Genetic Testing and Cancer

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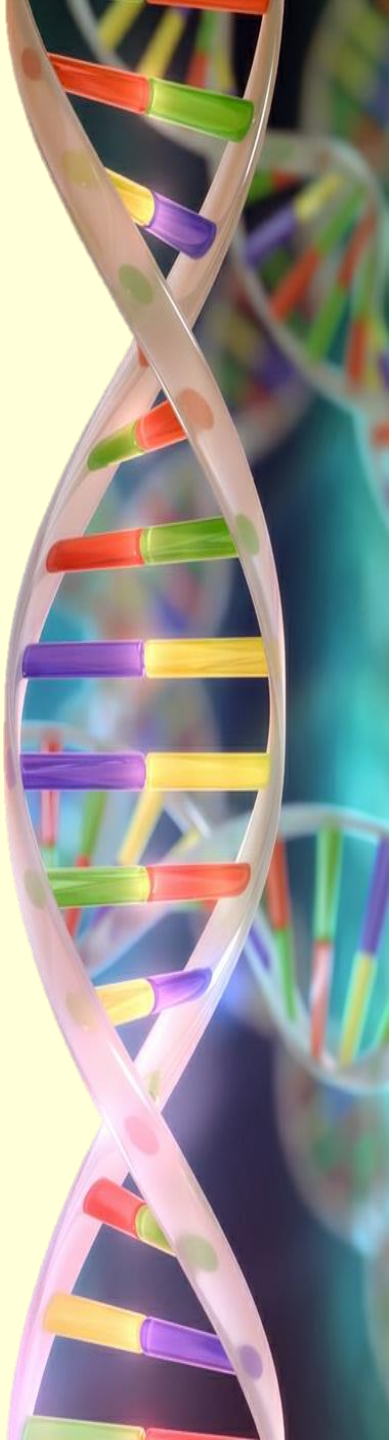
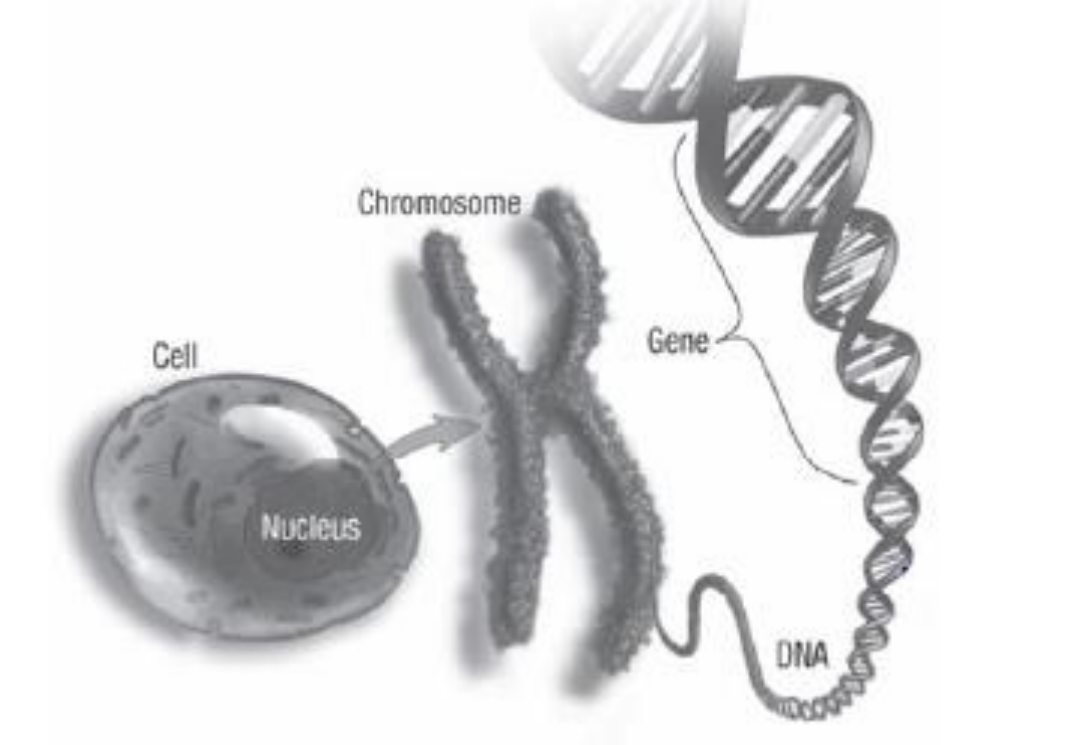
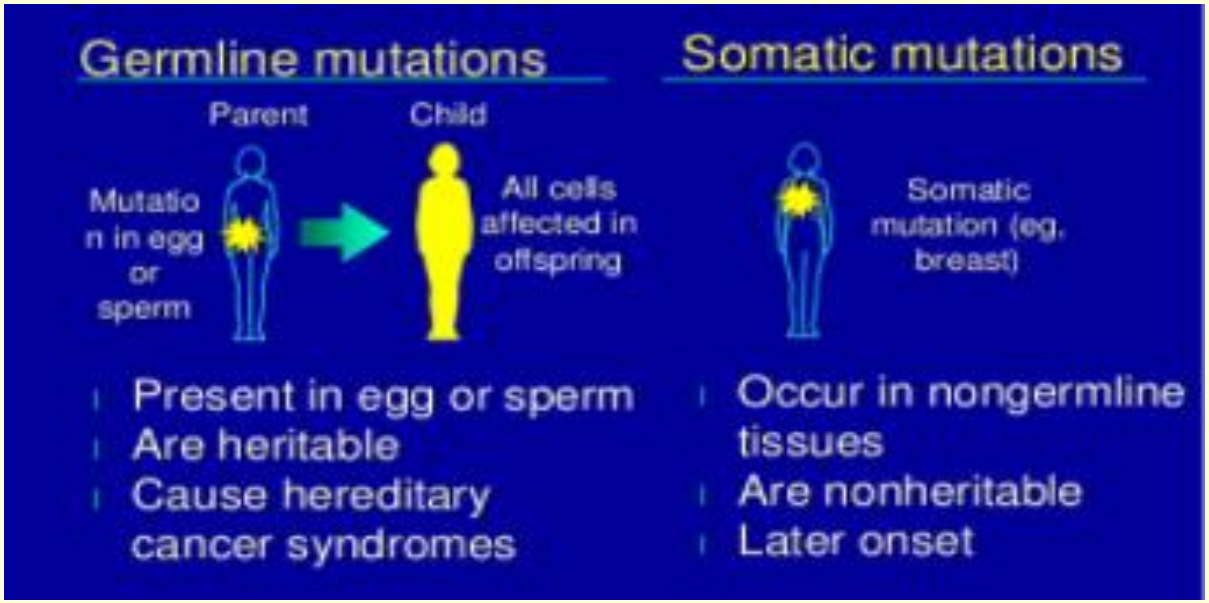


What is Genetic Testing?



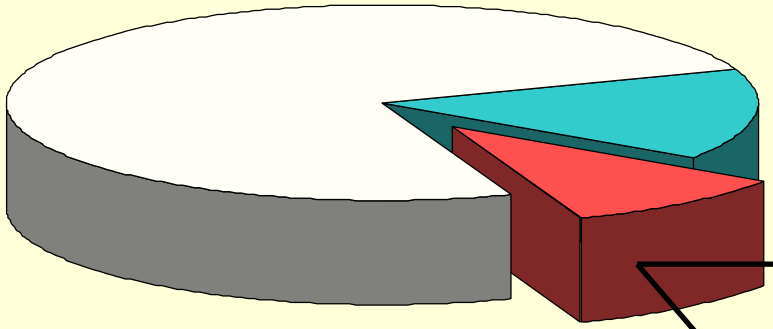
- Examines genes for changes, or mutations
  - Current terminology: mutation = pathogenic or likely pathogenic variant
- Genes are made of DNA
- Genes are present in almost all cells of our bodies, on structures called chromosomes
- We have two copies of most genes, one from each parent
  - Exception, the X and Y chromosomes in males

Two Types of Genetic Testing: Germline and Somatic



Somatic vs. Germline Testing

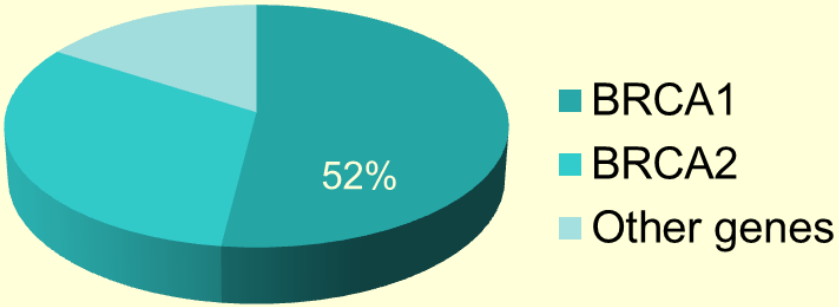
Somatic Testing	Changes in DNA in tumor	Not hereditary (not passed from one family member to another)	Found by testing the tumor
Germline Testing	Changes in DNA in all cells	Hereditary (passed from one family member to another)	Found by testing a blood sample



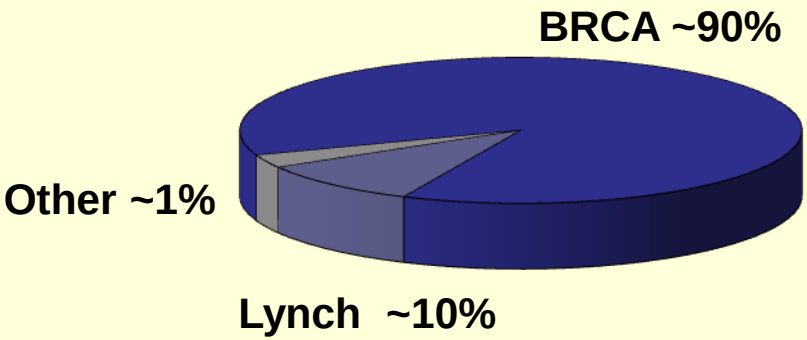
Hereditary cancers

Most Cancer is Not Hereditary

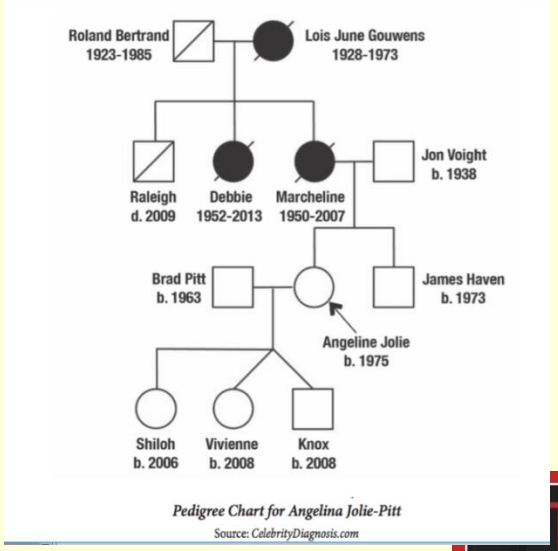
Hereditary Breast Cancer Etiology

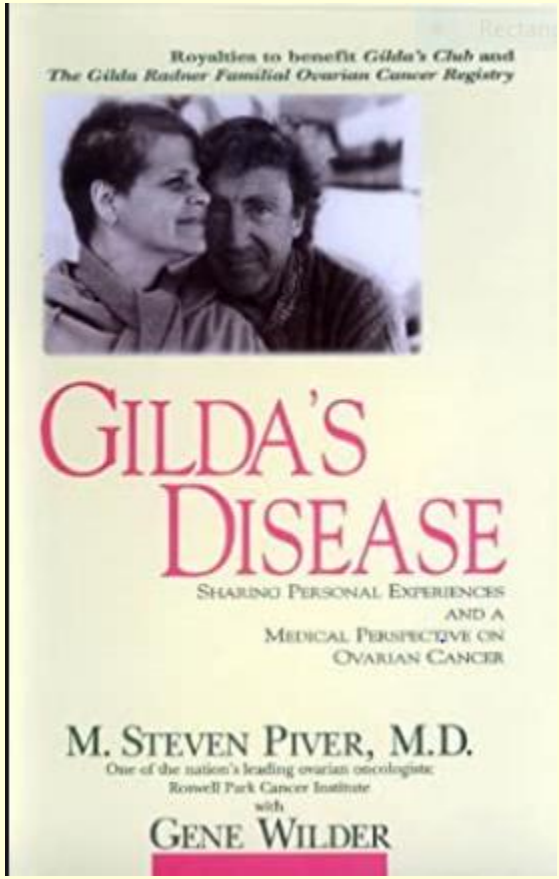


Hereditary Ovarian Cancer Etiology



Hereditary Cancer Testing (Germline) BRCA in the Media Spotlight

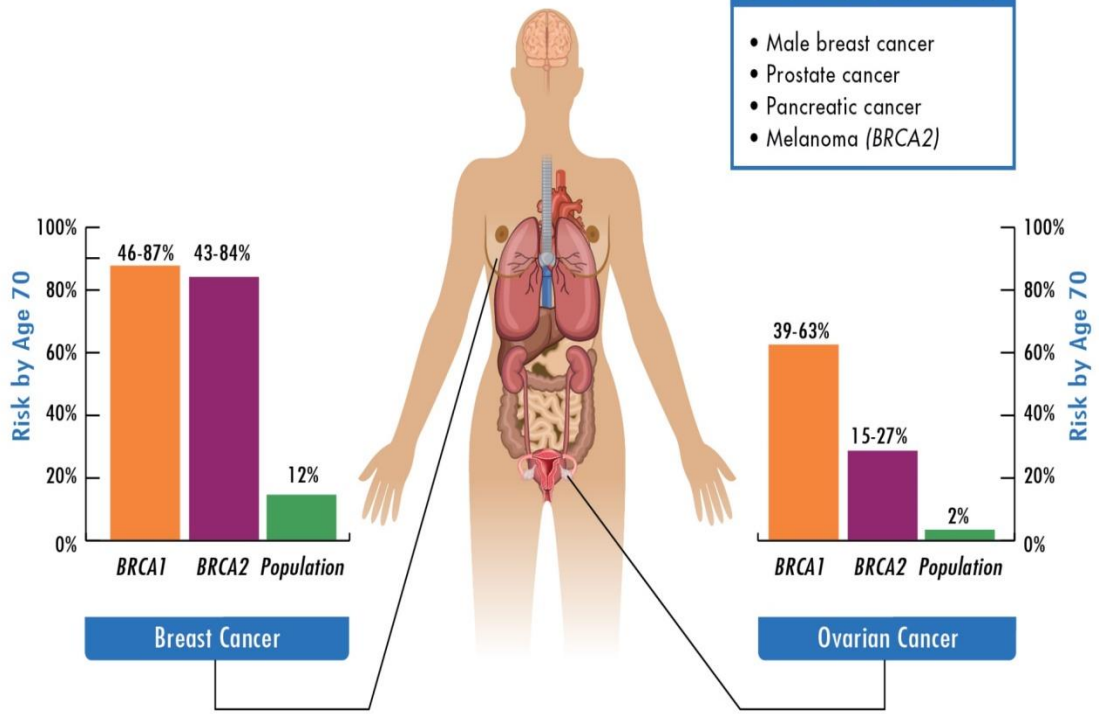




Hereditary Breast and Ovarian Cancer

Other Elevated Risks:

- Male breast cancer
- Prostate cancer
- Pancreatic cancer
- Melanoma *(BRCA2)*

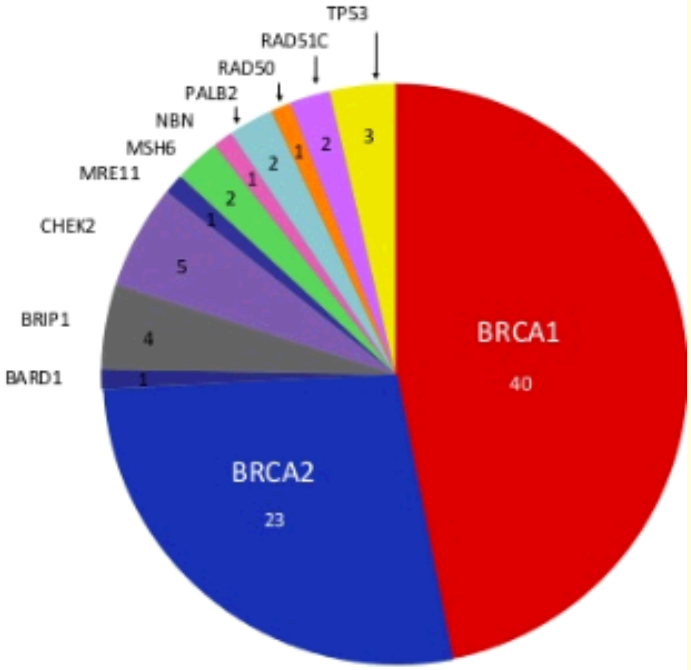


Greenwood Genetic Center

Other Genes Involved in Breast or Ovarian Cancer

BRCA1/BRCA2 mutations in ovarian cancer (UW, Seattle, USA)

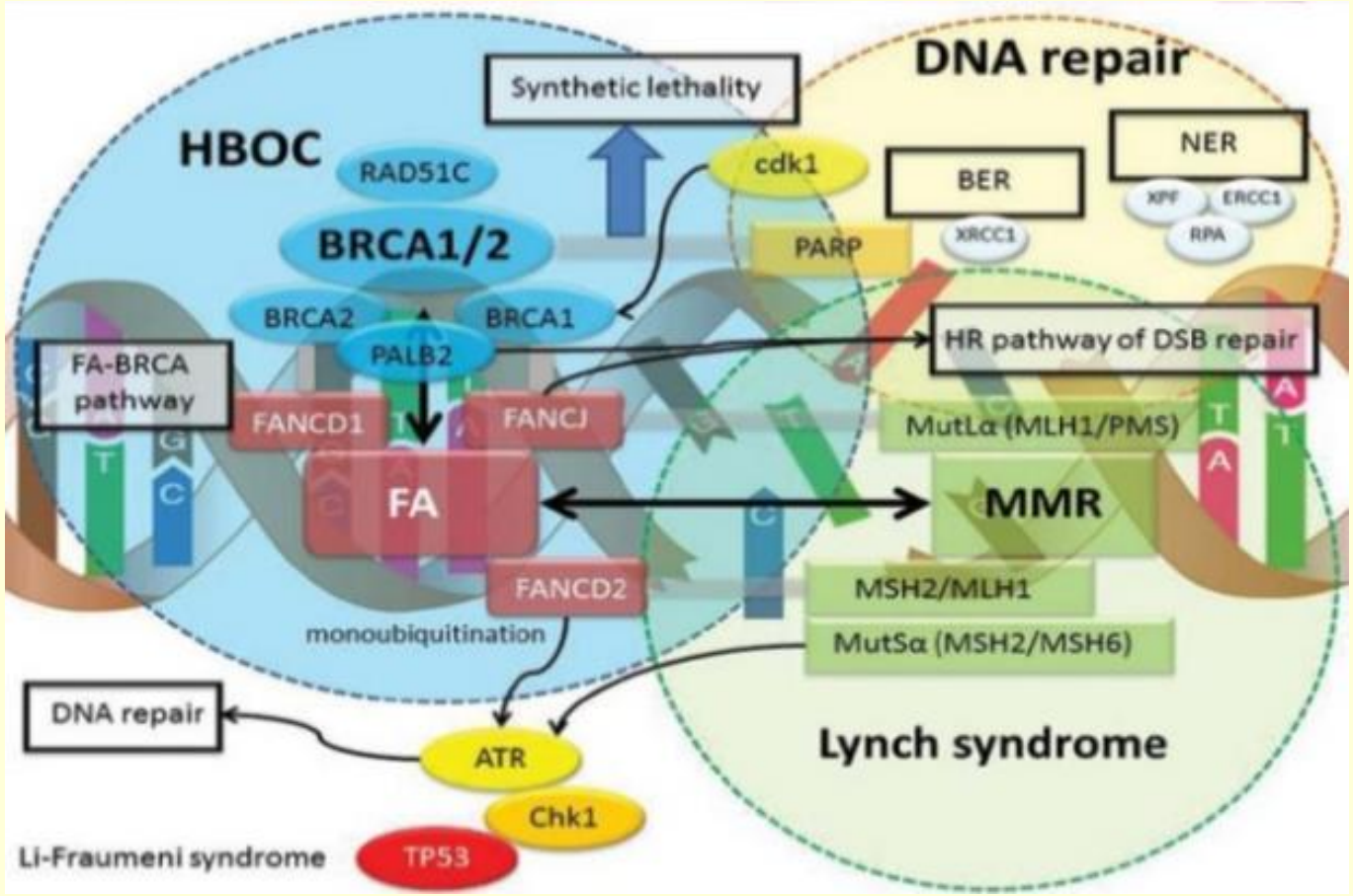
Ovarian cancer: BRCA1/BRCA2 mutations in **63/360 (18%)** patients not selected for family history or age at onset



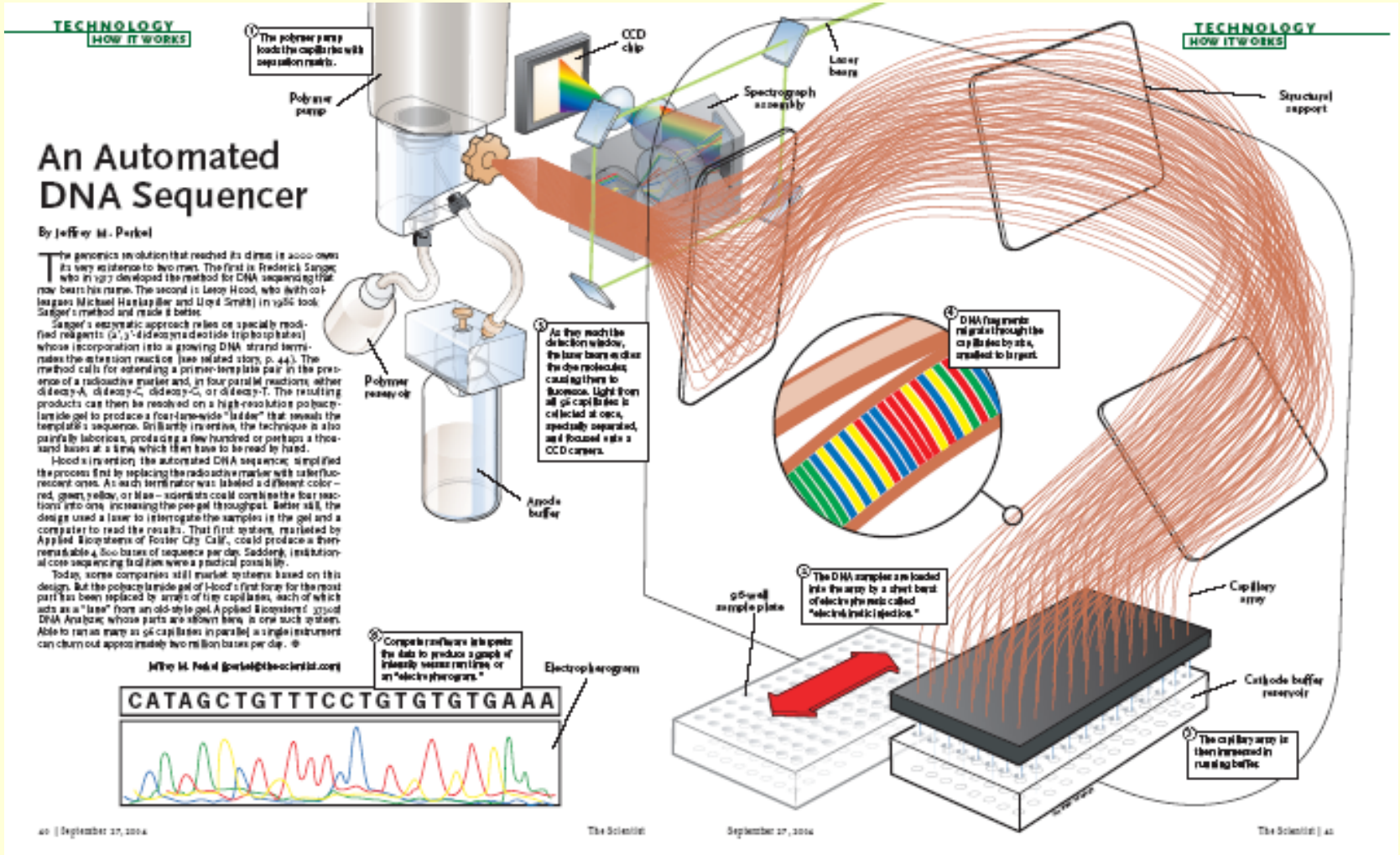
Courtesy of MC King, UW

Walsh, Swisher et al. *PNAS* 2011

BRCA Pathway



Next Generation Sequencing
Rapid and Efficient Analysis of Multiple Genes



Courtesy Dr. Matt Ferber, Mayo CIM Omics Course 2013

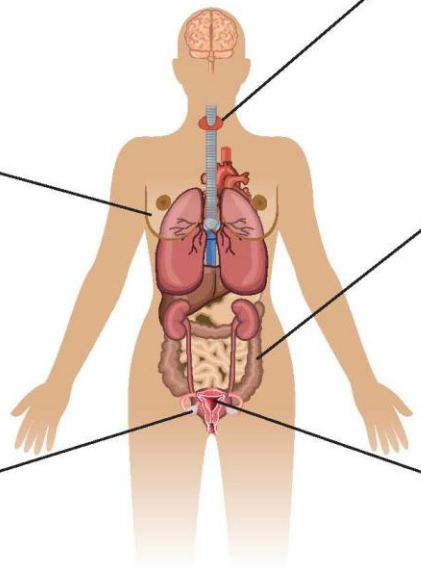
Examples of Hereditary Cancer Panels

Test code	Test name	# gene(s)	Gene list
Frequently Ordered Hereditary Cancer Panels			
01101	Invitae Multi-Cancer Panel ▶ Reflex to this panel Regardless of initial results Only if negative (no pathogenic/likely pathogenic results)	84	AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CASR, CDC73, CDH1, CDK4, CDKN1B, CDKN1C, CDKN2A, CEBPA, CHEK2, CTNNA1, DICER1, DIS3L2, EGFR, EPCAM, FH, FLCN, GATA2, GPC3, GREM1, HOXB13, HRAS, KIT, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RB1, RECQL4, RET, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WRN, WT1
01102	Invitae Common Hereditary Cancers Panel ▶ Reflex to this panel Regardless of initial results Only if negative (no pathogenic/likely pathogenic results)	47	APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, CTNNA1, DICER1, EPCAM, GREM1, HOXB13, KIT, MEN1, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PDGFRA, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, SDHA, SDHB, SDHC, SDHD, SMAD4, SMARCA4, STK11, TP53, TSC1, TSC2, VHL
01206	Invitae Breast Cancer Guidelines-Based Panel	11	ATM, BRCA1, BRCA2, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, STK11, TP53
	01206.1 Add-on gene with emerging data	1	BARD1
01204	Invitae Breast and Gyn Cancers Guidelines-Based Panel	19	ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53
	01204.1 Add-on gene with emerging data	1	BARD1
01252	Invitae Colorectal Cancer Guidelines-Based Panel	19	APC, AXIN2, BMPR1A, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53
	01252.1 Add-on gene with emerging data	1	RPS20
01701	Invitae Hereditary Breast and Ovarian Cancer Syndrome Panel	2	BRCA1, BRCA2

This testing will evaluate for hereditary cancer syndromes

Why Cancer Panel Testing

Cancer Syndromes by Primary Cancer Site



Thyroid Cancer
- Cowden syndrome
- Multiple Endocrine Neoplasia, Type 1
- Multiple Endocrine Neoplasia, Type 2
- Peutz-Jeghers syndrome
- Familial Adenomatous Polyposis

Breast Cancer
- Hereditary Breast-Ovarian Cancer
- Cowden syndrome
- Li-Fraumeni syndrome
- Peutz-Jeghers syndrome

Colon Cancer
- Hereditary Nonpolyposis Colon Cancer/Lynch syndrome
- Familial Adenomatous Polyposis
- *MUTYH*-associated Polyposis
- Cowden syndrome

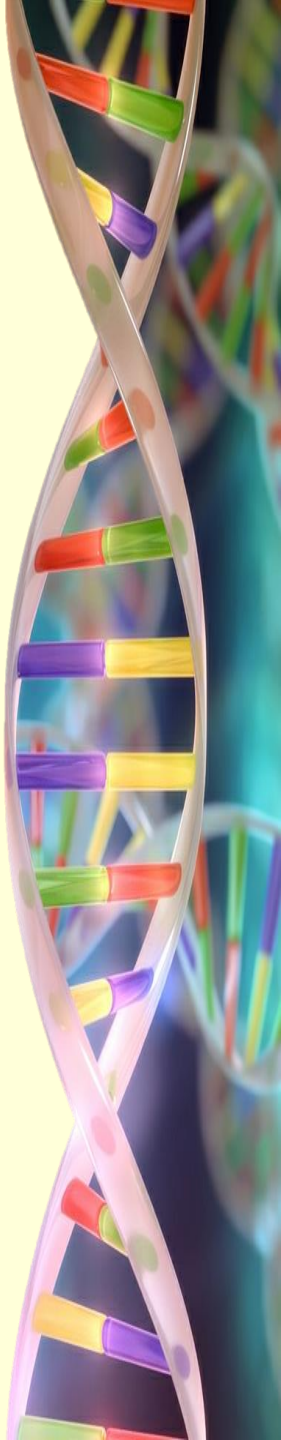
Ovarian Cancer
- Hereditary Breast-Ovarian Cancer
- Hereditary Nonpolyposis Colon Cancer/Lynch syndrome
- Cowden syndrome
- Multiple Endocrine Neoplasia, Type I

Uterine Cancer
- Hereditary Nonpolyposis Colon Cancer/Lynch syndrome
- Cowden syndrome
- Li-Fraumeni syndrome
- Peutz-Jeghers syndrome

Schneider, Katherine A. (2012) Counseling about cancer: Strategies for genetic counseling (3rd ed.). Hoboken, NJ: John Wiley & Sons, Inc.

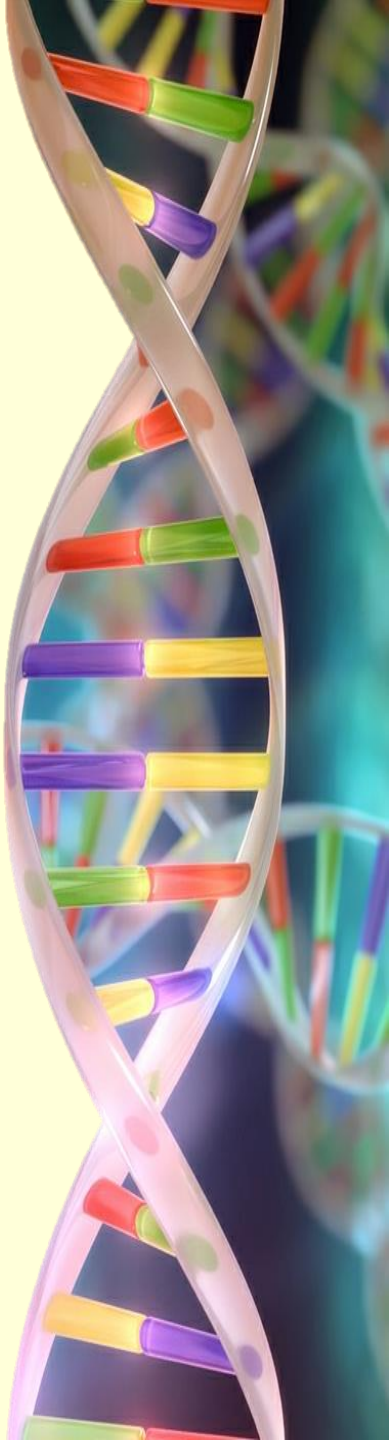
Advantages and Disadvantages of Panel Testing

- Advantages
  - Time and cost effective
  - Comprehensive information
  - Laboratory may offer familial testing without charge
- Disadvantages
  - Unanticipated findings
  - Cancer related risks of some genes not well defined
  - Equivocal results
    - Variants of uncertain significance (VUS)
      - 30% of tested individuals



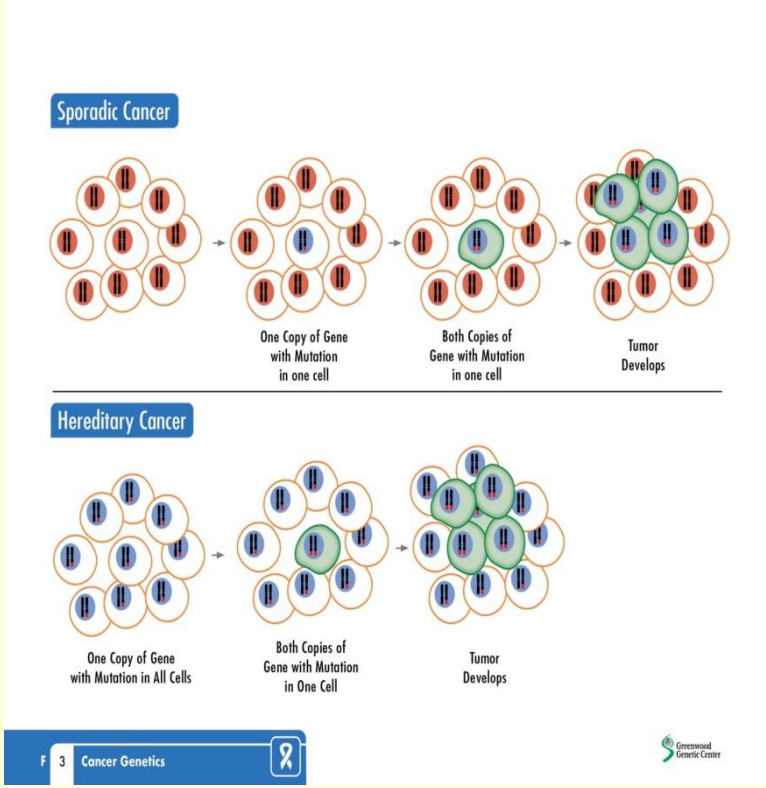
Hereditary Cancer Testing
Why is it important?

- Personal Risks
  - Cancer surveillance
- Family Risks
  - First degree family members at 50% risk
- Cancer treatment
  - PARP inhibitors

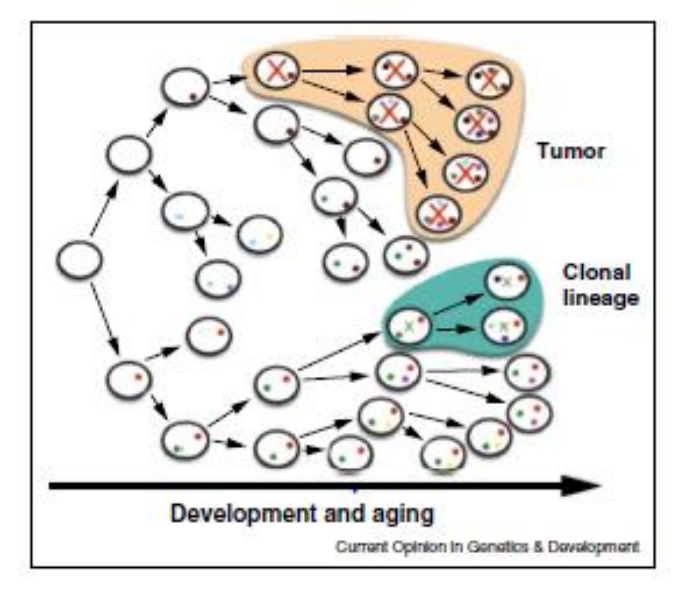


Tumor Testing

Tumor mutations (inherited or acquired) may also have therapeutic implications…



Tumors accumulate mutations
Acquired mutations are not hereditary



Current Opinion in Genetics & Development 2014, 26:141–149

Dr. Wahner Hendrickson will discuss mutations and therapeutics…

Thanks for your attention

Variant Classification

- Benign variant
- Variant, likely benign
- Variant of uncertain significance
- Variant, likely pathogenic*
- Pathogenic variant*

*Clinically actionable

Variants are common…