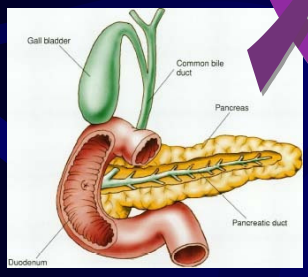
Genetics of Pancreatic Cancer: Identifying & Managing Increased Risk

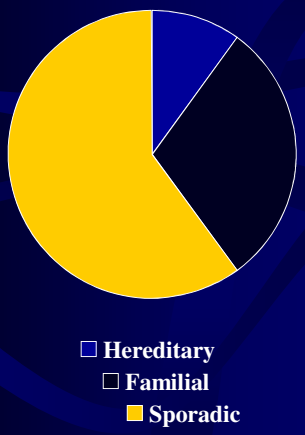


Jennifer E. Axilbund, M.S., C.G.C.
Cancer Risk Assessment Program
The Johns Hopkins Hospital

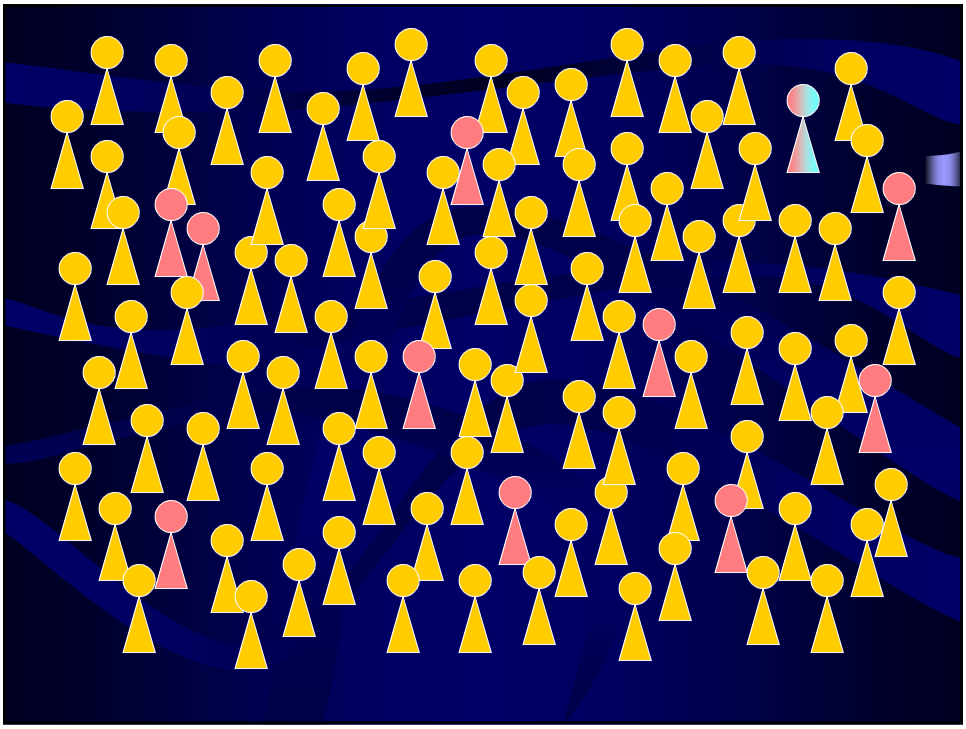
Risk Factors

- Cigarette Smoking
  - Doubles Risk
  - Causes 26% of pancreatic cancer
- Obesity
  - Increases risk by ~70%
- Diabetes
  - Longterm (>10yrs) 2-Fold increase (Everhart 1995)
  - 1% of new-onset diabetics develop pancreatic cancer within 3 years (Chari 2005)

What Percentage of Cancer is Considered to be Hereditary?



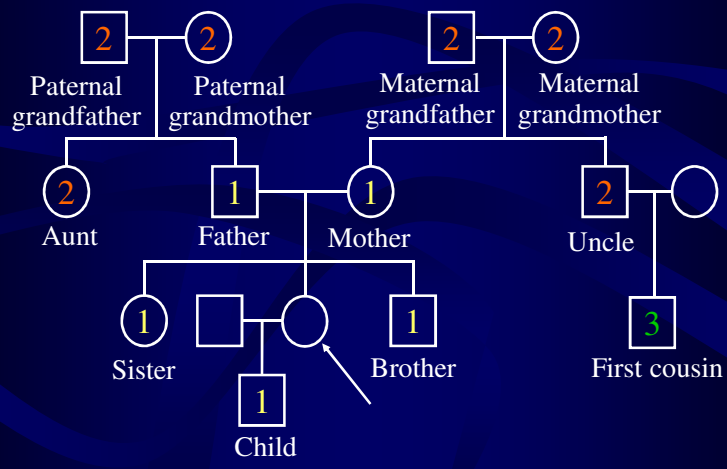
- 60-85% of cancer is thought to be sporadic
- 10-30% of cancer is thought to be familial
- 5-10% of cancer is thought to be hereditary



Family History Questionnaires

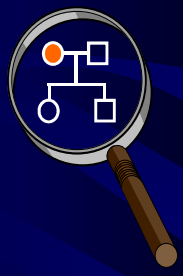
Name	Date of Birth	Age at dx/ Type of Cancer	Date of Death	Hospital
Davis, John	2/1/40	45/Colon	4/3/87	U. Minn.
Jones, Mary	4/9/42	52/Uterine	N/A	Franklin Med Ctr

1st, 2nd-, and 3rd-Degree Relatives



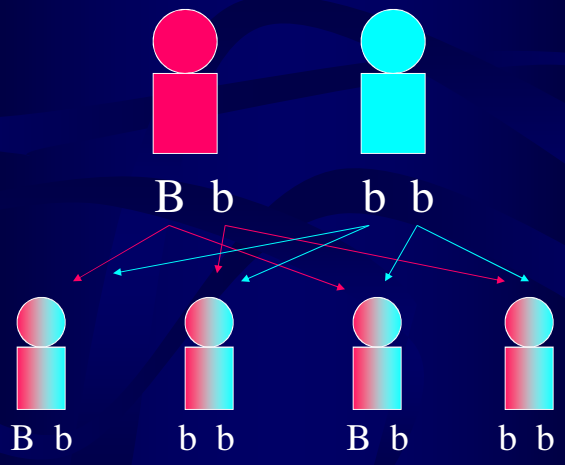
ASCO

When to Suspect a Hereditary Cancer Syndrome



- Cancer in 2 or more close relatives (on same side of family)
- Early age at diagnosis
- Multiple primary tumors
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with specific cancer syndrome (eg, breast and ovary)
- Evidence of autosomal dominant transmission

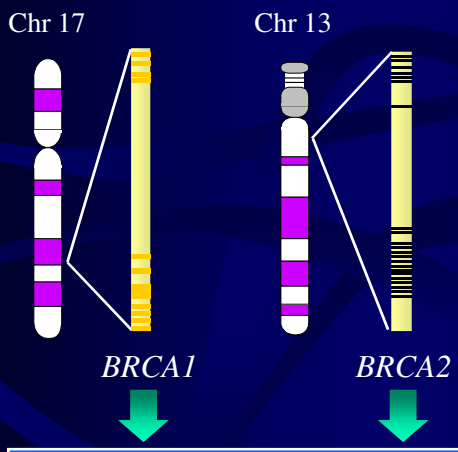
Autosomal Dominant Inheritance



Factors that Influence the Cancer Pattern within a Family

- Penetrance
- Gender
- Environment
- Genotype
- Risk-Reduction
- Early death
- Modifier genes

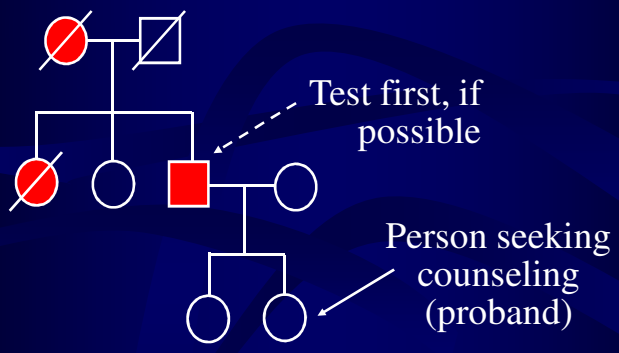
Genetic Heterogeneity



- Mutations in different genes can cause the same disease
- *BRCA1* and *BRCA2* account for half of all hereditary breast cancer

ASCO

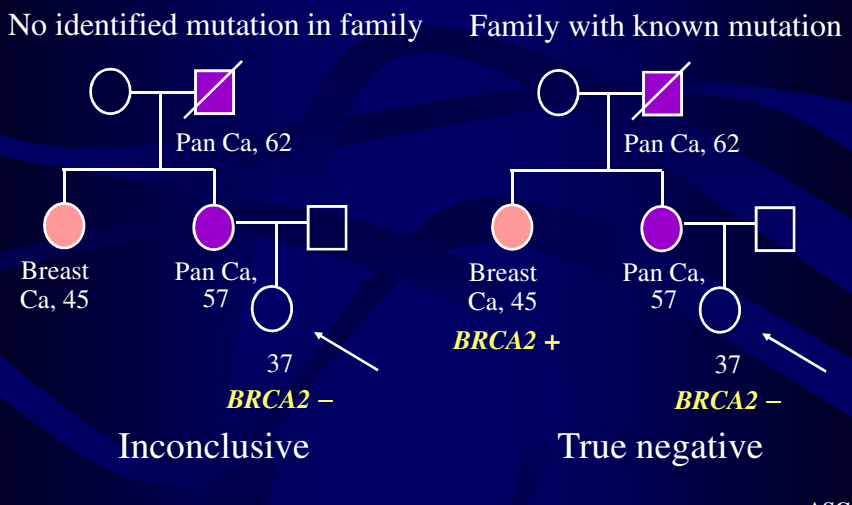
Ideally, Begin Testing With an Affected Person



If a mutation is found in an affected person, testing will be more informative for other family members

ASCO

Interpreting a Negative Result

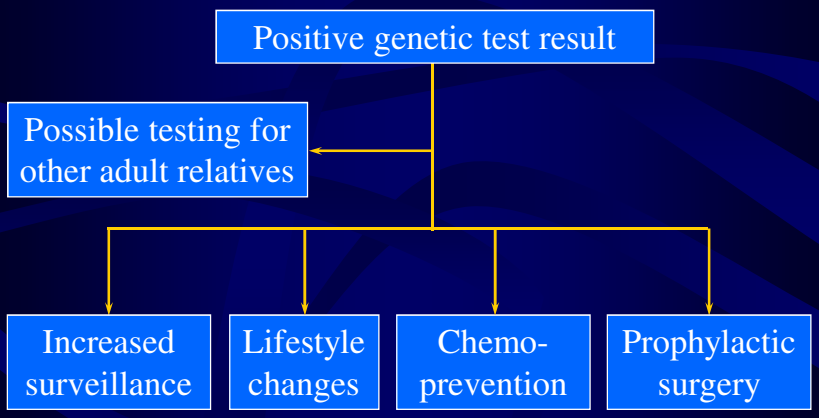


ASCO

In general, when Should Genetic Testing Be Considered?

- Patient has a reasonable likelihood of carrying an altered cancer susceptibility gene
- Genetic test is available that can be adequately interpreted
- Results will influence medical management or aid in the diagnosis of a hereditary cancer syndrome

Clinical Management of Mutation-Positive Patient



ASCO

Cost of Genetic Testing

Test:	Cost:
BRCA1/2 Sequencing	~$3400
BRCA1/2 Ashkenazi Jewish Panel	~$575
HNPCC Sequencing	~$3000
FAP (APC) Sequencing	~$2000
Large Deletion Testing	$400-750
Known Family Mutation	~$475

Insurance Coverage for Genetic Testing

- The vast majority of insurance companies cover *some* percentage of genetic testing
- Medicare does cover many cases, but Medical Assistance often does NOT
- Many laboratories offer pre-authorization services prior to committing to testing

Benefits of Genetic Testing

- Identifies high-risk individuals
- Identifies non-carriers in families with a known mutation (i.e. general population risk)
- Allows early detection and prevention strategies
- May relieve anxiety (positive or negative)

Risks and Limitations of Genetic Testing

- Does not detect *all* mutations and variants of uncertain significance
- Continued risk of sporadic cancer
- Efficacy of interventions unproven
- Psychosocial issues

Psychological and Ethical Issues in Adult-Onset Predisposition Testing

- Anxiety/fear
- Guilt
- Self-esteem
- Depression
- Stigmatization
- Grief and/or loss
- Family dynamics
- Right to know/right *not* to know
- Sharing of information
- Coercion
- Privacy
- Reproductive decisions
- Testing of minors

Variant of Uncertain Significance

- Prevalence: 5-15% in whites; 15-30% in other ethnic groups
- Effect on Risk Unknown
- Supporting Data:
  - Number of Unrelated Families
  - Seen with Deleterious Mutation
  - Co-segregation with Cancer
- Management based on Family History
- Do Not Test Unaffected Relatives

What Is Genetic Discrimination?

- Social or economic discrimination based on one's hereditary predisposition to disease
  - denial of access to or increased cost of insurance
  - loss of employment, educational, or other opportunities
- It is not clear that insurance discrimination based on cancer predisposition is a major issue

What Protection Exists?

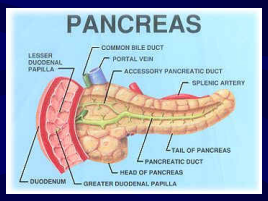
- GINA
  - Went into effect in May 2009
  - Health insurance and employment protections
- HIPAA:
  - Protects those with group health plans
  - Does not cover individual policies
- State Legislation:
  - Many states have laws that protect against all forms of health insurance discrimination
  - Limited for life, disability and long-term insurance

Familial Pancreatic Cancer

- 10% of cases have a positive family history of disease
- Represent a high-risk group that may benefit from early detection and risk assessment

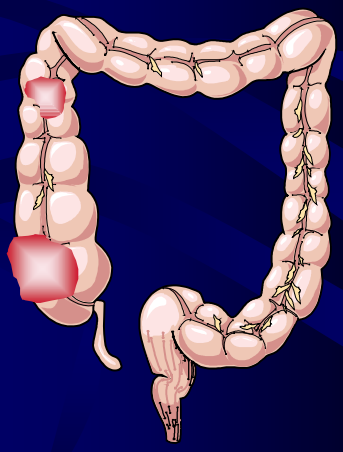
Familial Pancreas Cancer: Differential Diagnosis

- HNPCC
- FAP
- Peutz-Jeghers
- FAMMM
- Hereditary Pancreatitis
- BRCA1
- BRCA2
- PALB2
- Undiscovered Gene(s)

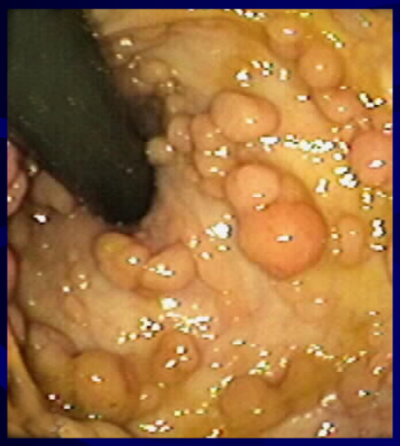


Hereditary Nonpolyposis Colorectal Cancer

- 70% are right-sided cancers
- 40% lifetime risk of endometrial cancer
- Average age at cancer diagnosis is 44 years
- Other associated malignancies (ovary, small bowel, urinary tract, stomach, biliary tract)

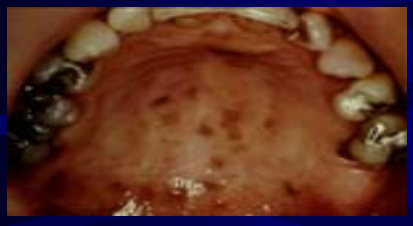


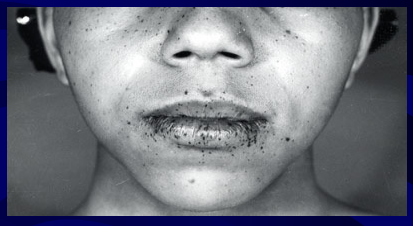
Polyposis Associated with Classic FAP



- >100 Adenomas
- Evenly distributed throughout colon
- Average age of polyp onset is 15 years
- Cancer risk approaches 100%
- Average age of cancer diagnosis is 39 years

Peutz-Jeghers syndrome

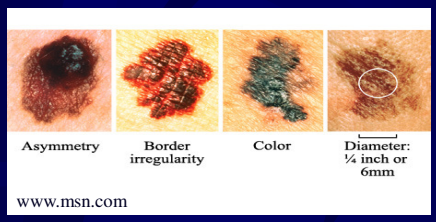




- Often presents as small bowel intussusception
- Melanin pigmentation
- Lifetime risk of *any* cancer is 93%
- Autosomal Dominant (STK-11)

Familial Atypical Multiple Mole and Melanoma (FAMMM)

- Characterized by a dominant pattern of melanoma and dysplastic nevi
- Risk for pancreas cancer is increased (22-fold)
- P16 gene
- Genetic testing is controversial



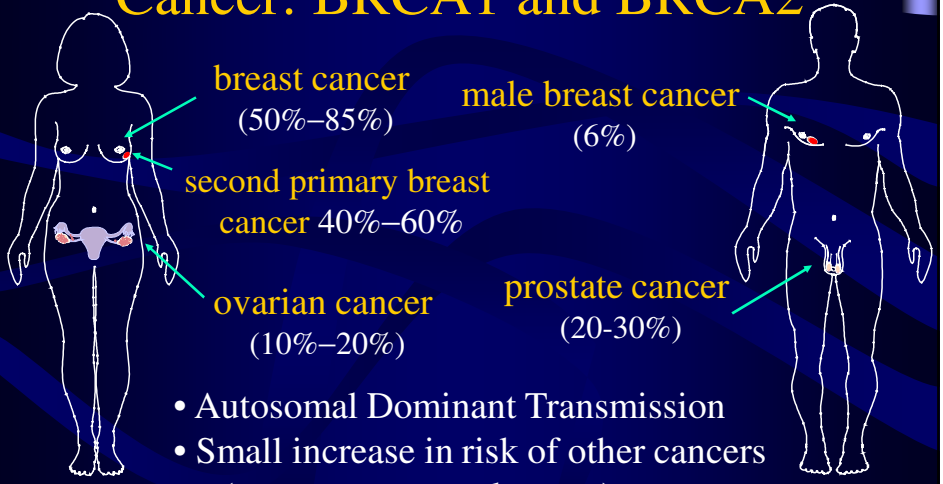
www.msn.com

Hereditary Pancreatitis

- Chronic pancreatitis following autosomal dominant pattern
- Risk of pancreas cancer approaches 40% by age 70 years
- Average age of onset is 39 years old
- Cationic Trypsinogen gene (PRSS1)

http://imagebank.ipcmedia.com

Hereditary Breast and Ovarian Cancer: BRCA1 and BRCA2



- Autosomal Dominant Transmission
- Small increase in risk of other cancers (e.g. pancreas, melanoma)

Adapted from ASCO

Risk of PC with BRCA2 mutations

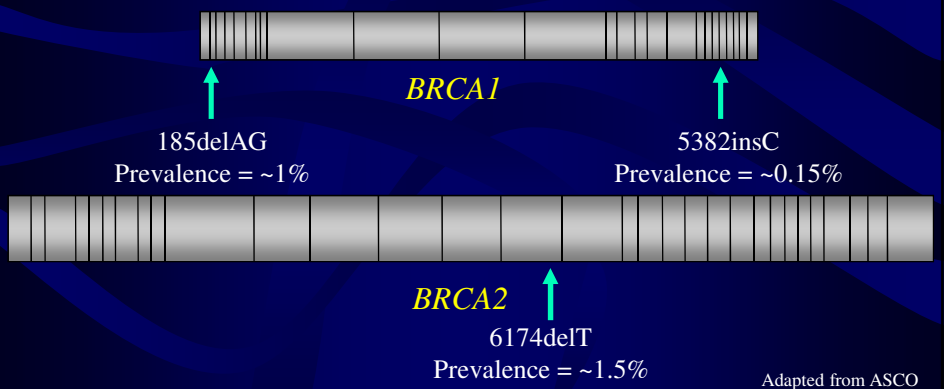
- J Med Genet. 2005 Sep;42(9):711-9
  - Overall RR = 5.9 (3.2-10 95% CI)
    - <65 y.o. RR = 37.1 (16-73.1 CI)
    - >/= 65 y.o. RR = 2.5 (1-5.2 CI)
- Breast CA Linkage Consortium (1999) JNCI
  - Carriers vs. Non-carriers vs. Unknown
    - Overall RR = 3.51 (1.87-6.58 95% CI; p = .0012)
    - 0-64 y.o. RR = 5.54 (2.72-11.32 CI)
    - 65-85 y.o. RR = 1.61 (0.45-5.72 CI)

BRCA2 Prevalence

- 7% of apparently sporadic pancreas cancer (Goggins et al. 1996)
- 10% of Ashkenazi Jewish patients with pancreas cancer (Ozcelik et al. 1997)
- 17% of kindreds with three or more relatives affected with pancreas cancer (Murphy et al. 2002)

BRCA1 and BRCA2 in the Ashkenazi Jewish Population

1 in 40 Individuals of Ashkenazi Jewish descent has a BRCA1 or BRCA2 Mutation



Adapted from ASCO

PALB2

- Official name "partner and localizer of *BRCA2*"
- Genome maintenance gene
- *PALB2* binds to *BRCA2* stabilizing it and anchoring it to structures in the nucleus allowing *BRCA2* to repair DNA

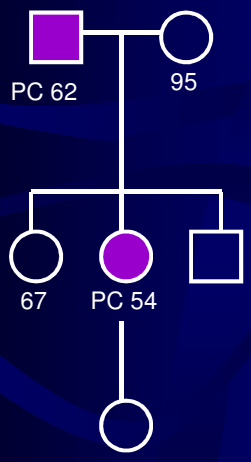
PALB2

- Sequence Analysis of 20,661 genes: *PALB2* mutated in one proband
- 3 of 96 additional FPC patients sequenced also had truncating *PALB2* mutations
- Co-segregation was observed
  - Two brothers with pancreatic cancer both had same PALB2 stop mutations
- 3 of 4 families also had history of breast cancer
  - Not all families had history of breast cancer
  - Prevalence of *PALB2* mutations higher than observed for HBOC families (3% vs 1%)

Jones, SciencExpress March 5, 2009

Most patients with a strong family history of pancreatic cancer do not fit into one of these recognized syndromes

Empiric Risk based on FDRs



- **One FDR = 4.5-fold**
- **Two FDRs = 6.4-fold**
- **Three FDRs = 32-fold**

Klein et al. Cancer Res. 2004

Ongoing gene discovery studies

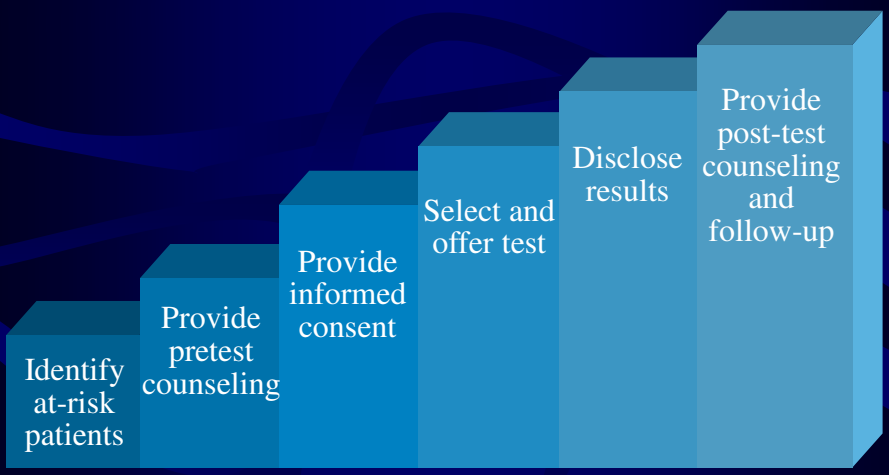
- PacGene

  Multi-center linkage consortium: Johns Hopkins, Mayo Clinic, Karmanos Cancer Institute, M.D. Anderson Cancer Center, University of Toronto, Dana-Farber Cancer Institute

- PANSCAN

  Genome Wide Association Studies: The Pancreatic Cancer Cohort Consortium; JHU, MD Anderson, Mayo, Mount Sinai, MSKCC, USCF, Group Health (Seattle WA)

Genetic Predisposition Testing Is a Multi-Step Process



ASCO

Cancer Genetics Centers

- National Society of Genetic Counselors
  - http://www.nsgc.org
- Gene Clinics
  - http://www.geneclinics.org
- National Cancer Institute
  - http://www.cancer.gov