From Recognition to Referral: Pediatric Cancer Genetic Syndromes in Practice

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Objectives

1) Recognize red flags for hereditary cancer genetic syndromes in the pediatric patient.

2) Develop tools to discuss a cancer genetics referral with families of pediatric patients.
Impacts on Pediatric Cancer Genetics

- Increasing recognition that genetic information can be helpful versus overwhelming to families
- New genes/syndromes being described
- Our understanding of known syndromes is expanding
- New genetic testing technologies are being developed
- Pediatric cancer screening guidelines developed
Clinical Cancer Research is proud to present a special collection of articles from the AACR Childhood Cancer Predisposition Workshop. The initial series of manuscripts was generated by an international cohort of leading pediatric cancer experts in order to provide recommendations for screening surveillance of childhood cancer predisposition syndromes in an effort to facilitate early detection and treatment of pediatric cancers. We hope you enjoy this series of freely available articles and continue to check back for additional relevant content and updated recommendations.

- The future of surveillance in the context of cancer predisposition: through the murky looking glass.

- Pediatric cancer predisposition and surveillance: an overview, and a tribute to Alfred G. Knudson Jr.
  Brodeur GM...Malkin D. Clinical Cancer Research June 2017.

- Pediatric cancer predisposition imaging: focus on whole-body MRI.

- Recommendations for surveillance for children with leukemia-predisposing conditions.

- Recommendations for childhood cancer screening and surveillance in DNA repair disorders

- Clinical management and tumor surveillance recommendations of inherited mismatch repair deficiency in childhood.
  Tabori U...Brugères L. Clinical Cancer Research June 2017

https://clincancerres.aacrjournals.org/pediatricseries
Genomic Studies in Pediatric Oncology

- Currently estimated that 10% of children with cancer will have an inherited cancer predisposition syndrome
  - Studies from BCM, St. Jude’s and University of Michigan
- Both well established cancer susceptibility conditions and previously unrecognized
- In the future, genetic testing may be offered to all children diagnosed with cancer

<table>
<thead>
<tr>
<th>Gene Mutation</th>
<th>Tumor Diagnosis and Relevant Medical History</th>
<th>Family History at Study Entry</th>
<th>Inherited From Parent</th>
<th>Tumor LOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous Mutation in Autosomal Dominant Disorder Associated With the Specific Childhood Cancer (n = 8)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WT1 (mosaic) c.865_867delinsAA, p.Y289Fs</td>
<td>Wilms tumor</td>
<td>None</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>DICER1 c.2062C&gt;T, p.R688X</td>
<td>Pulmonary pleuroblastoma</td>
<td>Multinodular thyroid disease</td>
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<td>ND</td>
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<tr>
<td>VHL c.499C&gt;T, p.R167W</td>
<td>Pheochromocytoma</td>
<td>None</td>
<td>Yes</td>
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<tr>
<td>VHL c.499C&gt;T, p.R167W</td>
<td>Pheochromocytoma</td>
<td>Von-Hippel-Lindau</td>
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</tr>
<tr>
<td>MSH2 c.1697delA, p.K566fs</td>
<td>Glioblastoma</td>
<td>Lynch syndrome tumors</td>
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<td>ND</td>
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<tr>
<td>TP53 c.743G&gt;A, p.R248Q</td>
<td>Neuroblastoma</td>
<td>Li-Fraumeni syndrome</td>
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<td>Yes</td>
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<tr>
<td>TP53 (likely pathogenic) c.470T&gt;C, p.V157A</td>
<td>Adrenocortical carcinoma</td>
<td>Adult cancers</td>
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<td>Yes</td>
</tr>
<tr>
<td>KRAS (likely pathogenic) c.194G&gt;T, p.S65I</td>
<td>Plexiform neurofibroma; multiple anomalies</td>
<td>None</td>
<td>No</td>
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<tr>
<td>Heterozygous Mutation in Autosomal Dominant Disorder Not Previously Associated With the Specific Childhood Cancer (n = 5)</td>
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<tr>
<td>SMARCA4 c.1156_1157del, p.E386fs</td>
<td>Neuroblastoma</td>
<td>None</td>
<td>ND</td>
<td>Yes</td>
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<tr>
<td>BRCA1 c.68_69delAG, p.E23fs</td>
<td>Neuroblastoma</td>
<td>Breast cancer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>BRCA1 c.697_698del, p.V233fs</td>
<td>Anaplastic medulloblastoma</td>
<td>Breast cancer</td>
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<td>No</td>
</tr>
<tr>
<td>BRCA2 c.1278delE, p.D427fs</td>
<td>Ewing sarcoma; short stature, anemia</td>
<td>Breast and ovarian cancer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CHEK2 c.1100delC, p.T367fs</td>
<td>Wilms tumor</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
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<tbody>
<tr>
<td>Autosomal Recessive Diagnosis Not Previously Associated With the Specific Childhood Cancer (n = 1)</td>
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<tr>
<td>TP2 (homozygous) c.817delE, p.A273fs*</td>
<td>Hepatocellular cancer, severe liver disease</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Considerations for Referral

- Family history of cancer especially with early ages of onset
- Diagnosis of cancer along with developmental delay or congenital anomalies
- Physical findings suggestive of genetic condition (e.g. café au lait macules, lip pigmentation, CHRPE, etc)
- Tumors associated with high likelihood of cancer predisposition
- Multiple primary tumors
- Specific subtypes of cancers (hypodiploid ALL, desmoplastic medulloblastoma)
- Polyposis conditions
- Treatment toxicity
Family History

- Three generation pedigree
- Important to ask about both adult and childhood cancers
- Early age of diagnosis (cancer under 50yrs)
- Multiple affected family members
- Bilateral disease or multiple primaries
- Consider the most informative relative to initiate testing
Case 1

- Breast cancer dx. 30yrs A/W 27yrs
- Osteosarcoma dx. 16yrs
- Astrocytoma dx. 6yrs A/W 8yrs
Li-Fraumeni Syndrome

- Caused by pathogenic variants in the *TP53* gene
- Autosomal dominant inheritance
  - 50% risk to offspring
- High-risk of diverse spectrum of both childhood and adult-onset tumors
  - Sarcomas
  - Pre-menopausal breast cancer
  - Brain tumors
  - Adrenocortical carcinoma
  - Choroid Plexus Carcinoma
  - Leukemia (Hypodiploid)
- Lifetime risk for cancer ≥70% for men and ≥90% for women
- Many individuals develop two or more malignancies over their lifetime
- Lifelong surveillance beginning in infancy
Case 2

Breast cancer
dx. 30yrs
A/W
dx. 16yrs
Osteosarcoma
A/W
27yrs
A/W
6yrs
A/W
8yrs
Predictive Genetic Testing for Adult-Onset Conditions in Children

• Common adult cancer predisposition syndromes include Hereditary Breast and Ovarian Cancer (BRCA1/BRCA2) and Lynch syndrome

• Screening typically does not begin until the early to mid-20s or 10 years before the earliest diagnosis in the family

• Standard of care is to NOT test minors until adulthood

• Families can be seen for genetic counseling to discuss recommendations
  – Discussion prior to referral to set expectations is important
Limitations of Family History

- *De novo* variants
- Mosaicism in parents
- Low penetrance
- Recessive inheritance
- Small/young families
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Features Suggestive of a Syndrome

- Abnormal pigmentation (hyperpigmentation, hypopigmentation, freckling in uncommon locations)
- Differences in hair and nails
- Macrocephaly/microcephaly
- Short stature/Overgrowth
- Hemihypertrophy
- Radial ray defects

1. www.merkmanuals.com
Case 3

• A 10 year old patient presents to the office based on recent episodes of blood in his stool.
• The patient has no significant past medical history.
• Upon exam, you notice mucocutaneous pigmentation.
• There is no family history of significant health concerns or others with the pigmentation.

Oral pigmentation

www.merkmanuals.com
Peutz-Jeghers Syndrome

- Caused by pathogenic variants in the STK11 gene
- Autosomal dominant inheritance
- Hamartomatous polyps most often found in the small intestine, but they can also occur in the stomach and large bowel
- Polyps can lead to intussusception
- Increased risk for cancers including colorectal, gastric, pancreatic, breast, and ovarian cancers
- Upper gastrointestinal endoscopy, video capsule endoscopy, and colonoscopy begin at 8 years of age or sooner if symptomatic
Considerations for Referral

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## Examples of High-Risk Tumor Types

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Condition</th>
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<tr>
<td>Retinoblastoma</td>
<td>Hereditary Retinoblastoma</td>
</tr>
<tr>
<td>Adrenocortical or choroid plexus carcinoma, hypodiploid acute lymphocytic leukemia</td>
<td>Li-Fraumeni syndrome</td>
</tr>
<tr>
<td>Atypical teratoid (ATRT)/rhabdoid tumor</td>
<td>Rhabdoid Tumor Predisposition syndrome</td>
</tr>
<tr>
<td>Pleuropulmonary blastoma</td>
<td>DICER1 syndrome</td>
</tr>
<tr>
<td>Optic glioma, malignant peripheral nerve sheath tumor</td>
<td>Neurofibromatosis Type 1</td>
</tr>
<tr>
<td>Acoustic of vestibular schwannomas</td>
<td>Neurofibromatosis Type 2</td>
</tr>
<tr>
<td>Medullary thyroid cancer</td>
<td>Multiple Endocrine Neoplasia Type II</td>
</tr>
<tr>
<td>Subependymal giant cell tumor (SEGA)</td>
<td>Tuberous Sclerosis</td>
</tr>
<tr>
<td>Retinal or cerebellar hemangioblastomas, endolyphatic sac tumor (ELSTs)</td>
<td>Von Hippel-Lindau syndrome</td>
</tr>
</tbody>
</table>
Retinoblastoma

- 1 in 20,000 children affected
- Unilateral or bilateral tumors develop in early childhood
- Occurs in heritable and nonheritable forms
- Identifying at-risk infants substantially reduces morbidity
- All bilateral cases are considered constitutional
- 13-15% of unilateral cases are constitutional
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Timepoints for Referral and Re-referral

- Diagnosis
- Adolescents
- Family Planning
Introducing a Genetics Referral

Important to have a discussion with the family prior to making the referral
Benefits of a Genetic Diagnosis

• May answer the question, “Why?”
• Can provide guidance for screening/surveillance
• Identify other family members at risk/not at risk
• Family planning
• Identify potential treatment options (rare)
Considerations When Introducing a Referral

- Family may be overwhelmed with current diagnosis/treatment
- Beliefs and attitudes about genetics
- Affects the family unit
- Issues of guilt/blame
- Raise concerns for the future
- Concerns about genetic testing and privacy
Genetics Visit

• Clinic may request medical records and previous genetic testing in advance.
• Gather family history
• Physical examination
• Detailed medical history
• Discussion of genetic testing options if appropriate
• Genetic testing may occur at the time of the visit or following visit
• All genetic testing is optional
Genetic Testing

- Most often a blood draw (in some cases a skin biopsy may be needed).
  - Saliva and buccal kits are becoming more common
- Standard genetic testing: 3-6 weeks
- Familial genetic testing: 2-3 weeks
- Exome sequencing (non-critical): approx 3 months
Insurance Coverage

• Visits for genetics evaluations are offered covered similar to a specialist visit (geneticist) if in-network.

• Genetic testing may require a prior-authorization/pre-determination process.
  • Letter of medical necessity
  • Peer to peer
  • Appeal
Genetic Information Nondiscrimination Act (GINA) of 2008

- Federal law
- Protects people from genetic discrimination in **health insurance** and **employment**.
- What does GINA not cover?
  - Insurance:
    - U.S. military who receive their care through Tricare.
    - Veterans who receive care through the veterans administration
    - The Indian Health Service
    - Federal employees enrolled in Federal Employee Health Benefits Plan
  - Employment:
    - U.S. military and federal employees
    - Employers with fewer than 15 employees

www.ginahelp.org
Cancer Genetics and Genomics Program

- **Pediatric Cancer Genetics Clinic**
  - Dr. Sharon Plon
  - Sarah Scollon, MS, CGC
  - Lauren Desrosiers, MS, CGC

- **Childhood Cancer Prevention and Screening Clinic**
  - Dr. Surya Rednam
  - Stephanie Gruner, APRN, MSN, CPNP

- **Precision Oncology Consultation Service**
  - Dr. Will Parsons
Summary

• Pediatric cancer genetics continues to be a growing field.
• Growing knowledge is leading to increased identification of patients with cancer predisposition syndromes.
• Identification of children at-risk for cancer predisposition can result in important changes to medical management.
• A cancer genetics evaluation can provide family with the information they need to make an informed decision about pursuing genetic testing.
Acknowledgements

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• The cancer genetics team at Texas Children’s Hospital
• Our patients and families
Questions and Comments

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