Keynote Lecture: *PTEN* Hamartoma Tumor Syndrome

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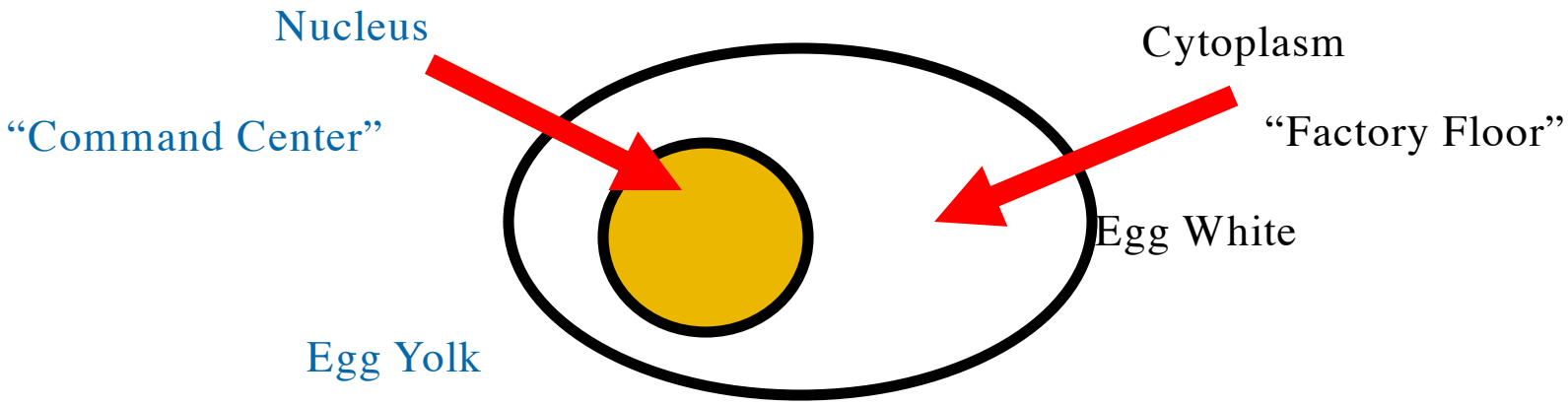
PTEN Patient Symposium, Mar. 26, 2018

Outline

- Genetics 101
- Overview of PTEN hamartoma tumor syndrome (PHTS)
- PHTS cancer risks
- Current cancer surveillance guidelines

Genetics 101 - Cells

- Cells = Basic Units of the Body
  - Like Bricks to a Building
- Cell has Nucleus & Cytoplasm



Genetics 101- Chromosomes & Genes

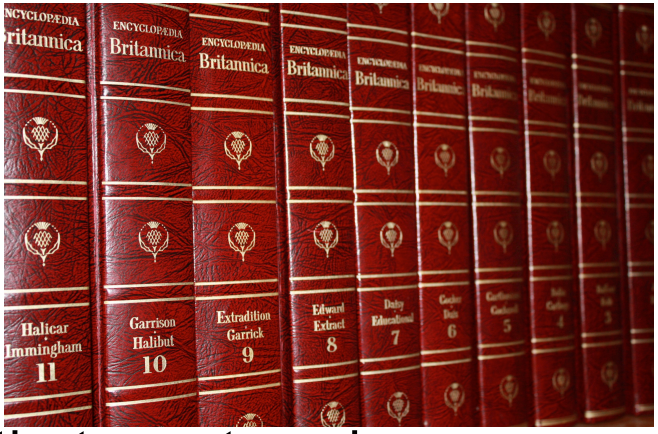
- Chromosomes in cell nucleus
- Genes reside on chromosomes
- Genes carry code for proteins
- Genetic Code = Alphabet of 4 letters
  - –A, C, G, T

Genetics 101- Proteins

- Housekeepers
- Workhorses on factory floor
- Under instructions from genes, proteins ensure cells behave properly
  - When to multiply (to get more cells)
  - When to stop multiplying

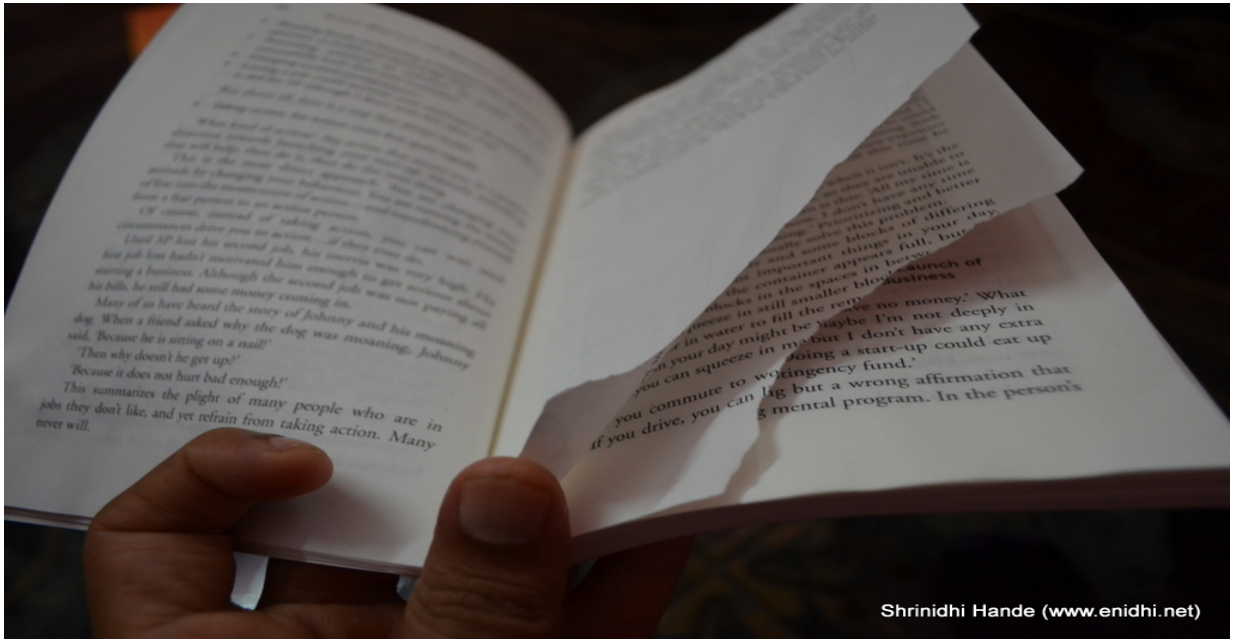
Genetics 101- Genes and Mutations in a Nutshell

- A gene is like an encyclopedia
  - 30,000 genes -> 30,000 encyclopedias
  - Some encyclopedias have 1 or a few volumes; others many volumes
    - ***PTEN has 9 volumes***
- Words, sentences & paragraphs have to read appropriately
- Gene Mutation = Typographical Error
  - Word Misspelled
  - Phrase(s)/Sentence(s) Missing
  - Whole Page(s) Missing



- Searching for a mutation: Looking for that one typo in a many volume encyclopedia
- Gene Mutation --> Absent Protein or Faulty Protein

We Can Read the Encyclopedia(s) and Look for Serious Errors* to Help Predict Those With Disease Outcome



Gene Testing to Look for Heritable Cancer Risk Like Reading our Body's Encyclopedias to Look for Serious Errors*

*Mutations or Alterations

Where's the *PTEN* Gene?

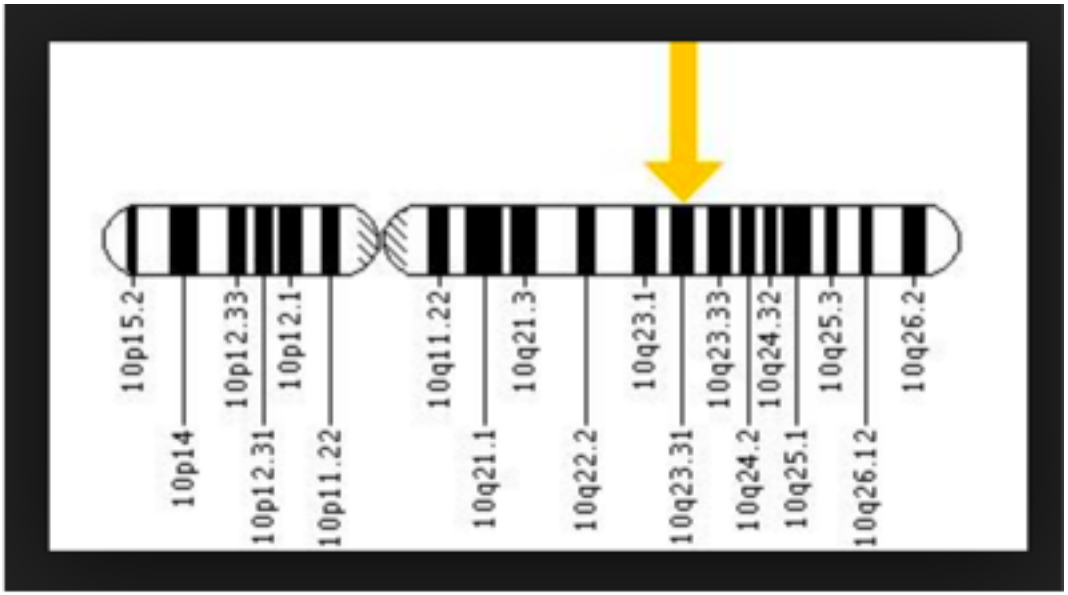
- Participation of 12 Cowden syndrome families in research
- Strict inclusion criteria per International Cowden Consortium

Pathognomonic criteria	Major criteria	Minor criteria
Mucocutaneous lesions • Facial trichilemmomas • Acral keratoses • Papillomatous papules	Macrocephaly Breast cancer Non-medullary thyroid cancer Adult-onset Lhermitte-Duclos disease (LDD)	Mental retardation (IQ ≤ 75) Goiter GI Hamartomas Lipomas Fibrocystic breast disease Fibromas GU tumor or malformation

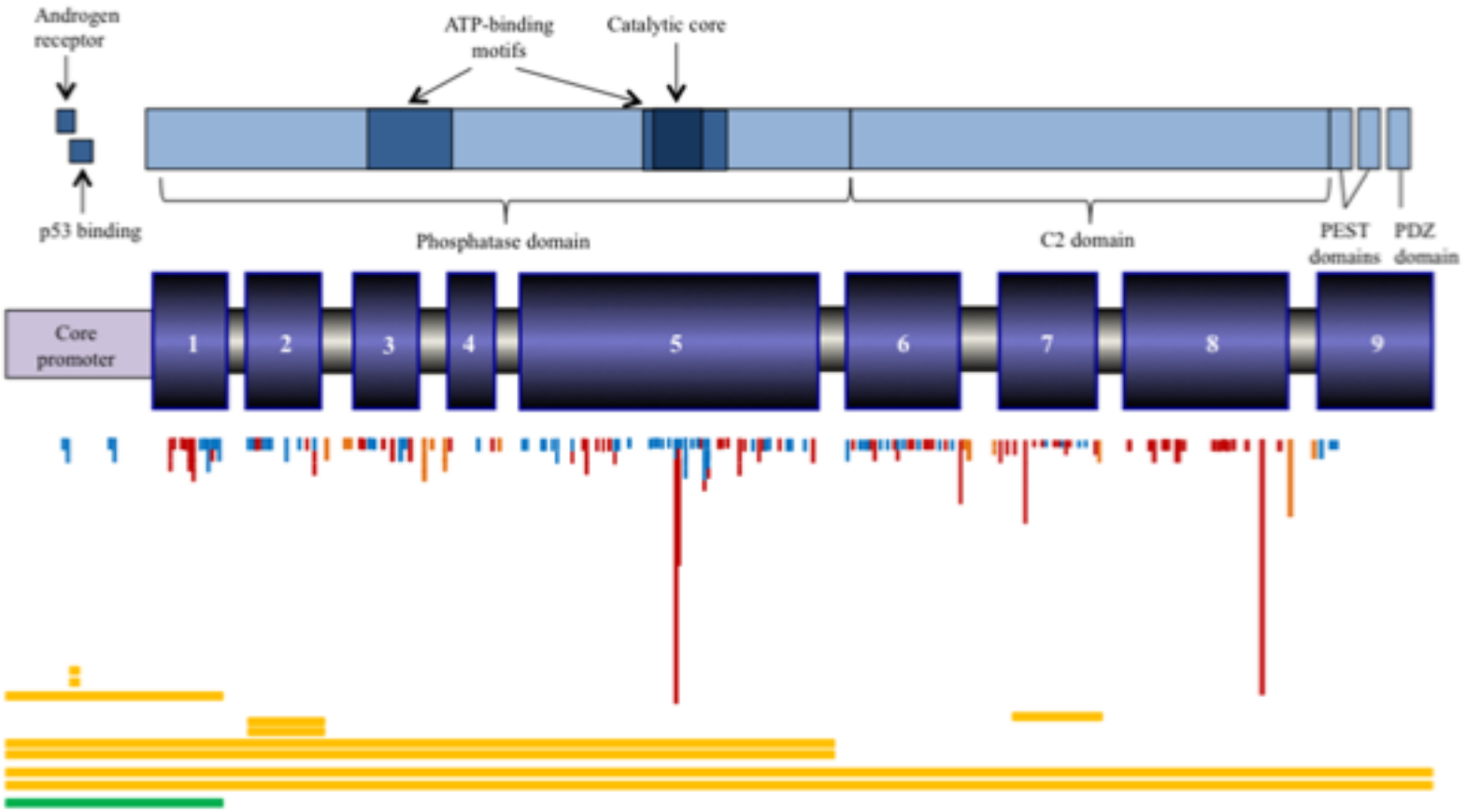
Operational diagnosis given to a person with:

1. Mucocutaneous lesions alone if:
   a. ≥ 6 facial papules, ≥ 3 being trichilemmomas, or
   b. Cutaneous facial papules + oral papillomas, or
   c. Oral papillomas + acral keratoses, or
   d. ≥ 6 palmoplantar keratoses
2. 2 major criteria, one being macrocephaly or LDD
3. 1 major + 3 minor criteria
4. 4 minor criteria

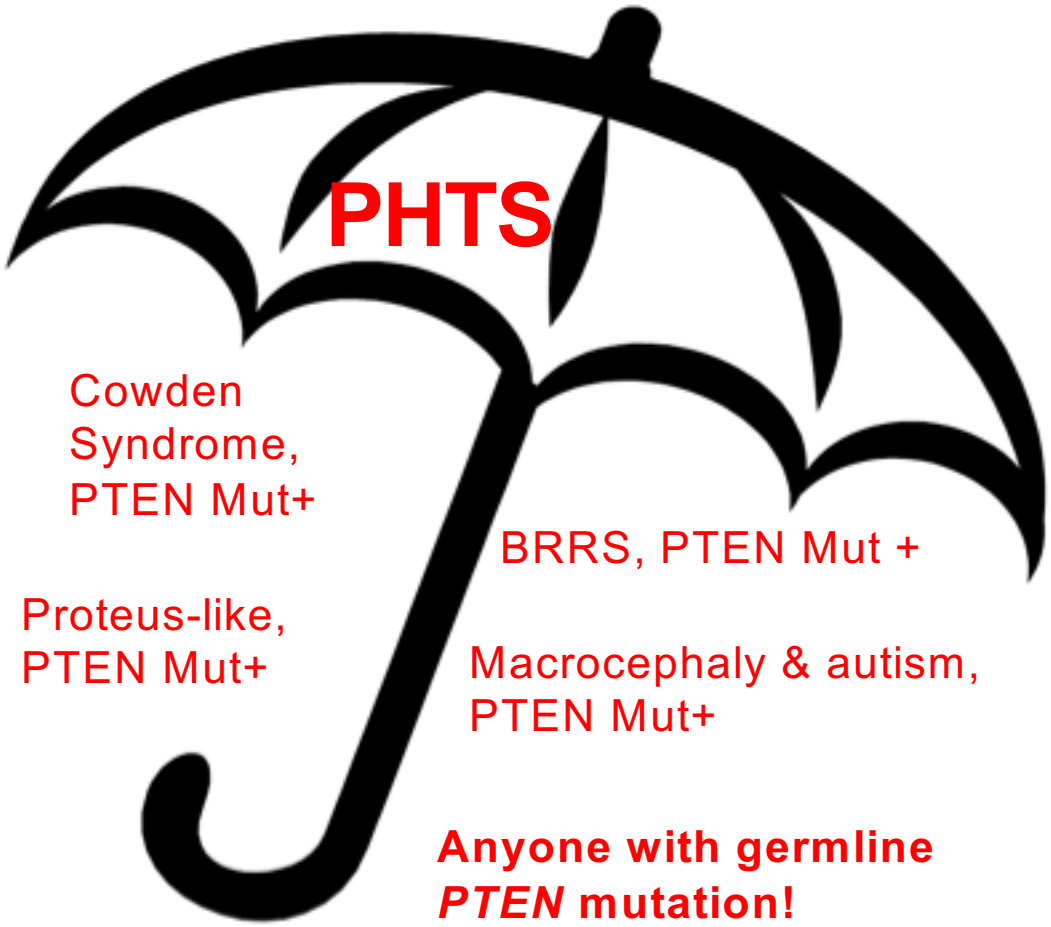
PTEN is a Gene on Chromosome 10



Many *PTEN* Mutations Identified



PTEN Hamartoma Tumor Syndrome (PHTS)



PTEN Hamartoma Tumor Syndrome (PHTS)

- Any patient with germline *PTEN* mutation
  - Cowden syndrome
  - Bannayan-Riley-Ruvalcaba syndrome (BRRS)
  - Proteus-like syndrome
  - Autism spectrum
- Areas of greatest clinical concerns
  - Increased malignancy risks
  - Benign tumors
  - Neurodevelopmental issues

Family History and PHTS

- Familial and sporadic (no apparent family history) cases reported

- PHTS has a high *de novo* (new) mutation rate
  - Minimum: 10.7%
  - Maximum: 47.6%

- No correlations with age, gender, or any clinical feature

Mester & Eng, 2012

How Important is Head Size?

- Overall: 94% with PHTS macrocephalic (“big head”)

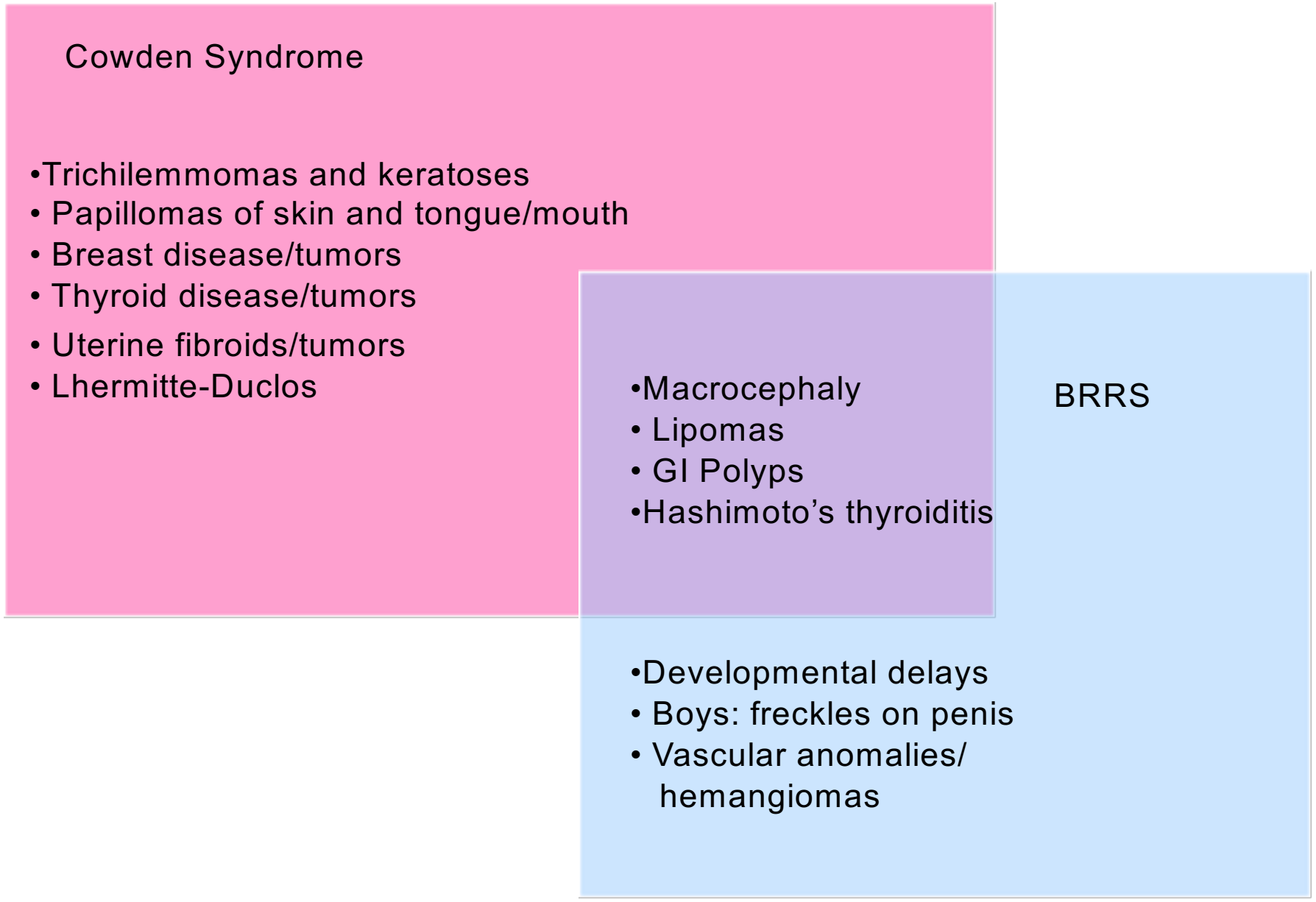
- Adults
  - Women: >57.8 cm
  - Men: >58.6 cm

- Dolicocephaly common

Nellhaus, 1968; Mester et al., 2011

Examples of Benign Growths in PHTS

- Skin and mucosa
  - Trichilemmomas (hair follicle bumps)
  - Keratoses (rough patches) on extremities
  - Papules on tongue, gums, inside nose
  - Lipomas (fatty bumps)
  - Fibromas
- Lhermitte-Duclos (benign tumor of the cerebellum)
- GI polyps
- Uterine fibroids, other genitourinary tumors
- Benign breast disease
- Thyroid nodules/goiter/ Hashimoto's thyroiditis
- Vascular anomalies/ hemangiomas


Cowden Syndrome
•Trichilemmomas and keratoses
• Papillomas of skin and tongue/mouth
• Breast disease/tumors
• Thyroid disease/tumors
• Uterine fibroids/tumors
• Lhermitte-Duclos
•Macrocephaly
• Lipomas
• GI Polyps
•Hashimoto's thyroiditis
BRRS
•Developmental delays
• Boys: freckles on penis
• Vascular anomalies/ hemangiomas

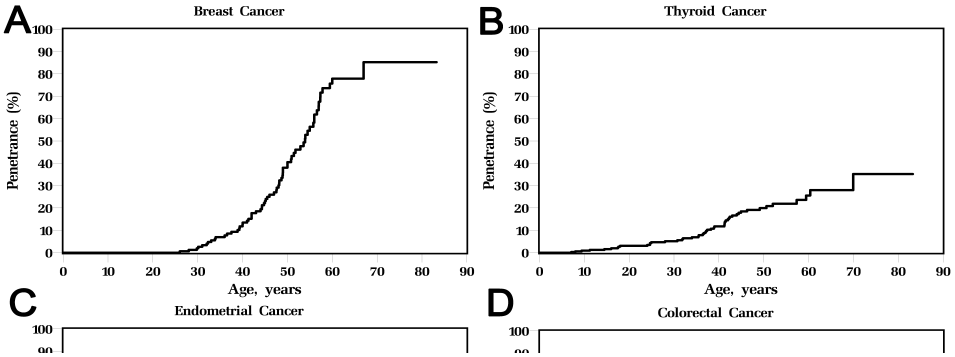
Mostly Pediatric-Onset	Mostly Adult-Onset
Macrocephaly	Lhermitte-Duclos
Developmental delays/autism	Most other skin lesions
Vascular malformations	Component cancers
Penile freckling	Fibrocystic breast disease
	Uterine fibroids
	GI polyps
Either: thyroid goiter/nodules/thyroiditis; lipomas	
Males	**Females**
Penile freckling	Breast cancer
	Fibrocystic breast disease
	Uterine cancer
	Uterine fibroids

Lifetime Cancer Risk Estimates in Prospective Series of PHTS Individuals

- Analyzing Cancer Risks in a Large Series of Research Participants Leads to:
  - Understanding Which Organs At Risk
    - Inform which organs need enhanced clinical screening
  - Age Cancer Risks Begin
    - Inform when enhanced clinical screening should begin
    - May inform when preventative surgery should be offered

Lifetime Cancer Risk Estimates in Prospective Series of PHTS Individuals

Based on 368 *PTEN* Mutation Positive Individuals *(from 3399 Prospectively Accrued Clinically Eligible Individuals)*



Cancer	General population risk	Lifetime Risk in CS with *PTEN* mutation
Breast	12%	85%
Thyroid	1%	35%
Endometrial	2.6%	28%
Renal cell	1.6%	34%
Colon	5%	9%
Melanoma	2%	6%

PHTS Cancer Risks and Current Enhanced Screening Recommendations

Cancer	General population risk	Lifetime Risk with PHTS	Screening
Breast	12%	~85% (avg dx 40s)	Starting at age 30: annual mammogram; consider MRI for patients with dense breasts
Thyroid	1%	35% (avg dx 30s/40s)	Annual ultrasound at dx age
Endometrial (uterine)	2.6%	28% (avg dx 40s/50s)	Starting at age 30: annual endometrial biopsy or transvaginal ultrasound
Renal cell (kidney)	1.6%	34% (avg dx 50s)	Starting at age 40: renal imaging every 2 years
Colon	5%	9% (avg dx 40s)	Starting at age 40: colonoscopy every 2 years
Melanoma	2%	6% (avg dx 40s)	Annual dermatologic examination

Tan et al., 2012, Ngeow et al. 2014

Is There/What is the Second Malignancy Risk in PHTS?

- 7-Year Multi-Institutional Prospective Study (2005-12)
  - 2912 Eligible Adult Research Participants
  - 2024 Invasive Cancer
- Comprehensive *PTEN* Mutation Analysis of Eligible CS and CSL Individuals
  - 114 of 2024 Germline Pathogenic *PTEN* Mutations
- Medical Record and Pathology Review
- Standardized Incidence Ratios (SIR) Calculated for all Second Malignant Neoplasms (SMNs)
  - Expected Rate Based on SEER

Second (Primary) Malignancies (SMNs) in PHTS

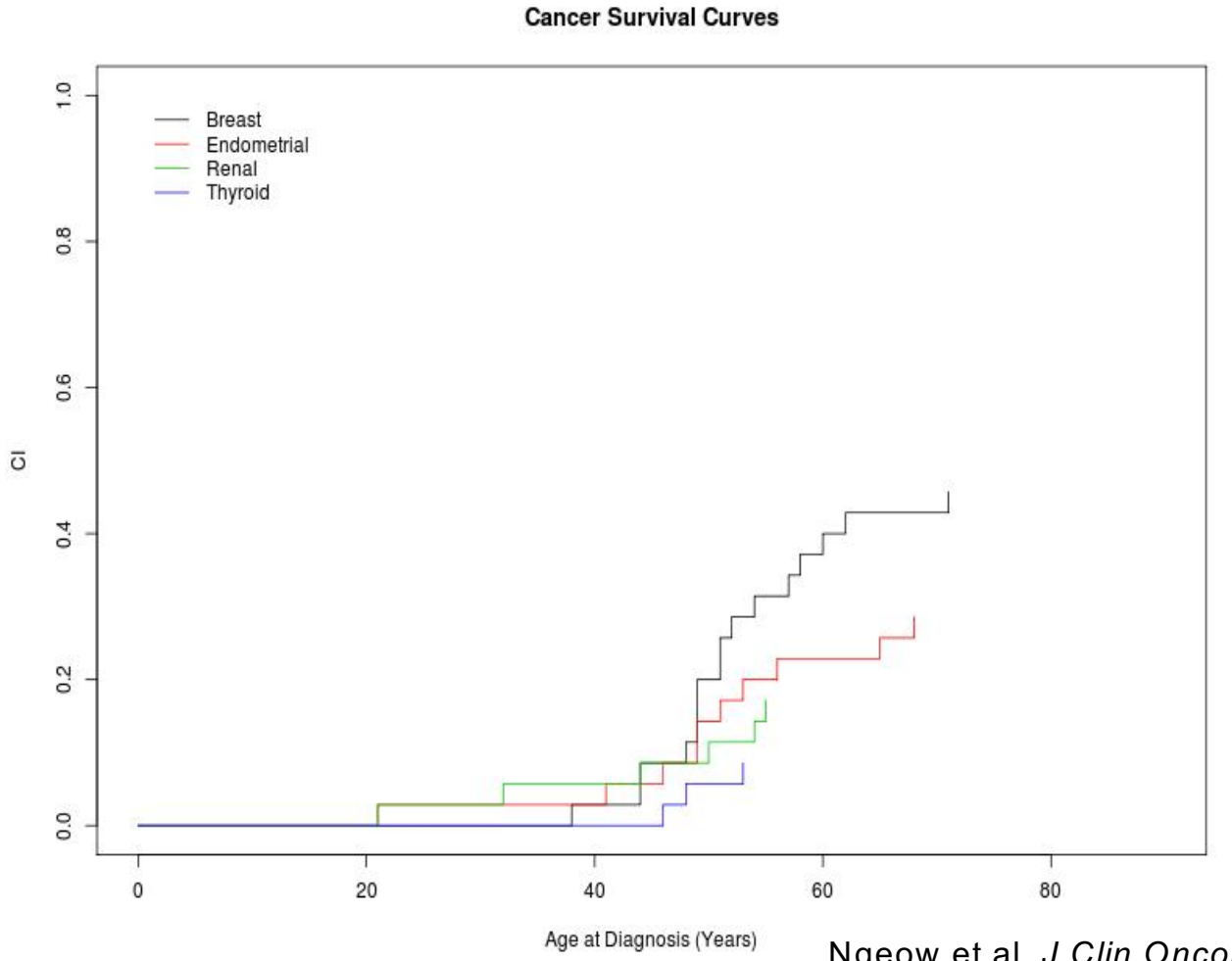
- Of 114 PHTS Adult Participants, 46 (40%) Had SMN
- Median Age at SMN = 50 yo (21-71)
- Median Interval between Primary Cancer and SMN = 5 years (<1-35 yr)

Risk of Second Malignancy in PHTS Patients

	Observed	Expected	SIR (95% CI)
All Cancers	52	6.72	7.74* (5.8-10)
Breast CA	24	2.69	8.92* (5.8-13)
Thyroid CA	12	2.06	5.83* (7-27)
RCC	2	0.49	4.09 (0.5-14)
Melanoma	2	0.47	7.41 (1.2-24.5)
Colon CA	3	0.48	6.2 (1.3-18)

Ngeow et al. *J Clin Oncol* 2014

Age-Related Penetrance Curves for Breast, Thyroid, Endometrial and Renal Cancers Presenting as Second Malignant Neoplasms in PHTS



Ngeow et al. *J Clin Oncol* 2014

SMN in PHTS: Take Home Messages?

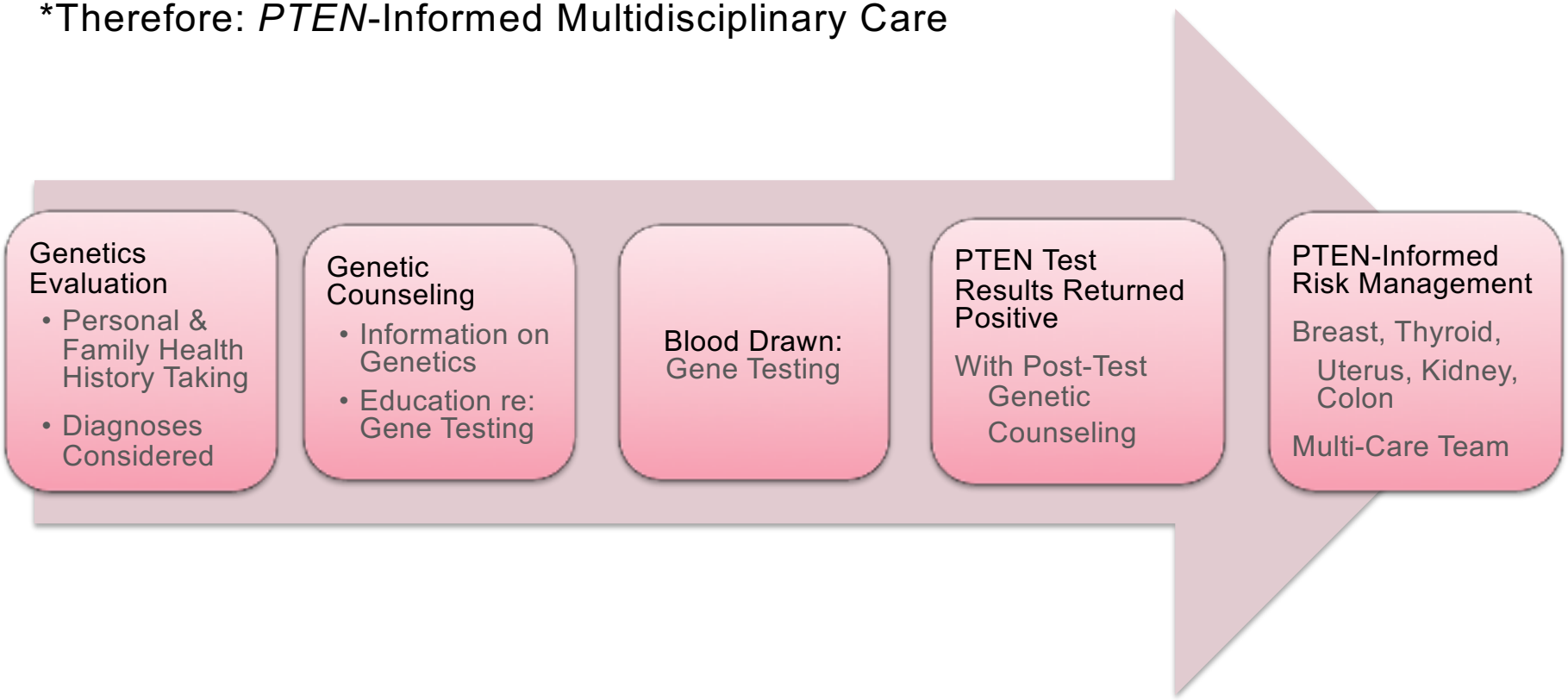
- Individuals with Germline *PTEN* Mutations at Increased Risks of SMN's vs General Population
- Lifelong Enhanced Surveillance Necessary
- Prophylactic Mastectomy Considered Given High Risk of Primary and Second Breast Cancers
- Longer Follow Up of Cohort Necessary
  - Increasing Sample Size Desirable
- Independent Validation by Another Group Desirable

Summary: *PHTS*

Knowledge is Power:

**PTEN* Germine Mutation Predisposes to Breast, Thyroid, Uterine, Kidney and Colorectal Cancer, and Melanoma

*Therefore: *PTEN*-Informed Multidisciplinary Care



PTEN Cowden Clinic

Overview

For children and adults with a confirmed or possible diagnosis of PTEN Hamartoma Tumor syndrome (PHTS), Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), or other conditions within the PTEN spectrum.

What Is PTEN?

PTEN is one of the body's many tumor suppressor genes. When they work properly, tumor suppressor genes help to control cell growth. When they are not functioning properly, cells can grow out of control and turn into either benign or malignant tumors. Many people with Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and a few other genetic conditions have been found to have PTEN gene mutations as the cause of their medical concerns. These conditions as a group are referred to as PTEN Hamartoma Tumor syndrome (PHTS). Dr. Charis Eng, our medical director and chairman of the Cleveland Clinic Genomic Medicine Institute, led the research team which in 1997 discovered the causative relationship between the PTEN gene and Cowden syndrome.

What Do We Do?

Some patients with PHTS, CS, or BRRS have health needs for which coordinated visits with multiple

GENOMIC MEDICINE INSTITUTE

Specialties

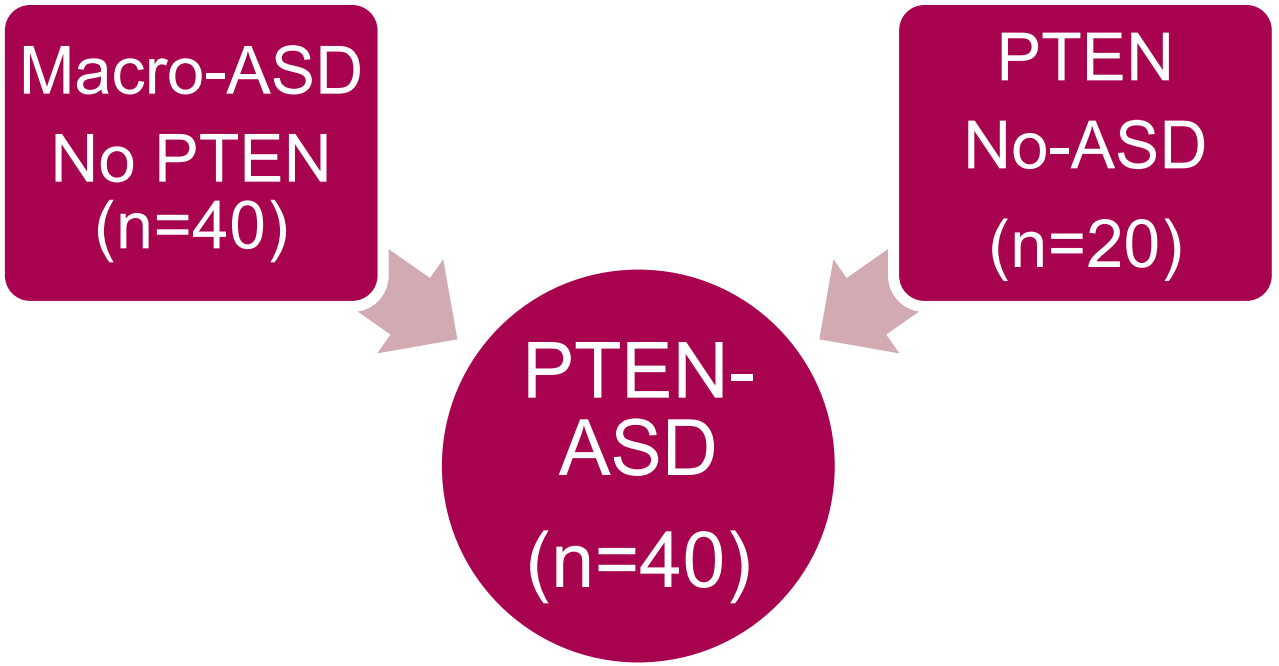
- Adult Genetics
- Pediatric Genetics
- Cancer Genetics
- Preconception & Prenatal Genetics
- Cardiovascular Genetics
- Lysosomal Storage Disease Program
- PTEN Cowden Clinic
- Paraganglioma & Pheochromocytoma Clinic

Who is Eligible for Our 8458 ("original") PTEN Study?

- Anyone with known *PTEN* mutation or variant of uncertain significance, or
- Anyone meeting "relaxed" International Cowden Consortium criteria, or
- Anyone with Cleveland Clinic (CC) PTEN risk score ≥ 10 or meeting separate pediatric testing criteria
- Study website: www.lerner.ccf.org/gmi/research/pten

Not to be confused with U54 Longitudinal Study

- 24-month, longitudinal study

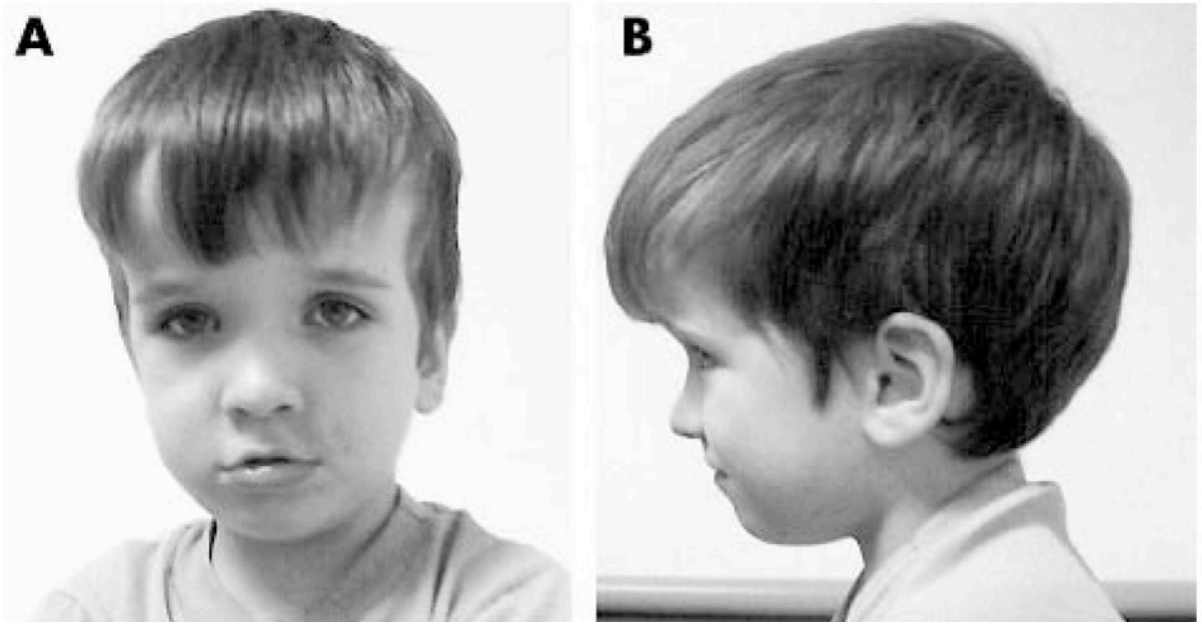


SHORT REPORT

Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline *PTEN* tumour suppressor gene mutations

M G Butler, M J Dasouki, X-P Zhou, Z Talebizadeh, M Brown, T N Takahashi, J H Miles, C H Wang, R Stratton, R Pilarski, C Eng

J Med Genet 2005;**42**:318–321. doi: 10.1136/jmg.2004.024646



Aim1: Cross-sectional (snapshot) and longitudinal (follow through over time) differences

- Cross-Sectional Neurobehavioral
  - cognitive
  - behavioral
  - adaptive functioning

- Longitudinal Neurobehavioral
  - 3 years
  - annual = cognitive
  - 6-months = symptoms

- Medical
  - cancer prevalence

Aim 2: Identify biomarkers specific to *PTEN* ASD

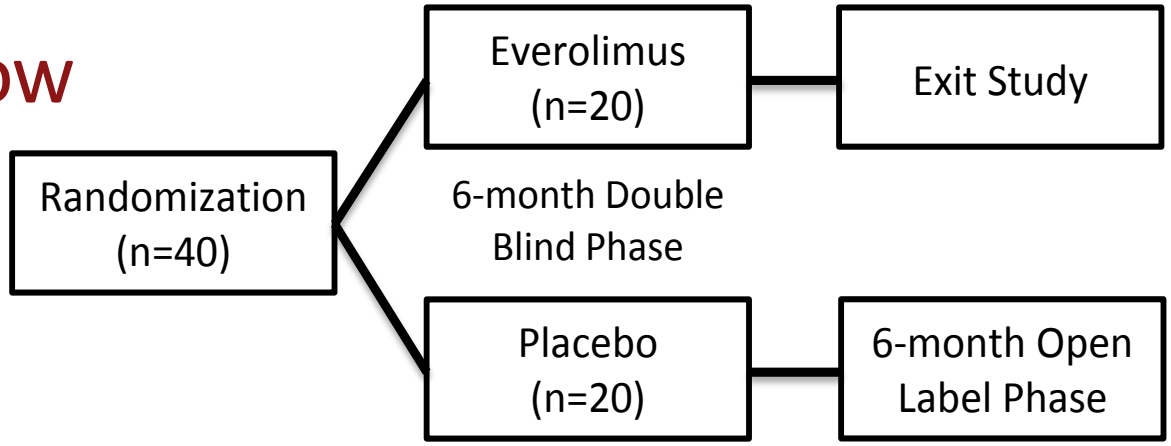
- Cognitive Markers
  - –reduced working memory
  - –reduced processing speed
- Imaging Markers
  - –white matter volume and hypo-intensities
  - –white matter integrity (DTI)
- Blood Markers (“peripheral markers of brain”)

Open: Pilot Randomized Controlled Trial of Everolimus in Individuals with ASD and *PTEN* Mutations

- Oral derivative of rapamycin in clinical development since 1986
- Approved for several indications:
  - Renal cell carcinoma (2009)
  - Pancreatic neuroendocrine tumors (2011)
  - Hormone receptor-positive HER2-negative breast cancer (2012)
  - Immunosuppressant: transplantation (kidney 2010; liver 2013)
  - Subependymal giant cell astrocytoma (SEGA) in TSC (2010)
- mTOR pathway abnormally upregulated affecting cell growth, proliferation, and function
- mTOR inhibitors reverse some deficits in Pten mouse models
- Selectively inhibits mTOR pathway: Blocks the abnormal up-regulation of mTOR that occurs as a result of PTEN loss

OPEN: Pilot RCT of Everolimus in Children and Adolescents with ASD and *PTEN* Mutations

Participants Flow



Developmental Synaptopathies Consortium
Multi-site trial:
Stanford University: 10
Cleveland Clinic: 20
Boston Children's Hospital: 10

Eng Lab PTEN/Cowden Team

- Alumni
- Debbie J. Marsh, PhD
- X. P. Zhou, MD, PhD
- **Min-Han Tan, MB, PhD**
- **Joanne Ngeow, MB, MPH**
- Kristi L. Bennett, PhD
- Jason He, MB, PhD
- Emily Nizialek, PhD
- Kevin Zbuk, MD

Genetic Counselor Coordinator
Shreya Malhotra, MS, CGC, LGC

Research Coordinators
Jen Mears (Alum) -> Holly Green (4/24)
Beth Crouser

- Current
- Ritika Jaini, PhD
- Ata Abbas, PhD
- Hyunpil Lee, PhD
- Ying Ni, PhD
- Madhav Sankhunny, PhD
- Iris N. Smith, PhD
- Lamis Yehia, MS
- Nick Sarn
- Stetson Thacker
- Tammy Sadler, MS
- Todd Romigh, MS
- Jin-Lian Chen, MS
- Qi Yu, MS
- Rose Kung, MS

Genomic Medicine Institute's Center for Personalized Genetic Healthcare

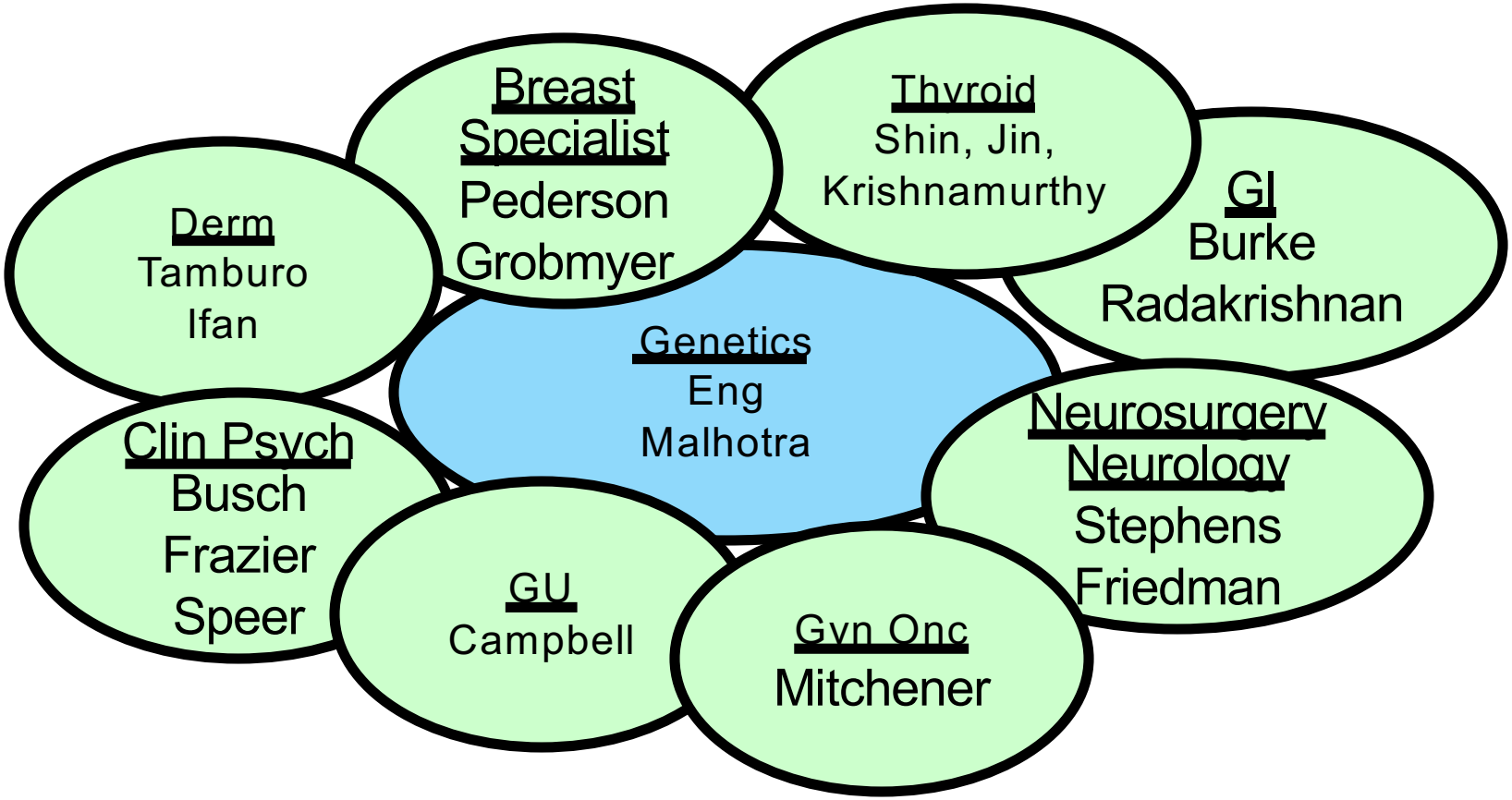
- Genomic Medicine Doctors
- Adnan Al-Sadah, MD
- *Charis Eng, MD, PhD
- Angelika Erwin, MD, PhD
- Marvin Natowicz, MD, PhD
- *Marc Shapiro, MD
- Vickie Zurcher, MD
- *Kevin Zbuk, MD, Fellow (05-07)
- *Holly Pederson, MD, Fellow (08-10)
- *Min-Han Tan, MB, PhD, Fellow (10-11)
- *Joanne Ngeow, MB, Fellow (10-14)
- *Pauline Funchain, MD, Fellow (11-15)
- Genomic Medicine Biorepository
  - Phyllis Harbor
  - Junying Lei
  - Brian McCue

- Genetic Counselors
- Diane Clements, MS, LGC
- *Brandie Heald Leach, MS, LGC
- *Shreya Malhotra, MS, LGC
- *Jessi Marquard, MS, LGC
- *Rebekah Moore, MS, LGC
- *Ryan Noss, MS, LGC
- Lauren Palange, MS
- Brittney Psensky, MS, LGC
- Christina Rigelsky, MS, LGC
- Allison Schreiber, MS, LGC
- Amy Shealy, MS, LGC
- Marissa Coleridge, MS, LGC

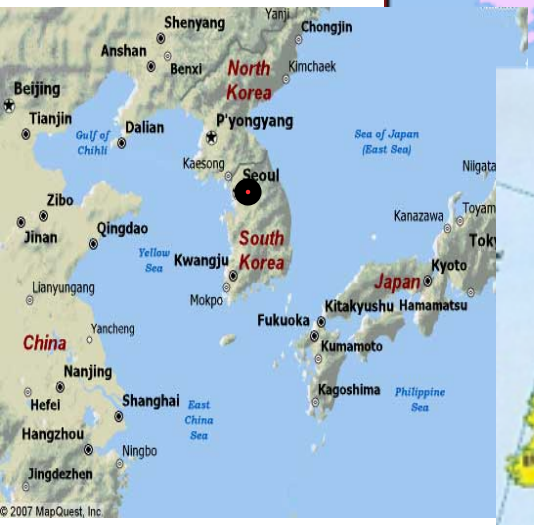
*Cancer Genetics Focus

Cleveland Clinic Cowden Syndrome and PHTS Multidisciplinary Team

http://my.clevelandclinic.org/genomics-genetics/subspecialties/pten-clinic.aspx



International Cowden Consortium



Protocol HQ

Accrual Centers

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American Cancer Society Clinical Research Professorship

American Cancer Society (1996-2007)

Cleveland Clinic-Hebrew University Center for Transformative Nanomedicine

Doris Duke Distinguished Clinical Scientist Award (2002-09)

National Cancer Institute (R01, R01, **P01**)

National Institutes of Health (R01, S10, U54)

Breast Cancer Research Foundation

Department of Defense US Army Breast Cancer Research Program (2010-13)

William Randolph Hearst Foundations (2008-13)

Susan G. Komen Breast Cancer Research Foundation

Lee Foundation Singapore (2010-12)

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Still

PTEN

Eng Lab 2016

Eng Lab 2017: PTEN n More

Thank YOU for Participating in Our PTEN Research
Thank YOU for Ensuring Knowledge is Power