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Hereditary GI Cancer Syndromes: Keys to identify high risk patients

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Objectives

- Recognize the characteristics suggestive of hereditary cancer syndromes.
- Distinguish between various hereditary cancer syndromes based on family history.
- Become familiar with the management of hereditary cancer syndromes for the patient and their relatives.

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Why is this important?

- Knowledge about how genomics impacts cancer development, prevention, and treatment is rapidly increasing.
- Number of genetic tests continue to increase
- Increasing interest from patients and their families

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Why is this important for nurses?

"Informed nurses can identify genetic cancer risk factors, educate patients about cancer risks and risk management/treatment strategies, and refer appropriate patients to a cancer genetics professional."

Aiello-Laws, L. 2011 Seminars in Oncology Nurses; 27:13-20

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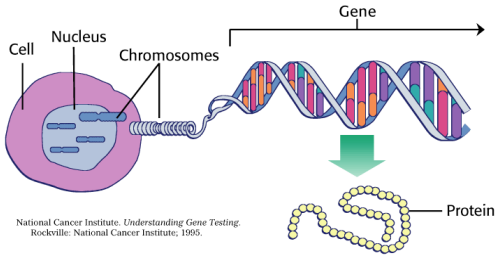
Genetics Review



National Cancer Institute. *Understanding Gene Testing.* Rockville: National Cancer Institute; 1995.

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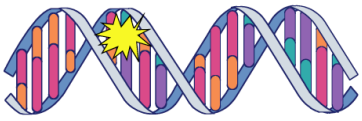
Modified from ASCO education slides

Gene mutations cause cancer

- A mutation is a change in the normal base pair sequence that affects the function of that gene's protein



- Many types of genes are important in the development of cancer including tumor suppressor genes, mismatch repair genes and oncogenes

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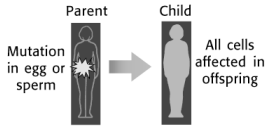
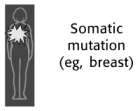
Gene mutations cause cancer

Germline mutations



- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Somatic mutations



- Occur in nongermline tissues
- Are nonheritable
- Acquired alterations common for all cancers

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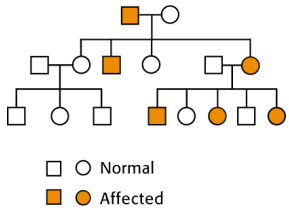
Autosomal Dominant Inheritance

- Equally affects men and women
- 50% chance offspring will inherit mutation



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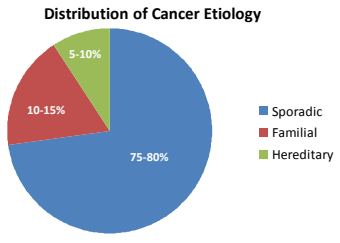
Distribution of Cancer Etiology



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When to suspect a Hereditary Cancer Syndrome

- Early onset
- Bilateral or multifocal disease
- Multiple primary cancers in one individual
- Cluster of cancer in a family
- Certain patterns of cancer in the family, usually multiple generations affected
- Rare cancers
- Precursor lesions

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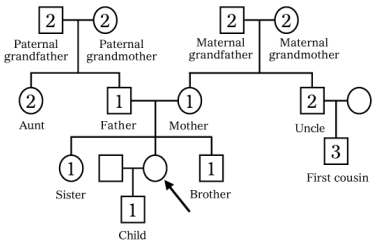
Family History

- Often the key to identifying a hereditary cancer family



Family History

- At least 3 generations
- Both maternal and paternal lineages
- Living and deceased
- Affected and unaffected
- Info to include for the patient :
  - Current age, cancer history, precursor lesions/biopsy results, surveillance practices, cancer risk factors

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Family History

Affected Relatives:

- Current age & screening practices
- Age at and date of diagnosis/ death
- Type and location of primary cancer(s), stage and laterality
- Second cancer: metastasis or new primary?
- Environmental exposures (eg, smoking, sun, radiation)
- Other medical conditions associated with cancers (ulcerative colitis, pancreatitis, diabetes, etc.)

Unaffected Relatives

- Current age
- Health status and history of significant illnesses
- Presence of other physical findings associated with cancer syndromes (benign tumors)
- Screening practices
- If deceased, cause of and age at death

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Family History Caveats

- Accuracy is key
- Family history is dynamic
- "No family history" is different than "negative family history"
  - Adoption, small family, lack of females, estranged relatives
- Hereditary cancer syndrome does not always lead to cancer in all relatives.

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GI Cancer Syndromes

- Hereditary Gastric Cancer
- Hereditary Pancreatic Cancer
- Hereditary Colorectal Cancer
  - Familial Adenomatous Polyposis
  - Lynch Syndrome

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Hereditary Gastric Cancer

- Genetic contribution
  - Mostly sporadic, some familial cases
  - 1-3% of gastric cancers are inherited
- Gastric cancers are part of many distinct hereditary cancer syndromes including Lynch syndrome, FAP, Peutz-Jeghers syndrome, Li Fraumeni
- Hereditary Diffuse Gastric Cancer

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Hereditary Diffuse Gastric Cancer

- Clinical Criteria:
  - 2 or more cases of DGC in first or second degree relatives, with at least one diagnosed before the age of 50
  - 3 or more cases of documented DGC in first/ second degree relatives, regardless of age of onset.

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Oliveira et al. Hum Mutat 2002;19:510-17.

Hereditary Diffuse Gastric Cancer

- 25-50% of families that meet clinical criteria will have an identified mutation
- *CDH1* gene, autosomal dominant inheritance
- Cancer Risks
  - Up to 80% risk of gastric cancer, average age of dx 37 yrs
  - Up to 60% risk of lobular breast cancer
  - Possible risk for colorectal and prostate cancers

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Fitzgerald et al. J Med Genet 2010;47:436-44

Management of HDGC

- Should include families with confirmed *CDH1* mutations and/or those that meet clinical criteria but have negative genetic testing.
- Surveillance
  - Annual endoscopy with random biopsies
  - Biannual clinical breast exam
  - Annual mammogram
  - Annual breast MRI
- Prophylactic Surgery
  - Consider prophylactic gastrectomy

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HDGC Criteria for further evaluation

- Single case of DGC dx <40 yrs of age.
- Two cases of DGC, one diagnosed less than 50 years of age.
- Three cases of DGC dx at any age.
- Combination of DGC and lobular breast cancer, one dx <50 yrs

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Hereditary Pancreatic Cancer

- May account for 15% of pancreatic adenocarcinomas
  - Genes responsible are largely unknown
  - Primarily autosomal dominant
- Hereditary Causes
  1. Hereditary cancer syndrome with PC as a feature along with other characteristics, usually other cancers
  2. Hereditary pancreatitis
  3. Familial pancreatic cancer

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Hereditary Syndromes and PC

	Gene	Relative Risk for PC	Additional Cancers
Breast and Ovarian cancer	*BRCA1, BRCA2*	3.5-10x	Breast, ovarian, prostate
Familial Atypical Multiple Mole Melanoma Syndrome (FAMM)	*P16*	15-65x	Melanoma
Peutz-Jeghers syndrome	*STK11*	130x	Esophageal, stomach, sm bwl, colon, lung, breast, ovarian
Lynch syndrome	*MMR genes*	2-8x	Colon, endometrial
Hereditary Pancreatitis	*PRSS1, SPINK1*	50x	—
PALB2 related-cancer	*PALB2*	Increased	Breast

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Familial Pancreatic Cancer

- 2 or more FDR with pancreas cancer
- 1 FDR with pancreas cancer, <50 yrs old
- 2 or more second degree relatives with pancreas cancer, one at any early age
- Cancer risk for relatives
  - 4.6-32 fold increase depending on fam hx

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Screening high-risk population

- No standard screening protocol
- Clinical trials underway to evaluate the use of EUS, CT and/or MRI with the goal of early detection in this high risk population.
- Who to screen?
  - Individual having a >10 fold increased risk
  - Lifetime risk is >16%

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Pancreatic Cancer Criteria for Further Evaluation

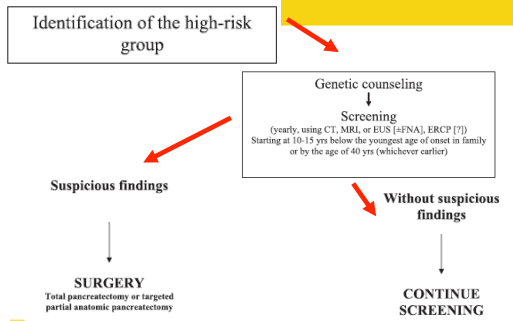

Figure 4. Proposed algorithm for the management of the individuals at high risk for PC development.

Sakorafas GH et al. Individuals at high-risk for pancreatic cancer development: Management options and the role of surgery. Surgical Oncology (2012). In press.

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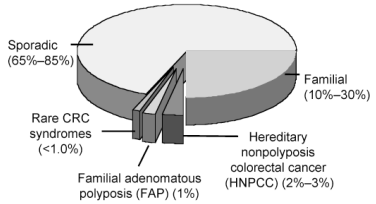
Causes of Hereditary CRC



Adapted with permission from Burt RW, Peterson GM. *Prevention and Early Detection of Colorectal Cancer.* London: WB Saunders; 1996:171-194.

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Modified from ASCO education slides

Familial Adenomatous Polyposis (FAP)

- 1% of all colorectal cancers
- Main feature
  - >100 polyps throughout entire colon, often thousands
  - Avg onset of polyps is 16 (range <10—30's)
- Cancer risk is ~100% if left untreated
  - Average age of colon cancer is 39 years.

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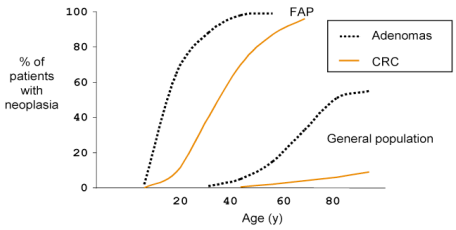
FAP: development of polyps and CRC



Adapted with permission from the American Gastroenterological Association, Clinical Teaching Project Unit, Colorectal Neoplasia II: Genetics and Prevention.

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FAP: Other Cancer Risks

- Small bowel: 4%-12%
- Pancreas (adenocarcinoma): ~1%
- Thyroid (papillary): 1%-2%
- CNS (medulloblastoma): <1%
- Liver (hepatoblastoma): 1.6%
- Bile duct: <1%
- Stomach (adenocarcinoma): <1% in Western cultures

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Attenuated FAP

- Fewer polyps
  - Average of 30
- Cancer dx later onset compared to classic FAP (average age 50-55 yrs)
- Can look like Lynch syndrome

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FAP Clinical Variants

- Turcot Syndrome
  - Colon polyposis with CNS tumors, often medulloblastomas
- Gardner Syndrome
  - Colon polyposis
  - Desmoid tumors (10%)
  - Osteomas
  - Dental anomalies
  - Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
  - Soft tissue skin tumors

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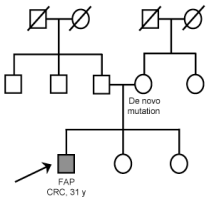
FAP Genetics

- *APC* gene; tumor suppressor
- Autosomal dominant inheritance
- 20-25% of individuals with FAP have no family history



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Management of FAP

Individuals with known FAP or at risk but not tested

- Birth-5 years: serum AFP and abdominal U/S, 3-6 mo
- 10-12 years: flexible sigmoidoscopy, 1-2 y
- Upper endoscopy by age 25, every 1-3 y
- Small bowel imaging when duodenal adenomas are detected or prior to colectomy, 1-3 y
- Physical palpation of thyroid annually, beginning late teens
- Annual physical exam

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NCCN. Colorectal Screening 2.2011

Management of FAP

Once polyps/cancer is detected:

- Proctocolectomy or colectomy
- If ileorectal anastomosis, then endoscopic rectum exam every 6-12 months
- If ileal pouch or ileostomy, then endoscopic evaluation every 1-3 years

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NCCN. Colorectal Screening 2.2011

FAP: Criteria for further evaluation

- >10 cumulative colon polyps
- CRC dx <50 yrs, regardless of family history
- CRC with a second primary (colon or non-colon)
- Presence of CRC and non-cancer features such as small bowel adenomas, desmoid tumors, osteomas, etc.

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Lynch Syndrome

- Formerly Hereditary Nonpolyposis Colon Cancer (HNPCC)
- ~3% of colorectal cancers
- Autosomal dominant inheritance
- Germline mutations in:
  - *MLH1, MSH2, MSH6, PMS2, EPCAM*
  - Mismatch repair genes

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Lynch Syndrome Cancer Risk

Cancer Type	General Population	Lifetime Risk
Colon	5%	54-74% (male) 30-52% (female)
Average age of dx	71 yrs	42-61 yrs
Endometrial	2%	28-60%
Average age of dx	62 yrs	47-62 yrs

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Modified from Weissman et al. J Genet Counsel 2011;20:5-19

Lynch Syndrome Cancer Risk (Cont)

Cancer type	General Population	Lifetime Risk with Lynch Synd
Stomach	<1%	6-9%
Ovarian	1%	6-7%
Urinary tract	Rare	3-8%
Small bowel	<1%	3-4%
Brain/CNS	<1%	2-3%
Pancreatic	1%	1-4%
Hepatobiliary	Rare	1%
Sebaceous skin	Rare	1-9%

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Modified from Weissman et al. J Genet Counsel 2011;20:5-19

Lynch Syndrome Cancer Risk (Cont)

- Second primary CRC
  - 30% after 10 years
  - 50% after 15 years
- Muir-Torre Syndrome
  - Lynch cancers AND sebaceous gland tumors or keratoacanthomas
- Turcot Syndrome
  - Lynch cancers AND CNS tumors (glioblastoma)

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Features of Lynch Syndrome

- Excess of right-sided tumors
- Histopathology
  - Mucinous/signet ring, poorly differentiated, medullary growth pattern, tumor infiltrating lymphocytes and Crohn's like lymphocytic reaction
- Progression from polyp to cancer occurs more quickly

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Lynch Syndrome Management

Surveillance

Intervention	Onset (age)	Interval (years)
Colonoscopy	20-25*	1-2
Endometrial sampling	30-35*	Annual
Transvaginal US	30-35*	Annual
Urinalysis with cytology	25-35*	Annual
Physical exam	21	Annual

* Or 10 years prior to earliest diagnosis in the family

Lindo et al. JAMA 2006;12:1507-17

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Lynch Syndrome Management

Surveillance

- After 15 years of follow-up:
- Surveillance decreased mortality by 65% (9 deaths in control group; 0 in case group)
- Decreased CRC by 63% (CRC rate 41% in controls, 18% in cases)
- Colonoscopy ever 1-3 years leads to earlier detection and improved survival

Jarvinen et al. Gastroenterolgoy 2000;118:829-34

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Lynch Syndrome Management

Prophylactic Surgery
- Colon
  - Limited role for prophylactic colectomy
- Uterus and ovaries
  - Consider total abdominal hysterectomy and bilateral salpingo-oophorectomy

Therapeutic Surgery
- Adenoma—polypectomy, option of prophylactic colectomy
- CRC—consider subtotal colectomy instead of segmental resection

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Identifying patients at risk for Lynch syndrome

- Clinical criteria (Family History)
- Tumor Studies
  - Immunohistochemistry (IHC)
  - Microsatellite Instability (MSI)

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Identifying patients at risk for Lynch syndrome

Amsterdam Criteria II Vasen et al. Gastroenterology. 1999:116:1453.
- 3 or more relatives with verified Lynch-associated cancer
  - Includes CRC, endometrial, small bowel, ureter or renal pelvis
  - one is a first degree relative of the other two
- 2 or more successive generations
- 1 cancer dx <50 yrs
- FAP excluded
- Caveat: At least 50% of patients with Lynch syndrome will be missed by using this criteria.

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Challenges with a Family History

- Family sizes are getting smaller
- Wider use of colonoscopies likely prevent many colon cancers
- Some gene mutations may have lower cancer risks
- Inaccurate information: patient recall, poor communication, adoption, estrangement

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Identifying patients at risk for Lynch syndrome

Tumor testing

- Not dependent on family history

Two options for tumor testing

- MSI testing
  - Abnormal in >90% with LS
  - Abnormal in 10-15% of sporadic CRC
- Abnormal MMR genes allow mismatch errors during DNA replication → variable lengths of DNA segments.

- IHC
  - Abnormal in >90% of LS
  - Abnormal in up to 20% of sporadic CRC
- Absence of protein expression suggests a mutation in the respective gene.

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Microsatellite Instability

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Revised Bethesda Criteria Guidelines

Tumors from individuals should be tested for MSI in the following situations

1. CRC dx <50 years of age
2. Presence of synchronous or metachronous CRC, or other Lynch related cancer, regardless of age
3. CRC with MSI-H histology diagnosed in a patient who is less than 60 years of age
4. CRC diagnosed in a patient with one or more first degree relative with Lynch related cancer, with one of the cancers being diagnosed under age 50 years
5. CRC dx in a patient with 2 or more first/second degree relatives with Lynch related cancers, regardless of age.

Umar et al. J Natl Canc Inst 2004;96:261-268

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Moving towards Universal Screening

- IHC and/or MSI screening of all colorectal cancers (and endometrial cancers), regardless of age of dx or family history has been implemented at some centers.
- Based on recommendations by the Evaluation of Genomic Applications in Prevention and Practice group from the CDC. EGAPP. Genet in Med 2009:11:35-41.
- Tumor screening has also been shown to be beneficial to patients and their at-risk relatives, and cost effective.

∞ Family History is not the only tool to use in screening for high risk families.

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Conclusions

- Obtaining a family history is a crucial first step in identifying high-risk families.
- An accurate family history makes all the difference
- Enhanced knowledge about the biology of hereditary cancers will allow for new and improved screening methods in the future.
- Appropriate identification of high-risk families can lead to prevention and early detection of cancer.

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Questions?

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