthyroidism

GeneReviews, Schultz et al, 2020

Carney Complex (PRKAR1A)

Major diagnostic criteria for CNC

- Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)
- Myxoma* (cutaneous and mucosal)
- Cardiac myxoma*
- Breast myxomatosis* or fat-suppressed MRI findings suggestive of this diagnosis
- Primary pigmented nodular adrenocortical disease (PPNAD)* or paradoxic positive response of urinary glucocorticosteroid excretion to dexamethasone administration during Liddle's test
- Acromegaly as a result of growth hormone (GH)-producing adenoma*
- Large-cell calcifying Sertoli cell tumor (LCCSCT)* or characteristic calcification on testicular ultrasound
- Thyroid carcinoma* or multiple, hypoechoic nodules on thyroid ultrasound in a child younger than age 18 years
- Psammomatous melanotic schwannomas (PMS)*
- Blue nevus, epithelioid blue nevus*
- Breast ductal adenoma*
- Osteochondromyxoma*

Baseline thyroid ultrasound after puberty and repeat as necessary.

Lifetime risk of thyroid cancer 6-25%

GeneReviews, Stratakis et al, 2018

MEN4

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2024
Neuroendocrine and Adrenal Tumors

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF HEREDITARY CANCER RISK ASSESSMENT AND GENETIC COUNSELING

Tumor Associations of Hereditary Endocrine Neoplasia Syndromes[b]

Syndrome (Gene)	Endocrine Neoplasia Manifestations	Other Manifestations	Surveillance
Multiple endocrine neoplasia type 4 *(CDKN1B)* [d]	Parathyroid adenoma/hyperplasia Pituitary adenomas PanNETs or duodenal NETs Papillary thyroid carcinoma	Meningiomas	Not available[1]
Neurofibromatosis type 1 *(NF1)*	PCC (3%) PanNETs (rare)	Neurofibromas Skin lesions (café-au-lait and freckling) Lisch nodules Gliomas GIST	NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic AAP Health Supervision Guidelines[3]
Tuberous sclerosis complex *(TSC1 and TSC2)*	Pituitary adenomas (rare) Parathyroid adenoma/hyperplasia (rare) PanNETs (rare)	Skin lesions Central nervous system tumors/cancers Renal angiomyolipomas Clear cell renal cancer Cardiac rhabdomyomas Lymphangioleiomyomatosis	NCCN Guidelines for Kidney Cancer (HERED-RCC-B)
von Hippel-Lindau (VHL) syndrome	PCC (10%–20%) PGL (10%–20%) PanNETs (5%–17%)	Hemangioblastomas (retinal or central nervous system) Clear cell renal cancer Endolymphatic sac tumors Cystadenomas	NE-G (7 of 8) and PanNET-11 VHLA Handbook[4] NCCN Guidelines for Kidney Cancer (HERED-RCC-B)

Syndromes with No Current Thyroid Guidelines

- TP53: 6-9% lifetime risk
- CHEK2: 3.7 – 6% lifetime risk

- Preliminary evidence genes:
  - FOXE1
  - HABP2
  - NKX2-1
  - SDHB, SDHD
  - SRGAP1

Thank you for your attention!

jjeter@coh.org