PTEN HAMARTOMA TUMOR SYNDROME (PHTS)

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PHTS OVERVIEW

PHTS is a rare syndrome caused by mutation of one copy of the Phosphatase and Tensin Homolog (PTEN) gene during embryo-fetal development.

PTEN is a tumor suppressor gene.

Mutation resulting in loss of PTEN expression increases activation of the PI3K/AKT/mTOR pathway.

- The syndrome has:
  - Significant co-morbidities that vary between patients.
  - Increased risk of cancer.

- Prevalence estimated at 1:200,000 but under-diagnosis is likely.
  - The American College of Medical Genetics recommend that the PTEN gene should be assessed in all patients undergoing genomic testing no matter what the primary indication for the genomic test.

PHTS MANIFESTATIONS

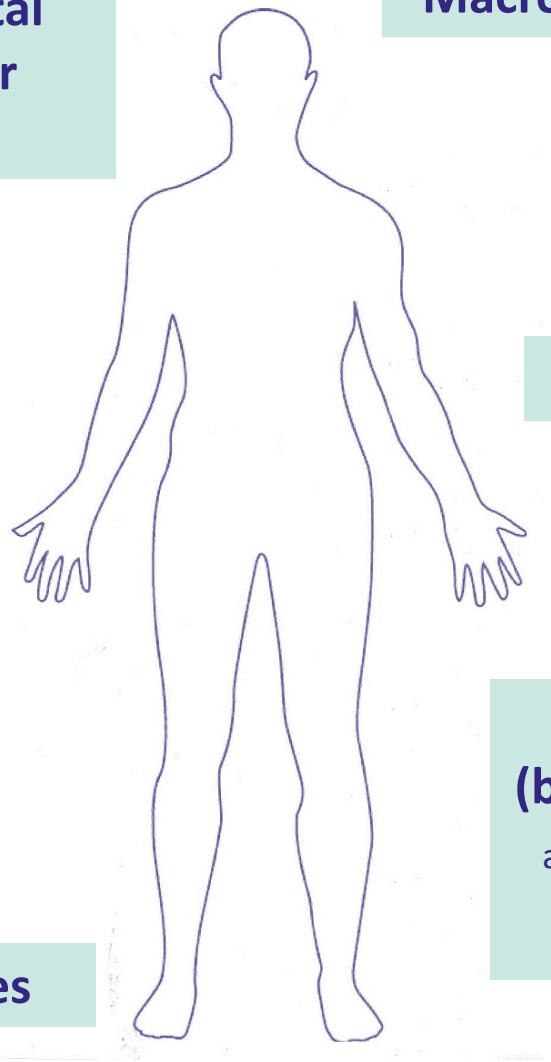
Developmental delay and/or autism

Macrocephaly

Increased risk of cancer

Lifetime risk:

- Breast cancer: 85%
- Thyroid cancer: 35%
- Endometrial cancer: 28%
- Kidney cancer: 34%
- Colorectal 16%
- Melanoma 5%



GI polyposis

Hamartomas (benign local overgrowths)

affecting skin, mucous membranes, thyroid, brain (Lhermitte-Duclos disease) and elsewhere

Vascular anomalies

DIAGNOSIS

PHTS diagnosis requires genetic confirmation of a mutation of the PTEN gene.

- Clinical criteria exist for referral for genetic assessment, but diagnosis is hampered due to:
  - low awareness of this rare disorder;
  - variable symptoms with age and gender;
  - overlap of clinical presentation with many other more common conditions.

Diagnosis and management by a range of clinicians due to the diverse manifestations of PHTS and differences in severity, including:

- Neurologists,
- Vascular surgeons,
- Interventional radiologists,
- Dermatologists,
- Oncologists.

MANAGEMENT

Current treatment is largely supportive, but guidelines recommend a comprehensive program of surveillance and early intervention for cancer in all patients with PHTS.

- Failure to recognize that a patient has PHTS may result in a missed opportunity to initiate surveillance and potentially, prophylactic surgery for cancer, which is the mainstay of cancer prevention in these patients.
- Specific ICD-10-CM codes will support appropriate access and coverage for cancer surveillance.
- There in an increasing interest in clinical trials for PHTS (Slide 8) and specific ICD-10-CM codes will support patient identification and recruitment.

HISTORICAL APPROACHES TO DIAGNOSIS ARE NOT ACCURATE

Prior to identification of the PTEN gene and genetic testing for PHTS, several syndromes were described based on clinical features:

- Cowden syndrome (CS),
- Bannayan-Riley-Ruvalcaba syndrome (BRRS),
- Proteus/Proteus-like syndrome (PLS),

However, only a subset of patients with these conditions have PTEN mutations/PHTS (i.e., there are other causes).

PTEN germline mutations have been identified in only a proportion of patients diagnosed:

- **BRRS (60%)**
- **CS (25-85%)**

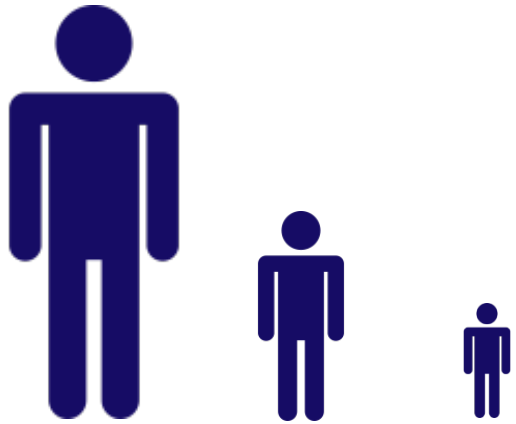
CLINICAL DIAGNOSIS IS BIASED BY AGE AND GENDER

In patients with a PTEN germline mutation, a clinical diagnosis of BRRS vs CS may occur as a result of age and gender-related variation in symptoms/signs

- E.g., endometrial cancer, which only occurs in females, is a feature of CS but not BRRS

Such patients should all be considered as having a PHTS diagnosis.

Example: Three male family members all with the same PTEN germline mutation. Younger ones are more likely to be diagnosed as having BRRS because features of BRRs (e.g., penile freckling) are apparent at a young age in males.



Age	37 years	47 months	27 months
BRRS features	Yes	Yes	Yes
CS criteria	Yes	No	No

Ref: Lachlan et al: Cowden syndrome and Bannayan Riley Ruvalcaba syndrome represent one condition with variable expression and age-related penetrance: results of a clinical study of PTEN mutation carriers. J Med Genet. 2007 Sep;44(9):579-85.

PHTS CLINICAL DEVELOPMENT IN PROGRESS

There is increasing interest in drug development for PHTS amongst both industry and academic investigators, specific ICD-10-CM codes will support patient identification and recruitment.

NCT Number	Short trial title	Intervention	Status
NCT02991807	RAD001 and neurocognition in PTEN hamartoma tumor syndrome	Everolimus /Placebo	Active, not recruiting (enrollment complete)
NCT04094675	Sirolimus for Cowden Syndrome with colon polyposis	Sirolimus	Recruiting
NCT00971789	Sirolimus to treat Cowden Syndrome and other PTEN hamartomatous tumor syndromes	Sirolimus	Completed
NCT02638389	Efficacy and safety of sirolimus in vascular anomalies that are refractory to standard care	Sirolimus	Recruiting

Table based on searches of the NIH clinical trials database for “PHTS” and “germline PTEN mutations” in October 2020; older studies and studies including mixed patient populations, are not included.

RATIONALE FOR PROPOSAL
NEW AND UNIQUE ICD-10-CM CODES FOR PHTS

PHTS fits the phakomatosis group (Q85), sharing many features of the two other classic phakomatoses that have their own codes (neurofibromatosis and tuberous sclerosis):

- Rare, hereditary disorder characterized by hamartomas of multiple tissues.
- Autosomal dominant pattern of inheritance with variable penetrance (but also sometimes due to new mutations).
- Associated with neurodevelopmental deficits.
- Associated with a predisposition to malignancy.

Further unique codes for PHTS are critical because:

- They clearly differentiate PHTS from other overlapping clinically diagnosed conditions where a PTEN germline mutation of known significant has not been identified.

RATIONALE FOR THE AMENDMENT

We do not believe combining 'other PHTS' in Q85.89 with Peutz-Jeghers Syndrome; Sturge-Weber(-Dimitri) syndrome; Von Hippel-Lindau syndrome is scientifically meaningful.

- These conditions do not share common gene involvement or medical management.
- In addition, it splits coding of PHTS between Q85.81 and Q85.89 with the latter code being shared with other conditions, thus hampering the use of the ICD-10-CM code to support more accurate PHTS prevalence estimates.

SUMMARY

The addition of new and unique codes for PHTS to ICD-10-CM would:

- Improve patient identification and diagnosis.
- Support patient access and coverage for cancer surveillance.
- Improve patient access to clinical trials and facilitate clinical research into new treatments for PHTS.
- Facilitate better understanding of epidemiology including disease prevalence and mortality.
- Promote PHTS natural history research.
- Facilitate laboratory research, improving the understanding of PHTS and other diseases.
- Be consistent with the approach already taken for tuberous sclerosis and neurofibromatosis type 1 and 2 as unique disorders.

CHALLENGES OF THE CURRENT PHTS CODING SUMMARY

Current coding of individuals with PHTS is inconsistent and heterogeneous

PHTS patients may be assigned codes that:

- describe differing clinical syndromes where diagnosis is influenced by both age and gender despite presence of a PTEN germline mutation.
- include multiple disorders with non-overlapping features.
- do not capture the multisystem effects of PHTS.

Consequences include:

- inconsistent records.
- missed diagnosis -> missed opportunity to initiate cancer surveillance in individual (and family members).
- inaccurate estimates of disease prevalence.
- hampered research.