PTEN-opathies: From Research to Clinical Care

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Epilepsy Genetics Keynote, Sept. 11, 2020
Disclosures

• None Relevant

• Over-Disclosing (No Relevance to Talk):
  – Co-Founder and (Pro Bono) CMO, Family Care Path, Inc.
  – Co-Founder and (Pro Bono) CMO, Covariance, LLC
Quickie Outline

• Setting the Stage – Genomics-Enabled Precision Care
  – Definitions

• Rachel Cowden and the Syndrome Honoring Her

• PTEN-opathy
  – PTEN Hamartoma Tumor Syndrome (PHTS)
  – Model for Genomics-Enabled Precision Medicine
True Healthcare Reform
Will need to shift the model from the practice of reactive medicine to proactive medicine

Genetics and Genomics will enable the shift to the less expensive and better quality of care of the proactive model

Source: Elias A. Zerhouni, M.D., FY 2007 Budget: NIH and the Transformation of Medicine House Appropriations Subcommittee on Labor/HHS/Education
Contributors to Premature Mortality

D.M. Cosgrove, MD, State of the Clinic 2008
April, 2009
Historical Imperative for Prevention

Superior doctors prevent the disease.
Mediocre doctors treat the disease before evident.
Inferior doctors treat the full blown disease.

*Nai-Ching (2600 B.C. 1st Chinese Medical Text)*
Nirvana of Genetic and -Omics-Based Individualized Healthcare for Cancer

Multidisciplinary Cancer Consult Including Genomic Medicine and Genetic Counseling

Multiple Generation Pedigree For Cancer Genetic Risk Assessment

Clinical Screening, Preventive Measures, Behavior Modification

Prioritization & Testing of Known High Penetrance Cancer Genes in Setting of Genetic Counseling

Select Multi-Agent Targeted Therapy With >99% Likelihood of Durable Response & <1% Likelihood Of Adverse Effects

Biopsy of Cancer

Histopathology

Germline Variant Profiling

Somatic Genomic Profiling of Cancer Epithelium & Stroma

Cleveland Clinic

Genomic Medicine Institute
What is Precision Healthcare (Medicine)?
One Definition: Precision Medicine

• “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person”

• Genomics-Enabled Precision Medicine = Genomic Medicine
What is Genomic Medicine?

Population of People

Omics Information

Subset of “People” At Risk for X

Research:
Who?
What?
When?
Where?
Why? How?
What is Genomic Medicine? Example Context: Heritable Fraction

Population of World: 7.3 Billion

At Risk for Genetic Disease: 600 Million

Help Stratify Those at Risk
Early Detection and Prevention: Only Those at Risk
One Example of Genomic Medicine Research: Research Evidence for Risk Stratification, Genetic Counseling and Gene-Informed Management

Example Tools:
* Family Health History
* Disease Predisposition Genes

Caveat: Non-genetics caregivers often do not take family histories or if taken, inaccurate
If Gene-Enabled Risk Assessment and Management are Successful, Then There are Previvors

• Previvors are individuals who are survivors of a predisposition to disease/disorder but who haven't had the disease
  – Corollary: Previvors also include those individuals whose gene-enabled management catches the disease early and mitigate or abrogate
The Story of Rachel Cowden (ca 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 & Denis, *Ann Intern Med* 1963)
  • Cowden Syndrome
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, Thyroid and Other Cancers
- International Cowden Consortium Diagnostic Criteria
  - Robust
  - Complex
Key Features of Cowden Syndrome (CS)

Papillomatous Papules

Trichilemmoma
(Pathognomonic Feature)
Mapping of the CS Gene

- International Cowden Consortium Study
- 12 Extended CS Families
- 40 Affected Individuals
- CS Mapped to 10q22-q23

Nelen et al. *Nature Genet* 1996
PTEN is the CS Gene

• 5 CS Families, Linkage to 10q22-q23
• Candidate Gene, PTEN, on 10q23.3
• Germline Mutations of PTEN, on 10q23.3, in 4 of 5 Families
  – Family “without” mutation had highest LOD score on prior linkage analysis (LOD>1)

Nelen et al. Nature Genet 1996
Liaw, Marsh et al. Nature Genet 1997
**PTEN**

- **Phosphatase, Tensin-Homologue, Deleted on Chromosome TEN**
  - 10q23.3
- **Tumor Suppressor Gene**
- **Dual-Specificity Phosphatase**
  - Lipid & Protein Phosphatase
  - Ser-Thr as well as Tyr Phosphatase
- **Multiple Roles in:**
  - Cell Cycle Arrest, Apoptosis, Migration, Polarity
  - Genomic Stability, Transcriptional Control
  - Etc

Reviewed in Yehia et al. *J Clin Invest* 2019
One Gene, Many Functions: PTEN Canonical and Non-Canonical Signaling Pathways

Many Germline *PTEN* Mutations Identified

Reviewed in Yehia et al, *J Clin Invest* 2019
PTEN Hamartoma Tumor Syndrome (PHTS) = PTEN-opathy

• Any patient with germline *PTEN* mutation
  – Cowden syndrome
  – Bannayan-Riley-Ruvalcaba syndrome (BRRS)
  – Proteus-like syndrome
  – Autism spectrum
  – *Whatever!*

• Areas of greatest clinical concerns
  – Increased malignancy risks
  – Benign tumors (mass effect)
  – Neurodevelopmental issues
**PTEN** Hamartoma Tumor Syndrome = Molecular (Genetic) Diagnosis
**PTEN**-opathy = Molecular (Genetic) Diagnosis

Cowden syndrome/BRRS/ASD = Clinical Diagnoses

- **PTEN** Mutation
  - Cowden Syndrome

- **PTEN** Mutation
  - BRRS

- **PTEN** Mutation
  - Autism Spectrum Disorder (ASD)

Reviewed in Yehia et al. *J Clin Invest* 2019
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, *Genet Med* 2012
Which Subset of Cowden-Looking Individuals has \textit{PTEN} Mutations

\begin{itemize}
  \item Population of People
  \item Omics Information
  \item Subset of “People” At Risk for X
\end{itemize}

\textbf{Research:}
- Who?
- What?
- When?
- Where?
- Why? How?
Based on >3,000 Cases, Created a Nomogram-Based Risk Score System to Help Identify À Priori Risk of PHTS

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)

Risk Calculator Website

• [http://lerner.ccf.org/gmi/ccscore/](http://lerner.ccf.org/gmi/ccscore/)

• A refined clinical scoring system for selecting patients for *PTEN* mutation testing is being proposed
  • Superior to existing legacy criteria
  • Utilized by clinical community (sometimes, patients)
What Organ-Specific Neoplasias and Ages of Risk in Individuals with PTEN Mutations?

Population of People

Subset of “People” At Risk for X

Research:
Who?
What?
When?
Where?
Why? How?

Omics Information
Lifetime Cancer Risk Estimates in Prospective Series of PHTS Individuals

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

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General population risk</th>
<th>Lifetime Risk in CS with PTEN mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>12%</td>
<td>85%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1%</td>
<td>35%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2.6%</td>
<td>28%</td>
</tr>
<tr>
<td>Renal cell</td>
<td>1.6%</td>
<td>34%</td>
</tr>
<tr>
<td>Colon</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Enhanced Surveillance for PHTS Cancer Risks Codified in National Practice Guidelines

<table>
<thead>
<tr>
<th>Medical Management Guidelines for PHTS (NCCN V.1.2020)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast (female)</strong></td>
</tr>
<tr>
<td>- Starting at age 18: Consistent breast awareness and self-exam</td>
</tr>
<tr>
<td>- Starting at age 25*: Clinical breast exam every 6-12 months</td>
</tr>
<tr>
<td>- Starting at age 30-35*: Annual mammogram and breast MRI with contrast. Discuss mastectomy, as needed and based on family history</td>
</tr>
<tr>
<td><strong>Thyroid</strong></td>
</tr>
<tr>
<td>- Starting at age 7: Annual thyroid ultrasound</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
</tr>
<tr>
<td>- Starting at age 40: Renal ultrasound every 1-2 years</td>
</tr>
<tr>
<td><strong>Endometrium</strong></td>
</tr>
<tr>
<td>- Starting at age 35: Consider cancer screening</td>
</tr>
<tr>
<td>Personalised management:</td>
</tr>
<tr>
<td>- Endometrial biopsy every 1-2 years</td>
</tr>
<tr>
<td>- Transvaginal ultrasound as needed (postmenopausal)</td>
</tr>
<tr>
<td>- Patient education; prompt response to symptoms</td>
</tr>
<tr>
<td>- Discuss hysterectomy with completion of childbearing</td>
</tr>
<tr>
<td><strong>Colon</strong></td>
</tr>
<tr>
<td>- Starting at age 35 (unless symptomatic)*: Colonoscopy every 5 years; more frequently if symptomatic or polyps are found</td>
</tr>
<tr>
<td><strong>Dermatologic</strong></td>
</tr>
<tr>
<td>Personalised management:</td>
</tr>
<tr>
<td>Annual dermatologic exam for melanoma and other cutaneous features recommended</td>
</tr>
<tr>
<td><strong>Developmental</strong></td>
</tr>
<tr>
<td>Starting at age of diagnosis: Consider psychomotor assessment in children; brain MRI if symptomatic</td>
</tr>
</tbody>
</table>

*5-10 years before the earliest known organ-specific cancer diagnosis in the family (whichever comes first)
Dilemma: Precisely Who is at Risk of What Phenotype in PHTS?

23% of PHTS patients have Autism Spectrum Disorder (ASD)

Hypothesis:
Genomic modifiers can impact PHTS clinical phenotypic outcomes on top of co-existing germline pathogenic PTEN mutations.
Is there precedence?

SDHx Variants Modify Cancer Risks in Individuals with Germline PTEN Mutations

- But: Only ~10% of PHTS patients have co-existing SDHx germline variants

Study Design: Genome-Wide Modifier Hunt in PHTS

- **PHTS patients** (n=481)
- Infinium Global Screening Array
  - ~660,000 markers
  - COSMIC, GO, clinical research content (ClinVar, PharmGKB, cancer, endocrine/metabolic, etc.)

  - Genotyping calls
  - Quality control
  - Analysis

  - Copy number variations (CNV)
  - Genome-wide association study (GWAS)
Copy Number Variation (CNV) 101

Deletion

Reference genes

Duplication

A copy of gene B has been deleted

A copy of gene B has been duplicated

NEJM Illustrated Glossary (2019)
CNVs in Multiple Brain-Related Phenotypes and in Cancer

Comparative Analyses of Copy-Number Variation in Autism Spectrum Disorder and Schizophrenia Reveal Etiological Overlap and Biological Insights

Itaru Kushima,1,2 Branko Aleksić,1 Masahiro Nakatomi,3 Tepppei Shimamura,1 Takaki Okaeda,1 Yota Urata,1,9 Makoto Morikawa,1 Karako Ishizuka,1 Tomoko Shino,1 Hiroki Kimura,1 Yuka Arakawa,1,9 Akira Yoshimura,1 Yuto Takasaki,1 Yanji Yu,1 Yukako Nakamura,1 Mami Yamamoto,1 Tatsuya Iida,1 Shoji Ito,1 Toshiyuki Iwashita,1 Manami Ogasawa,1 Emiko Ishikawa,1 Yuka Tsuchiya,1 Naoko Kawano,1,9 Yukako Ono,1,9 Tomo Yonehara,1 Tatsuki Ueno,1,9 Toshimichi Yamamoto,1 Masashi Iida,1 Ryota Hashimoto,1,9,10,11 Hidenao Yamamoto,1 Yuko Yashida,1 Toshiyuki Someda,1 Yukihide Watanabe,1 Jun Egawa,1 Ayako Nuncwaka,1 Masanari Itohata,1 Makoto Araki,9 Mitsuro Miyazaki,1 Akiko Kubota,1 Michio Suzuki,1 Tsutomu Takahashi,1 Masanobu Usami,1 Masayuki Kodama,1 Kyota Watanabe,1 Tsukasa Sasaki,1 Hitoshi Kusunoki,1 Mamoru Toguchi,1 Fumichika Tsuburaya,1,9

Cell Reports 34, 2838-2850, September 11, 2018 © 2018 The Authors.

Pathogenic Germline Variants in 10,389 Adult Cancers

Kuan-Hao Huang,1,2,4 R. Jay Masliah,1,2 Yige Wu,1,2 Deborah I. Pitter,1,2 Jaylin Wang,1,2 Clara Oh,1,2 Marta Paczkowska,1,2 Sheila Reynolds,1 Matthew A. Wyszynski,1,2 Ninad Oak,1,2 Adam D. Scott,1,2 Michel Krassowski,1,2 Andrew D. Chenick,1,2 Kathleen E. Houlihan,1,2 Reyoka Jaya-singhe,1,2 Liang-Bao Wang,1,2 Daniel Cui Zhou,1,2 Di Liu,2 Song Gao,2 Young Won Kim,1 Amanda Koral,1 Joshua F. McDermott,1 Vishwanathan Huang-thupayodge,1 Tae-Boon Kim,1,2 Abigail Hahn,1,2 Chen Wang,1,2 Michael D. McInerney,1,2 Fahid Al-Mulla,1,2 Kimberly J. Johnson,1,2 The Cancer Genome Atlas Research Network, Olivier Lichtarge,1 Paul C. Boutros,1,2 Benjamin Righelato,1,2 Alexander J. Lazar,1,2 Wei Zhang,1,2 Michael C. Wendl,1,2,11,12 Ramaswamy Govindan,1 Sanjay Jain,1 David Wheeler,1,2 Shashikant Kulkarni,1,2 John F. Dipeso,1,2,13 Jiri Reimand,1,2 Funda Meric-Bernstam,1,2 Ken Chen,1 Ilya Shmulevich,1,2 Sharon E. Plon,1,2 Feng Chen,1,2,14 and Li Ding1,2,1,2,14

Copy number variation in bipolar disorder

EK Green1, E Rees2, JTR Watts2, K-G Smith3, L Forty4, D Grozeva5, JL Moran5, P Sklar6, S Ripke7, KD Chamberlain7, G Genovese5, SA McCarroll1, J Jones1, L Jones1, MJ Owen5, MC O’Donovan5, N Craddock2 and G Kirov8

Large (> 100 kb), rare (< 1% in the population) copy number variants (CNVs) have been shown to confer risk for schizophrenia (SZ), but the findings for bipolar disorder (BD) are less clear. In a new BD sample from the United Kingdom (~2591), we have examined the occurrence of CNVs and compared this with previously reported samples of 6882 SZ and 8842 control subjects. When combined with previous data, we find evidence for a contribution to BD for three SZ-associated CNV loci duplications at 1q21.1 (P = 0.003), deletions at 3q29 (P = 0.03) and duplications at 1q11.2 (P = 2.3 x 10^-4). The latter survives multiple-testing correction for the number of recurrent large CNV loci in the genome. Genes in 20 regions (total of 55 genes) were enriched for rare exonic CNVs among BD cases, but none of these survives correction for multiple testing. Finally, our data provide strong support for the hypothesis of a lesser contribution of very large (>500 kb) CNVs in BD compared with SZ, most notably for deletions >1 Mb (P = 9 x 10^-8).

Molecular Psychiatry (2016) 21, 89–93, doi:10.1038/mp.2014.174; published online 6 January 2015
Demographic and Clinical Characteristics of 481 PHTS Patients

Analytical sample (EUR ancestry):

Group 1 = **ASD/DD** (n=113)

Group 2 = **No ASD/DD** (n=228)

Group 3 = **Cancer** (n=150)

**Abbreviations:**
ASD, autism spectrum disorder; DD, developmental delay
Genome-Wide CNV Burden Indicates Phenotype-Specific Patterns

Yehia L et al. JAMA Netw Open. 3(1):e1920415 (2020)
CNVs Involving Known Cancer Susceptibility Genes

- Genes associated with Cowden syndrome component cancers:
  - 46 genes
  - Breast, thyroid, kidney, endometrial, colon, melanoma
- Clinically actionable cancer-related genes:
  - 24 genes (*)
  - American College of Medical Genetics and Genomics (ACMG) guidelines

<table>
<thead>
<tr>
<th>Cancer susceptibility genes of component cancers (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK, APC, ATM, BAP1, BHD, BMPR1A, BRCA1, BRCA2, CDC73, CDK4, CDKN1C, CDKN2A, ERCC2, FH, HRAS, KLLN, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, NSD1, PHOX2B, PMS1, PMS2, POLH, PRKAR1A, RB1, RET, SDHAf2, SDHB, SDHC, SDHD, SMAD4, SMARC1, SMARCB1, STK11, TP53, TSC1, TSC2, VHL, WRN, WT1, XPC</td>
</tr>
</tbody>
</table>
NDD Patients Have Rare CNVs Involving Known Cancer Susceptibility Genes

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical Phenotypes</th>
<th>CNV Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCF00547-01-001</td>
<td>M</td>
<td>3</td>
<td>Macrocephaly, dysmorphic features, global developmental delay, tan macules on glans penis and penile shaft, juvenile polyps, congenital genitourinary tract anomalies, epilepsy</td>
<td>chr10:85624500-90412968 Length: 4.8 Mb Type: Deletion Gene: <strong>BMPR1A</strong> (OMIM 601299)</td>
</tr>
<tr>
<td>CCF03028-01-001</td>
<td>M</td>
<td>21</td>
<td>Macrocephaly, dysmorphic features, mental retardation, tan macules on glans penis and penile shaft, oral mucosa papilloma, adenomatous polyps, colon ganglioneuroma, arteriovenous malformation, inflammatory polyp, juvenile polyp, hyperplastic benign polyp, juvenile polyposis syndrome</td>
<td>chr10:87976544-91250370 Length: 3.3 Mb Type: Deletion Gene: <strong>BMPR1A</strong> (OMIM 601299)</td>
</tr>
<tr>
<td>CCF01852-01-001</td>
<td>F</td>
<td>6</td>
<td>Macrocephaly, dysmorphic features, global developmental delay, connective tissue nevus (NOS), lipoma</td>
<td>chr17:41256153-41319650 Length: 63.5 Kb Type: Deletion Gene: <strong>BRCA1</strong> (OMIM 113705)</td>
</tr>
</tbody>
</table>

**But:** No pathogenic or likely pathogenic (P/LP) CNVs involving known cancer-associated genes were identified in PHTS patients with cancer
CNVs Associated with Neurodevelopmental Disorders (NDD)

- **Previously reported P/LP CNV loci:**
  - Genomic disorders, congenital malformations, and neurodevelopmental phenotypes
  - Simons Foundation Autism Research Initiative (SFARI)
  - DECIPHER (DatabasE of genomiC variation and Phenotype in Humans using Ensembl Resources)
  - Developmental Disorders Genotype-Phenotype Database (DDG2P)
  - UK Biobank

- **Previously unreported CNV loci:**
  - Size and gene content (ACMG guidelines)
Enrichment of CNVs Associated with NDD in PHTS Patients with ASD/DD

<table>
<thead>
<tr>
<th>CNV Type</th>
<th>Comparison</th>
<th>(95% CI)</th>
<th>Without ASD/DD</th>
<th>ASD/DD Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD/DD associated</td>
<td>ASD/DD vs cancer</td>
<td>6.57 (1.59-44.50)</td>
<td></td>
<td></td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td>ASD/DD vs no ASD/DD</td>
<td>4.18 (1.43-13.70)</td>
<td></td>
<td></td>
<td>.008</td>
</tr>
</tbody>
</table>


PHTS patients with P/LP CNVs associated with NDD

- **ASD/DD** (11/113 or 10%)
- **No ASD/DD** (5/228 or 2.6%)
- **Cancer** (2/150 or 1.7%)
One Example Case Study: CNVs Involving CYFIP1

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Phenotype Group</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Neurodevelopmental and Cognitive Features</th>
<th>Other Clinical Features</th>
<th>CNV (Size)</th>
<th>Associated Genomic Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCF11952</td>
<td>ASD/DD</td>
<td>M</td>
<td>1</td>
<td>Global developmental delay</td>
<td>Macrocephaly, hemangioma, lipoma</td>
<td>15q11.1-q11.2 dup (3 Mb)</td>
<td>NA</td>
</tr>
<tr>
<td>CCF06207</td>
<td>ASD/DD</td>
<td>F</td>
<td>46</td>
<td>Variable delay</td>
<td>Macrocephaly, oral mucosa papilloma, lobular breast carcinoma in situ (age 44), benign breast disease, goiter, ovarian cysts, skin tag</td>
<td>15q11.2 del (916 Kb)</td>
<td>15q11.2 deletion syndrome (OMIM 615666)</td>
</tr>
<tr>
<td>CCF06601</td>
<td>ASD/DD</td>
<td>M</td>
<td>6</td>
<td>Autism spectrum disorder, global developmental delay</td>
<td>Macrocephaly, isolated hemihyperplasia, skin tag</td>
<td>15q11.2 dup (154 Kb)</td>
<td>NA</td>
</tr>
</tbody>
</table>
**CYFIP1 - Cytoplasmic Familial Mental Retardation-Interacting Protein 1**

Conclusions & Relevance

CNVs could act as genomic modifiers of the ASD/DD clinical phenotype in PHTS

- **ASD/DD** (11/113 or 10%)
- **No ASD/DD** (5/228 or 2.6%)
- **Cancer** (2/150 or 1.7%)
Biophysical Clues to Phenotype Dichotomy with Germline *PTEN* Mutations

*Differences in PTEN Biophysical Properties*

- *PTEN* Mutations Associated with Cancer Alone, ASD Alone, Either or Both (caveat: small sample size)

*Allosteric Alterations with Dichotomising *PTEN* Mutations

*Drugging Allosteric Sites

With Feixiong Cheng, Jun Qin, Nancy Wang, Shaun Stauffer

Smith IN et al. *Am J Hum Genet* 2019
Current Targeting Strategy: Downstream of Canonical PTEN Signalling

Precision Healthcare and Risk Stratification for PHTS

Population → Population-level risk → Individual-level risk

Modifiers

RISK

- PTEN
- Real life probability?
- Modifiers
- 0% or 100%

Prioritization & Testing of Known High Penetance Cancer Genes in Setting of Genetic Counseling

Clinical Screening, Preventive Measures, Behavior Modification

Select Multi-Agent Targeted Therapy With >99% Likelihood of Durable Response

Germline Variant Profiling

Multidisciplinary Cancer Consult Including Genomic Medicine and Genetic Counseling

Multiple Generation Pedigree For Cancer Genetic Risk Assessment

Cleveland Clinic

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- Ying Ni, PhD
- Iris N. Smith, PhD
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- Qi Yu, MS
- Rose Kung, MS
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- Ann Tushar
- Dennis Grencewicz

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