PTEN Hamartoma-Tumour Syndrome
Prof. Charis Eng

PTEN Hamartoma-Tumour Syndrome:

A Model for the Practice of Clinical Cancer Genetics

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Cleveland Clinic

Practice of clinical cancer genetics

- When faced with a patient with cancer:
  - Is it heritable?
  - Is it sporadic?
- Implications for patient
  - Which cancer(s) is this patient at risk for?
  - At what ages do these risks rise?
  - What to do for the patient?
- Implications for patient's family
  - Who are at risk for cancer?
  - What to do for each family member?

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Some clues suggesting heritable cancer

- Young age of onset
- Bilateral disease in paired organs
- Multi-focal tumors
- Association with other tumor types
- Familial clustering
  - (**But** not always)

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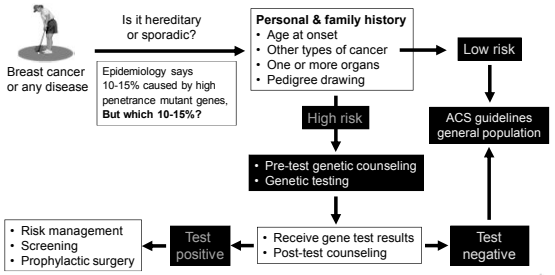
Clinical cancer genetics in 2013 can be powerful



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The story of Rachel Cowden (*c.* 1960's)

- Rachel Cowden died at 33 years of age
  - Metastatic breast cancer
  - Population average age at diagnosis of breast cancer: 60 years old
- Ms. Cowden also had unusual skin findings, thyroid neoplasias, *etc*.
  - No doctor knew what she had (1963)
- The new disorder was named in honor of Rachel Cowden (by Lloyd & Dennis, *Ann Intern Med.* 1963)
  - Cowden syndrome

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Cowden Syndrome (CS) as a model for cancer genetics practice

- The great mimic
- Difficult to recognize
- Under-diagnosed
- Autosomal dominant
- Multiple hamartomas
- High risk of:
  - Breast CA (50%)
  - Thyroid CA, especially FTC (10%)
- International Cowden Consortium diagnostic criteria
  - Robust
  - Complex

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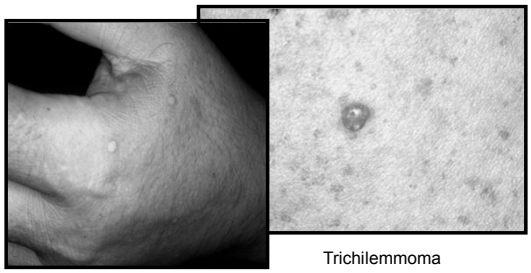
Key features of Cowden syndrome



Papillomatous papules

Trichilemmoma
(Pathognomonic feature)

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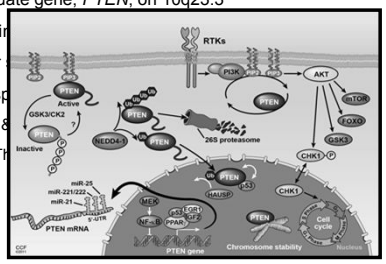
PTEN is the Cowden syndrome gene

- 9 CS families, linkage to 10q22-q26
- Candidate gene, *PTEN*, on 10q23.3
- Germlin
- Tumor
- Dual-sp
  - Lipid &
  - Ser-Th

Multiple roles in cell cycle arrest, apoptosis, migration, polarity, genomic stability, *etc.*



8 Nelen *et al*., *Nature Genet* 1996; Liaw, Marsh *et al*., *Nature Genet* 1997
Reviewed by Zbuk/Eng *Nat Rev Ca 2007*

A unifying term

- Subsets of different clinical syndromes, *e.g.* Cowden syndrome and BRRS, with germline *PTEN* mutation
- Common term *PTEN* Hamartoma-Tumor Syndrome (PHTS) was proposed (Marsh *et al*., *Hum Mol Genet* 1999)
- PHTS, one condition with variable expression and age-related penetrance

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International Cowden Consortium operational criteria

- First developed from retrospective family-based data; revised over last decade
- Developed to predict CS and Cowden-like patients
- Basis for current National Comprehensive Cancer Network (NCCN) criteria
- Suggested to have 85% positive predictive value for selection of patients with *PTEN* mutation

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Disadvantages of NCCN criteria

- With accruing clinical experience, lower performance when applied to community patients
- Unable to quantitatively distinguish patients other than binary classification of CS / non-CS
- Only adult criteria; no pediatric criteria
- Recent rapid expansion of phenotypic features recognized, including autism (2005) and polyposis syndrome (2010)

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Goals: recognition of PHTS

- To develop a clinical scoring system for selecting patients for *PTEN* gene testing through a prospective multi-national study

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Tan *et al.*, *AJHG* 2011

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Methods: research participants

- 3,042 Probands recruited at 2 tertiary cancer genetics centers from throughout N. America, Europe and Asia
  - Cleveland Clinic (2005 – 2010)
  - Ohio State University (2000 – 2006)
- Research participants met at least relaxed ICC operational criteria
  - (Criteria minus one)

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Methods: genotyping

- All individuals underwent full *PTEN* mutation analysis including promoter sequencing
- Selected individuals had MLPA deletion analysis performed

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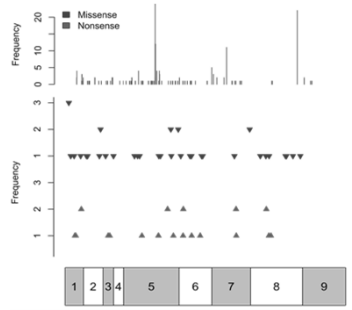
PTEN mutation spectra

Total of 290 patients with germline pathogenic mutations were detected in 3,042 patients



Tan *et al.*, *AJHG* 2011

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Age-specific criteria development

- Strong age-dependent expressivity of clinical features
- Therefore research participants divided into adult and pediatric subjects (<18 years)

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Tan *et al.*, *AJHG* 2011

Score derivation

- Frequency of each feature in mutation cohort evaluated relative to community estimates
- Weighted each feature with a pre-specified approach
  - RR relative to baseline of 1 to 5 corresponded to a weight of 1
  - RR of 5-10 with a weight of 2
  - RR of 10-25 with a weight of 4
  - RR of 25-50 with a weight of 6
  - RR of 50-100 with a weight of 8
  - RR >100 with a weight of 10
- High referral bias for individual features ("famous" features, *e.g.*, breast CA) were accounted for by adjustment of weight downward by one risk tier

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Tan *et al.*, *AJHG* 2011

Example score and weights by system: endocrine and genitourinary

	Population risk	Relative risk (referral/ community)	Relative risk (mutants/ community)	Weight
Endocrine				
Thyroid cancer:				
<20	0.01	90	480	10
20-30 [a]	0.06	46.7	48.3	4
30-40 [a]	0.13	44.6	51.5[b]	4
40-50 [a]	0.17	43.5	44.7	4
>50 [a]	0.57	17.7	6.7	1
Thyroid goiter, nodules or adenomas or Hashimoto's thyroiditis	5	7.1	14.4	4
Genitourinary				
Renal cell carcinoma	1.49	3.2	4.5	1

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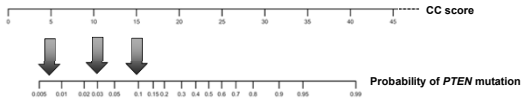
Example cases on the nomogram

Case 1: Breast cancer at age 55 (1) ;
Thyroid cancer at age 44 (4)

Case 2: Macrocephaly (6), breast cancer at age 38 (4)

Case 3: Single hamartomatous polyp (10);
Hashimoto's thyroiditis (4); skin lipomas (1)



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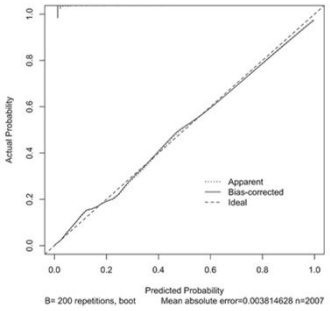
Tan *et al. AJHG* 2011

PTEN Cleveland Clinic score calibration



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Tan *et al. AJHG* 2011

Choosing a threshold score

- Choosing threshold for continuous score
  - Often challenging
  - Potentially statistically complex approach
- Acknowledging manifold issues, a threshold useful for practical implementation

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Tan *et al. AJHG* 2011

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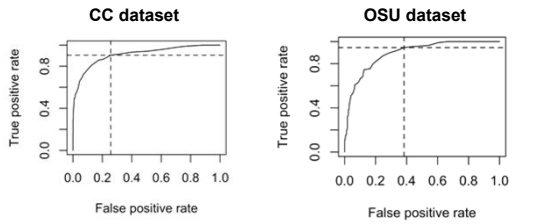
Excellent performance of *PTEN*-CC score at threshold of 10



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Tan *et al*. *AJHG* 2011

Conclusions

- A refined clinical scoring system for selecting patients for *PTEN* mutation testing
  - Superior to existing legacy criteria
  - Adult criteria and pediatric criteria
  - Easy to use

http://www.lerner.ccf.org/gmi/ccscore/

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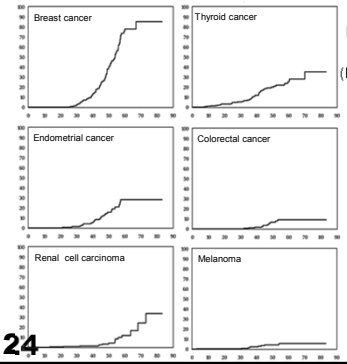
Tan *et al*. *AJHG* 2011

PTEN-associated age-related penetrances of component cancers help guide management



Based on 368 pathogenic *PTEN* mutation positive individuals (From 3399 prospectively accrued clinically eligible individuals)

Y axis – penetrance (%);
X axis – age (years)

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Tan *et al*. *Clin Cancer Res* 2012

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Recommendations for diagnostic workup and cancer surveillance in patients with *PTEN* mutations

	Pediatric (<18 y)	Adult male	Adult female
Baseline workup	Targeted history and physical examination Baseline thyroid ultrasound Dermatologic examination Formal neurologic and psychologic testing	Targeted history and physical examination Baseline thyroid ultrasound Dermatologic examination	Targeted history and physical examination Baseline thyroid ultrasound Dermatologic examination
Cancer surveillance			
From diagnosis	Annual thyroid ultrasound and skin examination	Annual thyroid ultrasound and skin examination	Annual thyroid ultrasound and skin examination
From age 30[a]	As per adult recommendations		Annual mammogram (for consideration of breast MRI instead of mammography if dense breasts) Annual endometrial sampling or transvaginal ultrasound (or from 5 years before age of earliest endometrial cancer)
From age 40[a]	As per adult recommendations	Biannual colonoscopy[b] Biannual renal ultrasound/ MRI	Biannual colonoscopy[b] Biannual renal ultrasound/MRI
Prophylactic surgery	Nil	Nil	Individual discussion of prophylactic mastectomy or hysterectomy.

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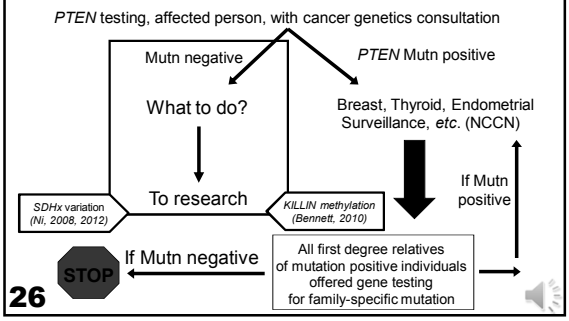
Tan *et al. Clin Cancer Res* 2012

Management is dependent on identification & risk assessment

Dependent on ability to find germline alteration



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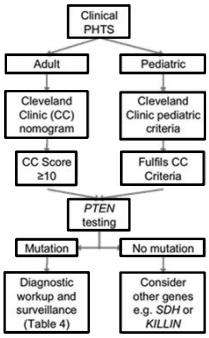
Decision tree for gene testing for individuals suspected to have *PTEN* hamartoma tumor syndrome



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Eng lab Cowden team

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- Debbie J. Marsh, PhD
- **Min-Han Tan, MB, PhD**
- X. P. Zhou, MD, PhD
- Kevin Zbuk, MD

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Jessi Moline, MS, CGC

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- Yu Wang, MB, PhD
- **Ying Ni, MS**
- Amanda Tilot, BS
- Emily Pontzer, BA
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- **Fusong Chen, MS**
- **Jin-Liang Chen, MS**

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Genomic Medicine Institute's Center for Personalized Genetic Healthcare

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- Vickie Zurcher, MD
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- *Holly Peterson, MD, Fellow (08-10)
- *Min-Han Tan, MB, PhD, Fellow (10-11)
- *Joanne Ngeow, MB, Fellow (10-)
- *Pauline Funchain, MD, Fellow (11-)
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*Cancer genetics focus

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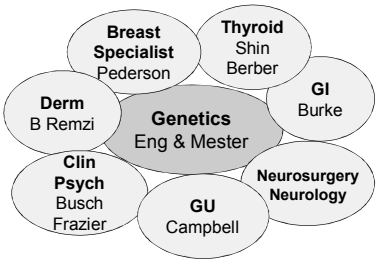
Cleveland Clinic Cowden Syndrome and PHTS Multidisciplinary Team



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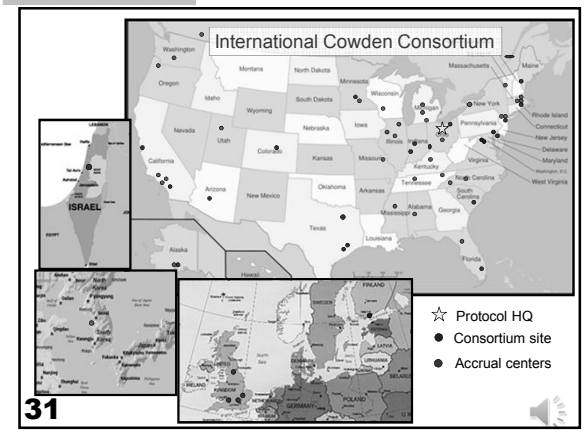

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