Julian A. Martinez-Agosto, MD, Associate Professor in Human Genetics at the University of California Los Angeles (UCLA) School of Medicine, discussed the benefits of multidisciplinary specialty clinics in providing optimal coordinated care for people with genetic conditions.

A gene contains a specific set of instructions which tell a protein how it should function. Sometimes, like in VHL, a variation (mutation) in a gene can cause a disease. For example, a small “mutation” in a cake recipe could result in using a CAP of sugar instead of a CUP of sugar. A properly functioning VHL gene makes a protein that alerts your cells when they need more oxygen. If the VHL gene is “broken” (mutated), cells think they are starving for oxygen and your body responds by producing more and more blood vessels (tumors).

A genetic disease can be inherited from a parent that has already has the mutation in their sperm or eggs and (except for mosaic cases) every other cell in their body. In 20% of people with VHL, the disease is acquired by a mutation that randomly occurs in one sperm or one egg. We call this a de novo case; the child will have VHL but the parents will not. Random gene deletions, like those that cause a de novo VHL mutation, occur more often in sperm than in eggs.

The multi-disciplinary clinic in which Dr. Martiz-Agosto participates helps people who have cancer predispositions. These clinics (and all other VHL Clinical Care Centers) are organized to improve testing, diagnosis, counseling, surveillance, and treatment for all affected family members. Their goal is to offer state-of-the-art coordinated care and also gather information to conduct research to help improve methods for other patients.
**Genetic Issues and Challenges in the Coordination of Care**

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**Hereditary Cancer Predisposition**

- 5-10% of all cancers are hereditary.
- Hereditary cancers are attributable to changes (or mutations) in specific genes that are passed from one blood relative to another.
- Individuals who inherit one of these gene changes will have a higher likelihood of developing cancer within their lifetime.

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**Genetic contribution to cancer risk**

- **UK Report in 1991**
  - Reviewed records of 16,564 cases of childhood cancer diagnosed from 1971-1983 reported to National Registry of Childhood Tumours in Great Britain
  - Genetic condition was listed for ~3% and when incorporating information about family history, total genetic fraction ~4.2%

Genetic contribution to cancer risk

Heritable cancer syndromes are genetic disorders in which germline mutations in one or more genes predispose individual to development of cancers

- Many caused by mutations in tumor suppressor genes, DNA repair genes, oncogenes
- One well-known example is familial breast and ovarian cancer syndrome

Von Hippel-Lindau

- Hemangioblastomas of the brain, spinal cord, and retina
- Renal cysts and clear cell renal cell carcinoma
- Pheochromocytoma
- Pancreatic cysts and neuroendocrine tumors
- Endolymphatic sac tumors
- Epididymal and broad ligament cysts

What are genes?

Global Vision
Normal Male Karyotype (46,XY)

Local View

Chromosomal Microarray (CMA)

Copy Number Variation (CNV)

Gametogenesis

VHL
Single Gene

Mutations

- Acquired mutations
  - Also called somatic mutations
  - Present only in the descendants of the cell that they originally occur in
  - Environmental agents, viruses
  - Usually repaired by DNA repair mechanisms

- Inherited mutations
  - Also called germline mutations
  - Present in every cell in the body

De novo mutations

Gametogenesis

Autosomal dominant inheritance in VHL

- 50% to offspring of affected individuals
- New change in family
- Variable expression
- Incomplete penetrance
Background

- An estimated 5-10% of pediatric patients diagnosed with cancer have an underlying cancer predisposition syndrome
  - Likely an underestimation because these studies were done in small cohorts and without the ability to perform thorough genetic assessments
  - Shorter environmental/carcinogenic exposures
  - More robust DNA repair mechanisms
  - What is the real scope of pediatric cancer predisposition?
**Hereditary Cancer Risk Assessment in Pediatric Oncology Follow-up Clinic**

- Patients from Cincinnati’s Cancer Survivor Clinic
- Family histories taken either in person by a genetic counselor or by completion of screening form
- 109/370 (29%) patients/families were considered eligible for genetics followup or referral


**Germline mutations in predisposition genes in pediatric cancer**

- St Jude’s study of 1,120 patients <20 years of age
- 52.5% leukemia, 21.9% CNS tumors, 25.6% non-CNS solid tumors
- Exome and/or whole genome sequencing and RNA sequencing on a subset
- 8.5% had cancer predisposing gene


**Genetic workup**

- Current practice in pediatric oncology
  - If a patient has striking family history of cancer, the oncologist may send off testing for one gene
  - Cost ~$2,000-$4,000
  - Takes ~4-6 weeks

**Role of sequencing in diagnosing cancer predisposition**

- Next-generation sequencing is a high-throughput DNA sequencing technology where millions or billions of DNA strands can be sequenced in parallel
- UCLA Clinical Genomics Center was the first academic medical center to offer Clinical Exome Sequencing
When to order clinical exome sequencing

- General indications for ordering CES for possible cancer predisposition
  - Targeted gene or panel sequencing has returned negative results
  - Targeted gene or panel sequencing test is more expensive and/or takes longer than CES
  - Clinical testing for suspected gene not available
  - A strong family history of cancer but pattern of cancers not consistent with one specific disorder
  - A specific phenotype associated with genetic heterogeneity

Pediatric Cancer Predisposition Clinic

- Established in August 2012
- Multidisciplinary clinic with medical geneticists, pediatric oncologists, genetic counselors, social workers, nurses
- Clinical mission: to offer state-of-the-art exome sequencing and interpretation for families with a possible genetic cancer predisposition syndrome.
- Research mission: create a biobank and registry to prospectively collect data on these high-risk families and increase our understanding of new genes and their function.

Yield of clinical exome sequencing

- 48.9% of cases have a pathogenic or likely pathogenic variant.
- 40.0% of cases have a variant of uncertain significance.
- 11.1% of cases have no clinically significant finding.

Effective cancer surveillance

- Graph showing the decline in cancer risk over time with annual surveillance.
Imaging

Effective cancer surveillance

- 18 y/o diagnosed with Von Hippel Lindau
  - Inherited cancer predisposition syndrome caused by mutations in VHL gene
  - Risk for tumors
  - Fluid-filled sacs throughout body
- Screening renal ultrasound shows right kidney mass
- Positive for clear cell carcinoma
- Early detection permits effective treated with surgery alone

Symptoms

- Cerebellar hemangioblastomas: headache, vomiting, gait disturbances, or ataxia.
- Spinal hemangioblastomas: pain, sensory and motor loss
- Retinal hemangioblastomas: vision loss.
- Pheochromocytomas: hypertension
- Endolymphatic sac tumors: hearing loss
- Renal cell carcinoma: 70% of individuals
- Pancreatic: asymptomatic

Surveillance

- MRI brain stem and spine at age 12, 15, and 18 years, then every 2 years
- If lesion detected, may be required annually
- Renal imaging annually from age 12 to 20 years
- Abdominal MRI at age 12, 15, and 18 years, with abdominal ultrasound in intervening years
- Abdominal MRI every 2 years from age 20 years
- Annual physical examination with blood pressure measurement from age 2 years
- Annual catecholamine assessment
- Annual ophthalmologic review from age 2 years
- Baseline audiometry at school entry
- Audiometry if symptomatic
What is involved in a Genetics Evaluation?

- Comprehensive approach to medical problem
- Defining Etiology
- Discuss implication of diagnosis
- Discuss implication for family members
- Giving bad news
- Combining diagnostic evaluation and counseling

Issues in VHL

- DNA testing for VHL
  - Confirm diagnosis
  - Test asymptomatic family members
  - Provide accurate genetic counseling
  - Avoid expensive, invasive testing of parents/siblings
- Clinical diagnosis/no DNA confirmation

Genetic Counseling

- Collection and interpretation of family and medical histories to assess the chance of disease occurrence or recurrence
- Education about inheritance, testing, management, prevention, resources and research
- Counseling to promote informed choices and adaptation to the risk or condition

Psychosocial Issues

- Anxiety of surveillance screening
- Family planning:
  - “If I had known I would not have had kids”
  - Preimplantation genetic diagnosis (PGD)/amniocentesis/chorionic villus sampling
- Impact on families
  - Partner support
  - Affinity with affected family members
  - Survivor’s guilt/transmission guilt
- Perceptions about limitations
- Caretaker exhaustion/isolation
Preimplantation Genetic Diagnosis (PGD)

- Single cells only visible up to 8-16 cell stage, before morula compaction
- The 8-12 cell stage is ideal
- Always confirmed by pregnancy testing

Psychosocial Issues

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Preimplantation Genetic Diagnosis (PGD)

- Many uses:
  - Recessive and dominant diseases
  - By multiplex fluorescent PCR with parent-specific polymorphic markers to identify allelic dropout
  - Chromosomal translocations
    - By FISH
  - Sex
    - X-linked diseases
    - By FISH only
  - No methylation testing

Psychosocial Issues

- Burden of genetic disorder
- Grief reaction
- Special needs
- Mobilizing community resources
  - Support groups
  - Internet supports
- Supporting physician and family
- Caring for individuals over lifetime
- Supporting unaffected siblings/family members
**Conclusions**

- VHL is a multi-organ genetic condition with specific tumor predisposition
- Surveillance has an impact on early detection and clinical outcomes
- Genetic testing is essential in facilitating family testing and planning
- Rare genetic conditions carry specific logistic and psychosocial barriers that require expert multi-disciplinary teams for optimal care

**UCLA PCPD Clinic**

- Multidisciplinary Clinic which provides diagnosis, genetic testing, genetic counseling, surveillance and social work
- Work with UCLA Neurology, Neurosurgery, Neuro-oncology, and the UCLA Prenatal Diagnosis Center
- To make an appointment: 310 206-6581
- To fax a referral: 310 206-8616