THE UNIVERSITY OF KANSAS
CANCER CENTER

NCI Designated Cancer Center

Updates in Cancer Genetics & Genomics

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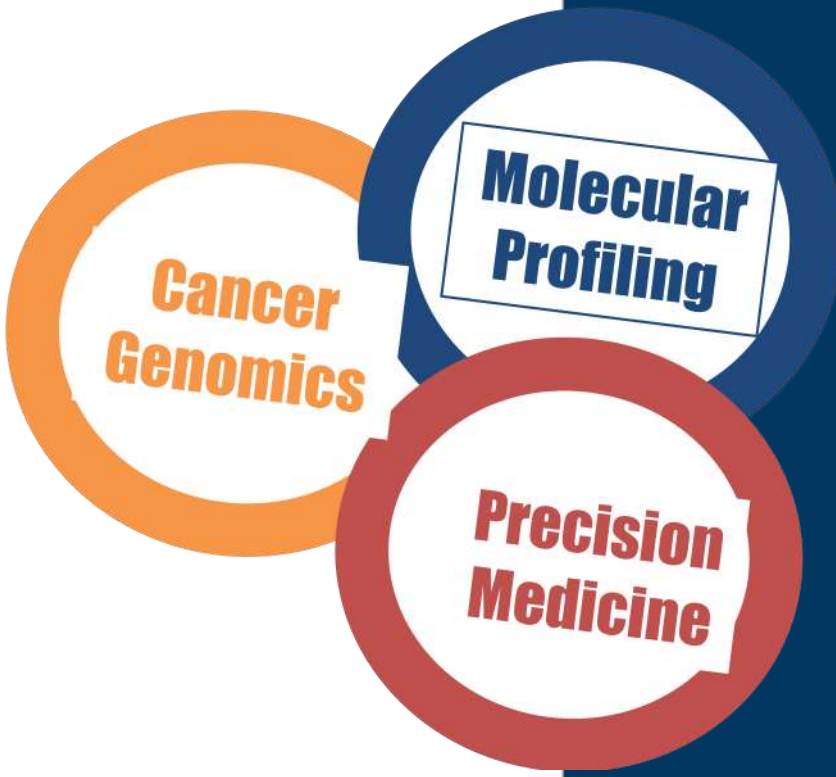
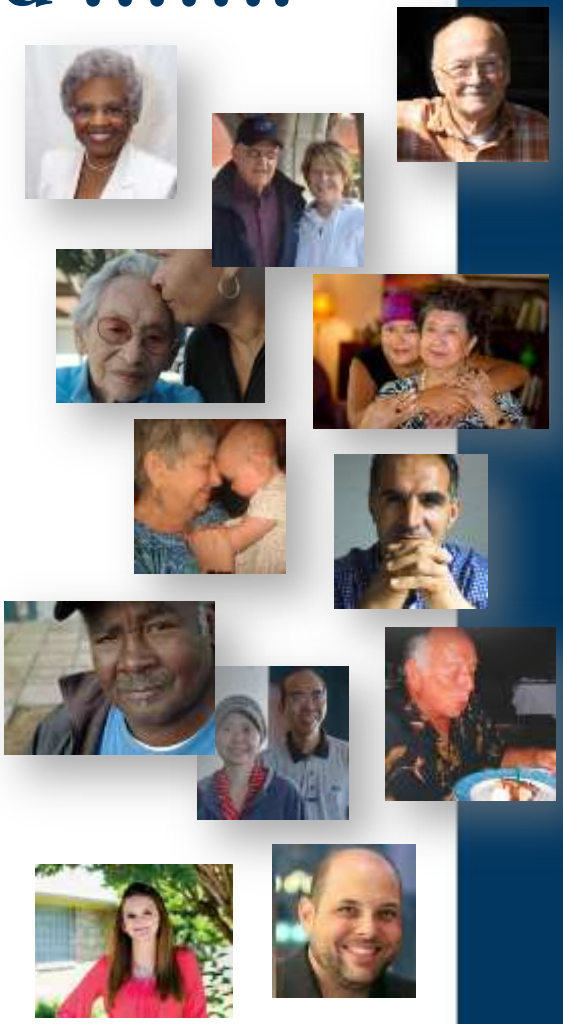


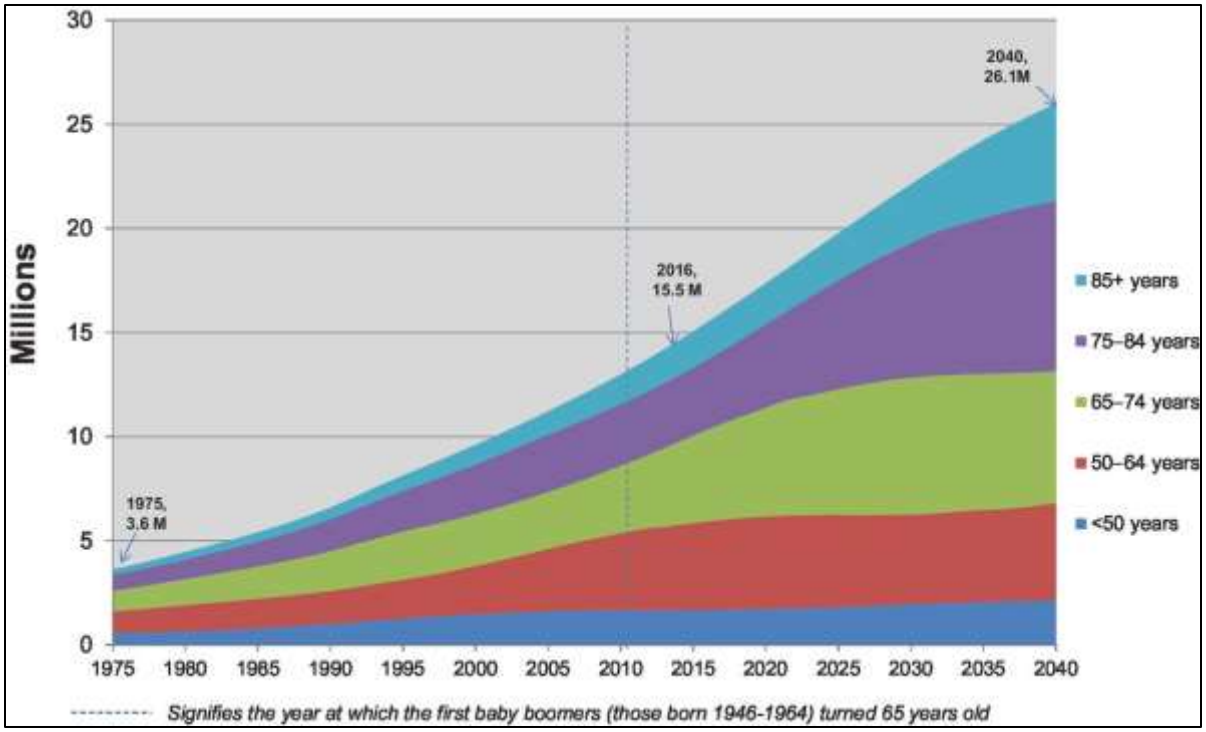
A Cancer Survivor is Anyone Diagnosed with Cancer and …….

- Living cancer-free for the remainder of life
- Living cancer-free for many years but experiencing one or more serious, late complications of treatment
- Living cancer-free for many years, but dying after a late recurrence
- Living cancer-free after the first cancer is treated, but developing a second cancer
- Living with intermittent periods of active disease requiring treatment
- Living with cancer continuously without a disease-free period



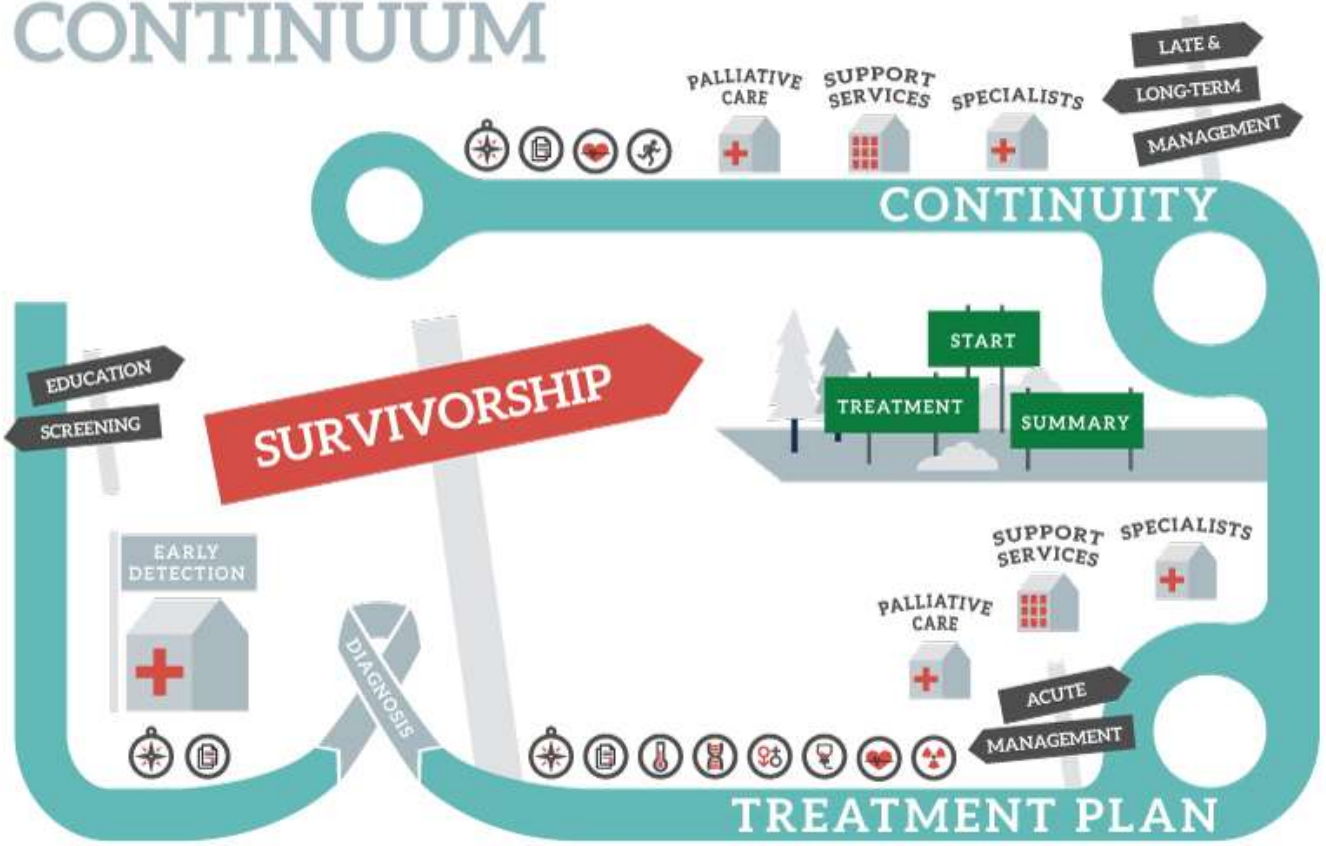
www.cancer.org

Growing Survivorship Population

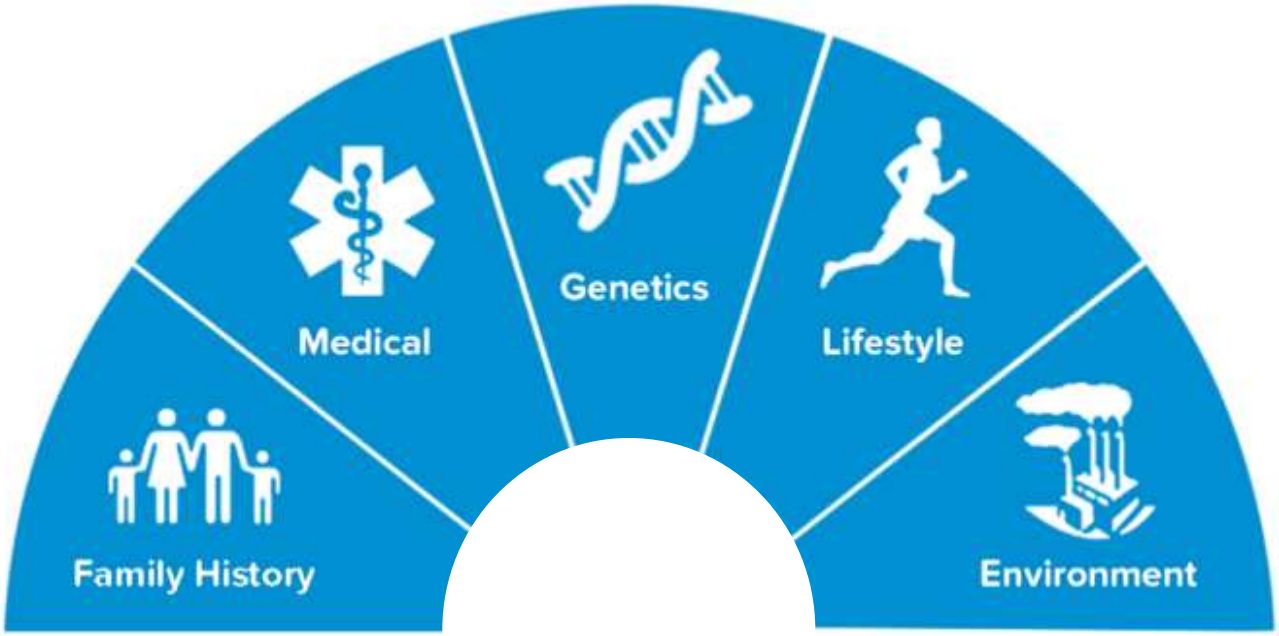


Bluethmann Cancer Epidemiol Biomarkers Prev 2016

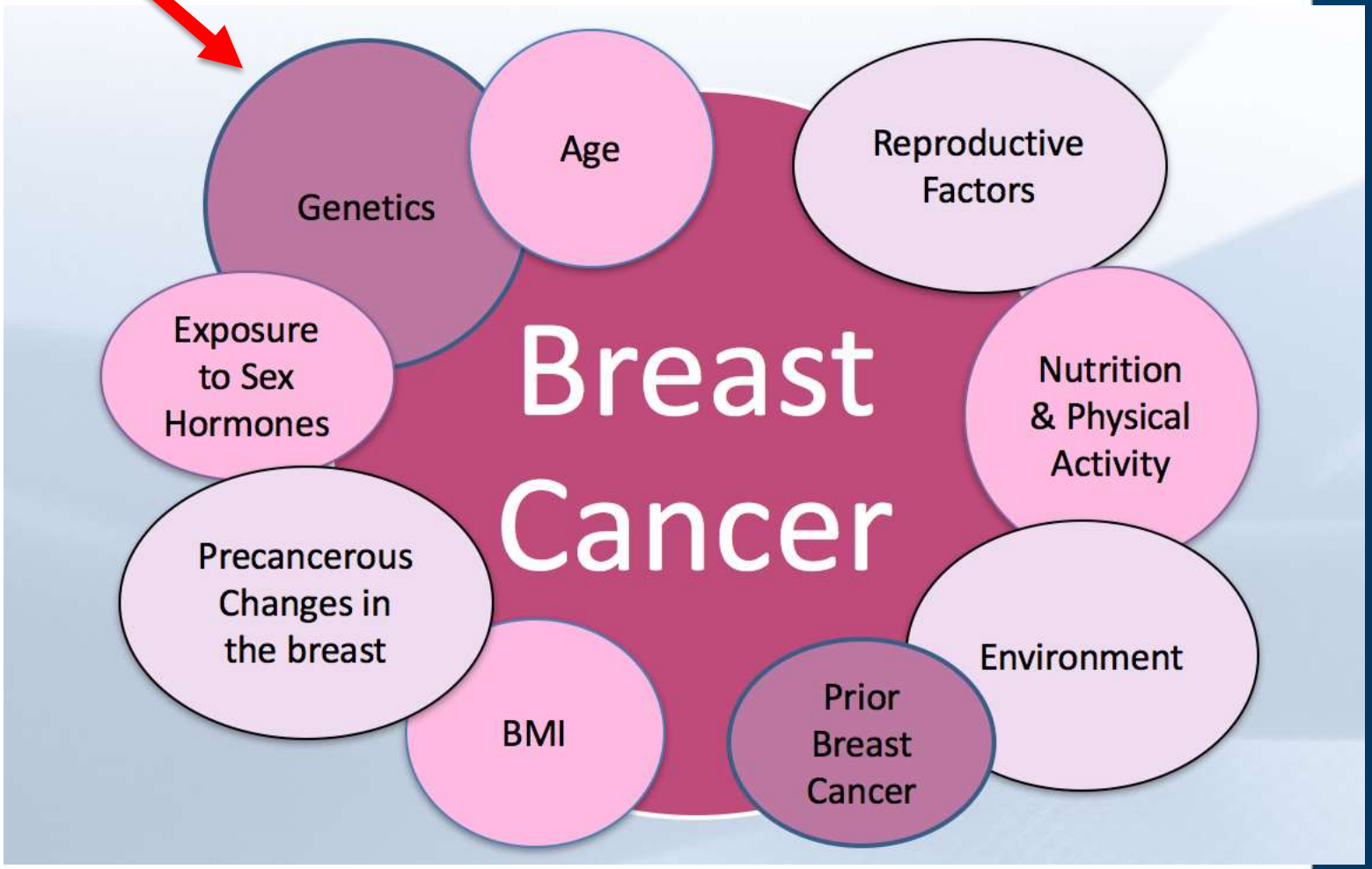
CANCER SURVIVORSHIP CONTINUUM

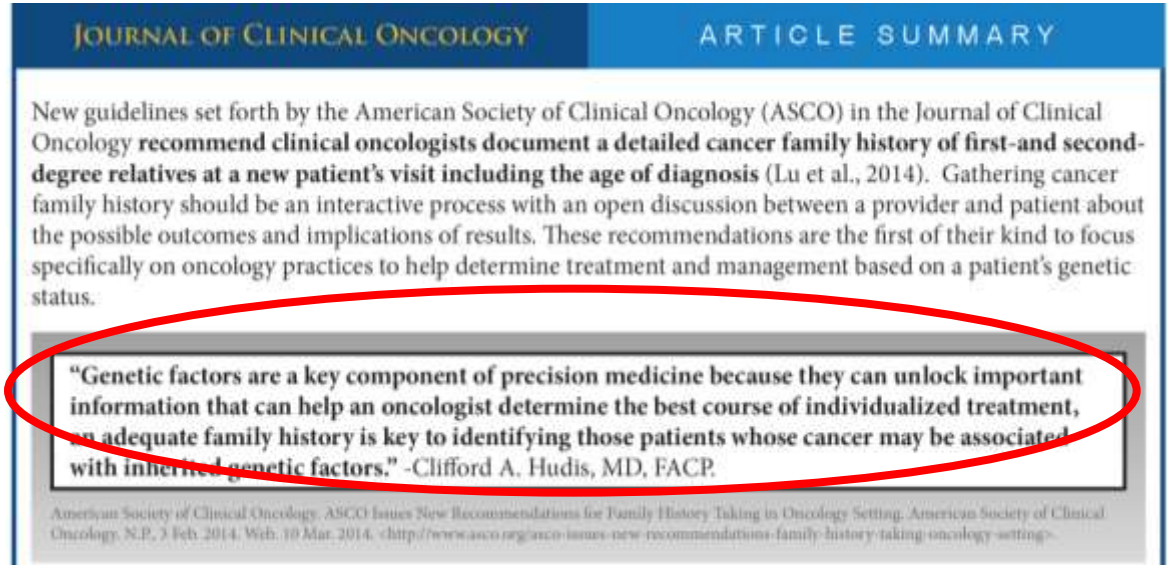


Precision Medicine: Risk Assessment and Tailored Treatment



Breast Cancer Risk is Multi-Factorial





JOURNAL OF CLINICAL ONCOLOGY | ARTICLE SUMMARY

New guidelines set forth by the American Society of Clinical Oncology (ASCO) in the Journal of Clinical Oncology **recommend clinical oncologists document a detailed cancer family history of first-and second-degree relatives at a new patient's visit including the age of diagnosis** (Lu et al., 2014). Gathering cancer family history should be an interactive process with an open discussion between a provider and patient about the possible outcomes and implications of results. These recommendations are the first of their kind to focus specifically on oncology practices to help determine treatment and management based on a patient's genetic status.

"Genetic factors are a key component of precision medicine because they can unlock important information that can help an oncologist determine the best course of individualized treatment, an adequate family history is key to identifying those patients whose cancer may be associated with inherited genetic factors." -Clifford A. Hudis, MD, FACP.

American Society of Clinical Oncology. ASCO Issues New Recommendations for Family History Taking in Oncology Setting. American Society of Clinical Oncology, N.P., 3 Feb. 2014. Web. 10 Mar. 2014. <http://www.asco.org/asco-issues-new-recommendations-family-history-taking-oncology-setting>.

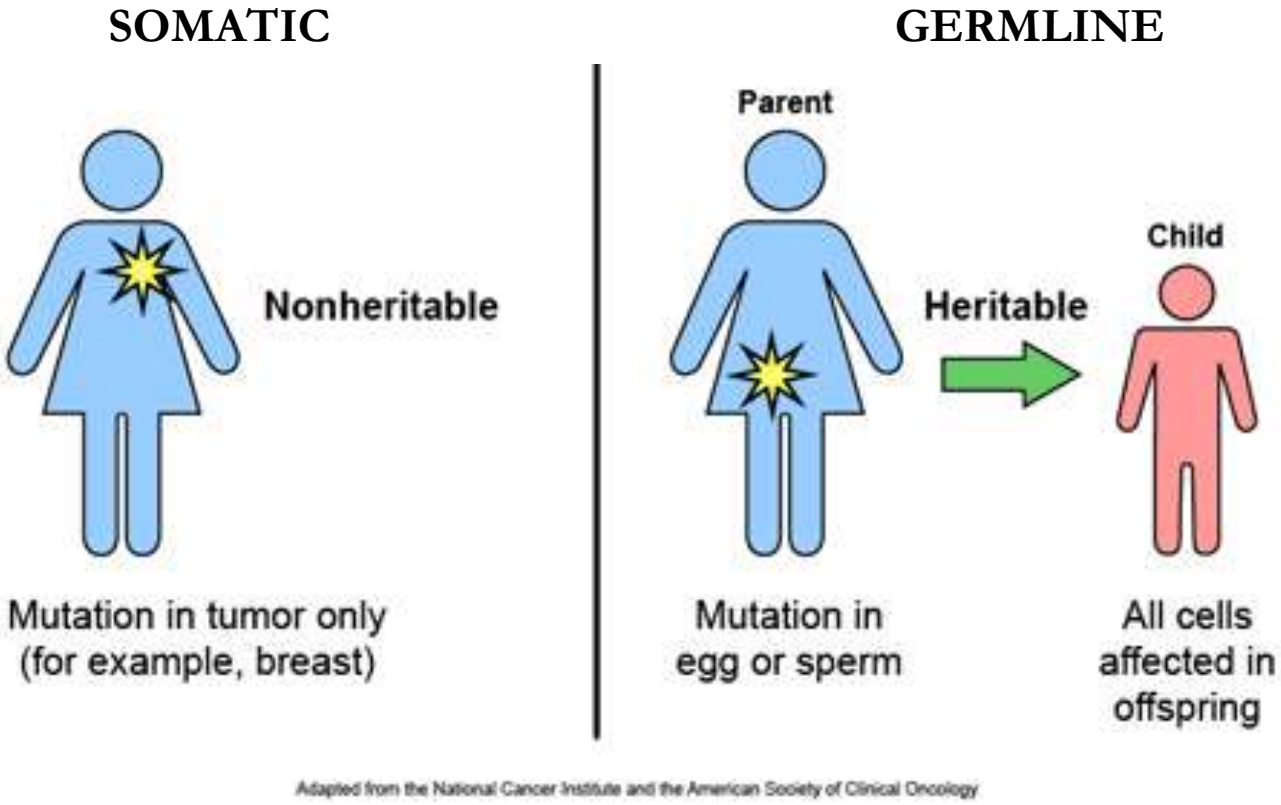
American Society of Clinical Oncology (ASCO)

"Genetic testing can have implications for management of the cancer patients, including: surgical treatment, chemotherapy choices, prognosis and risk for additional cancers. It is therefore important to assess the risk of a hereditary syndrome at diagnosis, at decision points along the cancer treatment trajectory and again when entering survivorship or surveillance."[1]

1 http://www.asco.org/practice-guidelines/practice-management-issues/genetics-toolkit/genetic-testing

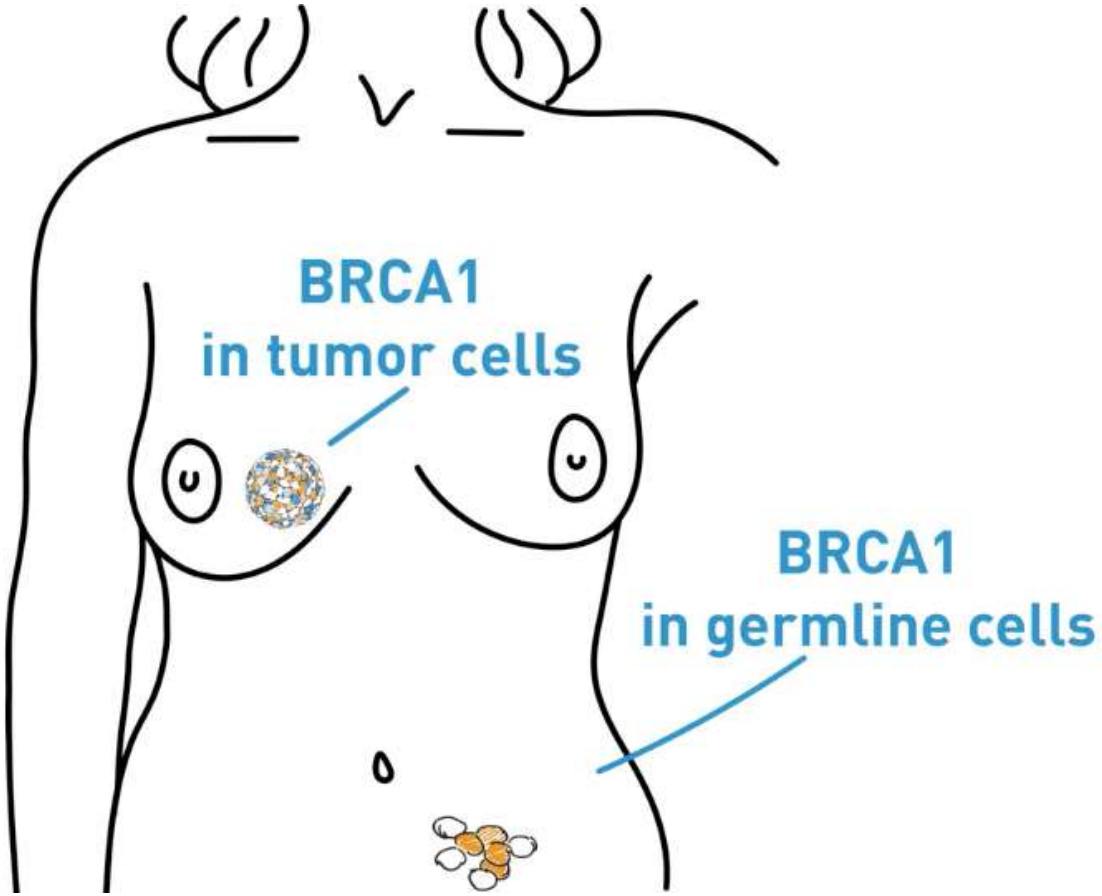
Slide courtesy of Jennifer Klemp, PhD

Differences Between Somatic & Germline Mutations



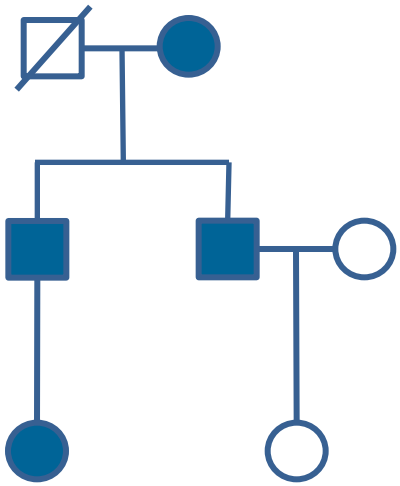
Adapted from the National Cancer Institute and the American Society of Clinical Oncology

Inherited or Acquired Genetic Variants

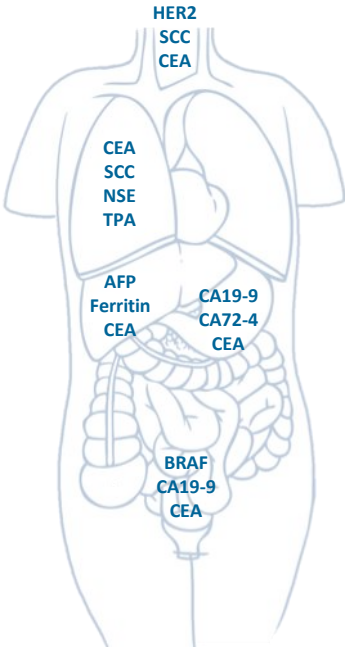


Genomics can increase diagnostic specificity

Germline Testing

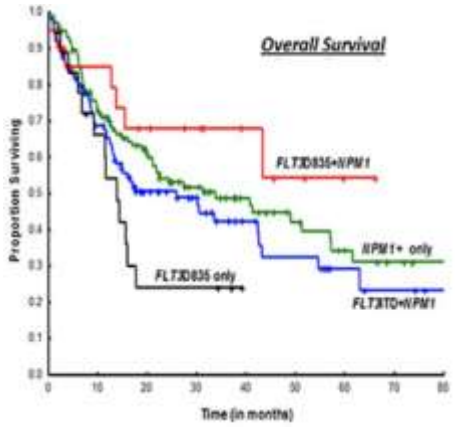


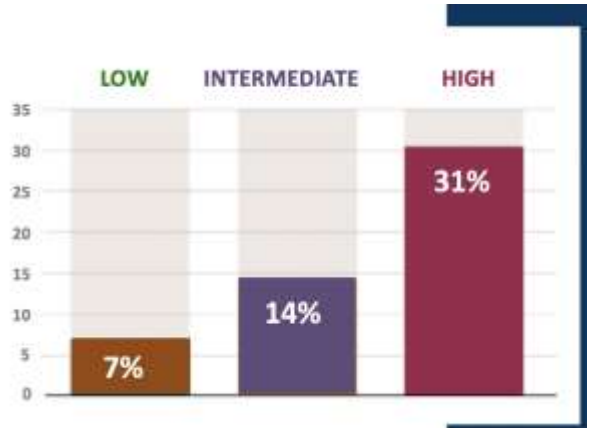
Targeted Biomarker Testing



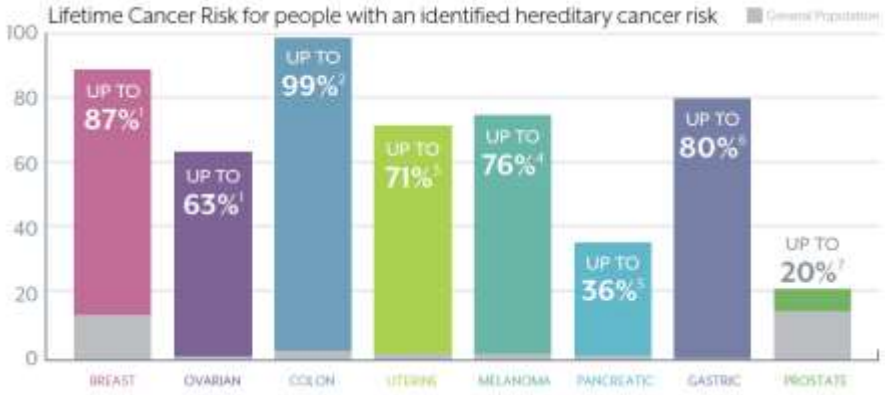
How Does Genetics Work in Cancer Treatment Decisions

Genomic testing can inform prognosis, adjuvant therapy, and targeted treatments



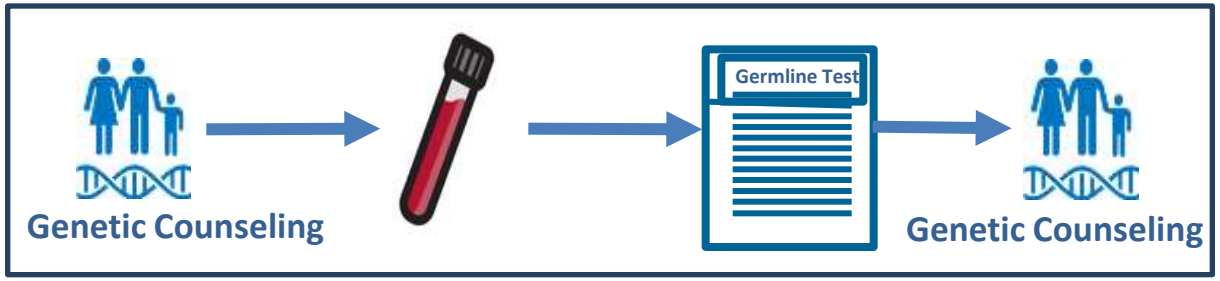


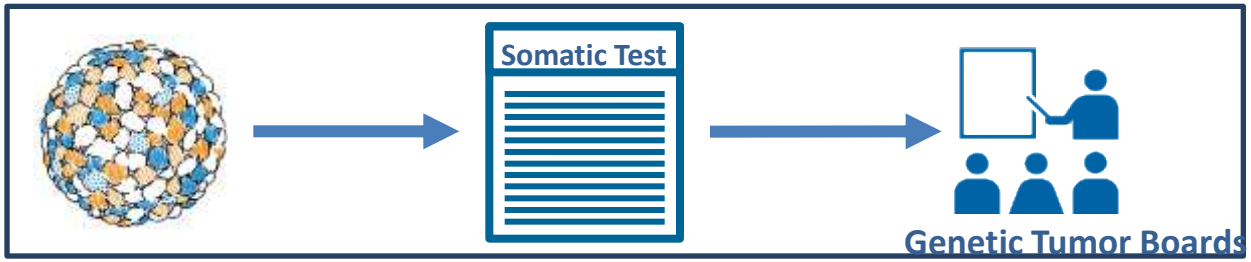
Germline testing can impact future cancer screening and prevention



1. Ford D, et al. *Lancet* 1994
2. Nielsen M, et al
3. Baglietto L, et al. *J Natl Cancer Inst* 2010
4. Begg CB, et al. *J Natl Cancer Inst* 2005
5. Provenzale D, et al.
6. Pharoah PD, et al. *Gastroenterology* 2001
7. Tai YC, et al. *J Natl Cancer Inst* 2007

Difference between Germline & Somatic Testing





THE UNIVERSITY OF KANSAS CANCER CENTER

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National Comprehensive Cancer Network® (NCCN®) Guidelines for Genetic Testing in Breast Cancer

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) 1.2019 for BRCA-Related Breast &/or Ovarian Cancer Syndrome

- Individual from a family with a known *BRCA1/2* pathogenic/likely pathogenic variant, including such variants found on research testing[b]
- Personal history of breast cancer[c] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - ◊ An additional breast cancer primary at any age[d]
    - ◊ ≥1 close blood relative[e] with breast cancer at any age
    - ◊ An unknown or limited family history[a]
  - Diagnosed ≤60 y with:
    - ◊ Triple-negative breast cancer
  - Diagnosed at any age with:
    - ◊ ≥1 close blood relative[e] with:
      - – breast cancer diagnosed ≤50 y; or
      - – ovarian carcinoma;[f] or
      - – male breast cancer; or
      - – high-grade (Gleason score ≥7) or metastatic prostate cancer;[g] or
      - – pancreatic cancer
    - ◊ ≥2 additional diagnoses[d] of breast cancer at any age in patient and/or in close blood relatives
  - Ashkenazi Jewish ancestry[h]
- Personal history of ovarian carcinoma[f]
- Personal history of male breast cancer
- Personal history of pancreatic cancer[i]
- Personal history of metastatic prostate cancer[g]
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with
  - ≥1 close blood relatives[e] with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer[g] at any age or breast cancer <50 y; or
  - ≥2 close blood relatives[e] with breast, or prostate cancer (any grade) at any age; or
  - Ashkenazi Jewish ancestry[h]
- *BRCA1/2* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
- Regardless of family history, some individuals with an *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment[j]
- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood[d] relative[k] meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

[a]For further details regarding the nuances of genetic counseling and testing.

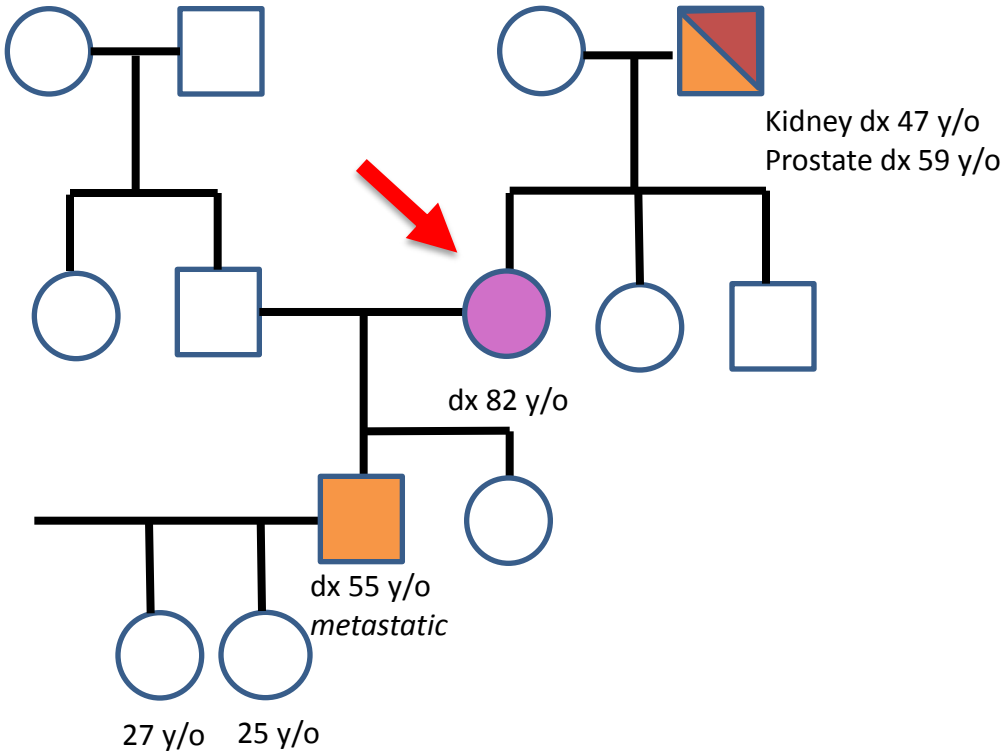
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer[1]

- For patients with HER2-negative tumors eligible for single-agent therapy, strongly consider germline *BRCA 1/2* testing
- Genetic counseling if patient is high risk for hereditary breast cancer

- This is a large number of survivors!
- What is your process for identification?

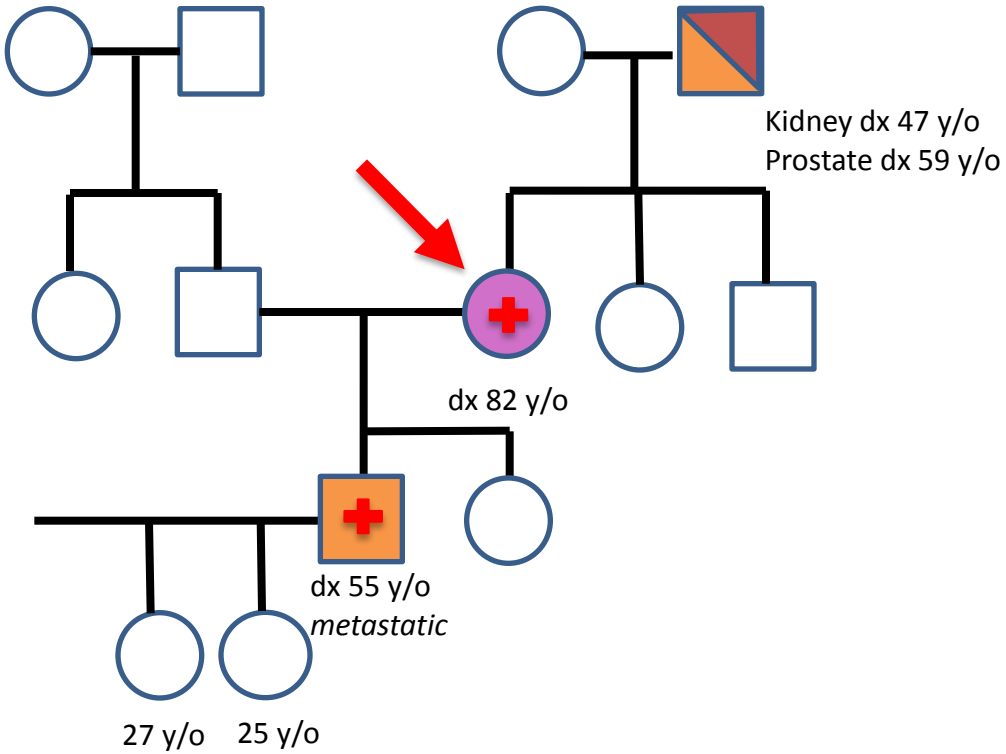
1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. Version 1.2019. http://www.nccn.org. Updated July 11, 2018. . Accessed July 13, 2018. **2.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 1.2018. http://www.nccn.org. Updated October 3, 2017. Accessed May 2, 2018.

Case 1



- Prostate cancer
- Breast cancer
- Kidney cancer

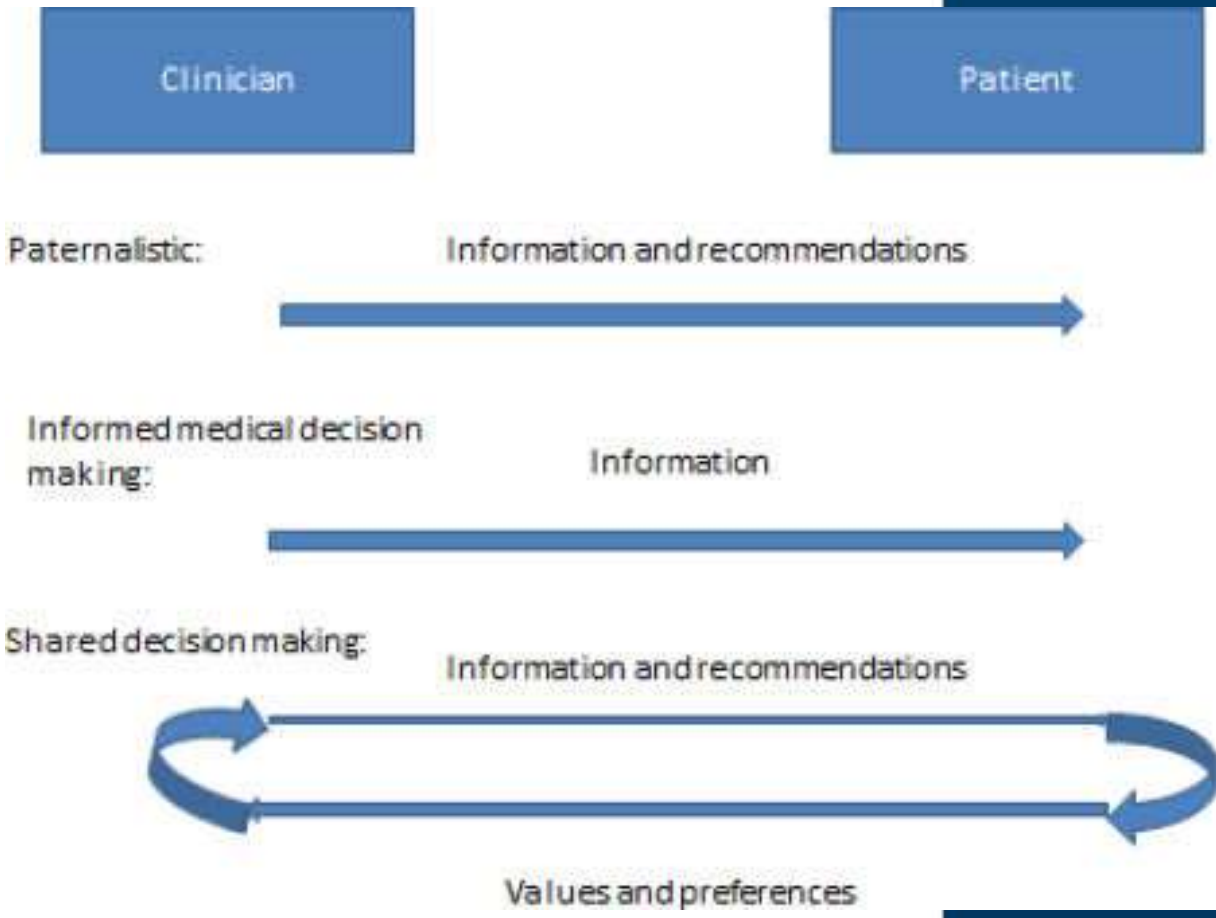
Case 1



Prostate cancer
Breast cancer
Kidney cancer

Shared Decision Making

- When the patient and the physician make decisions together regarding: care plan and management.
- Expectation is that patients are well informed and comfortable with the plan.



Schrager. *Family Practice Management*. 2017.

Share Decision Making

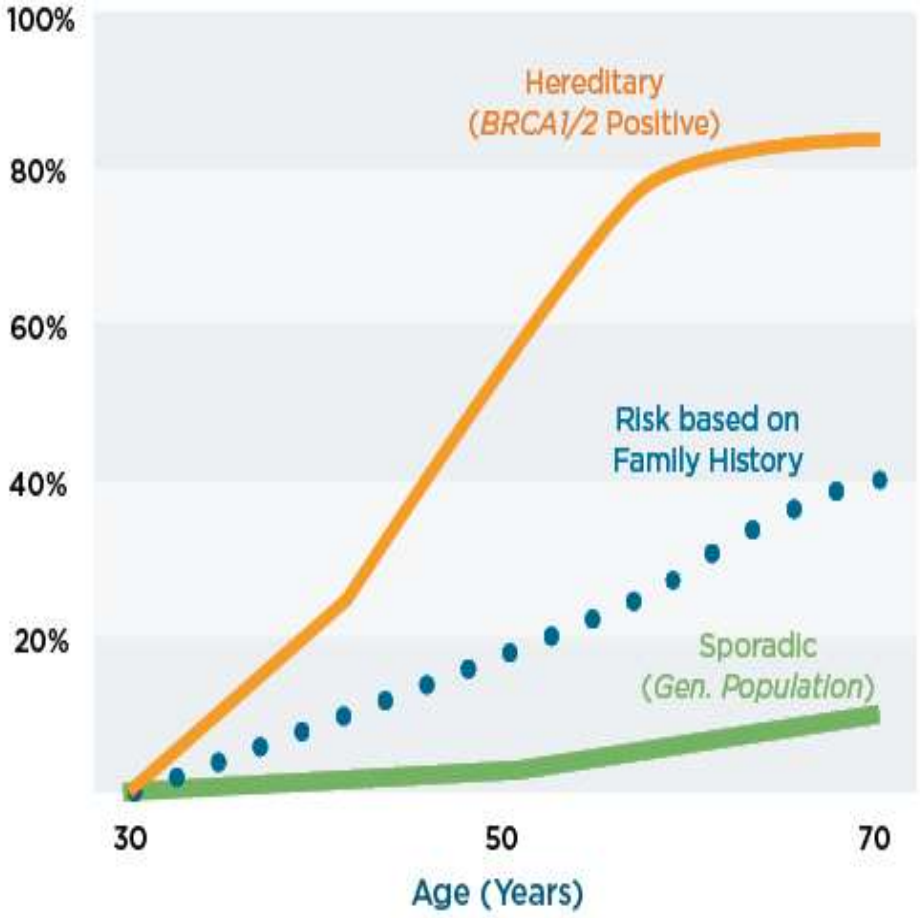
- Additional Considerations:
  - How will testing impact treatment?
  - How comfortable is the patient informing at risk family members if he is found to have a positive mutation?
  - How will testing impact their future cancer surveillance?
  - Psychosocial implications of testing.

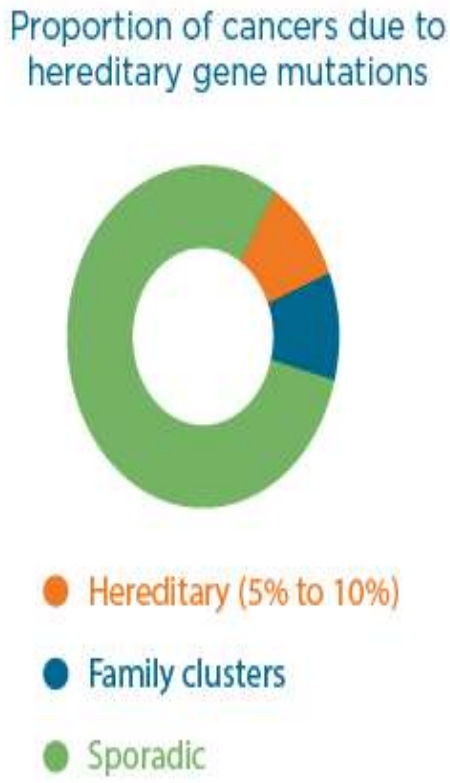
Case 1 + BRCA2

- Need to inform
  - Both daughters should be recommended for genetic counseling and testing.
  - A positive mutation would alter recommendations for breast and ovarian cancer screening including additional screening modalities and starting at a younger age.
  - A positive mutation would make them eligible to consider preventative measures including prophylactic surgeries.

Lana Blagg with her daughter Taylor McCord, and Taylor's daughter, Arianna.

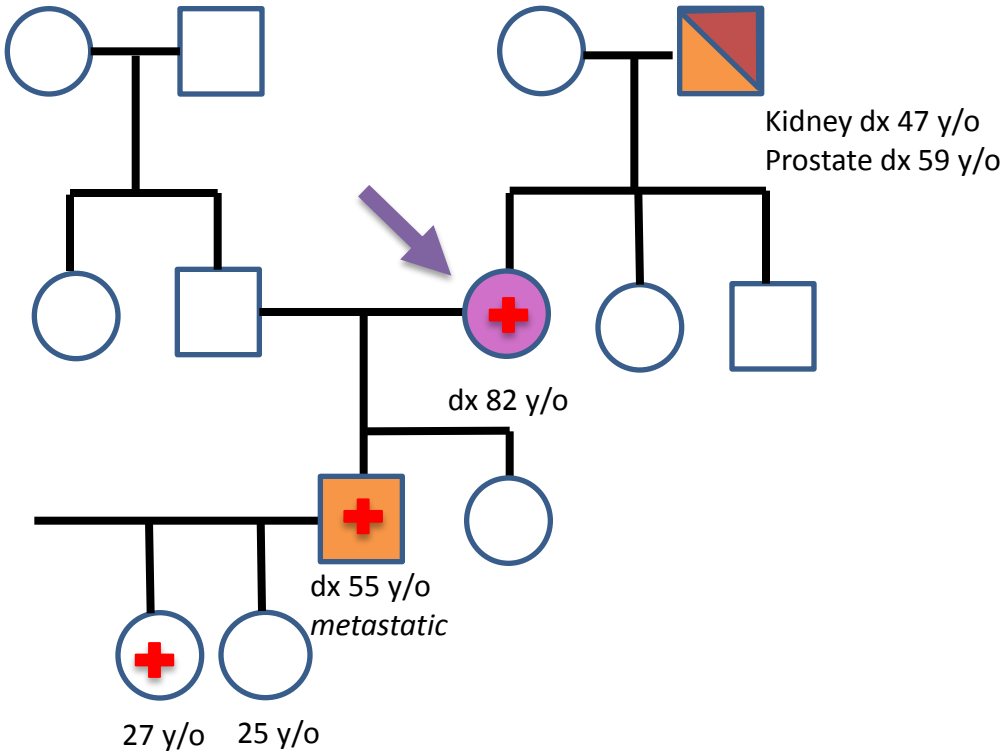
Breast Cancer Risk Comparison





Ponder B. et al. 1997
Berchuck A, et al. 1996
Lichtenstein P, et al. 2000

Case 1



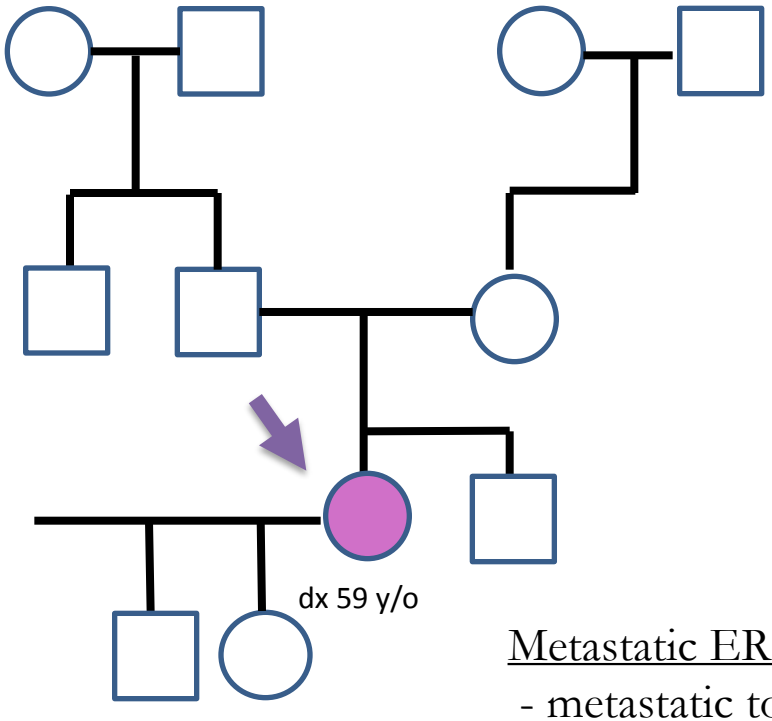
- Prostate cancer
- Breast cancer
- Kidney cancer

Recommended Counseling and Management
NCCN V1.2108

- Education/breast awareness by 18y/o
- Clinical breast examination annually or semiannually beginning at 25y/o*
- Breast imaging:
  - MRI beginning at 25y/o*
  - Mammogram + MRI from 30-75y/o*
- Preventive surgery
  - Risk reducing mastectomy (RRM)
  - Risk reducing salpingo-oophorectomy (RRSO) ~35-40y/o
- Ovarian cancer screening: (if did not undergo RRSO)
  - Transvaginal ultrasound + CA-125 blood test
  - Poor sensitivity, so at the clinicians discretion

*individual recommendations if breast cancer diagnosed under age 30 in the family

Case Study 2



Breast cancer

Metastatic ER+ HER2- Breast Cancer

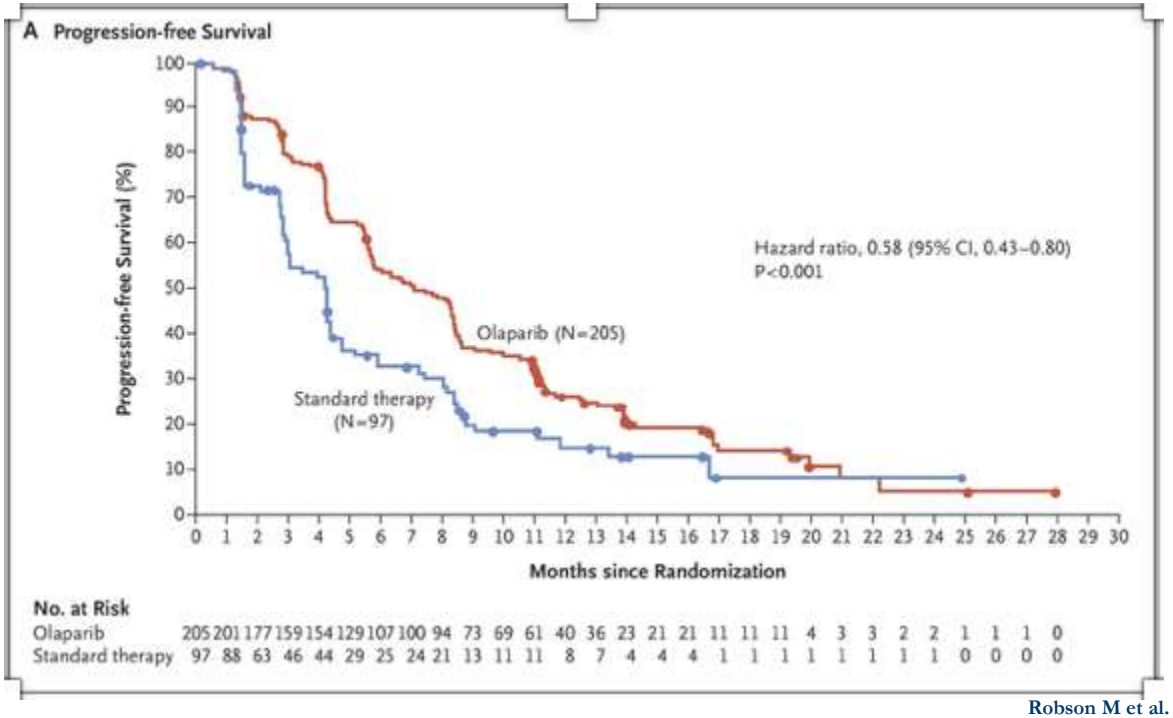
- metastatic to liver and bone
- received 2 lines of endocrine therapy
- received 1 line of chemotherapy
- **NGS done for clinical trial at outside institution *+ BRCA2 variant.***

Share Decision Making

Patients should be advised mutations may be detected that are not actionable.

Olaparib for Metastatic Breast Cancer in Patients with Germline BRCA Mutation

Kaplan–Meier Estimates of Progression-free Survival

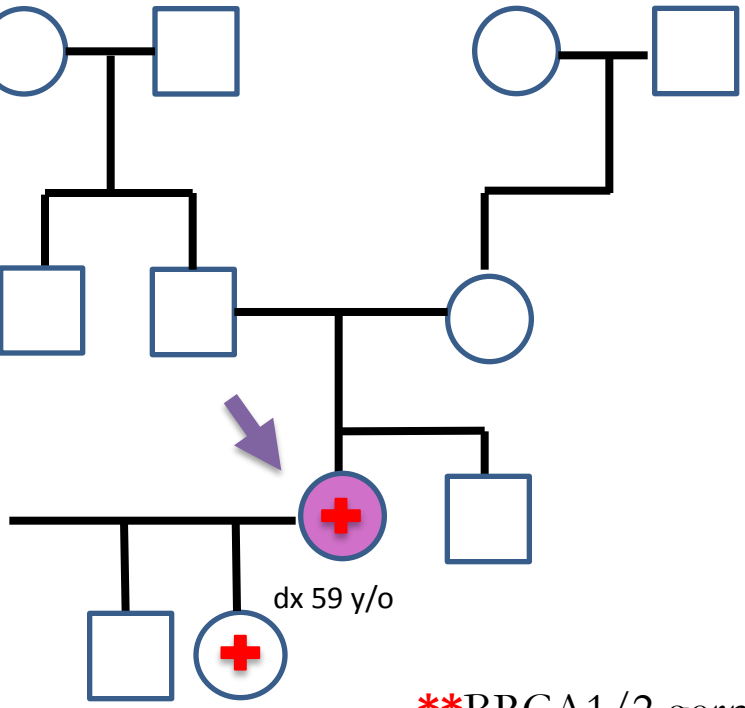


Robson M et al. N Engl J Med 2017

Olaparib approval for germline BRCA+ metastatic breast cancer

- January 12 2018 – FDA approved olaparib for treatment of patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative metastatic breast cancer who have received prior chemotherapy in the neoadjuvant, adjuvant or metastatic setting.
- The was approved with marketing authorization for the companion diagnostic, BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc).

Case Study: Post Germline Testing



Breast cancer

**BRCA1/2 germline testing is indicated if a BRCA1/2 mutation is identified on tumor profiling.

Concerns and Access to Care

- Access to genetic counseling
- Access to targeted therapies
- Common provider concerns:
  - "These syndromes are so rare and I almost never find a positive result"
  - "It won't affect how I manage this patient's care"
  - "My patient's don't want to know if the have a *bad gene*"
  - "I don't have time to get into this with my patients"
  - "I am worried about how complicated testing is- and which test(s) to order"
  - "Insurance will not cover this expensive test and the patient will be left with large out-of-pocket costs"

Discussion & Questions