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A Review of Genetic Counseling and Testing for Inherited Breast Cancer Risk

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Cancer Risk Factors

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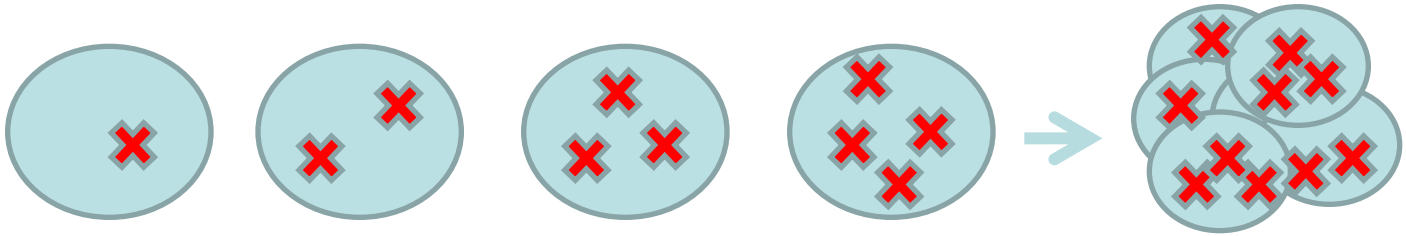
- **Increasing age**
- **Environmental exposures:**
  - Radiation, chemical & other carcinogens (incl. tobacco), viruses, alcohol, diet, excessive sun exposure
  - Hormones, chronic inflammation, obesity
- **Family history**
- **Inherited mutations**
- **All cancers arise from an accumulation of genetic alterations in a single cell over time.**



Hereditary Cancer Risk

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- Only ~5-10% of cancers are “hereditary”
  - Single gene, major effect on risk
- Inherited or de novo (new) mutation in a cancer susceptibility gene
- Most syndromes are autosomal dominant

Hereditary, Familial and Sporadic Cancers

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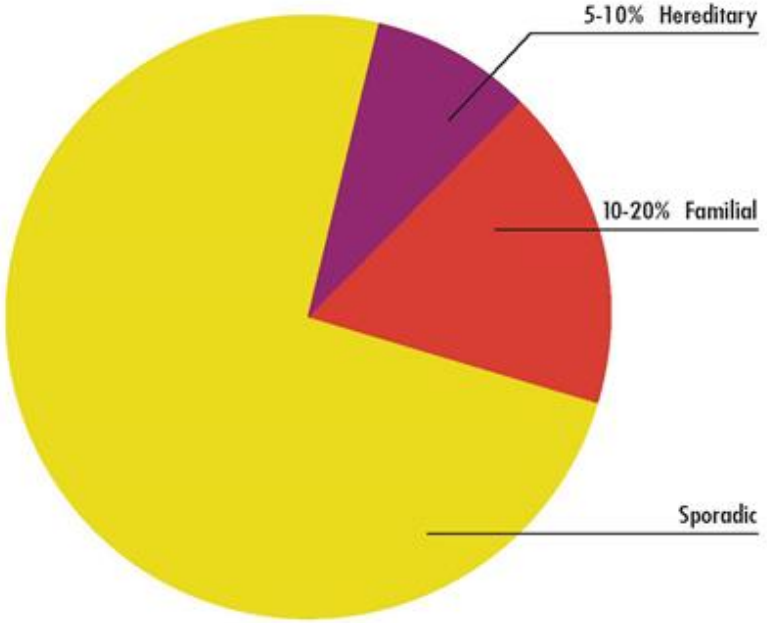
Distribution of Cancer



Hereditary
- Gene mutation is inherited in family
- Significantly increased cancer risk

Familial
- Multiple genes & environmental factors may be involved
- Some increase in cancer risk

Sporadic
- Cancer occurs by chance or related to environmental factors
- General population cancer risk

Features Suggestive of Inherited Breast Cancer Risk

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- Early Onset Cancers (prior to the age of 50)
- Same or related cancers in two or more close family members (breast, ovarian, metastatic prostate, pancreatic)
- Multiple generations are affected
- Multiple primary cancers in one individual (including bilateral cancers)
- Rare cancers
  - Ovarian, pancreatic, male breast, aggressive prostate
- Ashkenazi Jewish ancestry with a family history of breast, ovarian, and/or pancreatic cancer

Sporadic vs. Inherited Cancers

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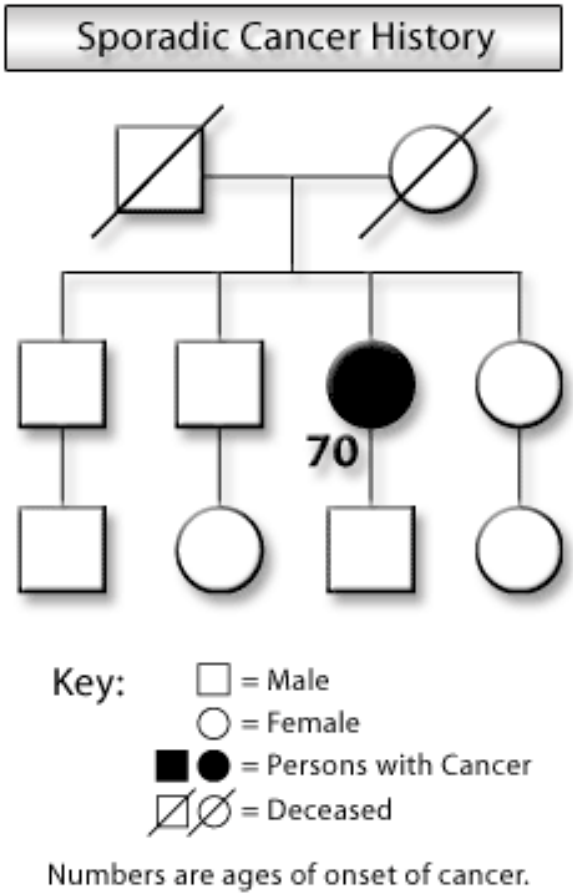
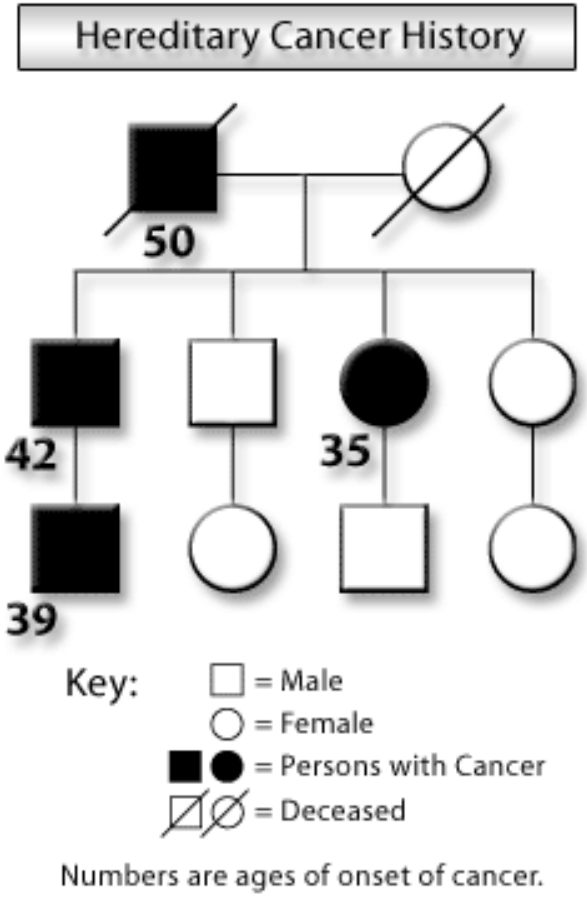


Sporadic = by chance, due to environmental factors, viral infections etc.



Inherited = genetic information passed down from one generation to another.

https://www.elcaminohospital.org/library/features-inherited-cancers

Cancer Genetic Counseling – What to Expect

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- Receive an individualized cancer risk assessment
- Personalized cancer screening recommendations and referrals
- Discuss risk, benefits, and limitations of genetic testing for you
- Options for reproductive planning based on genetic testing results
- Discuss psychosocial impact of genetic testing on you and other family members
- Review insurance coverage and concerns
- Resource for updated cancer genetic information

High Risk Breast Cancer Susceptibility Genes

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- BRCA1 and BRCA2 (Hereditary Breast and Ovarian Cancer Syndrome)
  - ~50-60% lifetime risk for female breast cancer
  - Up to 60% lifetime risk for ovarian cancer for BRCA1 carriers
  - Up to 20% lifetime risk for ovarian cancer for BRCA2 carriers
  - Increased risk for male breast cancer, pancreatic cancer, and melanoma
- PALB2
  - 24-48% lifetime risk for female breast cancer
    - Family history can influence breast cancer risk
  - Increased risk for pancreatic cancer, ovarian cancer, and male breast cancer

BRCA1 & 2 Founder Mutations

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Examples include:

- Ashkenazi Jewish: ~1/40 are carriers of one of three founder mutations
  - BRCA1
    - c.68_69delAG (187delAG)
    - c.5266dupC (5385insC)
  - BRCA2
    - c.5946delT (6174delT)
- Icelandic: BRCA2 999del5
- Portuguese: BRCA2 c.156_157insAlu

High Risk Breast Cancer Susceptibility Genes

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- CDH1 (Hereditary Diffuse Gastric Cancer)
  - Up to 80% risk for diffuse gastric cancer
  - Up to 50-60% lifetime risk for lobular breast cancer in females
- PTEN (Cowden Syndrome aka PTEN-Hamartoma Tumor syndrome)
  - Increased risk for kidney, breast, thyroid (follicular), and uterine cancer
  - Benign characteristics – large heads, specific skin features, uterine fibroids, thyroid nodules, learning disabilities, autism
- TP53 (Li-Fraumeni Syndrome)
  - ~90% lifetime risk to develop cancer
  - Increased risk for sarcomas, breast cancer, brain tumors, choroid plexus tumors, adrenal gland tumors, leukemias, GI, GU cancers
  - Usually have very early ages of onset (i.e. breast cancer before age 35)

Moderate Risk Breast Cancer Susceptibility Genes

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- **ATM**
- ~24-48% lifetime risk for breast cancer in females
- Increased risk for pancreatic cancer
- Possible increased risk for prostate cancer

- **CHEK2**
- ~18-36% lifetime risk for breast cancer in females
  - This risk varies depending on type of mutation
- Increased risk for colon cancer
- Possible increased risk for prostate, thyroid, kidney, and/or male breast cancer(s)

Newly Described Breast Cancer Susceptibility Genes

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- These genes have recently been thought to be associated with an increased risk for breast and/or ovarian cancer in females.
- The degree of cancer risk is still unclear – additional research is needed
  - BARD1
  - MRE11
  - NBN
  - RAD50

- No consensus guidelines currently exist for screening and/or risk-reduction in mutation carriers.
- As more research is done and we learn more about these genes, guidelines will likely evolve
- Rely on personal and/or family history for screening recommendations

Ovarian Cancer Susceptibility Genes

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High Risk:

- BRCA1 and BRCA2
- Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM)

Moderate Risk:

- BRIP1
  - ~8% lifetime risk for ovarian cancer
- RAD51C
  - ~6.5% lifetime risk for ovarian cancer
- RAD51D
  - ~7-12% lifetime risk for ovarian cancer

If we identify a mutation…what do we do next? NCCN guidelines version 3.2019

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- **Elevated surveillance**
  - Breast mammogram and breast MRI screening (typically each modality annually)
  - Option of ovarian cancer surveillance (CA-125 and transvaginal ultrasound), but significant limitations
- **Risk reduction options**
- **Surgical**
  - Bilateral mastectomies (removal of breast tissue)
  - Bilateral salpingo-oophorectomy (removal of the ovaries), typically between ages 35-45
- **Chemoprevention**
  - Tamoxifen and/or aromatase inhibitor (reduces breast cancer risk)
  - Oral contraceptives (reduces ovarian cancer risk)

Examples: Breast cancer susceptibility genes and NCCN guidelines version 3.2019

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Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of breat cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk, with insufficient evidence for recommendation of RRSO**	Unknown or insufficient evidence for pancreas or prostate cancer
	Comments: Insufficient evidence to recommend against radiation therapy. Counsel for risk of autosomal recessive condition in offspring.		

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
CHEK2	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	Colon • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comments: Risk data are based only on frameshift pathogenic/likely pathogenic variants. The risks for most missense variants are unclear but for some pathogenic/likely pathogenic variants, such as Ile157Thr, the risk for breast cancer appears to be lower. Management should be based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant.		

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
PALB2	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for ovarian cancer risk**	Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring.		

Cancer Syndromes Overlap

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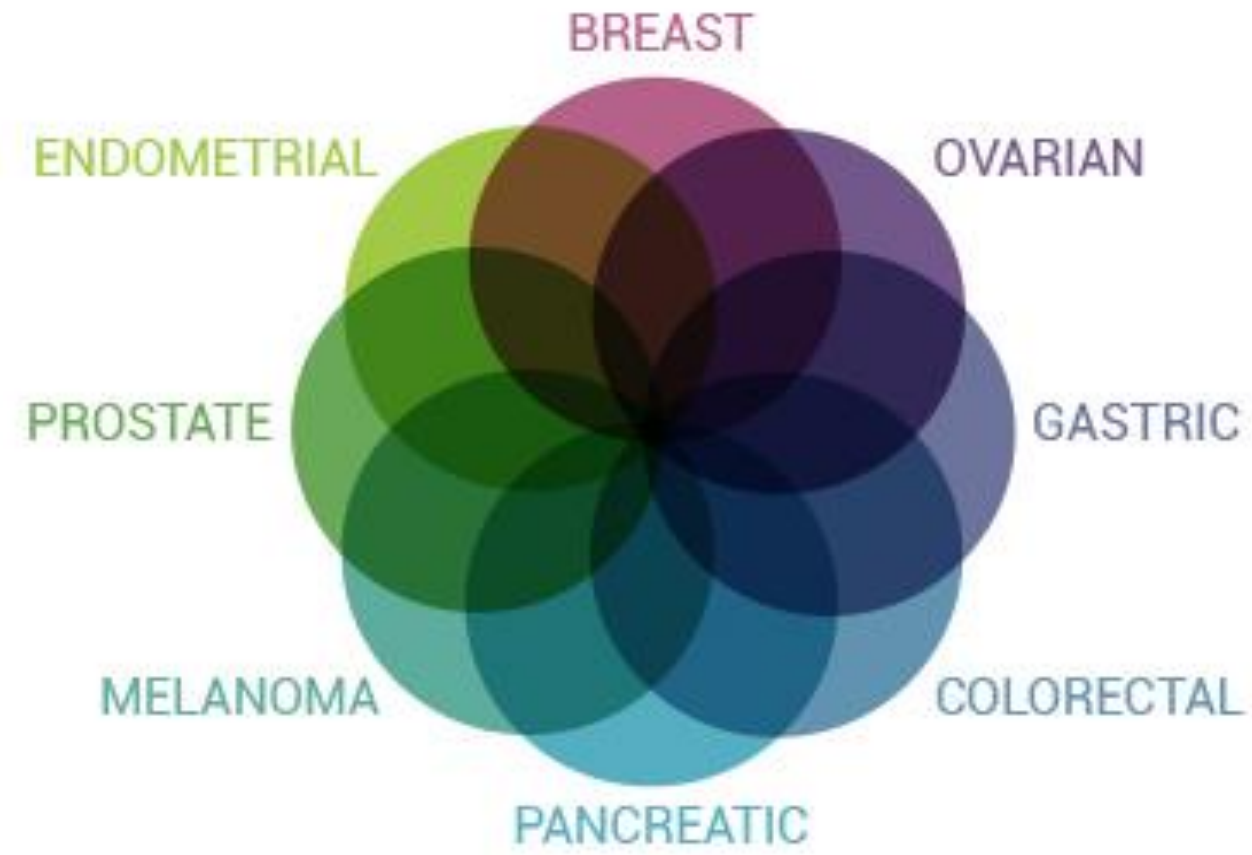

Image courtesy of: Myriad

Overview of Genetic Testing for Hereditary Cancer

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- Availability of multi-gene panels via Next-Generation Sequencing
  - Allows us to perform sequencing and deletion/duplication analysis on multiple genes at once
  - Reduces cost of genetic testing
  - Allows us to "cast a wide net" to evaluate possible hereditary cancer risk
- Most insurances cover genetic testing in individuals who fit criteria
- The most informative individual in a family to initially test is someone affected by cancer
- Testing allows for early screening and detection of cancer and allows family members to pursue genetic testing to determine cancer risks

- Our knowledge of genes is constantly evolving so genetic testing is NEVER 100%. We are only as good as our current understanding and technology!

Genetic Testing Benefits, Risks, Limitations, and Considerations

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Benefits

- Identifies high-risk individuals in a family
- May help inform treatment decisions
- Clarifies the risk to develop a new cancer
- Identifies non-carriers in families with known mutations
- Allows personalized early detection and prevention
- May relieve anxiety and uncertainty

Risks and Limitations

- Does not detect ALL mutations
- Does not eliminate risk for a new cancer
- May cause anxiety
- Some are not ready to handle genetic information
- Unclear recommendations for some genes
- Sometimes the effectiveness of interventions is unproven
- May create difficult situations within a family

Considerations

- Psychological impact
- A normal result could give false reassurance

Types of Results for Genetic Testing

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Positive	• A pathogenic mutation was identified • You are at increased risk for cancer(s) • Increased screening or risk-reducing surgeries may be recommended • Genetic testing recommended for family members
Variant of Unknown Significance	• A change was identified but it is unclear whether or not this increases cancer risk • Cancer risk and screening recommendations are based solely on personal/family history • Genetic testing is not recommended for family members for a VUS
Negative	• No mutation was identified • May be at increased risk for cancers based on family history • Screening recommendations are based on personal/family history

Implications of Genetic Testing on Relatives: Known Mutation in Family

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- Family members who test negative:
- Can generally be screened for breast cancer based on general population risk because they did not inherit the hereditary predisposition to cancer

- Family members who test positive:
- Should be screened/managed according to specific guidelines because they would have an increased risk for cancer

- At risk family members who do not want genetic testing:
- Should be screened as if they are positive

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- Genetic Information Nondiscrimination Act (2008)
- Protect individuals who pursue genetic testing from being discriminated against by employers and health insurance
  - In companies with at least 15 employees
- Does not apply to “luxury policies”
  - Life insurance
  - Disability
  - Long-term care

Personalized Medicine

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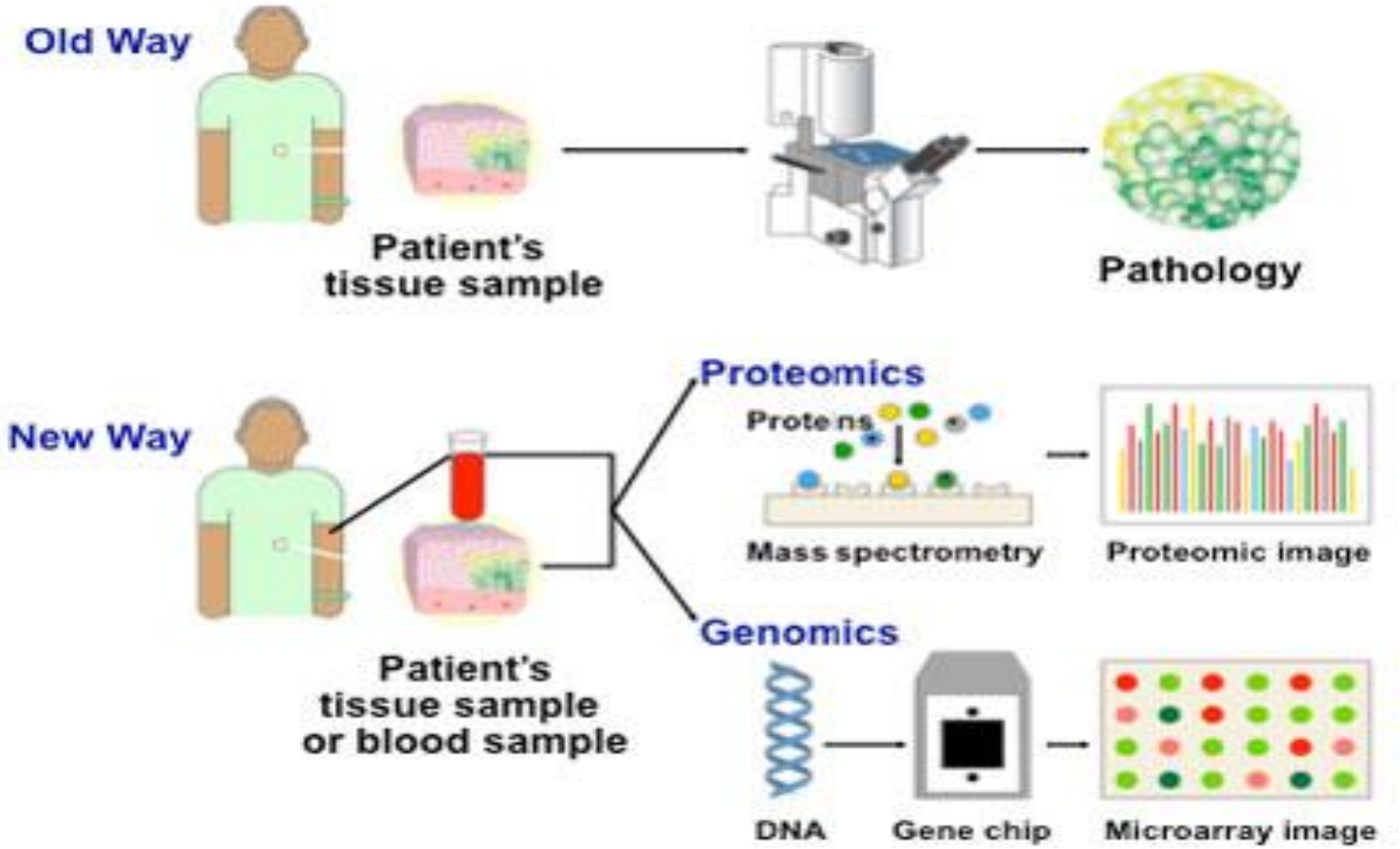

https://http://cisncancer.org/research/what_we_know/omics/personalized_medicine_07.html

Somatic Testing VS Germline Testing

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- **Somatic (Tumor Testing)**
  - Performed on tumor tissue
  - Affected cancer patients
  - Identifies mutations in the tumor (acquired changes)
  - Can identify treatment options and determine prognosis
  - Typically ordered by an oncologist

- **Germline (Inherited Testing)**
  - Performed on blood or saliva
  - Identifies mutations patients were born with
  - Patients may be affected or unaffected
  - Purpose is to identify possibly inherited mutations
  - Often ordered by a genetic counselor
  - Patients often receive counseling

Why Somatic Testing?

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Why Somatic (Tumor) Testing?

- Prognostic Information
  - tells healthcare providers about aggressiveness of tumor
  - higher or lower risk for developing metastatic disease
- Treatment Decisions
  - helps healthcare providers in making chemotherapy (or other) decisions
    - whether to give chemotherapy or immunotherapy
    - type of chemotherapy or immunotherapy
    - in people with advanced or refractory disease – new treatment options

Some somatic tests can identify people with hereditary forms of cancer

Take Home Messages

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- **Genetic counseling STRONGLY recommended for those with a personal and/or family history suggestive of an inherited cancer susceptibility.**
- **Information about cancer risks and medical management for the moderate and newly described genes will continue to evolve.**
- **Genetic testing available from several labs via a multi-gene panel.**
- **Personalized medicine, screening and treatments are on the rise.**

Inova Cancer Genetics Program

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- **Our Genetic Counseling Team**
  - **Tiffani DeMarco, MS, LCGC (IFH) – Director, Cancer Genetics Program**
  - **Kimberly Matthijssen, MS, LCGC (IFOH, ILH) – Senior Genetic Counselor**
  - **Amanda Schott, MS, LCGC (IFOH, ILH) – Senior Genetic Counselor**
  - **Dina Alaeddin, MGC, LCGC (IFH, IAH) – Genetic Counselor**
  - **Morgan Turner, MS, LCGC (IFH) – Genetic Counselor**
  - **Administrative Staff**
    - **Katherine Prince**
    - **Justine Farre**
    - **Tyler Stigall**

  - **Referral phone # (571) 472-0444**
  - **Referral email: cancergenetics@inova.org**
  - **Website: inova.org/cancergeneticcounseling**

THANK YOU!

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