Life before sarcoma:
Cancer predisposition in children, adolescents, and young adults

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Dana-Farber Cancer Institute
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Cancer predisposition in children and AYA: outline

I. Value of identifying a hereditary cancer risk
II. Evolving clinical practice of cancer predisposition care
   • Germline testing
   • Risk assessment and emerging phenotypes
   • Cancer surveillance
III. Novel approaches to cancer risk communication for AYAs
Identifying a germline cancer predisposition has significant implications

SOMATIC MUTATIONS ONLY

GERMLINE CANCER PREDISPOSITION
Identifying a germline cancer predisposition has significant implications

• May be at risk of additional tumors/cancers
• May be associated developmental anomalies
• May impact treatment decisions
• Risks to future generations
• Risks to other family members
Pediatric Cancer Genetic Risk Program

PCGRP Patients Seen

- Encounters
- Visits
- Unique patients

**PCGRP Team**
- Oncologists
- Nurse Practitioner
- Genetic Counselors
- Psychosocial providers
- Research coordinators

**FY14**
- Encounters: 75
- Visits: 75
- Unique patients: 68
Examples of cancer predisposition syndromes that include a risk of sarcomas

<table>
<thead>
<tr>
<th>GENE</th>
<th>SYNDROME</th>
<th>CANCER RISKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>Li-Fraumeni syndrome</td>
<td><strong>Soft tissue and bone sarcomas</strong>, breast cancer, brain tumors, ACCs, leukemias</td>
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<tr>
<td>DICER1</td>
<td>DICER1 syndrome</td>
<td>Pleuropulmonary blastoma, ovarian sex cord stromal tumors, thyroid cancer, <strong>cervix ERMS</strong>, <strong>ovarian sarcoma</strong>, cystic nephroma, <strong>renal sarcoma</strong>, <strong>CNS sarcoma</strong>, and others</td>
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<tr>
<td>RB1</td>
<td>Hereditary retinoblastoma</td>
<td>Retinoblastoma, pineoblastomas, <strong>bone and soft tissue sarcomas</strong>, skin cancers</td>
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<tr>
<td>SDHx, MAX, TMEM127</td>
<td>Paraganglioma-pheochromocytoma syndrome</td>
<td>Paragangliomas, pheochromocytomas, <strong>GIST</strong></td>
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<tr>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>CMMRD (Congenital mismatch repair deficiency)</td>
<td>Brain tumors, gastrointestinal and hematologic malignancies, <strong>bone and soft tissue sarcomas</strong></td>
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<tr>
<td>NF1</td>
<td>Neurofibromatosis I</td>
<td>JMML, <strong>rhabdomyosarcoma</strong>, MPNST, pilocytic astrocytoma</td>
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<tr>
<td>HRAS</td>
<td>Costello syndrome</td>
<td><strong>ERMS</strong>, rhabdomyosarcoma, bladder cancer</td>
</tr>
<tr>
<td>11p15 abn, CDKN1C</td>
<td>Beckwith-Wiedemann syndrome</td>
<td>Wilms tumor, hepatoblastoma, <strong>rhabdomyosarcoma</strong></td>
</tr>
</tbody>
</table>
When to suspect an underlying cancer predisposition

• Young age of onset
• Multiple primary cancers
• Strong family history of cancer
• Specific cancer that is a known feature of a hereditary syndrome
• Known genetic syndromes/mutations in family
• Associated developmental anomalies

• Tumor testing suggests possible germline mutation
Cancer Predisposition Care

At Each Step:

• Evolving clinical practice
• Challenges/areas for further research and collaboration
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Germline testing: from single gene to multi-gene panels

- Evolving clinical practice
  - FROM: syndrome recognition and iterative gene-by-gene testing for those meeting clinical criteria
  - TO: multiplex testing

- Concurrent need for genetic counseling shift from greater pre-test to greater post-test counseling
Germline testing: from single gene to multi-gene panels

PCGRP Pediatric Patients

Breast Cancer Patients
(n=5026) from Kurian AW et al.

Kurian AW et al. JAMA Onc 2018; 4:1066-1072
Li-Fraumeni syndrome (LFS): Example of a classic cancer predisposition syndrome:

- 1969: Li and Fraumeni examine medical records and death certificates of over 600 children with rhabdomyosarcoma
- Described families with a pair of children with soft tissue sarcomas, with other family members with cancers
- Earlier age of onset compared with non-hereditary tumors
- Core LFS tumors: **soft tissue and bone sarcomas**, brain tumors, adrenocortical carcinomas, leukemias, premenopausal breast cancer

Li-Fraumeni syndrome (LFS): Example of a classic cancer predisposition syndrome

- Associated with germline mutations in the tumor suppressor gene \( TP53 \)
Multigene testing allows for non-biased testing in families: LFS pedigree examples

“Classic” LFS with germline TP53 mutation

LFS with variable penetrance

LFS without TP53 mutation identified

Risk assessment and emerging phenotypes

Widespread use of tumor genetic testing may lead to an emerging understanding of phenotypes that are part of cancer syndromes.
DICER1 syndrome: example of an emerging syndrome

- Associated with germline mutations in DICER1, encoding an RNase III endoribonuclease.

Frio TR et al. JAMA 2011;305:68-77
DICER1-associated CNS sarcoma: somatic testing informing germline syndromes

- Histologically indistinguishable from pleuropulmonary blastomas
- Biallelic DICER1 mutations in tumors with characteristic inactivating and Rnase IIIb hotspot alterations
- Similar molecular genetic profiles to other DICER1 tumors
- Additional series described by Koelsche and colleagues (Acta Neuropath 2018; 136: 327-337)
- Seen in sporadic and hereditary cases
- Now recognized syndrome component

Kamihara et al. submitted
Screening and prevention

How do we best screen for cancers in the setting of a cancer predisposition syndrome?
Cancer Screening and Early Detection

- For most pediatric cancer syndromes, we continue to rely on consensus recommendations.
- 2016 AACR Workshop: Surveillance recommendations for pediatric cancer predisposition syndromes.

Developing a screening program:

- Age at highest risk, range
- Impact of early detection
- Risk of screening modality

Impact of early detection:
- Low/unknown
- High

Risk of screening modality:
- High
- Low

Impact of early detection:
- Common
- Rare

Risk of screening modality:
- Common
- Rare

Example: LFS surveillance recommendations

Birth to 18 years:
- Physical exams & prompt attention to symptoms
- US of abdomen/pelvis every 3-4 months
- Annual whole body MRI/brain MRI

Many remaining issues:
- Optimal timing and modalities
- Risks: Anesthesia, false positives
- Need better tests
- Psychosocial concerns
- Need prospective trials

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Adolescents and Young Adults (AYAs)

- WHO definition: Ages 12-24 years
- Significant social/developmental transitions
- Increasing desire for greater independence
- Transitions from pediatric to adult care
- Vulnerable population with traditional gaps of care
Focus group of AYAs with LFS to understand communication needs around cancer risk (n=17)

DEMOGRAPHICS

<table>
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<th>n (%)</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
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<tr>
<td>12-17</td>
<td>8 (47%)</td>
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<tr>
<td>18-24</td>
<td>9 (53%)</td>
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<tr>
<td><strong>Gender</strong></td>
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<td>M</td>
<td>7 (41%)</td>
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<td>F</td>
<td>10 (59%)</td>
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<td>Other</td>
<td>0 (0%)</td>
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<td><strong>Cancer in past</strong></td>
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<tr>
<td>Yes</td>
<td>8 (47%)</td>
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<td>No</td>
<td>9 (53%)</td>
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<td><strong>Age at learning of cancer risk</strong></td>
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<td>&lt;8</td>
<td>6 (35%)</td>
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<td>9-11</td>
<td>1 (6%)</td>
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<td>12-14</td>
<td>4 (24%)</td>
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<td>15-17</td>
<td>3 (18%)</td>
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<td>18-20</td>
<td>2 (12%)</td>
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<tr>
<td>&gt;20</td>
<td>1 (6%)</td>
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Focus group
AYA and parent surveys
AYA need for ongoing information about cancer risk
AYA survey (n=17)

KEY:
- Blue: Was discussed
- Orange: Should be discussed
- Green: Desire for more discussion

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<thead>
<tr>
<th></th>
<th>Diagnosis of cancer risk syndrome</th>
<th>Types of cancers at risk for in future</th>
<th>Likelihood of developing cancers</th>
<th>Ways to try to find cancers early</th>
<th>Risk to children in future</th>
<th>Emotional impact of diagnosis</th>
<th>Impact of diagnosis on current relationships</th>
<th>Impact of diagnosis on future relationships</th>
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Perspective on cancer risk evolves, and AYA express a desire for connection with others

How can we extend cancer genetic risk communication to AYAs?
How to help deliver complex information re: cancer risk to AYAs?

AYA-RISE (Risk Information and Screening Education)

HIPAA-compliant, clinical-grade:

• **CHATBOT**
  - For AYA with known cancer syndrome
  - Chatbot designed to present information about cancer genetic risk and screening
  - Standardized information initially, then further information can be explored depending on preference

• **PATIENT PORTAL**
  - Repository for personalized cancer risk and screening information over time

[Image of AYA-RISE website]

www.cleargenetics.com
Future Directions

• Broadening our understanding of genotype/phenotype (and the role of modifiers) will identify new at-risk populations and allow for more personalized risk prediction.

• Improving screening strategies including novel detection methodologies will allow for better early detection.

• Address ongoing communication needs of AYA and others with cancer genetic risk.

• Need for innovative strategies for cancer prevention.
Thank you

PCGRP Clinical and Research Teams and AYA-RISE Team

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