Integrating Genetic and Genomic Medicine Processes
For Systematic Identification of Neoplasias

Charis Eng, MD, PhD
Hardis/ACS Professor and Chairperson,
Genomic Medicine Institute
Director, Center for Personalized Genetic Healthcare
Cleveland Clinic

NHGRI Genomic Medicine Colloquium, Dec 5, 2011, 11 AM Session
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)*
MSI Analysis and Mismatch Repair Protein IHC for Lynch Syndrome Screening for All Resected Colorectal Cancers on Main Campus (80% Uptake to Genetics Clinics)

Implementation of MSI Analysis and Mismatch Repair Protein IHC for Lynch Syndrome Screening for All Endometrial Cancers on Main Campus (64% Uptake and Challenges)

Integration of Genetic Counselors in >25 Non-Genetics Specialty Clinics on Main Campus and Regional Practice

Prototype of Patient-Entered Cancer Family History Web-Based Tool
Today: Routine Screening for Heritable Pheochromocytoma and Paragangliomas

Charis Eng, MD, PhD
Cleveland Clinic
Katherine L. Nathanson, MD
University of Pennsylvania
Pheochromocytoma: Prototype Neuroendocrine Tumor

• Pheochromocytoma (Pheo)
• Tumor of Adrenal Medulla
  — Chromaffin Cells (Neural Crest)
  — Can Secrete Catecholamines
    — Hypertension
    — Headache, Palpitations, Pallor, Etc
    — Stroke, Sudden Death
Pheochromocytoma: Neoplasia of Adrenal Medulla
Paraganglioma (Extra-Adrenal Pheo)
10% Rule of Pheochromocytomas

• 10% Genetic
• 10% Bilateral
• 10% Malignant

But: Are these true?

Does it matter?

—Would it affect patient care?
Approximately 20-30% of All Pheo and PGL Presentations Have Genetic Etiology (Germline Mutations)

989 PC
20% Carry Germline Mutations

600 PGL
30% Carry Germline Mutations

Neumann et al. NEJM 2002, JAMA 2004, Cancer Res 2009,
Gene-Specific Neoplasia Risks Guide Management

Mutation Analysis

Mutn Negative

Mutn Positive

STOP

RET  VHL  SDHD  SDHB  SDHC  SDHA  SDHAF2  TMEM127

Gene-Dependent Clinical Tests and Surveillance for Patient

If Mutn +

All First Degree Relatives of Mutation Positive Individuals Offered Gene Testing for Family-Specific Mutation

If Mutn +

All First Degree Relatives of Mutation Positive Individuals Offered Gene Testing for Family-Specific Mutation
Genomic Medicine Institute
Center for Personalized Genetic Healthcare

Have Embedded Genetic Counselor in Main Campus
Endocrinology and Endocrine Surgery Clinics
SDHx Immunohistochemistry Screen?

• SDHB Null by IHC in PC and PGL with Germline SDHB, SDHC or SDHD Mutation
  – SDHB Expressed in Those with MEN 2, VHL and NF 1

• 6/316 PC/PGL SDHA Null by IHC – Germline SDHA Mutations

• Routinely Implemented at PennNET

• BUT: Cleveland Clinic Clinical Pathologists Inconsistent Results
  – My Lab: Blind Reading of SDHB Western Blot from Tumors from those With and Without Germline SDHx Mutations
    – Completely Random “Calls”