19 Years Old Man Who Presented Epigastric Soreness

Jung Min Lee

Department of Gastroenterology and Hepatology, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea

1. Case presentation

특이 병력 없는 19세 남자로 2달 전부터 시작된 속쓰림을 주소로 내원하여 local에서 시행한 위내시경, 대장내시경 상 oral cavity부터 장 전체에 diffuse polyp이 관찰되었다.

2. Diagnosis

조직 검사 상 hamartoma 확인되었고 이후 immunostain 상 PTEN 양성 소견으로 R/O Bannayan-Riley-Ruvalcaba Syndrome 의심된다.

3. Therapy and Clinical course

Treatments for symptomatic manifestations 및 Cancer surveillance하면서 10년간 경과 관찰 중이다.

4. Conclusion

polyposis의 진단 및 management, long term follow up시 해야 할 것이다.

Key Words: Polyposis; PTEN; Hamartoma

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Case

- M / 19

- 임 O O

- Chief complaints
  - epigastric soreness

    (o : 2 months ago)

- Present illness
  - 특이 병력 없는 분으로 2달 전부터 시작된 속쓰림을 주소로 내원하여 local에서 시행한 위내시경 상 multiple polyps 관찰되어 further evaluation 위해 내원함.

• Past history

- HTN / DM / Tb / Hepatitis (-/-/-/-)
- Admission / Op hx (-/-)
- Alcohol / Smoking (-/-)
- Medication (-)

• Family history : None

• Review of system

Fever / Chilling(-/-)

Headache / Dizziness(-/-)

Anorexia / Vomiting (-/-)

Epigastric soreness (+) Weight loss (-)

Hematochezi / Diarrhea (-/-)

• Physical examination

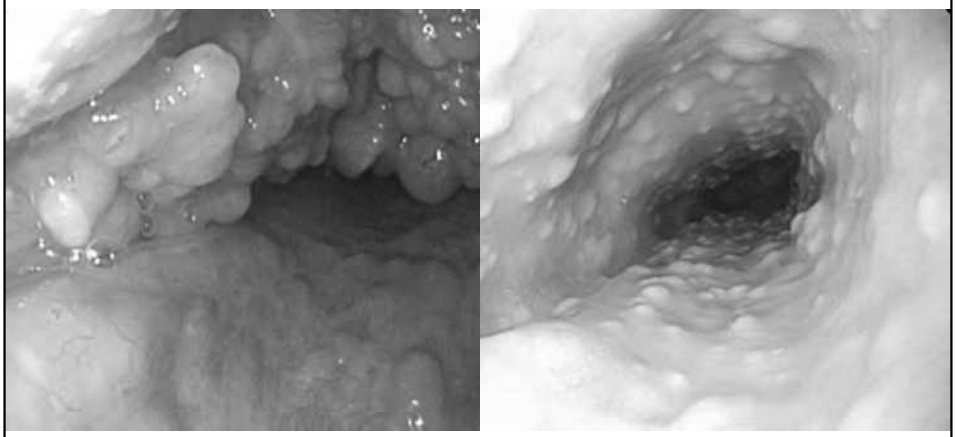
Clear Breathing sound w/o crackle, wheezing

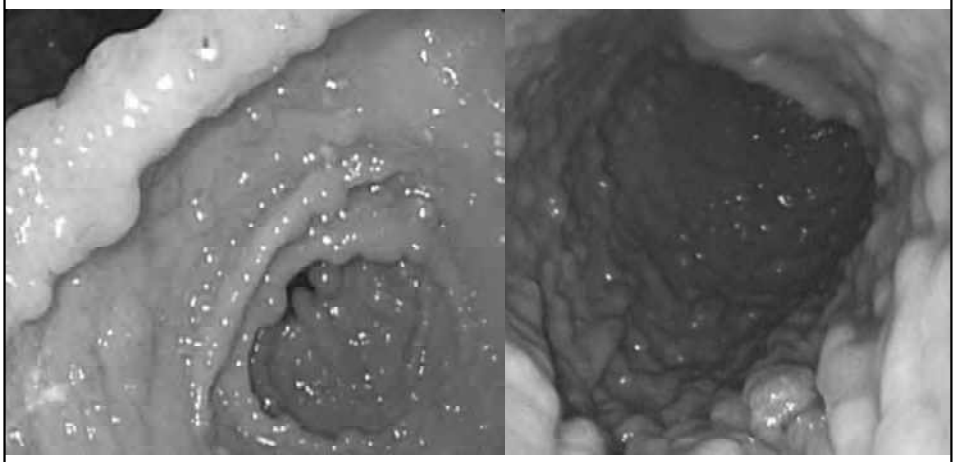
Abdomen td/rtd (-/-) Pitting edema (-/-)

• Lab findings

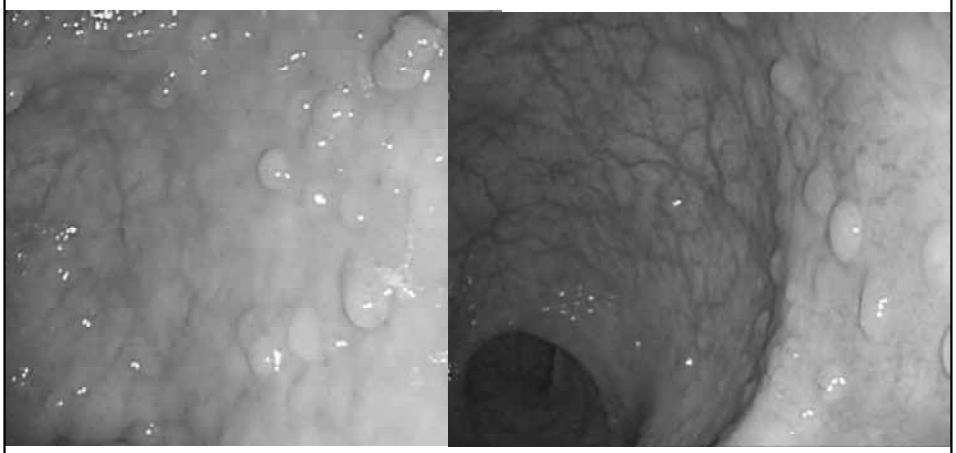
Hb 9.6 g/dL - WBC 5,800 /uL – PLT 181,000 /uL
Na 141 - K 4.4 – Cl 104 mmol/L
BUN / Cr 7.2 / 0.63 mg/dL ESR / CRP 7 mm/hr / 0.001 mg/L
Protein / Albumin 6.9 / 4.0 g/dL AST / ALT 9 / 14 IU/L ALP 28 IU/L
PT 95 %
CEA 0.7 ng/mL

Initial EGD

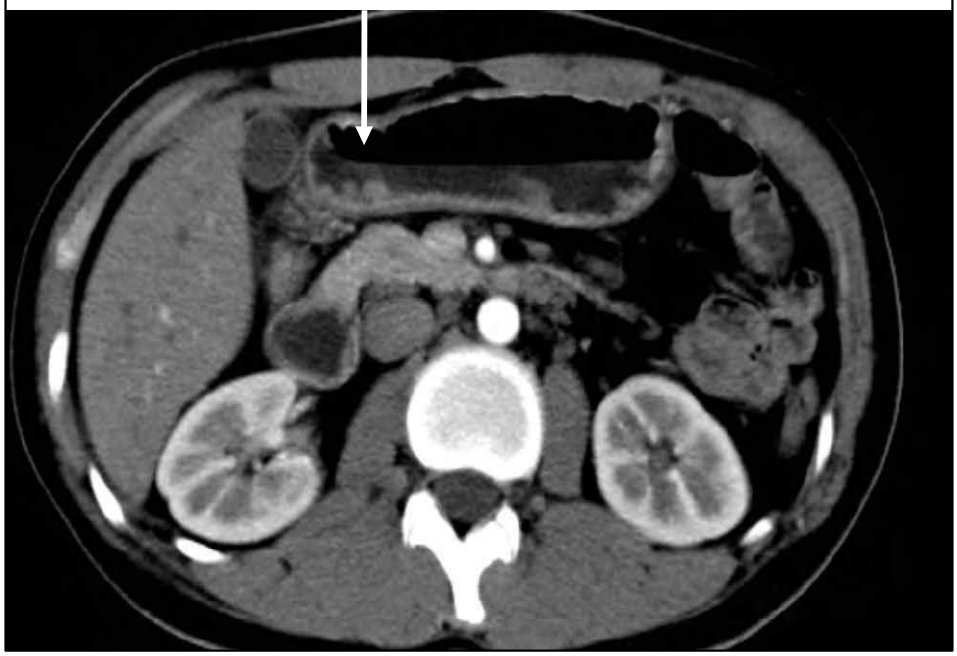




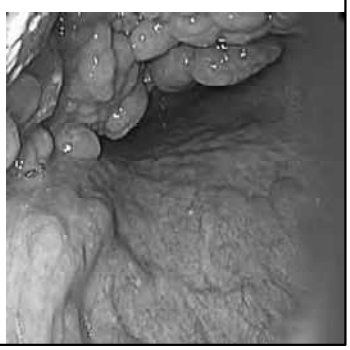
Initial Colonoscopy



Initial Abdomen CT



- Pathology
  - Stomach : hamartomatous polyp
  - Colon : hamartomatous polyp
  - Tongue : mucosal papilloma
  - Esophagus : squamous papilloma with koilocytotic atypia
  - *H.pylori* : positive



Polyposis

Hereditary	Non-hereditary

Pathologic type
Adenomatous polyp
Serrated polyp
Inflammatory polyp
Hamartomatous polyp
Other types

	Hereditary	Non-hereditary
Adenomatous polyp	Familial adenomatous polyposis	
	MUTYH - associated polyposis	
	Gardner's syndrome	
Hamartomatous polyp	Juvenile polyps	Cronkhite-Canada syndrome
	Peutz-Jeghers polyps	
	Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome	
Serrated polyp		Hyperplastic polyposis
Inflammatory polyp		Inflammatory polyposis
Other types		Lipomatous polyposis
		Lymphoid hyperplasia
		Multiple lymphomatous polyposis

- Initial impression

R/O Juvenile polyposis syndrome

R/O Peutz-Jegher's syndrome

R/O Cowden's syndrome

R/O Bannayan-Riley-Ruvalcaba Syndrome

	Genes	Hallmark features	Cancer by site	Mutation detection rate
Juvenile polyposis syndrome	SMAD4, BMPR1A	Multiple GI-polyps, epistaxis, telangiectasia	Colon, rectum and stomach	60%
PTEN-hamartoma syndrome: Cowden Syndrome	PTEN	Lhermitte-Duclos disease, trichilemmoma, skin hamartoma, macrocephaly	Breast, thyroid, uterus, colon	Up to 80%
PTEN-hamartoma syndrome: Bannayan-Riley-Ruvalcaba	PTEN	Macrocephaly, lipomatosis, pigmented macules of the glans penis	As above	60%
Peutz-Jeghers syndrome	STK11 (LKB1)	Mucocutanous melanosis and polyposis of the GI-tract	Colon, stomach, breast, pancreas (cervix, ovarian)	80%-94%
Hereditary mixed polyposis syndrome	BMPR1A, GREM1	Atypical polyposis with juvenile polyps, adenomas, hyperplastic and inflammatory	Colon and rectum	Unknown

The American Journal of Gastroenterology 100, 476-490 (2005)

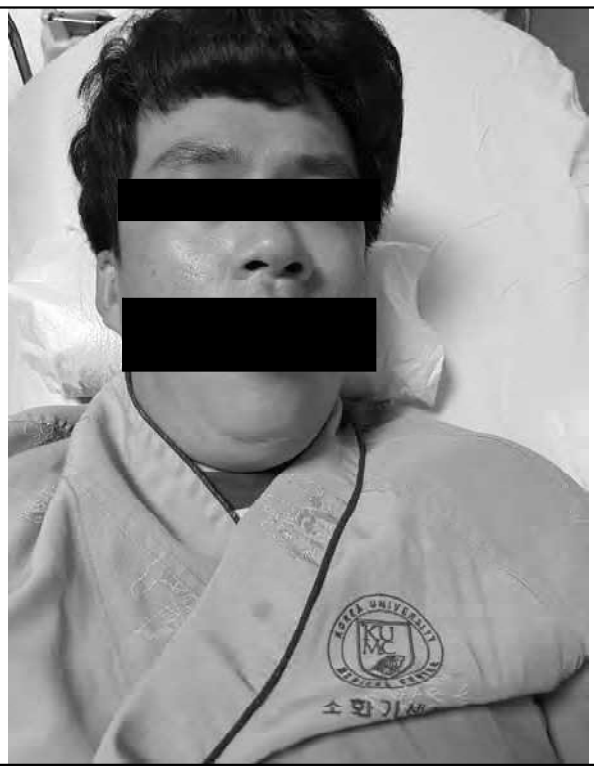
• Positive findings

: GI tract hamartomatous lesion

: Macrocephaly

: Oral cavity mucosal papilloma

: *Helicobacter pylori*



Cowden syndrome clinical diagnostic criteria

Major criteria
Breast cancer
Endometrial cancer (epithelial)
Thyroid cancer (follicular)
Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
Lhermitte-Duclos disease (adult)
Macrocephaly (≥97 percentile: 58cm for females, 60cm for males)
Macular pigmentation of the glans penis
Multiple mucocutaneous lesions (any of the following):
Multiple trichilemmomas (≥3, at least one biopsy proven)
Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
Mucocutaneous neuromas (≥3)
Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed

J Natl Cancer Inst. 2013 Nov 6;105(21):1607-16.

Cowden syndrome clinical diagnostic criteria

Minor criteria
Autism spectrum disorder
Colon cancer
Esophageal glycogenic acanthosis (≥3)
Lipomas (≥ 3)
Mental retardation (ie, IQ ≤ 75)
Renal cell carcinoma
Testicular lipomatosis
Thyroid cancer (papillary or follicular variant of papillary)
Thyroid structural lesions (eg, adenoma, multinodular goiter)
Vascular anomalies (including multiple intracranial developmental

- Operational diagnosis
  1. **3≤ major criteria, but 1 must include macrocephaly,** Lhermitte-Duclos disease, or gastrointestinal hamartomas; or
  2. 2 major and 3 minor criteria.
- Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a PTEN mutation:
  1. Any 2 major criteria with or without minor criteria; or
  2. 1 major and 2 minor criteria; or
  3. 3 minor criteria.

J Natl Cancer Inst. 2013 Nov 6;105(21):1607-16

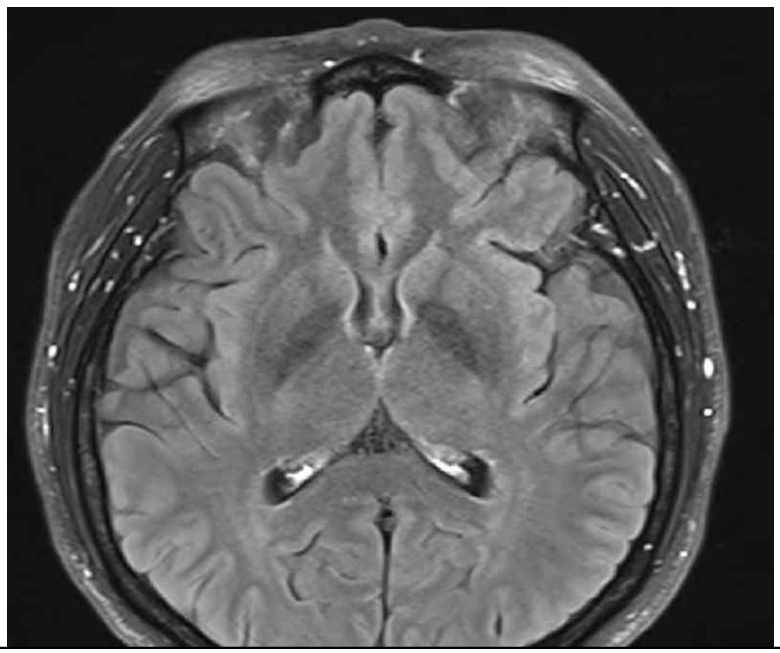
• Diagnostic plan

- PTEN gene mutation test
- Brain MRI
- Thyroid function test, thyroid ultrasound
- Need for evaluation of genitourinary tract

• Treatment plan

- *H.pylori* eradication treatment
- Polypectomy for symptomatic polyps
- Annual follow up for cancer surveilence

Brain MRI

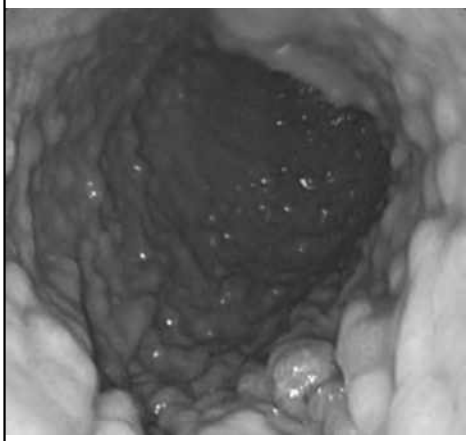


- Progress
  - Thyroid function test : WNL
  - Thyroid ultrasound : non-specific findings
  - Immunostain for PTEN : positive
  - PTEN Gene Mutation : Not Detected

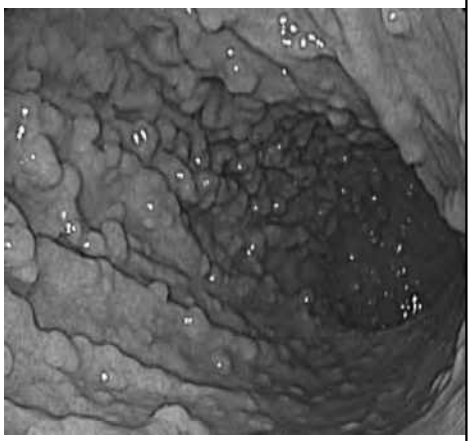
- Treatment plan
  - Polypectomy for symptomatic polyps
  - Follow up for cancer surveilence
    : colon, genitourinary tract and thyroid

EGD during 12 years

Initial

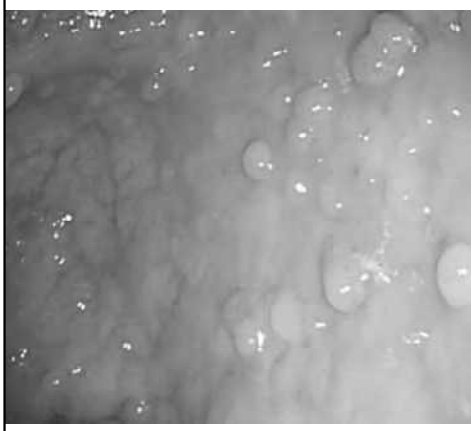


Follow up

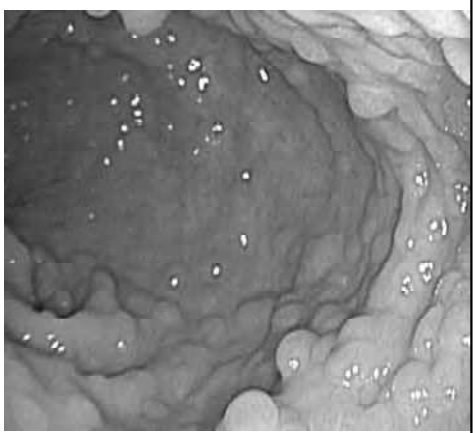


Colonoscopy during 12 years

Initial



Follow up



- Final diagnosis

  PTEN hamartomatous syndrome

  – R/O Cowden syndrome

- Next generation sequencing (NGS)

Screening Recommendations for Cowden's Syndrome

Screened Cancer	Age to Begin Screening*	Interval†	Diagnostic Tests‡
Colon§	15	2 years‡	Colonoscopy
Proximal GI tract/Small Intestine§	15	2 years	Upper Endoscopy
			UGI w/SBFT
Breast	21	Monthly	Self breast exam
	30	Annual	Mammography
Thyroid	Adolescence	Annual	Clinical exam plus baseline U/S

*Earlier if symptomatic.

†Annually if polyps are noted.

‡Screening intervals can be extended at age 35 in at-risk patients; gene carriers and affected cases should be kept under similar surveillance.

§A definitive consensus has not been reached.

Adapted from Attard, 2003, Boardman 2002, Burt 2002, McGarrity 2003 ([7,8,9,35]).

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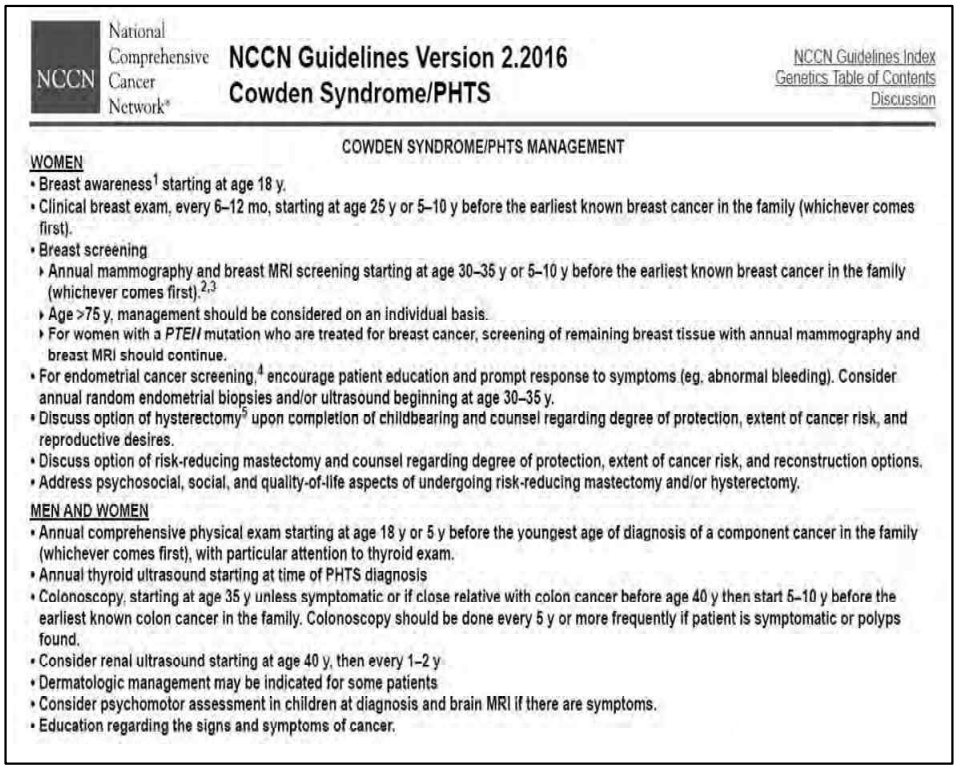

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Cowden Syndrome/PHTS

NCCN Guidelines Index
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COWDEN SYNDROME/PHTS MANAGEMENT

WOMEN

- Breast awareness[1] starting at age 18 y.
- Clinical breast exam, every 6–12 mo, starting at age 25 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).
- Breast screening
  - Annual mammography and breast MRI screening starting at age 30–35 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).[2,3]
  - Age >75 y, management should be considered on an individual basis.
  - For women with a *PTEN* mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.
- For endometrial cancer screening,[4] encourage patient education and prompt response to symptoms (eg, abnormal bleeding). Consider annual random endometrial biopsies and/or ultrasound beginning at age 30–35 y.
- Discuss option of hysterectomy[5] upon completion of childbearing and counsel regarding degree of protection, extent of cancer risk, and reproductive desires.
- Discuss option of risk-reducing mastectomy and counsel regarding degree of protection, extent of cancer risk, and reconstruction options.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy.

MEN AND WOMEN

- Annual comprehensive physical exam starting at age 18 y or 5 y before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to thyroid exam.
- Annual thyroid ultrasound starting at time of PHTS diagnosis
- Colonoscopy, starting at age 35 y unless symptomatic or if close relative with colon cancer before age 40 y then start 5–10 y before the earliest known colon cancer in the family. Colonoscopy should be done every 5 y or more frequently if patient is symptomatic or polyps found.
- Consider renal ultrasound starting at age 40 y, then every 1–2 y
- Dermatologic management may be indicated for some patients
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.
- Education regarding the signs and symptoms of cancer.

MEMO