

Genetic Cancer Risk Assessment (GCRA)

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Objectives

- ▶ Recognize the significance and burden of hereditary cancer
- ▶ Review underlying biology
- ▶ Understand individual risks and characteristics of high risk families
- ▶ Understand how to take an appropriate history and when to refer patient for GCRA

Cancers that may be hereditary

- ▶ Ovary 15% detectable mutations
- ▶ Breast 7% (3-5%BRCA)
- ▶ Pancreas >10%
- ▶ Colon 5% detectable mutation, 25% familial
- ▶ Endometrial 2%
- ▶ Kidney ~5%
- ▶ Melanoma >5%
- ▶ Stomach <5%
- ▶ Thyroid <5% (25% of medullary thyroid cancer)
- ▶ Prostate ~5%

Cancers that are rarely hereditary

- ▶ Lung
- ▶ Larynx
- ▶ Esophagus
- ▶ Bladder
- ▶ Leukemia
- ▶ Lymphoma
- ▶ Testicular
- ▶ Non-melanoma skin cancer

Cancers that are often hereditary

- ▶ Medullary thyroid cancer 25%
- ▶ Adrenocortical carcinoma up to 75%
- ▶ Pheochromocytoma

Case #1

A 52 year old woman is diagnosed with a triple negative breast cancer.

She denies a family history of breast cancer. Her mother died of “stomach cancer”. Her mother was an only child. The patient’s sister had Hodgkin’s Disease when she was 22 years old and received Radiation Treatments which unfortunately made her sterile. She is currently 43 years old and healthy.

Case #2

- ▶ A 36 year old man presents with a symptomatic anemia and is found to have a right sided colon cancer. He is taken to surgery for resection. He does well post-operatively. He has lymph node involvement so he receives adjuvant chemotherapy
- ▶ His father died of colon cancer at age 52. His sister had a “female cancer” but he knows no details. She is currently living and well. His uncle died in a traffic accident. His paternal grandmother died relatively young following abdominal surgery. He does not know why his grandfather was taken to surgery as he was just a child.

CASE #3

- ▶ A 54 year old woman is diagnosed with a stage 2 infiltrating ductal cancer of her left breast. Her grandmother had breast cancer at age 81. There is no other family history of cancer.
- ▶ Is this patient a candidate for a Genetic Cancer Risk Assessment referral?

Family History Documentation Tips

▶ Less helpful

- ▶ Mother and aunt had breast cancer.

▶ More helpful

- ▶ Mother had breast cancer at age 65. Paternal aunt had breast cancer at age 41. No family history of other breast, ovarian, colorectal cancers in any first or second degree relatives. Not of Ashkenazi Jewish ancestry.

Importance of Maintaining Current Family History

- ▶ When taking care of patients as a primary care provider it is recommended that the family history be reviewed each year with respect to first and second degree relatives.
- ▶ Maintenance of the family history can help in the early detection of genetic mutations that significantly increase the risk of cancer.
 - ▶ Once diagnosed, preventive strategies can be instituted.

Patient “Relations”

- ▶ First Degree Relatives
 - ▶ Mother, Father, Sister, Brother
- ▶ Second Degree Relatives
 - ▶ Grandmother, Grandfather, Aunt, Uncle, Niece, Nephew
- ▶ Third Degree Relatives
 - ▶ Cousin

Why is GCRA important in Cancer Prevention?

The vast majority of non-smoking related cancers are SPORADIC.

What makes Genetic Cancer Risk Assessment important is that it identifies individuals who may be carriers of a mutated gene that significantly increases the risk of both breast and ovarian cancers (HBOC) as well as colon and endometrial cancers (HNPCC) or Lynch syndrome. There are also a variety of other less common malignancies that are due to various other genetic mutations.

Etiology of Cancer

- ▶ **SPORADIC** - 70-80% of cancer. Cause felt to be “environment” and chance
- ▶ **FAMILIAL** - 10-25% of cancer. Cause felt to be heredity and environment.
- ▶ **HEREDITARY** – 5-10% of cancer. Cause mostly heredity.

Risk of breast cancer

	Percent of population	Percent of all breast cancer cases	Average risk of breast cancer to age 70
Positive family history breast cancer*	~10	15 to 20	10 to 13 percent*
Positive BRCA1 or 2 mutation	~0.1	5 to 6	50 to 85 percent ^Δ
General population without positive family history or BRCA mutation	~90	80 to 85	7 [◇] percent

* Breast cancer in a first-degree relative.

• Data from: Colditz G, et al. JAMA 1993; 270:338.

Δ This range represents the range of lifetime risk quoted by genetic specialists.

◇ Data from: the American Cancer Society, Cancer Statistics, 2010. (CA Cancer J Clin 2010; 60:277).

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Hereditary Breast and Ovarian Cancer (HBOC)

- ▶ Majority associated with mutations of either BRCA 1 or BRCA 2 gene.
 - ▶ Less commonly associated with other hereditary cancer syndromes such as the Cowden Syndrome (TP53 mutation) or the Li-fraumeni Syndrome (PTEN mutation).
- ▶ BRCA 1 and 2 are due to mutations of “Tumor Suppressor” genes. These genes normally play a role in the maintenance of genome integrity. They are involved in repair of damaged DNA.

Who to Consider for GCRA?

Personal history of breast cancer before age 50

Patient with 2 separate primary breast cancers

Epithelial ovarian cancer at any age

Personal history of both breast and ovarian cancers

Ashkenazi Jewish Ancestry with breast/ovarian cancer in family and early age at onset

Personal or family history of any cancer before age 50

2+ relatives on same side of family with same type of cancer

DETAILED Family History Essential

- ▶ Not enough to know “history of breast cancer” in family
 - ▶ Need to know age at diagnosis
 - ▶ Need to know relationship to patient
 - ▶ Need to see pathology reports if available
- ▶ Grandmother having breast cancer at age 78 is noteworthy, but not suggestive of a germline mutation.
- ▶ Mother having breast cancer at age 38 is very significant
- ▶ Is family history adequate on which to base recommendations?

Think Genetic mutation when you see

- ▶ Multiple primary cancers
- ▶ Early onset cancer such as premenopausal breast cancer or colon cancer diagnosis < age 50
- ▶ Bilateral cancer or multifocal disease
- ▶ Multiple family members affected in multiple generations
- ▶ Families with both breast and ovarian cancer
- ▶ Families with both colon and endometrial cancer
- ▶ Rare tumors such as adrenocortical carcinoma or duodenal cancer
- ▶ Unusual presentation such as male breast cancer
- ▶ Ethnicity associated with a high risk for hereditary cancer such as Ashkenazi Jewish ancestry.

Benefits of Genetic Testing

- ▶ Better understanding of cancer risk
 - ▶ Improved surveillance
 - ▶ Risk reducing therapies
 - ▶ May influence treatment decisions
 - ▶ Potential information about risk for family members

Importance of GCRA

- ▶ Prevention of cancer
 - ▶ Prophylactic surgery
 - ▶ Increased and more aggressive surveillance
 - ▶ Certain medications proven to reduce risk
- ▶ Prevention of Cancer is *so much better* than treatment of cancer.

Limitations of Genetic Testing

- ▶ Patient may have a “VUS”. (Variant of Uncertain Significance)
- ▶ May not provide a definitive answer about cancer risk.
- ▶ May be uninformative
- ▶ Sometimes the family phenotype is such that a genetic mutation seems inherent.....but all of the testing is negative. This patient/family must be treated as if they had positive tests.

Genetic Cancer Risk Assessment

- ▶ **Pre-test counseling** – Provide an assessment based on personal and family history. Mathematical models can be used to help estimate cancer risk. Discuss the potential risks, benefits and limitations of genetic testing.

Exactly what happens when a patient has a GCRA.

▶ RISK ASSESSMENT

▶ Personal and Family History

- ▶ Review differential diagnosis
- ▶ A personal pedigree is created with as much detail as possible.
- ▶ Detailed family history taken. Includes first, second and third degree relatives.
 - ▶ Include types of cancer
 - ▶ Bilaterality
 - ▶ Age at diagnosis
 - ▶ Medical record documentation
 - ▶ Any chemoprevention or risk reducing surgery?

Risk Calculation Tools in Breast Cancer

- ▶ The Likelihood of developing breast cancer
 - ▶ Gail model
 - ▶ Claus model
 - ▶ BRCAPRO
 - ▶ Tyrer-Cuzick model

Risk Calculation Tools in Breast Cancer

- ▶ **Likelihood of carrying a BRCA mutation**
- ▶ BRCAPRO
 - ▶ BOADICEA
 - ▶ Tyrer-Cuzick model
 - ▶ UPENN II
 - ▶ Myriad Risk Tables
 - ▶ Pedigree analysis

GAIL Model Risk Factors

- ▶ Current age
- ▶ Age at menarche
- ▶ Age at first live birth or nulliparity
- ▶ Number of first degree relatives with breast cancer
- ▶ Number of previous benign breast biopsies
- ▶ Atypical ductal hyperplasia on prior biopsy
- ▶ Race
- ▶ www.nci.nih.gov
 - ▶ NCCN Guidelines for breast cancer screening and diagnosis

Gail Model

- ▶ If Risk Score is $>1.7\%$, consider Tamoxifen or Raloxifene for breast cancer risk reduction.
 - ▶ Google the “Gail Model”. Very easy to use. Takes less than 5 minutes online.
- ▶ Limitation – Only considers first degree relatives. Underestimates the risk in 50% of families with cancer in the paternal lineage and doesn’t take into account the age of onset of breast cancer.

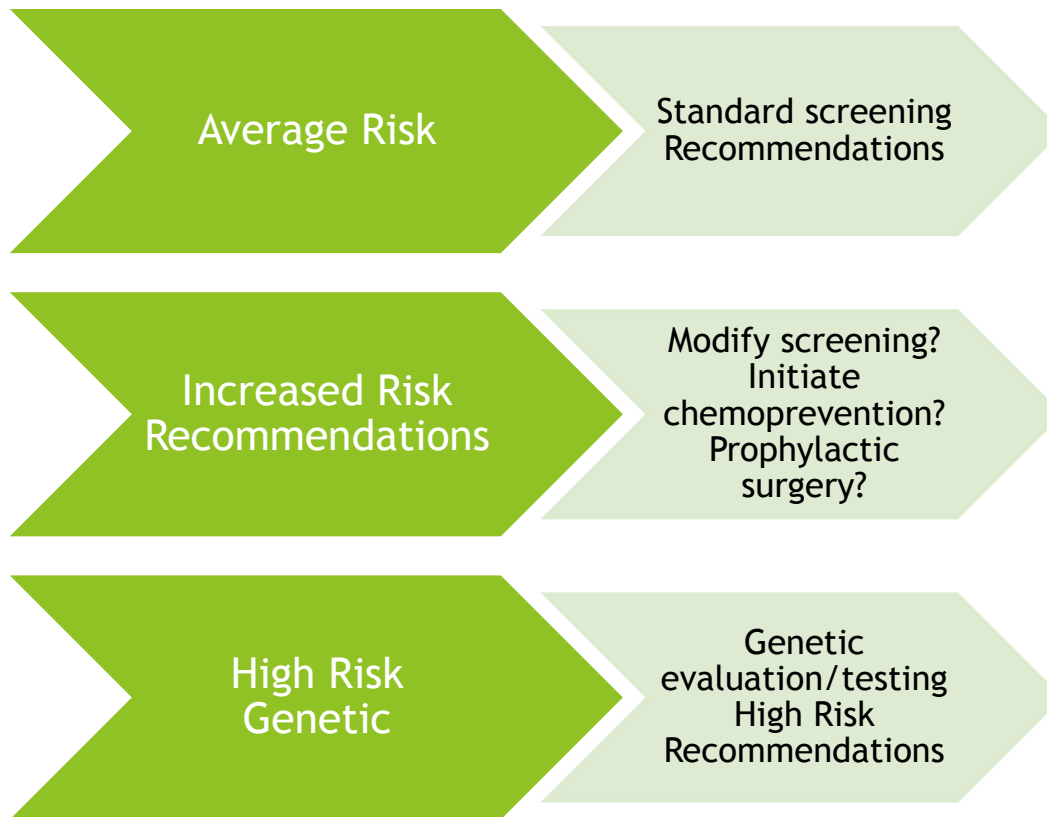
Risk Factors for Breast Cancer

- ▶ Family History
- ▶ Early menarche
- ▶ Late menopause
- ▶ ADH (atypical ductal hyperplasia) or LCIS (lobular carcinoma in situ) on patients breast biopsy
- ▶ Prior history of breast cancer
- ▶ Age at parity
- ▶ Obesity
- ▶ Prior thoracic radiation therapy

Risk Factors for a Hereditary Breast Cancer Syndrome

- ▶ Family history of breast cancer
- ▶ Early age at onset of breast cancer
- ▶ Bilateral breast cancer
- ▶ Male breast cancer
- ▶ Relationship degree
- ▶ Multiple cases of breast cancer on one side of the family
- ▶ Other tumors such as ovarian cancer, sarcoma, diffuse gastric or uterine cancer
- ▶ Number of affected individuals in the family

Who Needs What? Family history can define Risk Classification



Guidelines Required by National Cancer Associations

- ▶ American Society of Clinical Oncology ASCO
- ▶ National Society of Genetic Counselors NSGC
- ▶ Oncology Nursing Society ONS

- ▶ Guidelines outline the standards for the practice of cancer risk counseling, risk assessment and genetic testing

Importance of GCRA

- ▶ Family Planning
- ▶ Decreased worry
- ▶ Can benefit multiple generations in a family
- ▶ **SAVES LIVES**
- ▶ Cancer is more likely curable when diagnosed in the earlier stages.

Major Hereditary Cancer Syndromes

Hereditary Breast and Ovarian Cancer (HBOC)

Lynch Syndrome (HNPCC) – hereditary non-polyposis colon cancer

Cowden Syndrome

Familial Adenomatous polyposis

Li-Fraumeini Syndrome

Hereditary Breast and Ovarian Cancer Syndromes (HBOC)

- ▶ Germline mutations found in < 10% of women with breast cancer and <15% of women with ovarian cancer.
- ▶ The vast majority are due to BRCA1 or BRCA2 genetic mutations
- ▶ Breast cancer also seen in other syndromes such as Li-Fraumeni and Cowden syndromes.

BRCA1 and BRCA2

- ▶ Autosomal dominant, highly penetrant genetic mutations
- ▶ BRCA1 is located on chromosome 17
- ▶ BRCA2 is located on chromosome 13
- ▶ The prevalence of these deleterious mutations varies among ethnic groups and geographic area. “Founder Effect”
 - ▶ Examples Ashkenazi Jews, Icelandic, French Canadian, Mexican. Specific founder mutations

Cancer Risks

- ▶ Studies have identified varied risks dependent upon study populations, risk-modifiers such as oophorectomy, parity status and BCP usage.
- ▶ Lifetime risk of Breast Cancer is higher with BRCA1 and the mean age at diagnosis is also younger.
- ▶ Mean age of diagnosis of ovarian cancer for BRCA1 is 52y while it is 62y for BRCA2.

BRCA1 – Lifetime Risk of Associated Cancers

- ▶ Female Breast Cancer 50-85%
- ▶ Male Breast Cancer 1-5%
- ▶ Ovarian Cancer 20-40%

- ▶ Second primary breast cancer 40-60%
- ▶ Colon Cancer 10-15%
- ▶ Pancreatic cancer 2-3%
- ▶ Possible increase for other cancers such as gastric or endometrial.
- ▶ No evidence for increased risk for prostate cancer, but some evidence of earlier onset

BRCA2 - Lifetime Risk of Associated Cancers

- ▶ Female breast cancer 50-85%
- ▶ Male breast cancer 6%
- ▶ Ovarian Cancer 10-20%
- ▶ Second primary breast cancer 40-60%
- ▶ Pancreatic cancer 3-5%
- ▶ Prostate cancer 15-25%
- ▶ Melanoma 3-5%
- ▶ Possible increases for gastric or endometrial cancer.

Meta Analysis of 10 Studies in High Risk Clinics

- ▶ Breast – The cumulative risk of breast cancer by age 70 years
 - ▶ BRCA1 57% (95%CI 44-66%)
 - ▶ BRCA2 49% (95%CI 40-57%)

Ovarian – The cumulative risk of breast cancer by age 70 years

- BRCA1 40% (95%CI 35-46%)
- BRCA2 18% (95%CI 13-23%)

National Comprehensive Cancer Network criteria for consideration of BRCA1/2 genetic testing

A. Individual from a family with a known deleterious BRCA1/BRCA2 mutation**^Δ
B. Personal history of breast cancer[◇] plus one or more of the following:
<ul style="list-style-type: none"> Diagnosed age ≤45 years Diagnosed age ≤50 years with ≥1 first-, second-, or third-degree blood relative (on the same side of the family) with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age, or with a limited family history^Δ Two breast primaries[§] when first breast cancer diagnosis occurred ≤50 years Diagnosed ≤60 years with a triple negative breast cancer Diagnosed ≤50 years with a limited family history^Δ Diagnosed at any age with ≥1 first-, second-, or third-degree blood relative (on the same side of the family) diagnosed with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer ≤50 years Diagnosed at any age with ≥2 first-, second-, or third-degree blood relatives (on the same side of the family) with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age Diagnosed at any age with ≥2 first-, second-, or third-degree blood relatives (on the same side of the family) with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age First-, second-, or third-degree male blood relative (on the same side of the family) with breast cancer For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish), no additional family history may be required[‡]
C. Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
D. Personal history of male breast cancer
E. Personal history of pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age with ≥2 first-, second-, or third-degree blood relatives (on the same side of the family) with breast and/or ovarian cancer and/or pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
F. Family history only[‡]:
<ul style="list-style-type: none"> First- or second-degree blood relative meeting any of the above criteria Third-degree blood relative with breast cancer[◇] and/or ovarian/fallopian tube/primary peritoneal cancer with ≥2 first-, second-, or third-degree blood relatives (on the same side of the family) with breast cancer (at least one breast cancer ≤50 years) and/or ovarian/fallopian tube/primary peritoneal cancer

* One or more of these criteria is suggestive of hereditary breast/ovarian cancer syndrome that warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. The maternal and paternal sides should be considered independently. Melanoma has been reported in some hereditary breast/ovarian cancer families.

• Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA. If available, DNA should be extracted from a fibroblast culture. If the source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.

Δ Individuals with a limited family history, such as fewer than two first- or second-degree female relatives or female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of a familial mutation.

◇ For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

§ Two breast primaries include bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

¥ Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or other hereditary breast/ovarian cancer criteria are met. Founder mutations exist in other populations.

‡ Clinical judgment should be used to determine if the patient has reasonable likelihood of mutation, considering the unaffected patient's current age and the age of the female unaffected relatives who link the patient with the affected relatives. Testing of unaffected individuals should only be considered when an appropriate affected member is unavailable for testing. Significant limitations of interpreting test results for an unaffected individual should be discussed.

National Comprehensive Cancer Network, v3.2013 (www.nccn.org).

HBOC and LYNCH Syndrome (HNPCC)

....the two most common hereditary cancer syndromes

HBOC

- ▶ 1 in 400-500
- ▶ Accounts for 7% of breast and 14% of ovarian cancer
- ▶ Age at onset and family history of related cancers important
- ▶ Risk development of multiple site primary tumors
- ▶ Breast cancer patients have up to 64% risk of a contralateral breast cancer by age 70 and a 10-fold increased risk for ovarian cancer.

LYNCH SYNDROME

- ▶ 1 in 400-500
- ▶ Accounts for 2-4% of colorectal, endometrial and ovarian cancers.
- ▶ Early age of onset and family history important
- ▶ Genetic testing can help assess the risk of developing additional cancers. Colon cancer patients with Lynch syndrome have up to a 50% risk of developing a second colon cancer in the next 15 years

HBOC and LYNCH SYNDROME, similarities

- ▶ High prevalence
- ▶ At least 20% of all breast and colo-rectal cancer patients should be evaluated for HBOC of Lynch syndrome, respectively
- ▶ Significantly elevated risk for developing a second primary cancer
- ▶ Hallmark cancers
- ▶ Autosomal Dominant Inheritance
- ▶ Test results can allow for personalized medicine and preventative strategies reducing both morbidity and mortality

Think Lynch Syndrome when you see:

- ▶ More than one primary colon cancers in same individual
- ▶ Colon and endometrial cancers in the same family
- ▶ Greater than 10 adenomatous polyps
- ▶ More than 2 melanomas
- ▶ Cancer of the pancreas
- ▶ Age at diagnosis of cancer younger than usual age

Autosomal Dominant Inheritance

- ▶ Germline mutation of a MISMATCH REPAIR (MMR) gene
 - ▶ MSH 2
 - ▶ MLH 1
 - ▶ MSH 6
 - ▶ PMS 2
- ▶ MSH 2 or MLH 1 account for about 90% of the germline mutations in Lynch syndrome.
- ▶ Women with Lynch Syndrome have a 27-71% lifetime risk of endometrial cancer and a 3-14% risk of ovarian cancer.

Risk Reducing Surgery

- ▶ TAH-BSO appears to be effective in preventing endometrial and ovarian cancers in women with Lynch syndrome. It is suspected that the gynecologic cancers associated with Lynch syndrome may have biologic differences from those in other women.

COLON CANCER IN LYNCH SYNDROME

- ▶ Occurs at an earlier age than usual
- ▶ Predominantly RIGHT sided colon tumors
- ▶ 10% patients have SYNCHRONOUS or METACHRONOUS tumors.
- ▶ 90% of colon cancers caused by Lynch syndrome have high levels of microsatellite instability (MSI).

High MSI is also seen in 15% of sporadic colon cancers

Lynch Families with High Risk of Extracolonic Tumors

- ▶ Endometrial Cancer
- ▶ Ovarian Cancer
- ▶ Gastric Cancer (diffuse)
- ▶ Small Bowel
- ▶ Hepatobiliary System
- ▶ Renal pelvis or Ureter (TCC)

Surveillance in Carriers and Family Members

- ▶ Colonoscopy is recommended to begin at age 20-25 years, or 10 years younger than the earliest diagnosis of colon cancer in the family. Since the onset of cancer is later in families with the MSH 6 mutation, surveillance in these families can begin at age 30.
- ▶ Total or subtotal colectomy with continued surveillance is recommended for patients with colorectal cancer or a high grade adenoma.

Surveillance for Extracolonic Tumors

- ▶ Annual screening for endometrial cancer with endometrial biopsy, transvaginal ultrasound and CA125. Begin at age 30-35 or 10 years younger than the first diagnosis in the family.

PTEN hamartoma tumor syndrome, including COWDEN syndrome

- ▶ PTEN is a tumor suppressor gene and loss of normal function contributes to oncogenesis.
- ▶ Germline mutations of the PTEN gene is inherited in autosomal dominant fashion.
- ▶ Patients have a variety of skin manifestations such as trichilemmoma, oral fibromas.
- ▶ Increased risk of breast, endometrial, thyroid, kidney and colorectal carcinomas.

Features of Cowden Syndrome

- ▶ Incidence is 1/200-250,000
- ▶ Clinical features included
 - ▶ Enlarged Head Circumference
 - ▶ Benign Neoplasms of the face, hands and feet
 - ▶ A variety of mucocutaneous abnormalities are seen.
 - ▶ Breast Cancer
 - ▶ Kidney Cancer
 - ▶ Thyroid Cancer
 - ▶ Many of the above features are seen in the general population and this diagnosis is often missed.

Li-Fraumeni Syndrome

- ▶ An inherited autosomal dominant disorder which is manifest by a wide variety of cancers that appear at an unusually early age.
- ▶ Mutation of the TP53 gene which is located on chromosome 17.
- ▶ TP53 is a tumor suppressor gene that plays a role in determining the fate of cells that contain damaged DNA. In the absence of normal P53, cells with damaged DNA survive and proliferate
- ▶ Also known as the SBLA Syndrome. (Sarcoma, Breast, Leukemia and Adrenal Gland
- ▶ Patients with this mutation who develop cancer are at a markedly increased risk of developing a second cancer.

Case #1

A 52 year old woman is diagnosed with a triple negative breast cancer.

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CASE #3

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Thank you