Genes and Cancer

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Children's National Health System

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Children's National

Disclosure

No Relevant Financial Relationships with Commercial Interest

Objectives

- 1) Overview of the most common cancer predisposition syndromes
- 2) Criteria that can be used to identify at risk children so they can be referred to the cancer genetics clinic for testing
- 3) an overview of the CNHS Cancer Genetics clinic, and how a shared care approach could be used to improve screening compliance in at risk patients

Cancer is not a heritable disease

BUT Cancer Predisposition Is Heritable

Pediatric Cancer

- More than 12,000 children and teens are diagnosed with cancer each year in the U.S.A.
- **At least 10% of these kids likely have a cancer predisposition syndrome.**

Inherited Cancer Predisposition Syndrome

- A mutation in a cancer gene that increases one's risk of cancer above the population risk.
- The lifetime risk of cancer can be up to 100% depending on the gene involved.
- **Affected children can inherit a gene mutation from a parent, or they can be the first in the family.**

Cancer Promoting Genes

- Most cancers likely start with a single mutation
- All cancer-promoting genes have a role in normal development but have the potential to mutate to a form that is pathogenic
- Three major classes of cancer-promoting genes:
  - Oncogenes
  - DNA repair genes
  - Tumor suppressor genes

Oncogenes

- **Proto-oncogenes:** normal genes that determine whether or not it is appropriate for a cell to enter the cell cycle
  - Examples: *WNT, RAS, MYC*
- **Oncogenes:** A mutated form of a proto-oncogene that turns the cell into a cancer cell. Mutations are **activating mutations** that will:
  - Affect a protein sequence
  - Activate overexpression OR
  - Create a new fusion protein

  Oncogenes act in a **Dominant** manner

  Oncogenes have **gain of function** that causes cells to abnormally progress through cell division

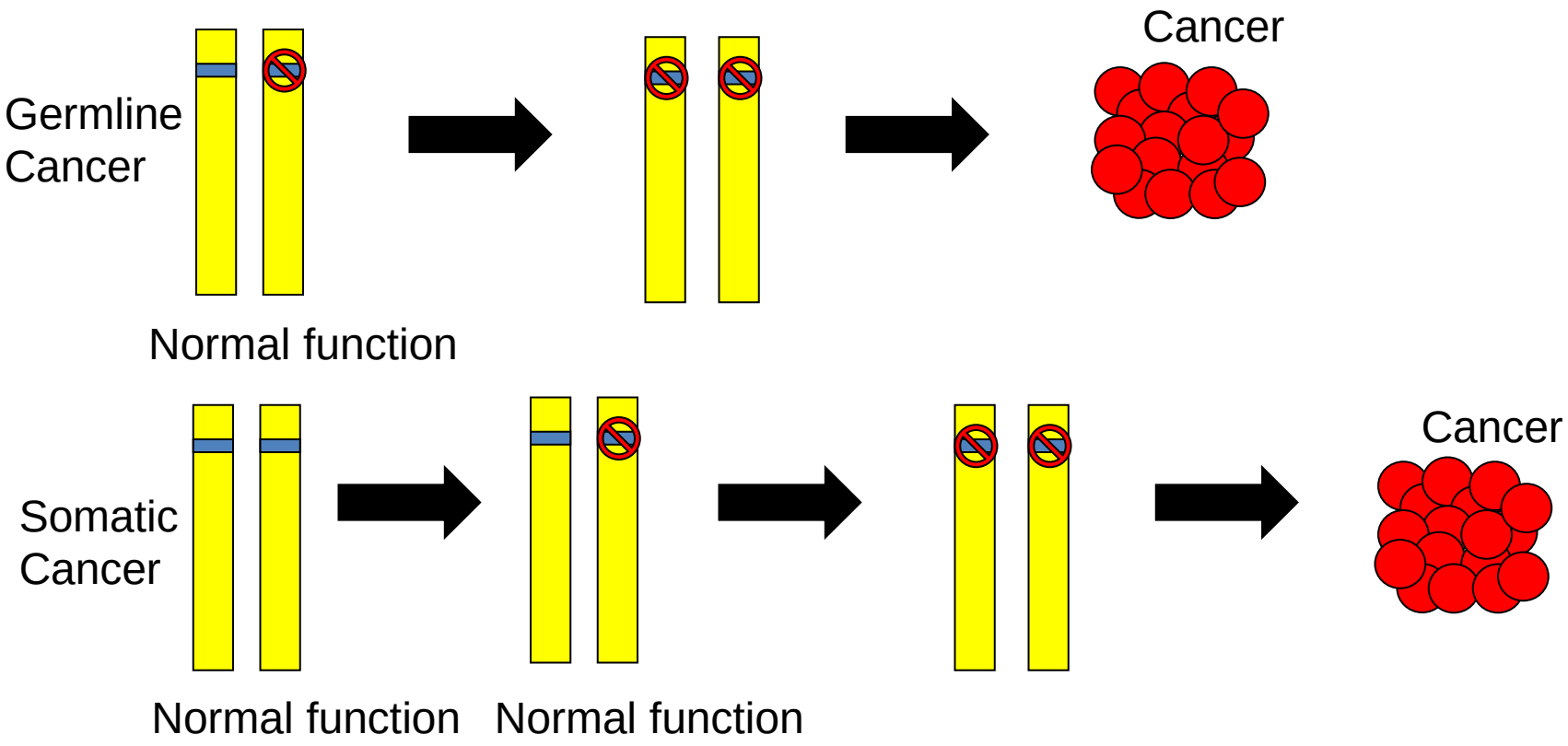
DNA Repair Genes

- DNA repair genes identify and correct damage to DNA that occur either during normal metabolic activities, or external factors (i.e. radiation).
- Examples: Genes with roles in mismatch repair (*MSH2, MLH1, PMS2, MSH6*), genes that sense DNA damage and regulate DNA repair pathways and homologous recombination (i.e. *BRCA1*)
- Loss of DNA repair capacity leads to accumulation of mutations resulting in accelerated cell division or migration as is seen in cancer cells

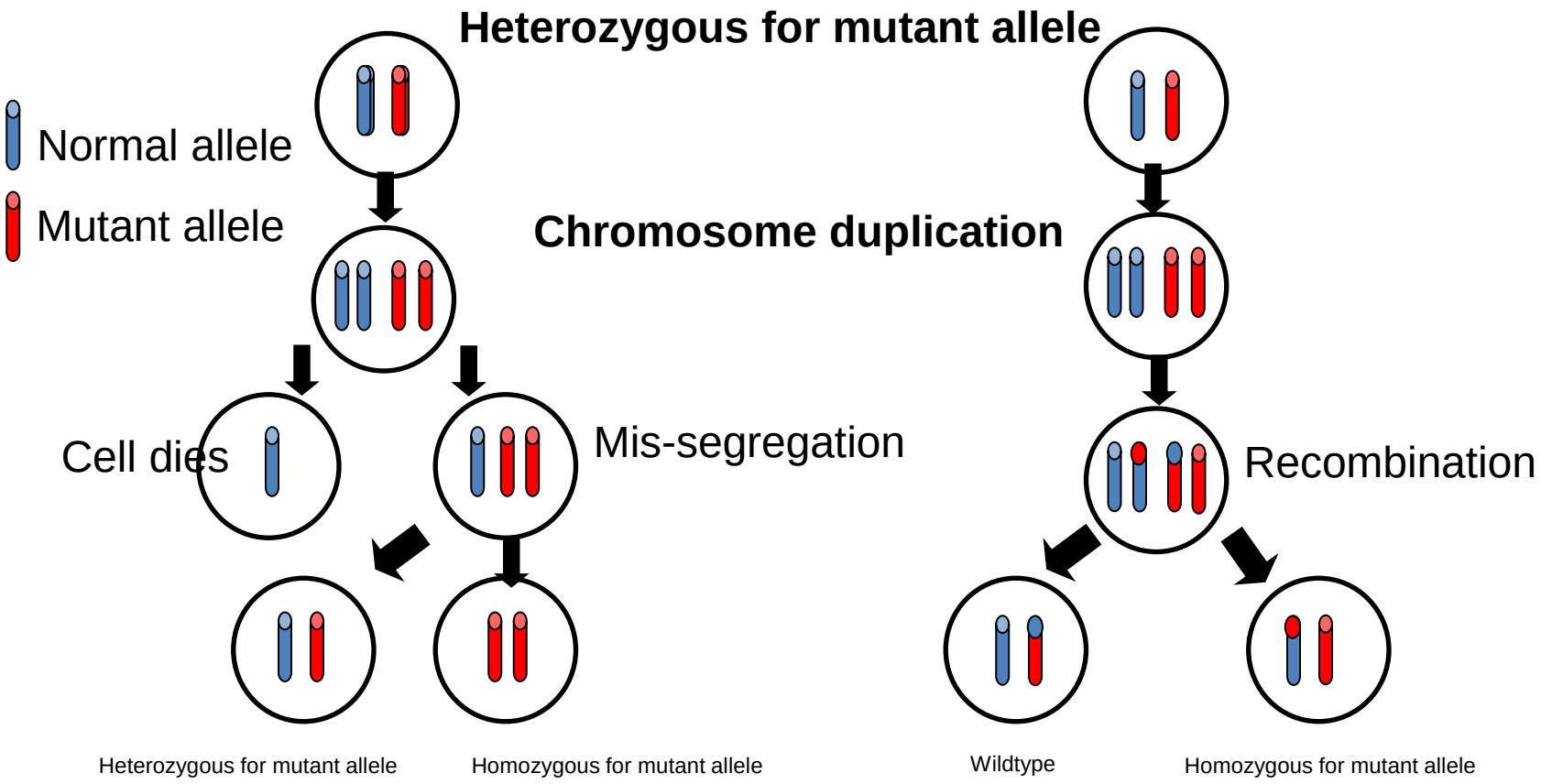
Tumor Suppressor Gene

- Genes that prevent cells from moving through the cell cycle because it is not the developmentally appropriate, or because DNA damage has been detected and it is unsafe to proceed (triggers apoptosis)
  - Examples *TP53, RB, NF1*
- Act in a **Recessive** manner
- **Loss of function** causes cells to continue through cell division

“Two-hit Hypothesis”



LOH


Heterozygous for mutant allele
Normal allele
Mutant allele
Chromosome duplication
Cell dies
Mis-segregation
Recombination
Heterozygous for mutant allele
Homozygous for mutant allele
Wildtype
Homozygous for mutant allele

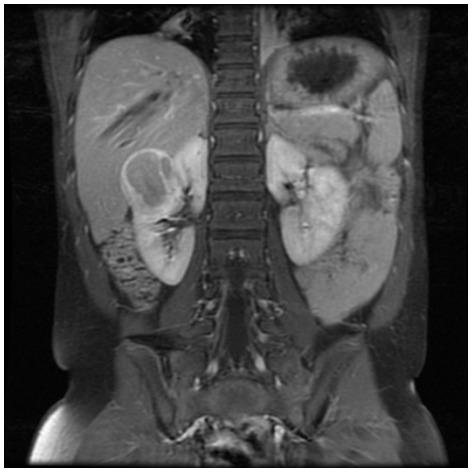
Case report #1

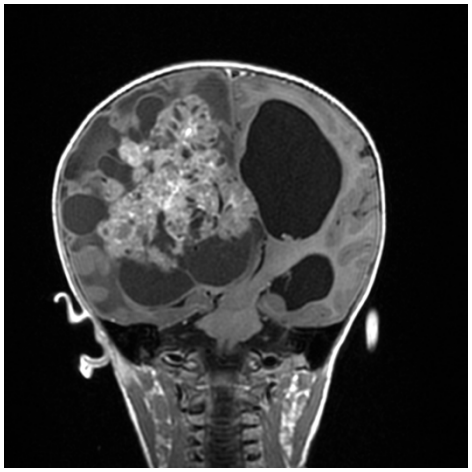
Li Fraumeni Syndrome

- *TP53* gene mutation
- Autosomal Dominant inheritance with high cancer penetrance
- 85-90% inherited, 10-15% De Novo mutations
- 50% chance of cancer by 30 yrs of age, 90% chance by 60 yrs of age

Li Fraumeni Syndrome

- Associated with Multiple Tumors
  - Leukemia
  - **Adrenocortical Carcinoma**
  - Brain tumors (**Choroid plexus carcinoma,** astrocytoma, medulloblastoma, etc.)
  - **Breast cancer**
  - Colorectal Cancer
  - Kidney Cancer
  - Lung Cancer
  - Melanoma
  - Neuroblastoma
  - **Sarcoma**





- Non-Cancer association
  - Colon Polyps

Toronto Screening Protocol

- Children
  - Complete physical exam every 3-4 months
  - US of the abdomen every 3-4 months
    - Labs if needed: Testosterone, DHEAS, androstenedione
  - Annual brain MRI
  - Annual WBMRI
  - Leukemia labs (CBC, LDH) with any symptoms
- Adults
  - Complete physical exam every 6 months
  - Breast awareness (18+)
    - Clinical breast exam twice a year (20+)
    - Annual breast MRI (20-75)
    - Consider bilateral mastectomy (after childbearing years)
  - Annual Brain MRI
  - Annual WBMRI
  - Annual US abdomen/pelvis
  - Upper endoscopy and colonoscopy every 2-5 years (20+)
  - Annual dermatologic examination

Kratz et al, *CCR*, 2017

Tumor Screening-Li Fraumeni Toronto Protocol

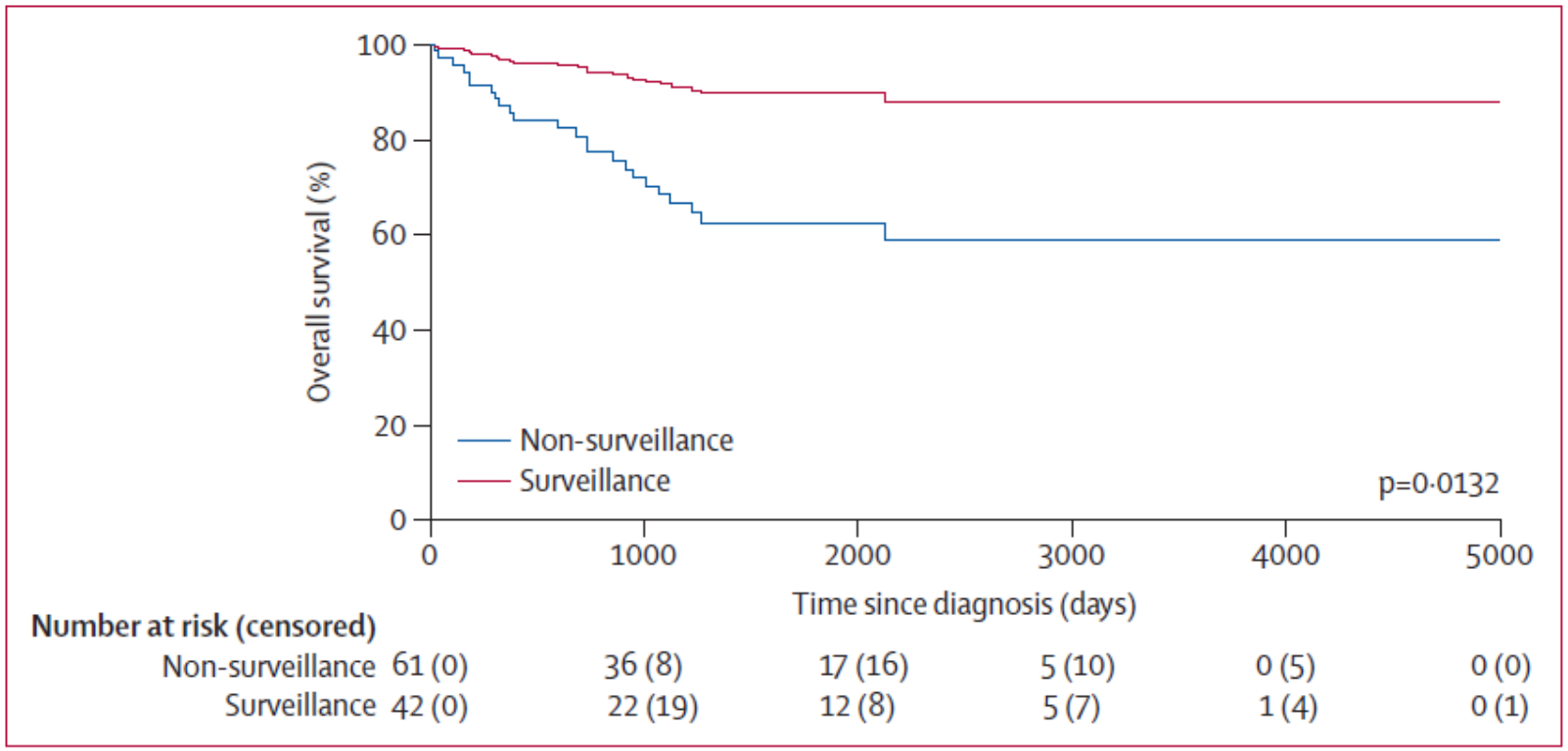


Figure 1: **Overall survival in the surveillance and non-surveillance groups**
Number at risk refers to the number of tumours, not individuals.

Villani et al, Lancet, 2016

Case Report #2

Beckwith-Wiedemann Syndrome

- Epigenetic and genomic alterations at 11p15 OR gene mutations in *CDKN1C*
- Sporadic (90%+)
- Autosomal Dominant (*CDKN1C)*
  - Only 5% of all BWS, but 40% in familial cases
- Overall cancer risk depends on the molecular subgroup (from 2.6%-28.1%)
- Risk for cancer decreases significantly after 7 years of age

Beckwith-Wiedemann

Diagnosis (>=4 points or >=2 points + molecular confirmation)

- Cardinal Features (2pts/feature)
  - Macroglossia
  - Exomphalos
  - Lateralized overgrowth
  - Multifocal and/or bilateral Wilms tumor or nephroblastomatosis
  - Hyperinsulinism
  - Pathology findings: adernal cortex cytomegaly, placental mesenchymal dysplasia or pancreatic adenomatosis
- Suggestive features (1pt/feature)
  - Birthweight >2 SDS above mean
  - Facial naevus simplex
  - Polyhydramnios and/or placentomegaly
  - Ear creases and/or pits
  - Transient hypoglycemia (lasting <1 week)
  - Typical BWS tumors
  - Nephromegaly and/or hepatomegaly
  - Umbilical hernia and/or diastasis recti

Beckwith-Wiedemann

- Tumor Association
  - Wilms Tumor
  - Hepatoblastoma
  - Neuroblastoma (*CDKN1C)*
  - Rhabdomyosarcoma
  - Thyroid Cancer
  - Melanoma
  - Pancreatoblastoma
  - Adrenocortical carcinoma
  - Phaeochromocytoma
  - Leukemia (ALL)
  - Hemangiotheloma

BWS Screening Protocol

- Based on molecular subgroup
- Complete abdominal ultrasound every 3 months from diagnosis until 7 years of age
- +/- Serum AFP from diagnosis until 4 years of age

Brioude et al, *Nature Reviews,* 2018

Case Report #3

Familial Adenomatous Polyposis

- *APC* gene mutation
- Autosomal Dominant
- Nearly 100% chance of developing cancer
- Average age for colon cancer is 39 for classic FAP

Familial Adenomatous Polyposis

- Tumor Association
  - Colorectal Cancer
  - Colorectal Adenomatous Polyposis
  - Thyroid cancer (often papillary)
  - Hepatoblastoma
  - Medulloblastoma
  - Pancreatic cancer
  - Small bowel cancer
  - Stomach cancer
  - Desmoid tumors
  - Epidermal cyst
  - Fundic gland polyp (stomach)
  - Fibromas
  - Osteoma (often in the jaw or skull)
  - Small bowel adenoma

Familial Adenomatous Polyposis

- Non-Cancer Associations
  - Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
  - Extranumerary teeth/dental anomalies

FAP Screening Protocol

- Birth- 4 years of age: Serum AFP every 4-6 months
- Birth-7 years of age: Complete abdominal ultrasound every 4-6 months
- 10-15 years of age until surgery: Colonoscopy q1 year (or more frequent if needed)
- 15-19 years of age: Thyroid Ultrasound q1 yr
- Abdominopelvic MRI if family hx of desmoids

Case Report #4

Constitutional (Biallelic) Mismatch Repair Syndrome

- Biallelic *MLH1, MSH2, MSH6, PMS2, EPCAM*
- Autosomal Recessive
- Monoallelic (Autosomal dominant) mutations in the same genes = Lynch Syndrome
- High incidence of early onset tumors

Constitutional (Biallelic) Mismatch Repair Syndrome

- Tumor Association:
  - Brain tumors (**anaplastic astrocytoma, glioblastoma,** medulloblastoma, primitive neuroectodermal tumors)
  - Leukemia or Lymphoma (often T-cell)
  - Neuroblastoma
  - Osteosarcoma
  - Rhabdomyosarcoma
  - Wilms Tumor

Constitutional (Biallelic) Mismatch Repair Syndrome

- Non-Cancer Associations
  - Café au lait spots and other hyper/hypopigmented skin lesions
  - Mild immunodeficiency

Lynch Syndrome

- Lynch syndrome associated tumors:
  - Colorectal cancer (colorectal adenomatous polyps)
  - Small bowel cancer (small bowel adenomatous polyps)
  - Urinary tract cancer (ureter, renal pelvis, bladder)
  - Stomach cancer
  - Ovarian cancer
  - Pilomatricoma

BMMRD Screening Protocol

- Birth: Brain MRI q6 months
- 1 years of age: Abdominal US and CBC q6mo
- 6 years of age: colonoscopy q1 year, then q6 months once polyps are detected; WBMRI q1 year
- 8 years of age: Upper endoscopy colonoscopy q1 year
- 20 years of age: Gyn exam, transvaginal US, UA q1 year

Case Report #5

Neurofibromatosis Type 1

- *NF1* gene mutation
- Autosomal Dominant
  - 50% sporadic, 50% familial
- Diagnostic Criteria
  - 6 or more café-au-lait spots. These spots must be more than 5 millimeters (mm) in diameter in young children and more than 15 mm in diameter after puberty.
  - 2 or more neurofibromas or 1 plexiform neurofibroma
  - Freckling around the armpits or groin
  - Optic glioma, which is a tumor on the optic nerve in the brain that effects vision
  - 2 or more Lisch nodules, which are tumors on the iris of the eye
  - Specific bone changes, including sphenoid dysplasia, which is an abnormality of 1 of the bones forming the skull, or thinning of the long bones
  - A parent, sibling (brother or sister), or child with NF1

NF1 Presentation

Infants (0-1)	Café au lait spots
	Plexiform neurofibroma
	Pseudoarthrosis
Toddler/Pre-School (2-5)	Decreased growth
	Macrocephalus
	Lisch nodules
	Neuropsychological deficits
	Gliomas (Optic)
	T2 Hyperintense MRI lesions of unknown significance
	Other malignancies
Children (6-10)	Skin neurofibromas
	Scoliosis
Adolescents (11-16)	MPNST

NF1 Screening

- Brain MRI following diagnosis (typically between 18mos-3 years of age)
- Eye exams yearly until at least 8 years of age
- Physical exam yearly
- Breast awareness at 18 years of age
- Yearly breast exam every year starting at 20
  - May soon early breast MRI/mammogram

Other Cancer Predisposition Syndromes

J Genet Counsel
DOI 10.1007/s10897-017-0077-8

REVIEW PAPER

A Comprehensive Review of Pediatric Tumors and Associated Cancer Predisposition Syndromes

Sarah Scollon[1] · Amanda Knoth Anglin[2] · Martha Thomas[3] · Joyce T. Turner[4] · Kami Wolfe Schneider[5]

[*Pediatr Ann*. 2018;47(5):e204-e216.]

Recognizing and Managing Children with a Pediatric Cancer Predisposition Syndrome: A Guide for the Pediatrician

Stephanie A. Coury, MS; Katherine A. Schneider, MPH; Jaclyn Schienda, ScM; and Wen-Hann Tan, BMBS

Identifying Patients At Risk

- Childhood Cancers
- Family Cancer History
- Physical Exam

Childhood Cancers

- Adrenocortical carcinoma
- Atypical teratoid rhabdoid tumor
- Basal cell carcinoma
- Cardiac rhabdomyoma
- Cerebellar gangliocytoma
- Choroid plexus carcinoma
- Colon cancer
- Cystic nephroma
- Desmoid tumor
- Endolymphatic sac tumors
- Ependymoma
- Gastrointestinal stromal tumor
- Hemangioblastoma
- Hepatoblastoma
- Hepatocellular carcinoma
- Juvenile granulosa cell tumor
- Juvenile myelomonocytic leukemia
- Hypodiploid acute lymphoblastic leukemia
- Malignant peripheral nerve sheath tumor
- Medullary thyroid carcinoma
- Medulloblastoma
- Melanoma
- Neurofibroma
- Optic glioma
- Ovarian Sertoli-Leydig cell tumor
- Pancreatic islet cell tumor
- Paraganglioma/pheocyromocytoma
- Pleuropulmonary blastoma
- Pituitary blastoma
- Pineoblastoma
- Renal cell carcinoma
- Retinoblastoma
- Rhabdoid tumor
- Sarcoma (bone or soft tissue)
- Schwannoma
- Subependymal giant cell tumor
- Wilm’s tumor (especially if bilateral)

Family History

- Only 1/3 of cancer survivor's providers regularly collect family history
- Most FHs are 2 generation, and focus on adult cancers
- Barriers: Lack of time, alternative priorities, perceived lack of relevance, lack of confidence

Wakefield et al, *Pediatr Blood Cancer,* 2018

Family History

- Early age of onset for any type of cancer (<50)
- Multiple family members with the same type of cancer
- Multiple family members with cancer clusters (i.e. breast, pancreatic, thyroid)
- Multiple family members with a similar physical feature (i.e. large head, café au lait spots)

Physical Exam

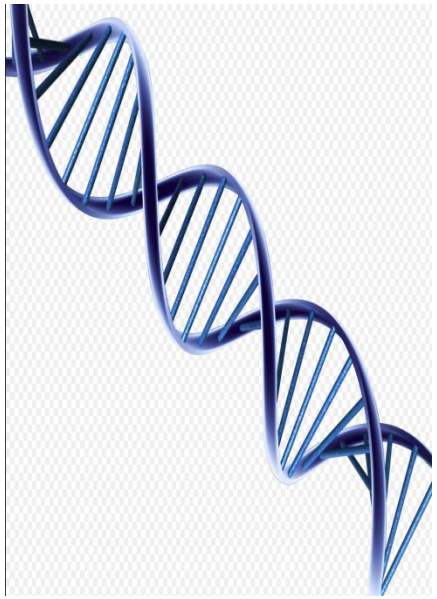
- Congenital anomalies
  - Dental anomalies, skeletal anomalies, congenital heart defect, urogenital abnormalities
- Cutaneous and subcutaneous lesions
  - Hyper or hypopigmented lesions, shagreen patch, tumors of the skin, palmar/plantar pitting, nevus flammeus or other vascular anomalies
- Dysmorphic features
  - Ear creases/pits, coarse facial features, broad forehead, abnormal placement of the ears
- Endocrine anomalies
  - Precocious puberty, primary hyperparathyroidism, hypercalcemia, hypo/hyperthyroidism with nodules

Physical Exam

- Growth abnormalities
  - Overgrowth, stunted growth, hemihypertrophy, macro or microcephaly, macroglossia
- Hematologic disorders
  - Pancytopenia, anemia, thrombocytopenia, leukopenia
- Immune deficiency
  - Frequent infections, autoimmune disorders
- Neurodevelopmental or neurologic concerns
  - Autism spectrum disorder, developmental delay, seizures
- Ophthalmologic anomalies
  - Congenital hypertrophy of the retinal pigment epithelium, coloboma, aniridia, optic disc pallor

Genetic Counseling and Testing Process

- Review of personal medical history & family history
- Risk assessment
- Discussion of inheritance and chance of recurrence
- Review of syndrome
- Pros and cons of testing, potential outcomes
- Appropriate testing medium (blood, skin, tumor)
- **Screening, prevention, treatment, surveillance**



Cancer Genetics Clinic Information

- Miriam Bornhorst, MD
  - Pediatric Neuro-Oncologist
  - Specialized training in Neurofibromatosis and other Cancer Predisposition Syndromes
- Joyce Turner, MS, CGC
  - Certified Genetic Counselor
  - Specialized training in cancer genetics counseling

- For appointments
  - Joyce Turner (jturner@cnmc.org)
  - Phone: 202-476-4685

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