



*Familial and Genetic Risks for
Breast Cancer*

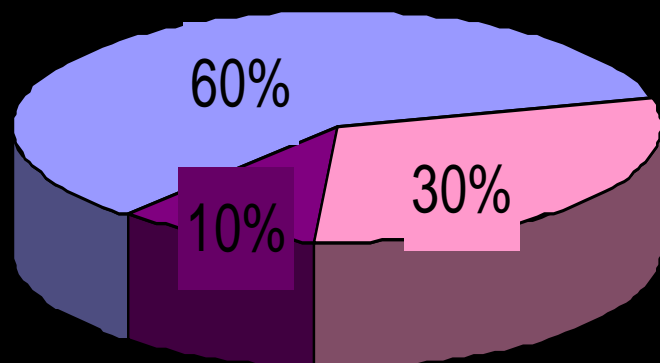
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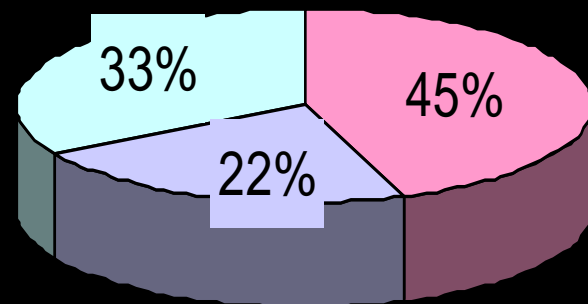
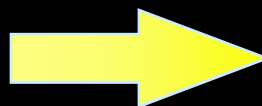
Update in cancer Genetics

- ◆ Review hereditary breast cancer syndrome
- ◆ Discuss updates in genetic testing
- ◆ Discuss new genetic tests
- ◆ Review screening and management recommendations for hereditary breast cancer

Hereditary Breast Cancer



■ Sporadic Breast cancer
■ Familial Breast Cancer
■ Hereditary Breast Cancer



■ BRCA1
■ BRCA2
■ other



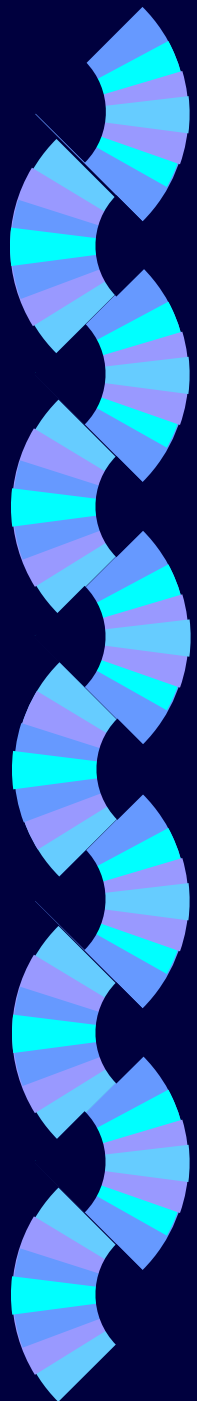
Cancer – the facts

- ◆ The majority of cancers are sporadic.
- ◆ Hereditary or genetic factors may increase an individual's risk for cancer.
 - 5-10 percent of cancers are hereditary- a single gene passed from generation to generation
 - 10-30 percent are familial- multiple low susceptibility genes and environment.

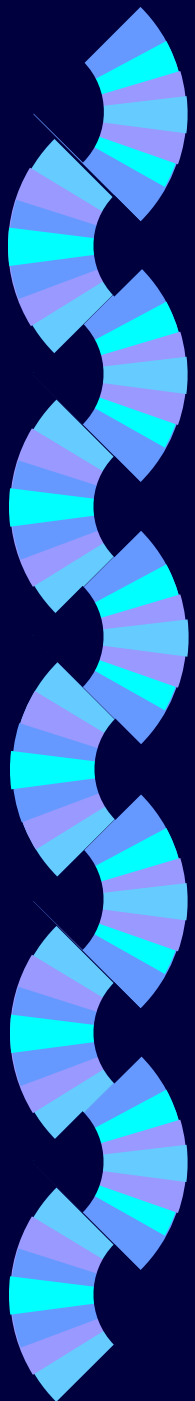


Features of Hereditary Cancers- *Questions to ask your relatives*

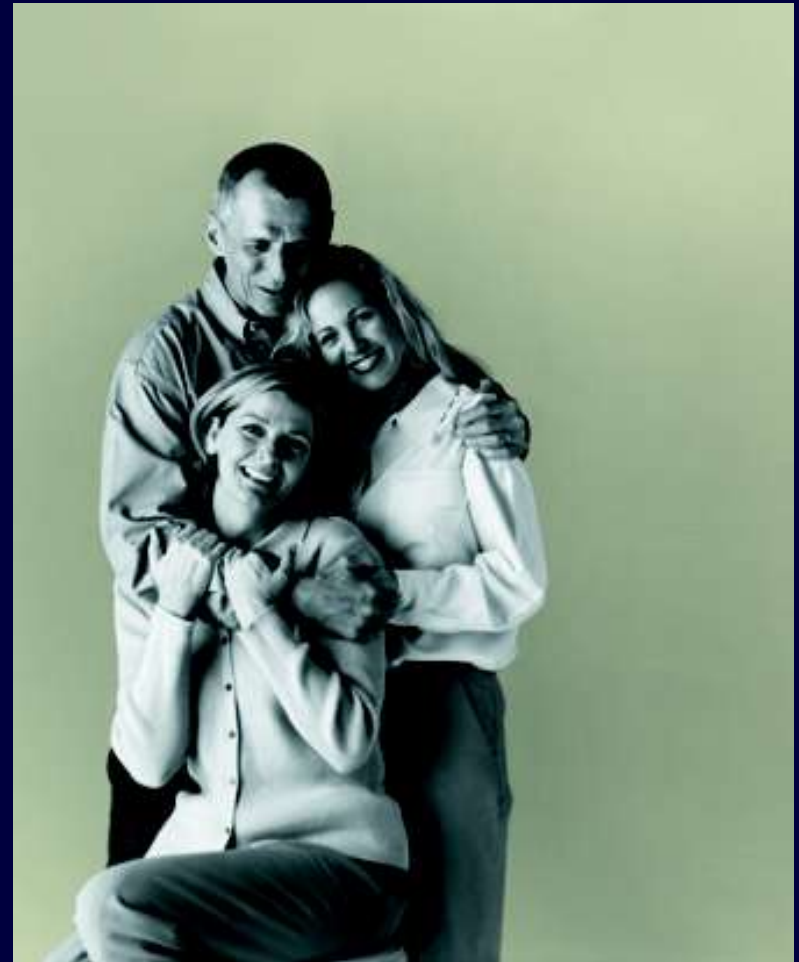
- ◆ **Who had cancer?**
 - Occurs in more than one generation prior to the age of 50.
- ◆ **How old were they at the time of diagnosis?**
 - Occurs at a much younger age than average
 - Less than age 50
- ◆ **If they had breast cancer was it in one breast or both?**
 - Bilateral disease (cancer occurs in both breast) or synchronous cancer
- ◆ **What cancer did they have?**
 - More than one type of cancer occurs in the same close relative
 - breast and ovarian; endometrial and colorectal
 - Occurs in the less commonly affected sex
 - male breast cancer
 - Several rare cancers occur in a family.

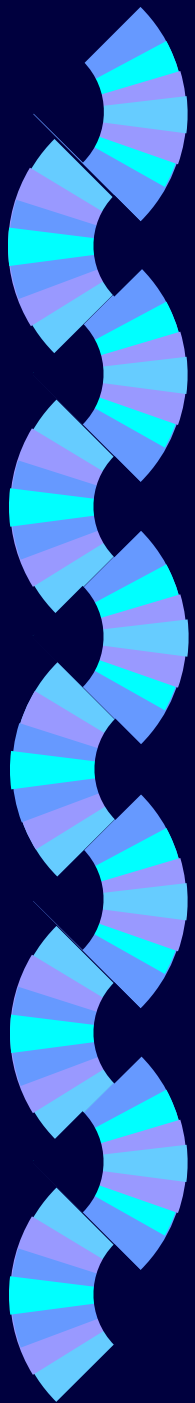


*Jane is 41 and she was
diagnosed with breast cancer at
age 40.*

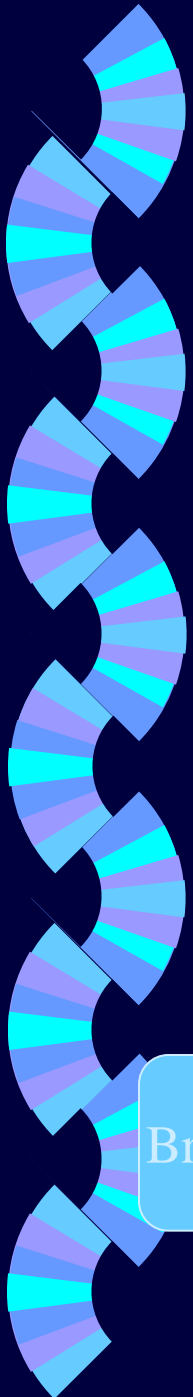


- ◆ Jane has a:
 - 34 year old sister
 - 38 year old brother
 - 60 year old mother
 - 61 year old father
 - No family history of cancer (mom, dad brother and sister)





Jane's mother Marjorie was diagnosed with ovarian cancer at age 61, shortly after Jane's diagnosis.



Ovarian Cancer at 61



Breast Cancer at 40



38



34



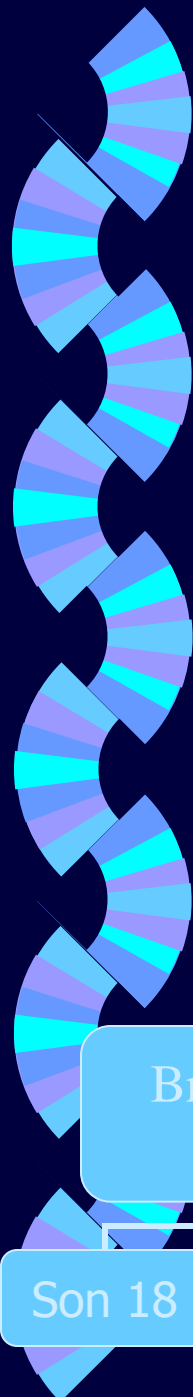
Genetic Testing

- ◆ Based on Jane's personal history of breast cancer and family history of ovarian cancer the option of BRCA1/2 testing was discussed.
- ◆ Jane elected to proceed with Genetic Testing
 - Alteration was noted in the BRCA2 gene



Who Else Has Jane's Gene

- ◆ Genetic testing is offered to all first degree relatives which means, mom, dad, brother, sister, and children if at least 18 years of age.
- ◆ Genetic testing is also offered to all second degree relatives- aunts, uncles, grandparents.



Ovarian cancer 61-
BRCA2



Breast cancer 40-
BRCA2



38- negative for
BRCA2 alteration



34- BRCA2

Son 18

Daughter 16

Son 15

Daughter 14

Daughter 10

Son 8

Son 6

BRCA1-2 Mutations Increase the Risk of Early-Onset Breast Cancer

By age 40



By age 50



By age 70



Population Risk 0.5%

2%

7%

Hereditary Risk 10%-20%

33%-50%

56%-87%

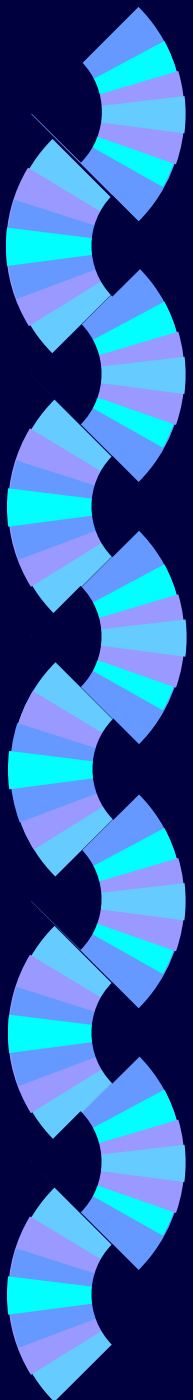
BRCA1-2 Mutations Increase the Risk of Ovarian Cancer

By age 70



Population Risk 1%

Hereditary Risk ~44% (*BRCA1*)
27% (*BRCA2*)





Risks of Other Cancers

- ◆ Male breast cancer (*BRCA1*, *BRCA2*)
 - $\leq 6\%$ by age 70
- ◆ Prostate (*BRCA2*, possibly *BRCA1*)
 - 20% by age 80; 3- to 7-fold increase in relative risk
- ◆ Pancreatic cancer (*BRCA2*)
 - 2-3% by age 80; 3- to 4-fold increase in relative risk
- ◆ Colon
 - Little or no increased risk

Am J Hum Genet 1997;61: 120-8

JNCI 1999;15:1310-6

Dis Colon Rectum 1999;42:1041-5



BRCA1 and BRCA2 Mutations Increase the Risk of a Second Cancer

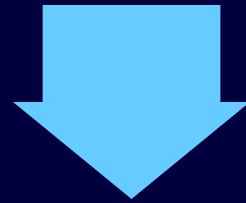
- ◆ Increased risk of ovarian cancer following breast cancer
 - 10-fold increase in risk compared to women without mutations
 - lifetime risk is at least 16%
- ◆ Increased risk of second breast cancer
 - 20% (*BRCA1*) or 12% (*BRCA2*) within 5 yrs
 - Up to 64% (*BRCA1*) or 52% (*BRCA2*) by age 70

JNCI 1999;15:1310-6
J Clin Oncol 1998;16:2417-25
Lancet 1998;351:316-21
J Clin Oncol 1999;17:3396-402
Lancet 1994;3343:692-5



Chemoprevention of Breast Cancer

Tamoxifen



- “High risk” women without cancer:
45% reduction in breast cancer
- Breast cancer patients with *BRCA1-
BRCA2* mutations:
*75% reduction in risk of contralateral
breast cancer*

“We believe that tamoxifen will also reduce the occurrence of primary cancers in *BRCA1* and *BRCA2* mutation carriers.”

Lancet 2000; 356:1876-81

JNCI 1998; 90:1371-88



Prophylactic Mastectomy

- ◆ Removes most but not all breast tissue
- ◆ Total (simple) mastectomy appears more effective than subcutaneous mastectomy
- ◆ Shown to reduce risk of breast cancer in women with *BRCA* mutations



Prophylactic Oophorectomy

- ◆ Reduces risk of ovarian cancer by ~95% in women with *BRCA* mutations

“The risk of ovarian cancer in women from families with hereditary ovarian cancer syndromes...is sufficiently high to recommend prophylactic oophorectomy in these women after child-bearing is completed.”-

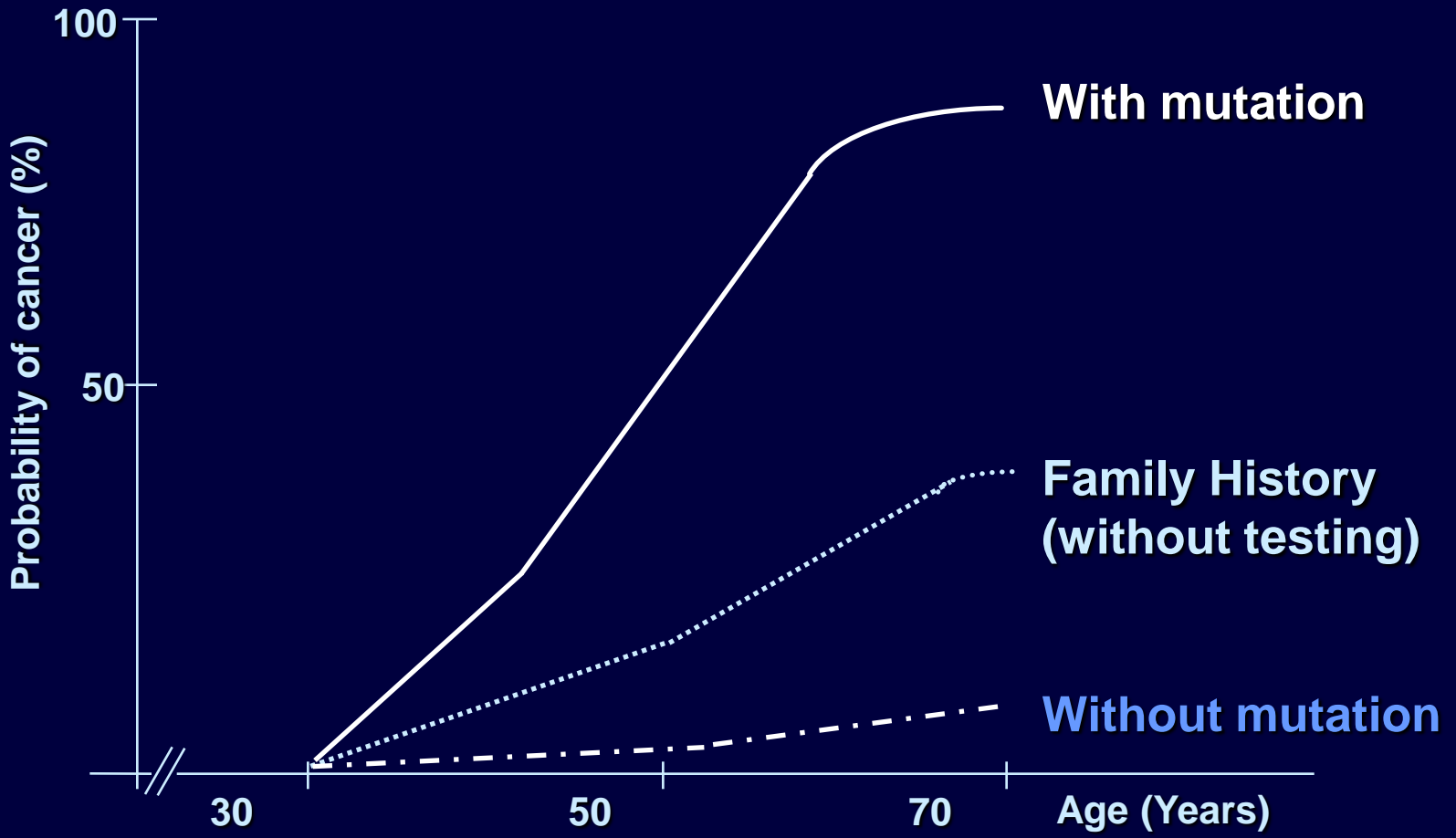
NIH Consensus Guidelines, *JAMA* 1995;273:491-7

- ◆ Prophylactic oophorectomy also reduces the risk of breast cancer in women with *BRCA* mutations by nearly 50%

AJHG 2000;67(S2):59

JNCI 1999; 91:1475-9

The Importance of Genetic Diagnosis



Each child of a carrier has a 50-50 chance of being at increased risk (or not).

Adapted with permission from Ponder B: Genetic Testing for Cancer Risk. *Science* 1997; 278:1050-4.
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What is new in HBOC

- ◆ BART analysis- large rearrangement analysis
 - Ordered separately from comprehensive DNA sequence analysis.
 - Occur in a small percentage of patients tested for HBOC
 - Large rearrangement in BRCA1 and BRCA2 account for:
 - 16% of alterations in high risk African Americans
 - 10% of high risk Latin Americans
 - 9.4% of high risk Central European descent
 - 10.1% of Western European descent
- ◆ Only 66% of hereditary families are attributed to BRCA1/ BRCA2- 33% from rare genes or genes that are yet to be identified
 - Family history is the key
 - Family history and genetic testing together determine screening



*BRCA1/BRCA2 are not the only genes
for hereditary breast cancer*

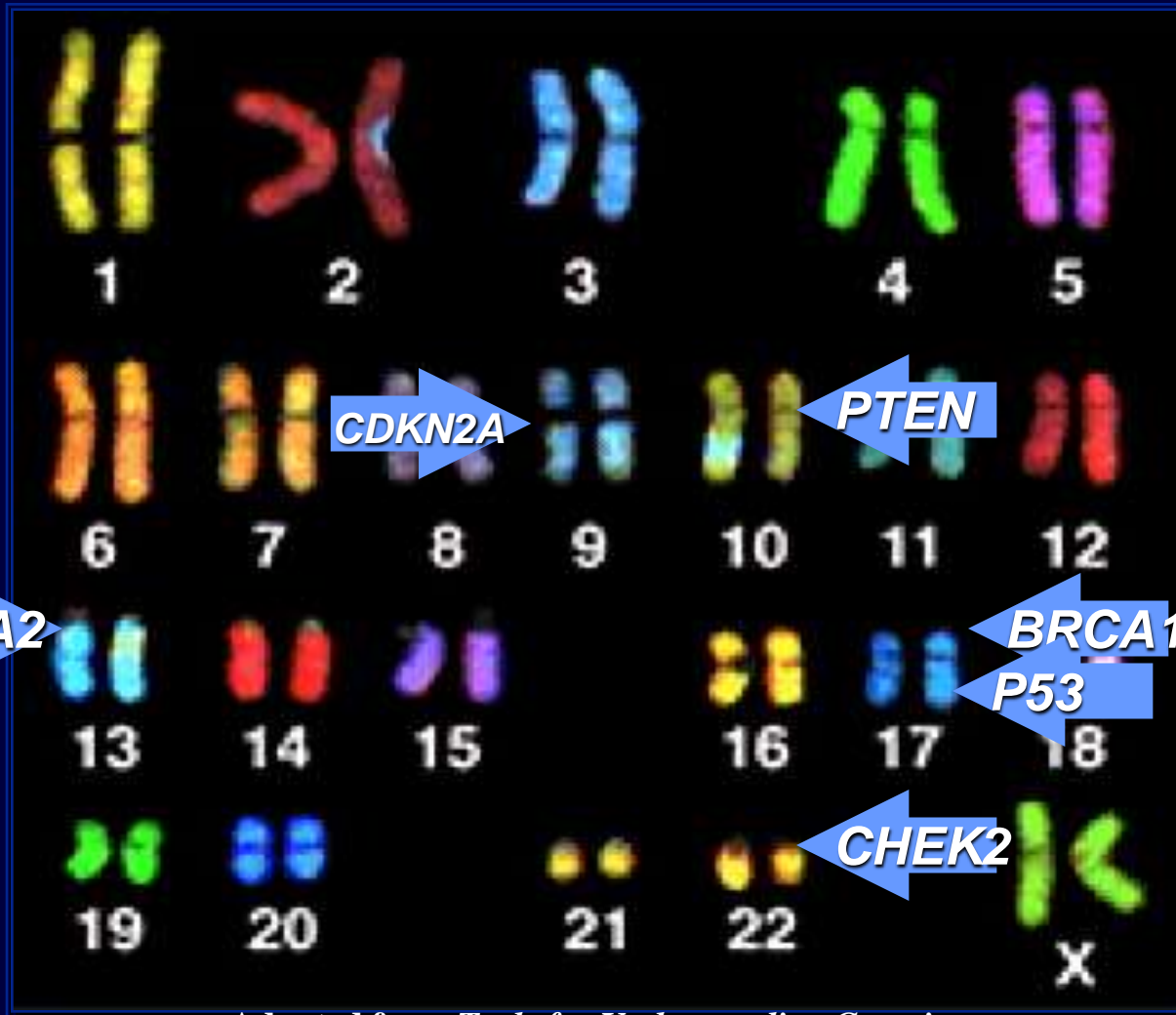
- ◆ Family history determines what genes are the best to test for and sequence of testing
- ◆ Family history also is the key for management and screening recommendations



Inherited Breast Cancer Syndromes

- ◆ Hereditary Breast and Ovarian Cancer
 - BRCA1 and BRCA2 Genes
- ◆ Hereditary Breast Cancer
 - Cowden Syndrome
 - PTEN Gene
 - Li-Fraumeni Syndrome
 - P53 Gene
- ◆ Other Genes- Questionable clinical utility- helpful in screening and management
 - P16
 - CHEK2

Cells Have Two Copies of Every Gene



Adapted from *Tools for Understanding Genetics*
National Human Genome Research Institute
Office of Science Education and Outreach
www.nhgri.nih.gov/DIR/VIP



Cowden Syndrome

- ◆ Associated with alterations in the PTEN gene
 - Increased risk for
 - Breast Cancer- 25-53% risk of breast cancer
 - Thyroid Cancer- 5-10% of thyroid cancer
 - Endometrial (Uterine) Cancer- 5-10% risk of uterine cancer
 - Colon cancer
 - Clinical and research testing available



Benign tumors associated with Cowden Syndrome

- ◆ **Breast**
 - Fibrocytic breast
 - Fibroadenoma
 - Papilloma
- ◆ **Thyroid**
 - Multinodular goiter
 - Thyroid nodules
- ◆ **Uterus**
 - Fibroids
- ◆ **Colon**
 - Polyps
- ◆ **Skin**
 - Lipomas- fatty tissue deposits under the skin
 - Papillomas- wart like growths on the skin
 - Trichilemmomas- growths of the hair follicle



Li- Fraumeni

- ◆ Associated with alterations in the P53 gene

Associated Cancers

- Early onset sarcoma- soft tissue cancer
- Early onset Breast cancer- before age 30
- acute leukemia
- brain tumors
- adrenocortical carcinoma
- unusually early onset of other adenocarcinomas
- other childhood cancers



Updates Li-Fraumeni Syndrome

- ◆ New literature suggests that some individuals who carry the gene may not develop cancer or may develop cancer at an older age.
- ◆ Previous to this it was always thought that individuals who carried the gene developed cancer prior to 45 and most often had more than one cancer prior to 45



Hereditary Breast and Melanoma

- ◆ Familial atypical mole malignant melanoma syndrome (FAMMM)
 - Associated with alterations in the CDKN2A/p16 gene
 - Accounts for 20-40% of melanoma prone families
 - Screening recommendations
 - Based on family history
 - Skin screening and sun protection
 - Breast screening
 - pancreatic screening- no proven way to screen for pancreatic cancer still being evaluated in research setting



Hereditary Breast Cancer

- ◆ CHEK2 alterations

- 1100delC

- Breast cancer risk

- Carriers have a 37% cumulative risk of developing breast cancer by age 70

- Concern with testing arise from:

- Other associated cancers risks not clearly defined yet

- There have been reports of increased risk for colon, prostate, lung but these have not been characterized with the same level of detail as breast cancer risk.

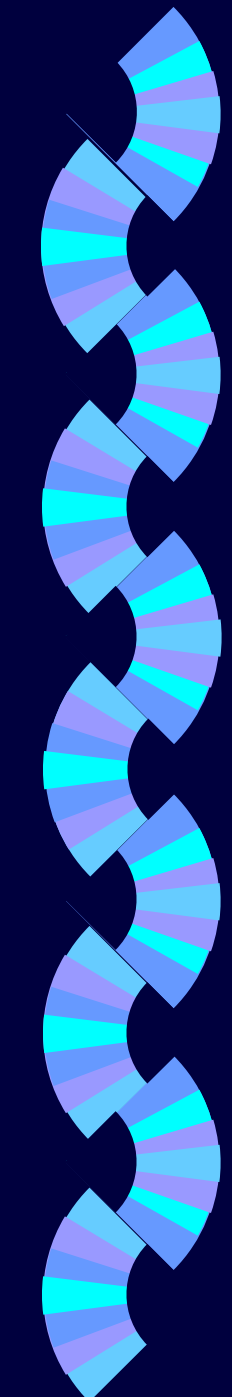
- How do you screen?

- Increased breast surveillance- this would be recommended based on family history
- Risk for other cancers unknown
- Therefore screening and management are not altered



Susceptibility genes marketed as SNPs for personalized medicine

- ◆ 23 and me
 - Carrier status on 24 conditions
 - Drug response – 19 types
 - 48 traits
 - 98 disease risks
- ◆ Decode genetics-
 - Assess the risk for common forms of breast cancer, and allows a woman concerned about breast cancer to better understand her lifetime risk of developing the common forms of the disease.



Know what the test can and cannot tell you

- ◆ 23 and me
 - Under Disease risk
 - Breast cancer risk*
 - Breast cancer risk modifiers
 - * = established research reports give you information about conditions and traits for which there are genetic associations supported by multiple, large peer-reviewed studies. Because these studies are regarded as reliable 23 and me uses them to develop a quantitative estimates and explanations of what they mean for you.
 - = preliminary research reports- based on peer-reviewed published research where the findings still need to be confirmed by the scientific community and include topics with contradictory evidence.



Decodeme

- ◆ You request the test you want
 - Cancers, heart and circulation, blood, bones, joints muscles, digestive and metabolic, etc
 - Breast cancer- test based on seven DNA sequence variations, called SNPs,



*Comments from Debbie Saslow, PhD,
director of breast and gynecologic cancer*

- ◆ "The manufacturer's supporting materials are incorrect and mischaracterize the American Cancer Society guideline for breast screening using MRI.
- ◆ The materials grossly overestimate the lifetime risk of breast cancer associated with the relative risks calculated using the test.
- ◆ The manufacturer claims that the test will provide relative risk assessment values ranging from 0.4 to 4.0, meaning it can indicate if women are at as low as 40 percent of the average risk, or up to four times the risk.
- ◆ The manufacturer claims that the test will be helpful in identifying the 5 percent of women at the highest risk, who can then consider breast MRI screening or drugs to lower the risk of breast cancer (e.g.: tamoxifen).



Are we ready

- ◆ Research is still needed on SNP's and how they will alter medical management
- ◆ Individuals who have done both tests received very different risks
 - One stated no risk for cardiac disease and increased risk for prostate cancer
 - Other one stated no risk for cancer but significant risk for cardiac disease



Recommendations for MRI- ACS

- ◆ The American Cancer Society guideline on screening women at high risk for breast cancer does not recommend for or against screening women with a 4 to 6 fold increased risk, such as women with a history of atypical hyperplasia or women who have extremely dense breasts.
- ◆ This is in part because that risk is considered moderately increased rather than high
- ◆ And in part because there are no MRI screening trials that included women with these clinical factors.
- ◆ All of the evidence supporting MRI screening for women at increased risk is derived from women at high risk based on family history or BRCA mutation status.



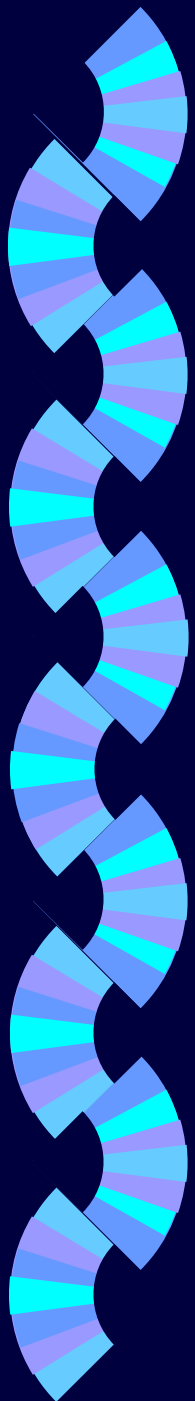
Genetic testing and discrimination

- ◆ Legal issues: Genetic Discrimination
 - Employability
 - Health insurance
 - HIPPA, GINA and state laws
- ◆ Insurance coverage and payment for commercial genetic testing
- ◆ Test results disclosure and follow-up. Who will you tell?



Closing Remarks

- ◆ Family History is the key
- ◆ Cancer Family Histories tend to be complex and they change over time.
- ◆ Documentation of medical records is essential for good cancer risk assessment.
- ◆ It is critical to discuss the risks, benefits and limitations of genetic testing.
- ◆ Discuss Genetic Discrimination and laws to protect against discrimination.



*Knowledge
is Power.*

And Hope.

