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Cancer Predispositions in Pediatric Patients

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Speaker Disclosure

- I have nothing to disclose

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Learning Objectives

- Describe what a cancer predisposition is.
- Identify which cancers are associated with some of the syndromes discussed.
- Apply family screening into practice.

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Pediatric Cancer Statistics

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Pediatric Cancer Statistics

- In 2023, estimated 15,190 new cases of cancer were be diagnosed among children birth to 19 yrs.
  - 1590 children will die
  - Third leading cause of death in children 1-19yrs (after accidents and firearms)
- Most common types:
  - Acute Lymphocytic Leukemia (ALL)
  - Brain and other CNS tumors
  - Neuroblastoma
  - Lymphoma

National Cancer Institute, 2023/NEJM, 2022

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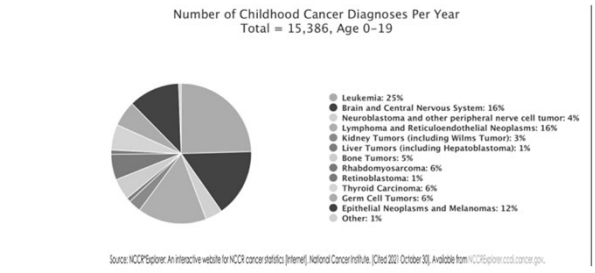
Incidence of Pediatric Cancers (2021)



Source: NCCR*Explorer: An interactive website for NCCR cancer statistics [Internet]. National Cancer Institute. [Cited 2021 October 30]. Available from NCCRExplorer.ccdi.cancer.gov.

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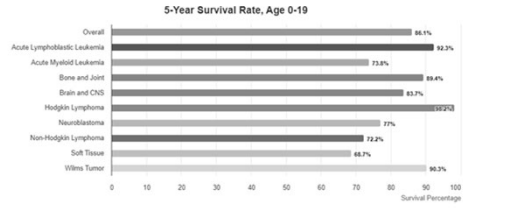
Survival Rates of Pediatric Cancers



Source: NCCR*Explorer: An interactive website for NCCR cancer statistics [Internet]. National Cancer Institute. Accessed at nccrexplorer.ccdi.cancer.gov on May 23, 2023, 09:14:31 AM.
Years: 2012-2018. By Cancer Site, Both Sexes, All Races, Ages <20.

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Genetics 101

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Genetic Basics

- 1865-Gregor Mendel-demonstrated inheritance of factors on pea plants
- Human Genome Project started 1990 and finished in 2003
  - Over 90% of DNA sequenced
  - In 2022, Telomere to Telomere consortium announced it completed the sequence
- DNA (a genome) contains the code for building and maintaining an organism
- Genes are small sections of the DNA long chain
- Half of our genome comes from biological mother and father

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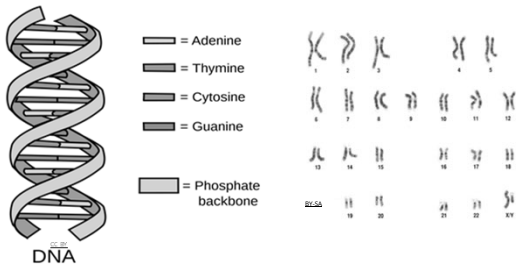

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Genetic Basics

- Genetic testing began 1959 Trisomy 21, Turners, Klinefelter syndrome, monosomy X and XXY
- Systemic genetic screening began in 1960's
  - PKU-→newborn panels
- 1980's second trimester maternal blood testing for Trisomy 18, 21 and neural tube defects
- 2007-ACOG recommends prenatal screening before 20 wks
- Whole exome/genome sequencing (Next generation sequencing)

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How do genetic diseases develop

- Changes in the DNA sequence are called genetic variants
- Autosomal dominant disorders
- Autosomal recessive disorders
- X-linked disorders
- Y-linked, codominant and Mitochondrial

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Who Gets Cancer?

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Causes

- Cause of most childhood cancers is unknown
- Inherited genetic changes (8-10%)
  - Inherited pathologic variant in a cancer predisposition gene
  - Li-Fraumeni, Beckwith-Wiedemann, Noonan, etc.
- Genetic changes early in development
  - Broken, missing, extra or rearranged chromosomes
  - Trisomy 21
- Environmental causes have been difficulty to link
  - Maybe exposures in early childhood development

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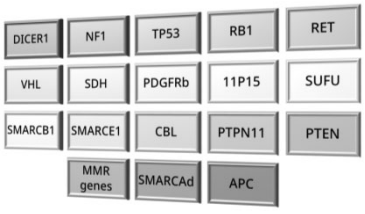
Next Generation Sequencing



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Pediatric Cancer Predispositions

- Familial Adenomatous Polyposis
- Li Fraumeni's
- Hereditary Retinoblastoma
- Beckwith-Weideman
- Gorlin Syndrome
- Noonan's Syndrome
- Hereditary Breast and Ovarian Syndrome (BRCA 1/2)
- Lynch Syndrome
- Turner's Syndrome
- DICER1 syndrome
- Fanconi's Anemia
- NF-1/NF 2
- Tuberous Sclerosis

American Cancer Society, 2017

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Li Fraumeni's

- Autosomal dominant disorder
- Germline mutation of p53 tumor suppressor gene
- Classification of LFS requires:
  - One family diagnosed before 45 yrs with sarcoma
  - First degree relative diagnosed with any major cancer before age 45yrs
  - Third member of family (1st/2nd degree relative) with any type of cancer before age of 45yrs
- Lifetime risk of cancer with LFM is 90% by age of 60yrs

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Familial Adenomatous Polyposis (FAP)

- Autosomal dominant disorder
- APC gene: adenomatous polyposis coli
- More than 1000 different mutations of the APC gene associated with FAP
- 92x's higher risk of medulloblastomas

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Beckwith-Wiedemann Syndrome

- Multiple abnormalities in two imprinting domains of genes that regulate 11p15 chromosomes
- ~ 1 in 130,000-may be an underestimate due to mild phenotypes undiagnosed
- Wilms Tumor
- Hepatobastoma

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Neurofibromatosis 1

- Autosomal dominant
- Mutation of the NF 1 gene
- Neurofibromin-protein encoded by the NF1 gene
- Signs: café-au-lait spots, axillary and inguinal freckling, Lisch nodules and neurofibromas
- Plexiform neurofibromas
- Optic nerve gliomas
- Rhabdomyosarcomas
- AML, MDS, Myeloproliferative syndromes

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Hereditary Retinoblastoma

- Mutation of RB1 gene on 13th chromosome
- Other cancers
  - Osteosarcomas
  - Soft tissue sarcomas
  - Malignant melanoma

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Fanconi's Anemia

- Autosomal recessive
- Mutations in one of at least 17 FA genes (FANCA to FANCQ)
  - Pancytopenia
  - Congenital abnormalities (microcephaly, triangular facies, short neck, hypo/hypertelorism, renal/urinary/gonadal malformations)

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Ethics of Genetic Testing in Pediatrics

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Policies

- Joint statement of AAP and ACMG in 2013
  - Testing should focus on the medical best interest of the child
  - Take into consideration the potential psychosocial benefits and harms to the child/family
  - Some families cannot live without knowing or adolescents may want to know
  - Benefits vs. Harms
- This policy has not been revised but it does recognize that whole genomic sequencing is out of the scope (only research tool at time)

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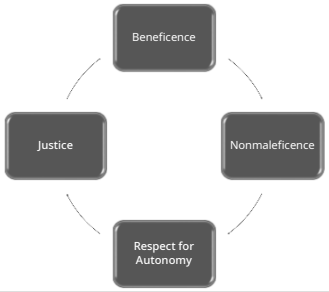
Principles of Ethics



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Protections with Genetic Testing

- Health Insurance Portability and accountability Act (HIPPA)
- Genetic Information Nondiscrimination Act of 2008 (GINA)

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How to Address in PC?

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Problems with assessment

- Guidelines for evaluating children are lacking (last policy 2013)
- Providers don't have time or tools to assess
  - EHR FH taking abilities
- Most providers don't have the expertise to do an adequate assessment
- Need to have access to pre-testing counseling

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Red Flags for Screening

- Several first-degree FM with cancer
- FMs on one side with same type of cancer
- Cluster of cancers know to be associated with gene mutation
- FM with more than 1 type of cancer
- FM who had cancer at a younger age than normal for that type
- Rare cancer in family
- Close relative with known hereditary cancer syndrome
- Specific race/ethnicity
- Physical finding linked to inherited cancer
- Known genetic mutation in one or more FM who have had genetic testing
- Lab tests of cancer cells with features linked to a gene mutation

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What can PNPs do in practice?

- Good family history
  - Note each relative of child with cancer (type, age, maternal/paternal side)
  - Any prior genetic testing?
  - 3 generations if possible
- If it is believed that testing would be beneficial, should refer to specialist/genetic counseling.
  - All US children's hospitals have cancer predisposition clinics to do counseling and testing
  - Assisting with getting insurance to cover referral

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Direct to Consume Genetic Testing

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DTC Genetic Testing

- ACMG and AAP does not recommend using in pediatrics

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Problems

- Little oversight for these companies
- Cannot promise that results mean will have the disease
- No pre or post-test counseling
- Letter to consumers to take to PCP for interpretation
- Risk of inaccurate results or poor interpretation
- Makes parents responsible for giving results to child
- Privacy concerns (information shared with researchers, sold to other companies)
- Potentially harmful consequences with results
  - Depression/suicide, insurance

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Thank you!

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