Breast Cancer and Genetics

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Objectives

- Discuss breast cancer: hereditary and non hereditary breast cancer
- Discuss risk factors that increase breast cancer
- Discuss the genetics of breast cancer

At a Glance

Estimated New Cases in 2018	266,120
% of All New Cancer Cases	15.3%

Estimated Deaths in 2018	40,920
% of All Cancer Deaths	6.7%

Female Breast Cancer Statistics Facts

SEER Data 2018

(Surveillance, Epidemiology, End Results Program)

Prevalence

In 2015, there were an estimated 3,418,124 women living with female breast cancer in the United States.

In 2018, it is estimated that there will be 266,120 new cases of female breast cancer and an estimated 40,920 people will die of this disease.

SEER 2018

Symptoms

According to the American Cancer Society, any of the following unusual changes in the breast can be a symptom of breast cancer:

- swelling of all or part of the breast
- skin irritation or dimpling
- breast pain
- nipple pain or the nipple turning inward
- redness, scaliness, or thickening of the nipple or breast skin
- a nipple discharge other than breast milk
- a lump in the underarm area

Types of Breast Cancer

- Invasive/Infiltrating Ductal Carcinoma
- Inflammatory Breast Cancer
- Ductal Carcinoma in situ (DCIS)
- Lobular Carcinoma in situ (LCIS)
- Phalloides Tumor
- Paget's Disease

Male Breast Cancer

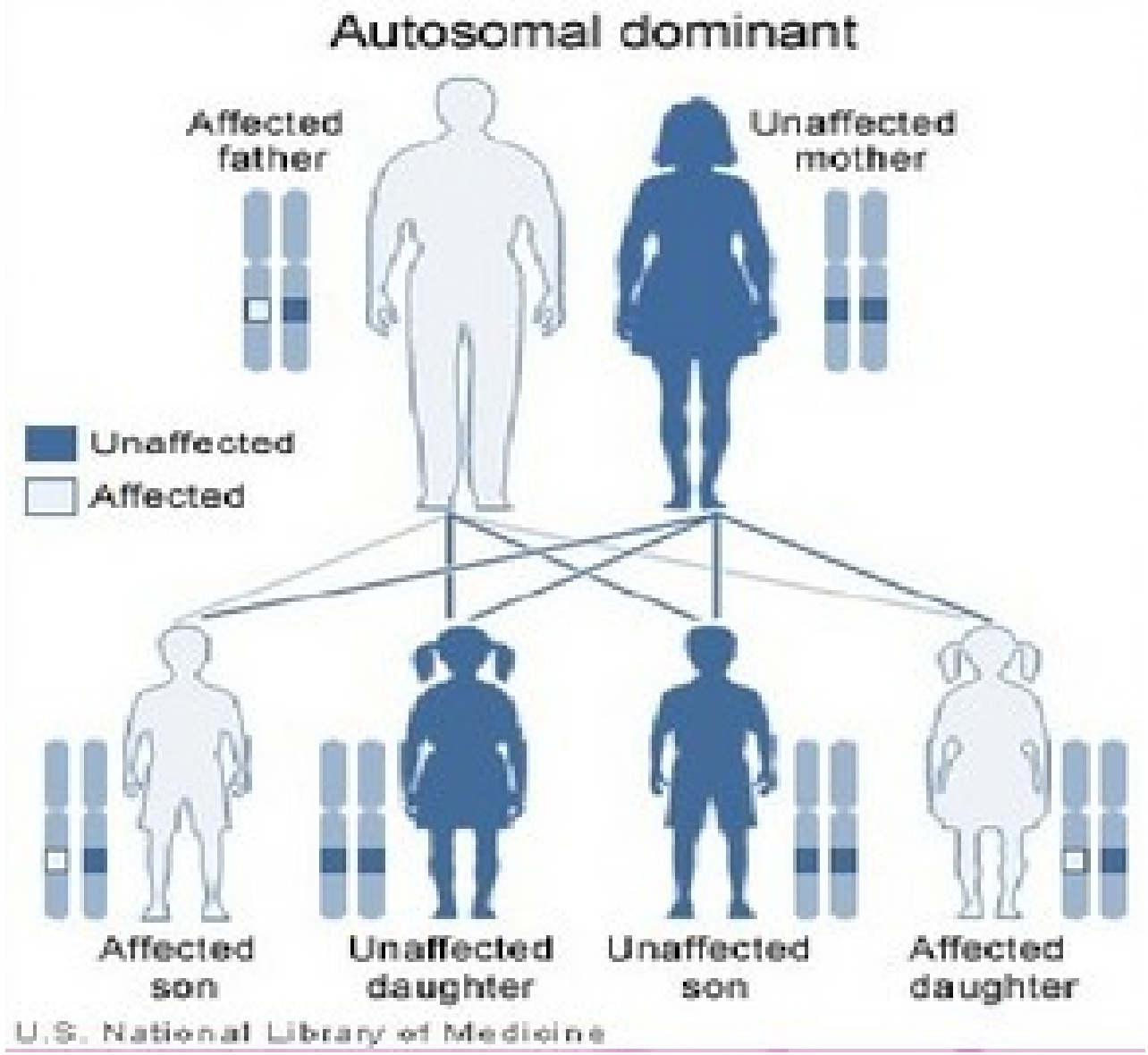
- Incidence – rare disease; 1% cases
- Jewish men have higher incidence (2-3/100,000 per year) than other white ethnic group

Breast Cancer

- Of all cases of breast cancer -90% are sporadic
- Hereditary breast cancer is – 5-10% of the cases

Risk Factors

- Age (incidence increases with age)
- Family History
  - 15-20% of MBC pts have a close relative with BC
  - If First-degree relative, risk increases 2-3 times
- Lifestyle: Obesity & Alcohol Intake
- Disease: Liver disease & Testicular Disorders
- Environmental Influences:
  - Radiation exposure
  - Hot environments
  - Exhaust fumes
- Hormonal
  - Estrogen & Prolactin



Hereditary Breast cancer

In this case there is only one non working gene

Genetic Mechanism:

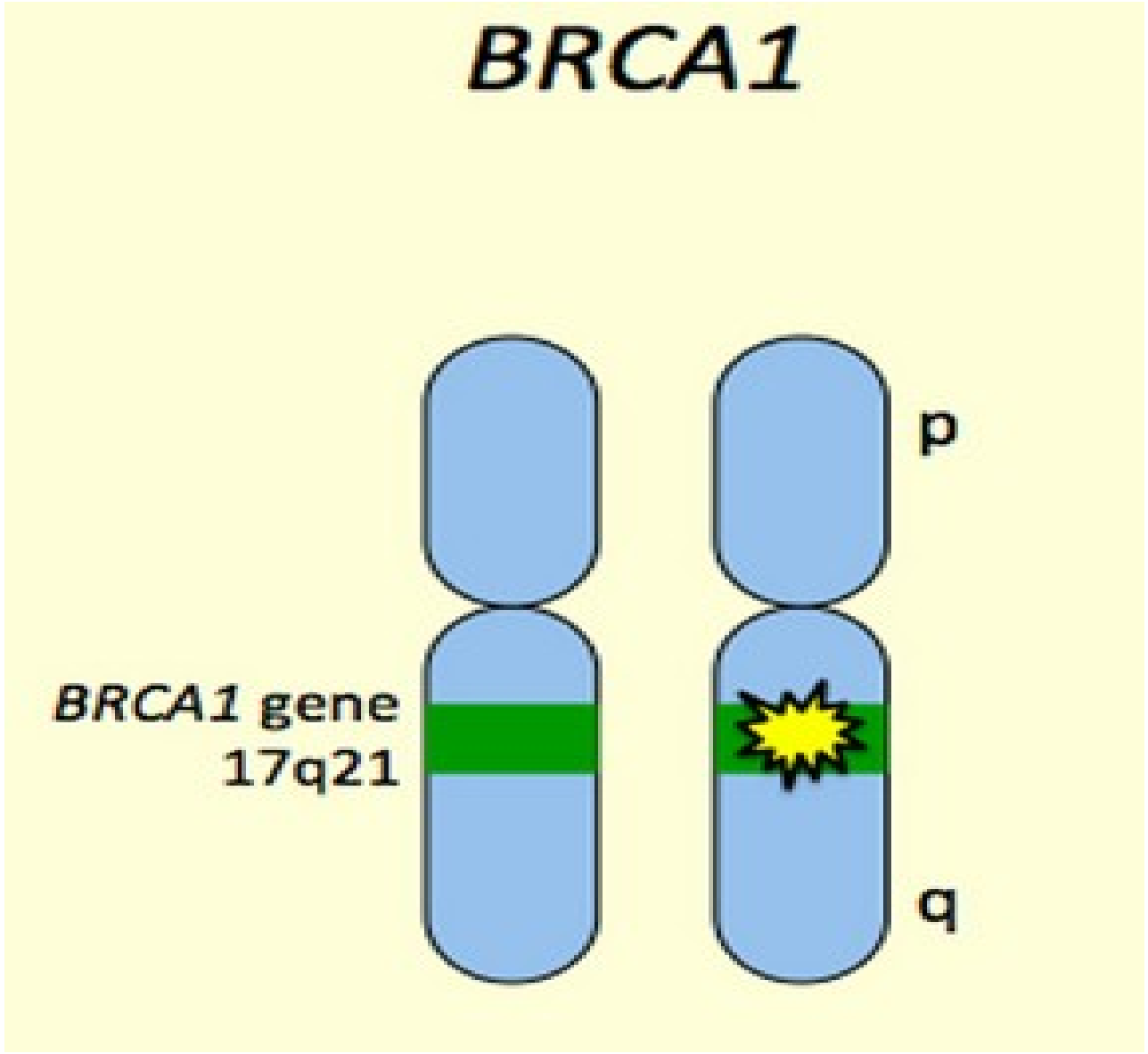
- Development of breast cancer usually occurs through disruptions of signal transduction pathways or DNA repair mechanism
- Cancer cells arise from mutations in genes that encode or control transcription factors, cell cycle checkpoint proteins, growth factors, repair proteins or telomerase may disrupt the cell cycle

Contd. Genetic mechanism:

- Breast cancer is multifactorial (approximately 90%)
- Partial genetic & environmental factors
- Had many mutations (nonsense & frameshift)
- Polymorphic & incomplete penetrant

Mechanism of action

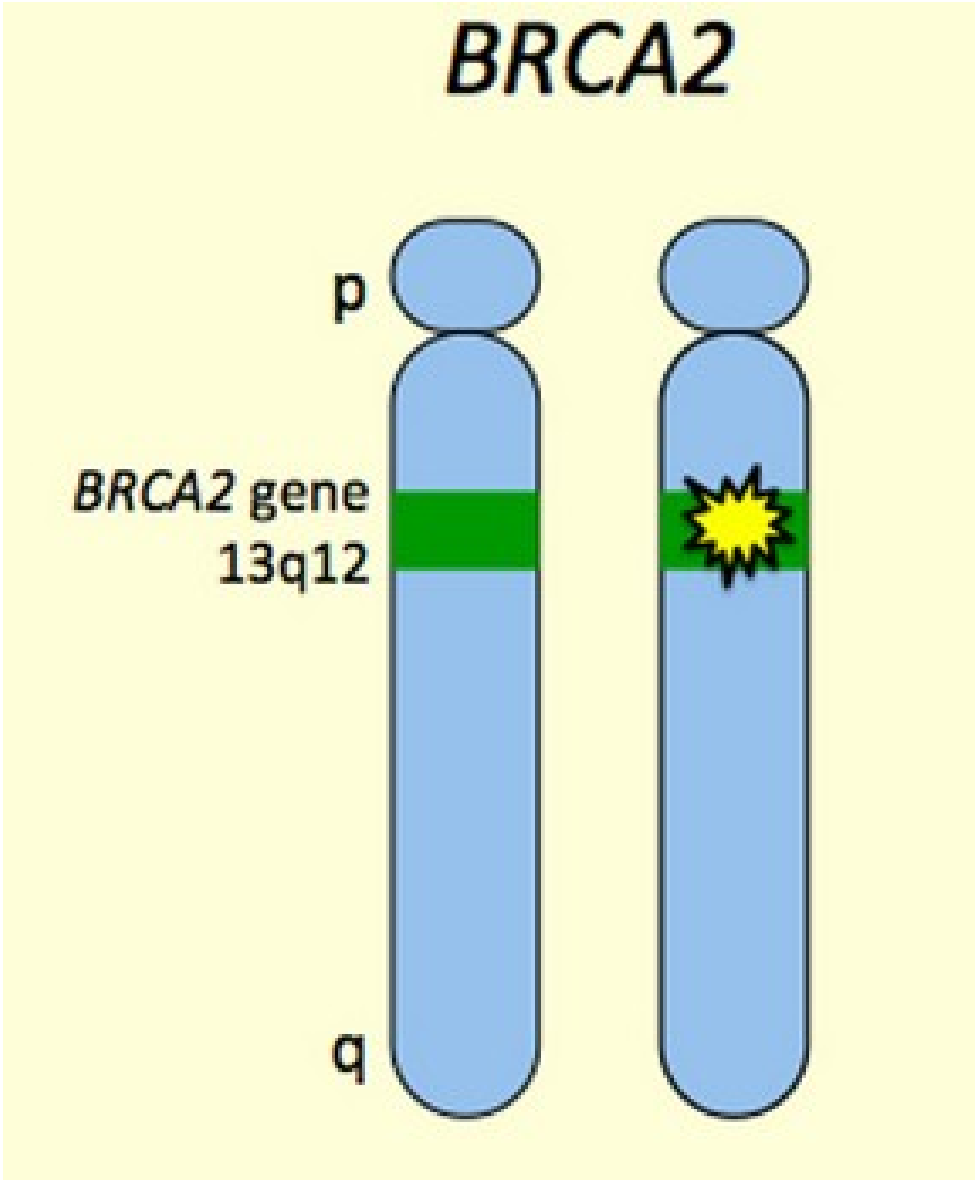
- BRCA 1 & 2 are tumor suppressor genes
- Common mutation of these genes result from deletion of two adjacent bases, altering the reading frame & shortening of protein
- Mutations of these 2 genes account for 30-50% of hereditary breast cancer



BRCA1- chromosome 17 (17q21) OMIM 113705

Encodes a nucleic protein activating transcription of the genes that respond to p53 protein

Necessary for DNA repair (mending the double stranded breaks that threatens chromosome stability



BRCA 2-chromosome 13 (13q12)
OMIM 600185

Encodes a nucleic protein larger than BRCA1

Work similar to BRCA1, pulls apart daughter cells as mitosis completes (explain-aneuploidy in cancer)

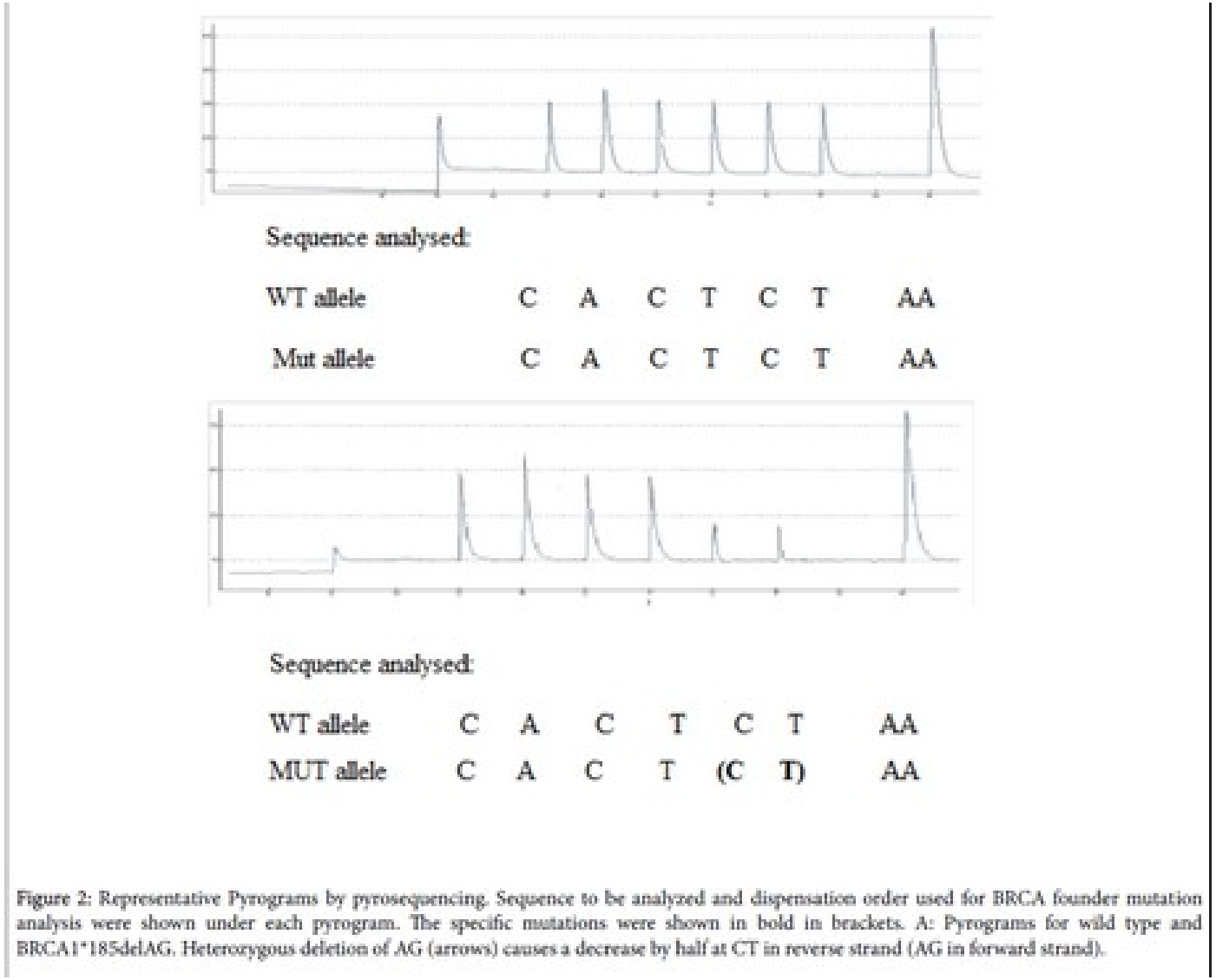


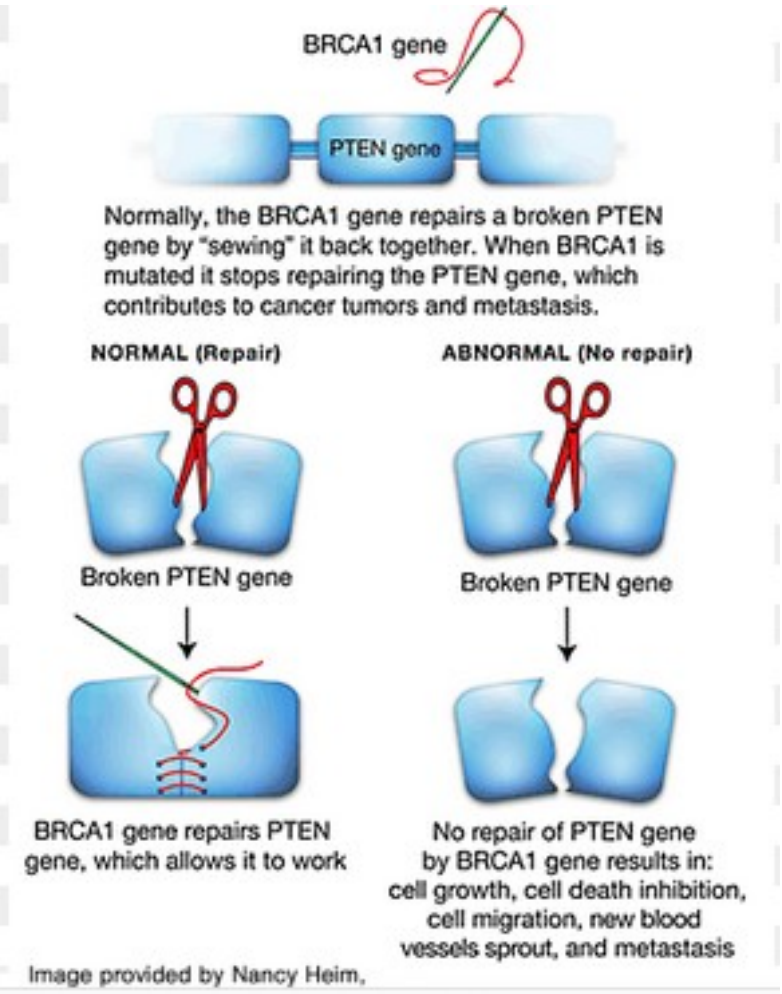
Figure 2: Representative Pyrograms by pyrosequencing. Sequence to be analyzed and dispensation order used for BRCA founder mutation analysis were shown under each pyrogram. The specific mutations were shown in bold in brackets. A: Pyrograms for wild type and BRCA1*185delAG. Heterozygous deletion of AG (arrows) causes a decrease by half at CT in reverse strand (AG in forward strand).

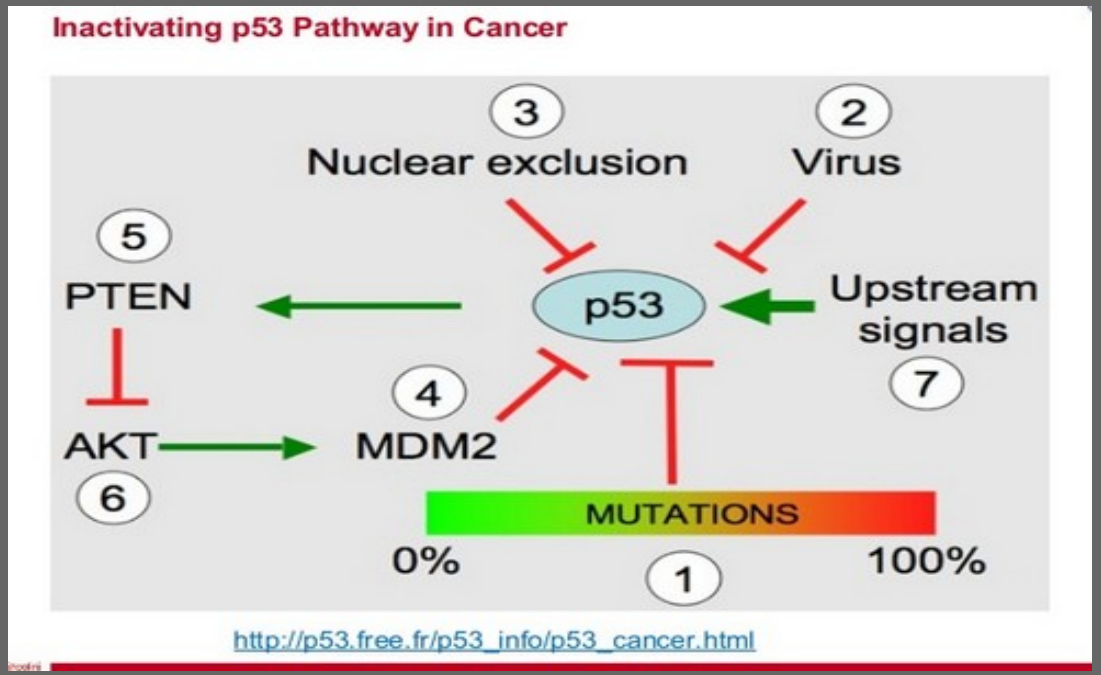
More mechanism….

Most alterations are unique & associated with a common haplotype likely descended from a common ancestor "founder mutations"

Detected in Icelanders, Ashkenazi Jews, Finns & French-Canadians

Propensity to acquiring the same mutation may stem from the composition of bases around the mutation or secondary/tertiary structure of the protein





Other genes

P53-mutation present in Li-Fraumeni syndrome

PTEN mutations – rare on male breast cancer unless Cowden syndrome

Other genes:

- PTEN mutations
  - Rare in MBC unless Cowden syndrome
- P53 mutations
  - Li-Fraumeni syndrome
  - Uncommon in MBC
- CHEK2
  - Encodes a checkpoint serine/threonine kinase which responds to DNA damage via the ATM-P53 pathways

Role of nurse practitioner

Role of nurse practitioner in risk assessment screening

Gail Model - The model is an interactive tool designed by scientists at the National Cancer Institute and at the National Surgical Adjuvant Breast and Bowel Project to estimate 5 years lifetime risk (up to 90yo) of developing invasive breast cancer.

- Focus on non-genetic risk factors
- Limitation: age of onset, 2nd degree relatives, paternal history, ovarian cancer

http://brca.nci.nih.gov/brc/start.htm

Contd…risk assessment model:

Claus Model

- Lifetime breast cancer risk estimates are based on family history
- Considers the number and ages of onset of breast cancer in first- and second-degree relatives.
- Distinguishes between maternal and paternal relatives (up to 2 relatives)

Claus.EB et al.Cancer 73:643.651 (1994)

Myriad Risk Tables

- Identifies the chance of detecting a BRCA 1 or 2 mutation in women with family history of early onset breast or ovarian cancer
- Limitations: >50 years old not included, clinical data not validated

www.myriad.com

Educate patients and community about the symptoms of breast cancer

Prevention & early detection

Diagnosis

- Clinical Breast Examination
- Imaging
    - Screening/Diagnostic Mammogram
    - Tomosynthesis (3D MMG)
    - Ultrasound
    - MRI -Magnetic Resonance Imaging
- Biopsy (Surgical excision or FNA)

Hereditary Breast Cancer Management

- Surveillance (CBE, yearly mammogram)
- Chemoprevention – Tamoxifen, aromatase Inhibitor
- HRT data remains insufficient in BRCA 1-2 mutations
- Lifestyle modification (exercise, weight-loss, less alcohol, increase fiber and vegetable in diet
- Prophylactic surgery
- Genetic Counseling & or genetic testing

Staging

- Helps to determine appropriate treatment, assess whether treatment is effective, establish prognosis and outcomes, and evaluate the approach to care
- System used for MBC is similar to the one used for FBC
  - TNM: Tumor, Node, Metastasis

Testing

- Cancer diagnosis utilizes DNA microarrays to scan both genotype and gene expression patterns
- Estrogen / Progesterone Receptor Tests
- HER2 Tests

Genetic Testing

- Breast cancer, typically tests for the mutant genes (BRCA 1/ 2)

- Considered for following reasons:
  - Female breast cancer before age 50
  - 2+ women on the same side of the family, diagnosed with BC before age 50
  - Multiple primary tumors
  - Ovarian cancer
  - Ashkenazi Jewish ancestry and one relative diagnosed with either breast or ovarian cancer
  - Male breast cancer (any age)
  - Early-onset breast cancer (before 50) and ovarian cancer in the same blood line
  - Pancreatic cancer and a family history of breast cancer before age 50
  - Early-onset prostate cancer (before 55) and a family history of breast cancer before 50
  - Family member with a known mutation in a breast cancer susceptibility gene

Cost of Genetic Testing

90-94 percent of insurance company covers genetic testing including Medicare

- Comprehensive testing $3120
- 3 mutation testing $535
- Single site $440

Payment plan is available

www.Myriad.com

Treatment of Breast Cancer

- Chemotherapy
  - Medications include Cyclophosphamide, methotrexate, and fluorouracil most commonly with a 5 year survival rate of more than 80% following surgery

- Hormone therapy (Phenotypic treatment)
  - First hormonal therapies were ablative: orchidectomy, adrenalectomy, and hypophysectomy
  - Tamoxifen, which blocks estrogen receptors, is given to patients for 5 years following surgery
  - Uses of aromatase inhibitors are useful in treatment of FBC but have insufficient research in MBC
  - Used also for advanced metastatic disease: main treatment for the past 5 decades

- Targeted therapy (Genotypic treatment)
  - HER2 positive tumors
    - treated with trastuzumab (Herceptin), which is a monoclonal antibody
    - prevents the activity and arresting the growth of HER2 cells
    - drug is high cost and tolerance considerations

PARP Inhibitors

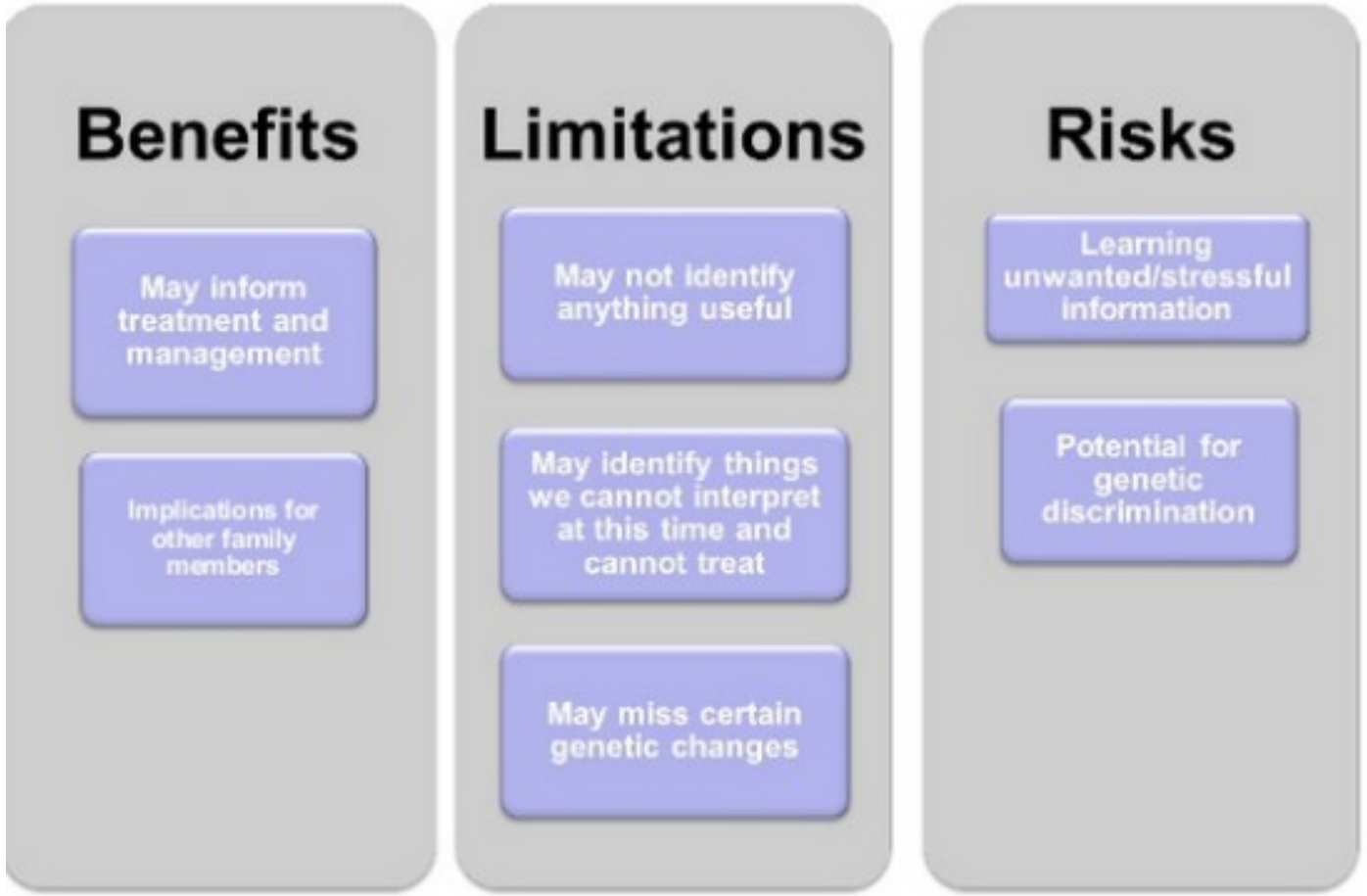
First FDA approved drug cleared for the treatment for patients with advanced breast cancer caused by BRCA1 & 2 mutations

- Belongs to the class PARP inhibitors that block the enzyme involved in repairing damaged DNA
- Also approved in certain ovarian cancer treatment

McGinley, L. January 12, 2018 Washington Post

Cont'd. Treatment

- Radiation therapy
  - Men with nonmetastatic breast cancer were 6 times more likely to receive radiation therapy than women
  - Radiation therapy has not been shown to improve survival, in fact some studies showed 3-20% locoregional recurrence rates for radiotherapy in men



Genetic Testing Outcome???

Legal???

Legislation that protects against genetic discrimination

Would you do it?

Breast Cancer

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References

Thank you