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VIRGINIA PIPER CANCER INSTITUTE

Cancer Genetic Counseling Services: What is it? Is it for me?

You can't help those who are at risk unless you find them!
WHY IT MATTERS FOR THOSE WITH and without CANCER and for their families.

DID YOU KNOW?

- HOW MANY OF YOU KNEW YOU WERE HIGH RISK FOR BREAST CANCER?
- HOW MANY HAVE HAD A GENETIC TEST?
- IF IT WAS NORMAL, IS THAT GOOD NEWS?
- WHY?

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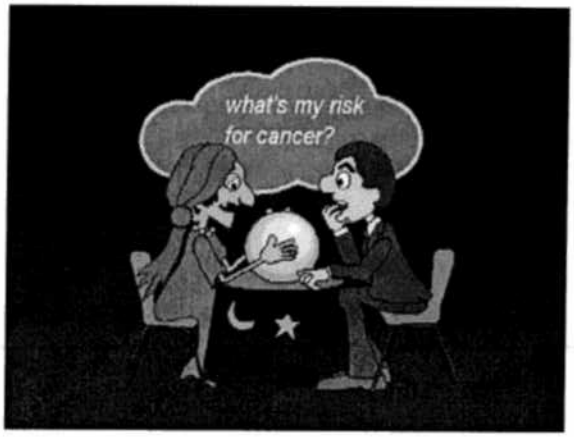

What filled your glass?

- Cancer: filled with risk factors

- Density(4-6 vs 1 for HRT) 14/15-BRCA

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NCCN GUIDELINES:

Breast Screening and DX(2012)

- Women with lifetime risk of >20% dependent on family hx(Claus, Tyrer-Cusick,BRCAPRO,BOADICEA): annual mammo, CBE q 6-12 mo, consider annual MRI; start at 30
- For mutation carriers(BRCA & other highly penetrant genes) : follow guidelines(usually start at 20-25)
- For those with thoracic RT< 25, start 8-10yrs post treatment

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Highest Risk

- BRCA+: 11-15X
- TP53,PTEN: >10x
- Extremely dense breast (75-100%)-4-5X (Lowest density 1% over 3 yrs vs. 2.4% with highest density) Some data suggest RR 6—also informs BRCA related risks
- LCIS—6-10X
- RT<20
- ADH/ALH-4-5X

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	RR	Gail	Claus	BRCAPro	IBIS	BOADICEA
Age	30	x	x	x	x	x
Body Mass Index	2				x	
Birth order	1.24					
Age menarche	2	x			x	
Age 1st live birth	3	x			x	
Age menopause	4				x	
HRT use	2				x	
OCP use	1.24					
Breast feeding	0.8					
Plasma estrogen	5					
Breast biopsies	2	x			x	
ADH	3(4-5)	x			x	
LCIS	4-210				x	
Breast density http://www.bcfa.ucsf/breast/risk.htm	6					
1st degree relative	3	x	x	x	x	x
2d degree relative	1.5		x	x	x	x
Age of breast ca	5		x	x	x	x
Bilateral breast ca	5			x	x	x
Ovarian ca	1.5			x	x	x

RISK MODELS

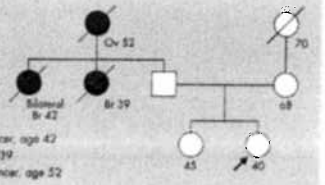
- All have limits
- Use a tool/model that includes the risk factor of concern AND know the limits of each model or risk evaluation may be in error and result in wrong management decisions i.e. over screening some and under screening others.
- often may need to use > 1
- Those with ALH, LCIS, significant density, prev. BC may face significant risks BUT ACS— "can't argue for or against..MRI"-meets PBC guidelines (20%)
- Remember—pedigree analysis!!

Case 1

all 3 from Aug 2009, Oncology Genetics: Community Oncology

Case 1

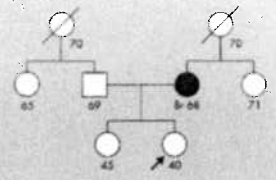
40-year-old Caucasian; premenopausal; height, 5'3"; weight, 150 pounds
Menarche, age 13
First live birth, age 25
No breast biopsies
Family history:
- Paternal aunt: bilateral breast cancer, age 42
- Paternal aunt: breast cancer, age 39
- Paternal grandmother: ovarian cancer, age 52



Breast cancer risk	Gail model	Claus extended model	IBIS model
Five-year risk	0.6%	3.0%	3.3%
Ten-year risk	1.5%	6.2%	6.3%
Lifetime risk (age 70)	6.9%	23.2%	18.2%

Case 2

Case 2
40-year-old Caucasian; premenopausal; height, 5'5"; weight, 150 pounds
Menarche, age 12
First live birth, age 25
Two benign breast biopsies
Family history:
- Mother: breast cancer, age 68



Breast cancer risk	Gail model	Claus extended model	IBIS model
Five-year risk	2.8%	0.6%	1.8%
Ten-year risk	7.3%	1.3%	3.1%
Lifetime risk (age 70)	21.3%	6.6%	13.5%

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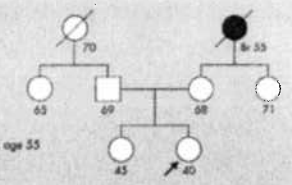
Case 3

Case 3
40-year-old Caucasian; premenopausal; height, 5'5"; weight, 150 pounds
Menarche, age 9
Nulliparous
Biopsy: atypical hyperplasia, age 39
Family history:
- Maternal grandmother: breast cancer, age 55



Breast cancer risk	Gail model	Claus extended model	IBIS model
Five-year risk	2.0%	0.6%	5.3%
Ten-year risk	5.2%	1.2%	11.2%
Lifetime risk (age 70)	18.9%	6.3%	53.4%

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Cancer Risk: It is not just about Genes

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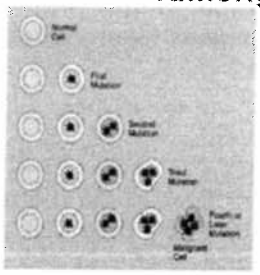
Multi-step Process of Tumorigenesis



- Multiple "hits" needed in single cell for tumorigenesis
- General population cancers have all somatic mutations
- Hereditary cancers have inherited "head start" followed by somatic mutations

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CANCER IS IN THE GENES

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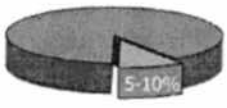
Hereditary Cancer is Rare



Sporadic Cancer
Hereditary Cancer

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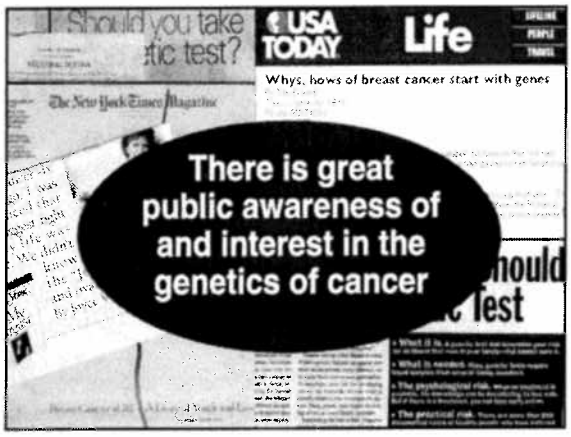

BE AWARE.....

Familial cancer risk assessment

DOES NOT ALWAYS EQUAL GENE TESTING**

The Goal of Testing is not to test as many people as possible it is to test the right people

**you can be high risk with a normal gene test

AND IT'S NOT JUST ABOUT BRCA1/2

Why is it Important to Identify Families with Hereditary Cancer Syndromes?(ONLY ~10% of All Cancers)

- High risk for cancer
- Multiple organ systems may be involved
- Increased risk for second primary cancer
- Increased risk of cancer to relatives
- Possible treatment(targeted therapy- PARPinhibitors for BRCA; need for CT, surgery; avoid RT withTP53; ?mTor inhibitors for PTEN,STK11)
- The ultimate goal is treatment or prevention or early detection of cancer- for patient and FAMILY

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10 yr risk of CBC

AGE@DX	Graeser-JCO 2009	Hooning-SABC-2009
BRCA 1 <30	30.7%	54%
31-40	30.7%	39%
41-50	10.6%	26%
>50	7.9%	17%
BRCA 2 ≤40	20.7%	28%
41-50	12.8%	19%
>50	9.2%	10%

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Don't forget the other BRCA cancers

- Pancreatic
- Melanoma: cutaneous and ocular
- Prostate: high grade; excess <65. IMPACT study
- ?stomach and other GI
- ?colon
- ?some head and neck
- ? HGPSU cancer(embryonic rests vs mets from FT)

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BRCA

- ~20-23% of high grade pap serous OC due to BRCA (~1/3 are in women with no other family hx)
- ?~70% are actually from the fimbria(native tissue is serous)
- Risk for breast cancer ranges from ~37%-70+% but could be further stratified by gene modifiers and density
- Risk for ovarian cancer by age 30 with BRCA 1 is 1% or less(~2/1000 for BRCA 2)BUT 1.6-3.4% between 30 and 40 for BRCA 1
- PROSE study: HRT not contraindicated in those without cancer, at least until natural menopause. Decrease in BC risk with BSO> for nat. menopause and postmenopausal BSO also protects against BC (AACRfor cancer Research may7,2012;Kotsopoulos etal)

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TH/BSO vs BSO

- ??TAM
- HRT vs ERT
- Theoretical risk in proximal tube
- ?is HGPSU related cancer

- HYSTERECTOMY NOT NECESSARY BUT NOT UNREASONABLE

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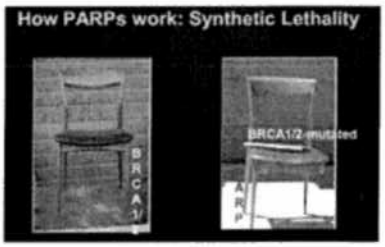

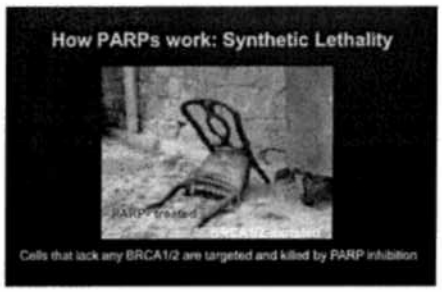

Screening for "Familial Cancer"

- Help your doctor collect appropriate Family History Details:
  - Type of primary cancer(s) in each relative(not mets)
  - PATHOLOGY
  - Age of disease onset in each relative
  - Cancer status in 1st ,2nd and 3rd degree relatives-minimum
  - Cancer/precursors in both sides of the family
  - Ethnic background on both sides
  - Other medical/environmental findings – benign tumors, congenital abnormalities, preventive surgery etc.
  - Update often: hx dynamic

Confounders

- Incomplete penetrance
- Hx incomplete/inaccurate
- False paternity
- Adoption
- Sporadic Ca's among familial ones
- Early non-CA death of informative relative
- Those w/ PM/PSO - mask susceptibility
- Absence of medical records
- Pedigree too small

Family History Collection Tools

Surgeon General's Family History Health Initiative
http://www.hhs.gov/familyhistory/

www.nsgc.org

Hereditary Breast and Ovarian Cancer Syndrome: Who to Refer

Breast Cancer (BC)

- Dx ≤ 45y
- ➡ Dx ≤ 50y with ≥ 1 close blood relative with BC ≤ 50y and/or ovarian/fallopian tube/primary peritoneal cancer at any age
- Two breast primaries with first dx ≤ 50y
- ➡ Dx ≤ 60y with triple negative breast cancer
- ➡ Dx ≤50y with a limited family history
- Dx any age, with ≥ 2 close blood relatives with BC and/or epithelial ovarian/ fallopian tube/ primary peritoneal cancer at any age(or 1 rel with BC≤50)
- Male with or close male blood relative with BC
- Personal history of epithelial ovarian/ fallopian tube/ primary peritoneal cancer
- Ethnicity associated with higher mutation frequency i.e. Any Ash. Jewish woman with breast cancer

Hereditary Breast and Ovarian Cancer Syndrome: Who to Refer

Other Personal History

- Epithelial ovarian/fallopian tube/primary peritoneal cancer
- BC or ovarian cancer at any age with ≥ 2 close blood relatives with pancreatic cancer at any age OR HIGH GRADE PROSTATE
- Pancreatic cancer at any age with ≥ 2 close blood relatives with BC or ovarian and/or pancreatic cancer at any age

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Who Might benefit due to Breast Cancer Concerns?

- Consider with criteria of other syndromes: TP53, PTEN, STK11,CDH 1 etc.
  - Consider also with family hx of multiple breast cancers, pancreatic cancers or other **cancers(sarcomas, brain tumors etc); consider measuring OFC**
- **Always if patient is concerned about cancer risk to self/family**

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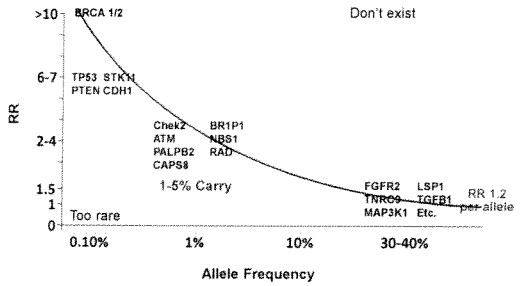
BREAST CANCER GENES



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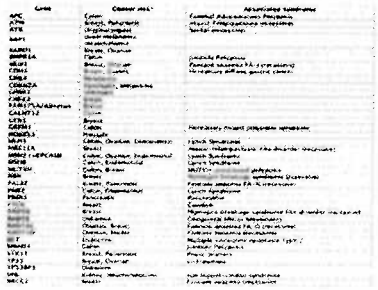
Other Breast Cancer Genes besides BRCA 1 and 2(only 13 of 43 researched & published extensively)



Summary: It's not just BRCA!!

- Only ~10% of BC is due to major heritable risk
- Mutations in BRCA 1 and 2 account for only ~5% of all BC
- Offit: ¾ of familial BC NOT BRCA 1 and 2
- New multigene panel may account for another ~20%
- Currently known low penetrant/common alleles(less than 1oz in glass) account for 25% of population attributable risk but only ~5% of familial aggregations
- NO BRCA 3
- Likely ~50 genes expected to account for rest of clusters
- ?Environment??epigenetics

Next-gen Panels

-Cheaper(low cost)	-Moderate accuracy (techniques may add coverage but some genes more comprehensively covered than others)
-Many Genes(mutations in any one of a number of genes can meaningfully elevate risk).	-Lack of clinical utility proven for some genes esp moderate risk ones(no good data on outcome, specific risks)
-Not hypothesis driven	-Only some of the genes have proven interventions available(may not have specific recommendations &/or may not be covered by ins.)
-Good when more than one dx possible OR multiple unrelated cancer i.e .when phenotype of pt or family is unable to clearly direct testing	-Some ins. Consider these investigational
-May learn more broad phenotypes: (for moderate penetrance genes = opportunity&challenge)	-High rate of VUS
-Most associated with at least mod risk for other cancers.	

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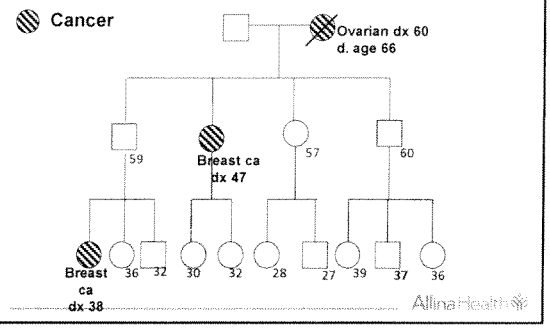
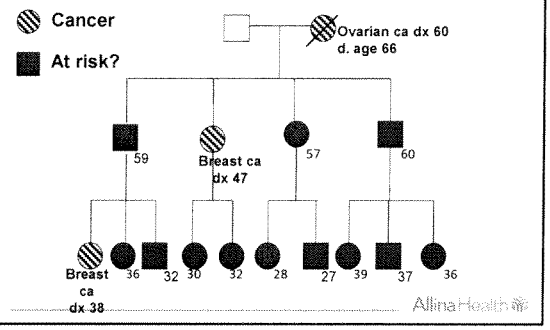
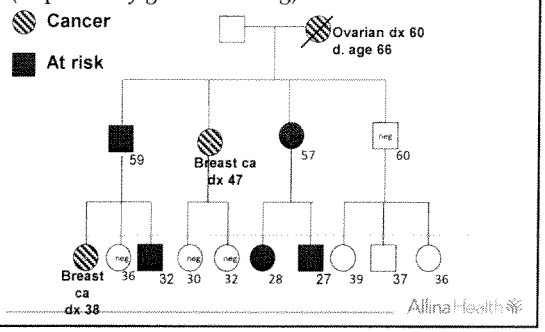
HBOC Family History



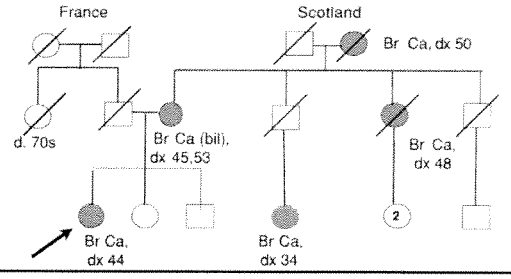
Other "At-Risk" Relatives



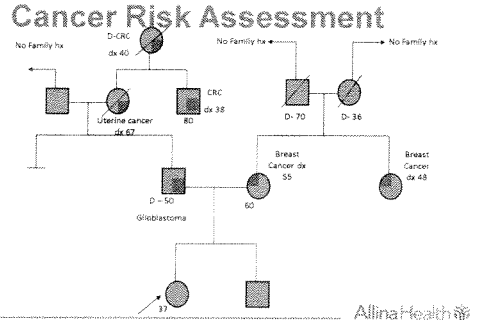
Other "At-Risk" Relatives
(impacted by genetic testing)



Uninformative Results: No *BRCA1* or *BRCA2* Mutation Identifiable



Case 4: Referral for Breast Cancer Risk Assessment



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Case 4: Follow-Up

- Breast cancer risks evaluated; high risk management instituted; no gene test unless mutation found in mom
- Because paternal hx suggestive of Lynch, pt had colonoscopy
- Villous adenoma found in cecum**
- Genetic testing sought and family management changed
- **GENETIC COUNSELING CAN SAVE LIVES

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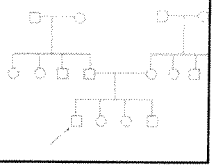
What Goes on during Cancer Genetic Counseling

Before Consult:
- Gather three-four generation family tree
  - Confirm diagnoses through medical records

During Consult:
- Assess hereditary cancer risk
- Provide management options in light of personal risks(refer to appropriate resources).
- Discuss possible genetic syndromes IF indicated.
- Address the option of genetic tests
  - If indicated and choose best to test
  - Help informed decision making
  - All risks, concerns, limits, benefits



Genetic Counseling

- After Testing if done:
- Interpret test result for patient and family
- Discuss continuing care with screening/surgeries/prevention
- Encourage conversation with family members
- Address psychosocial issues for both patient and family

- Goals:
- Eliminate the burden of cancer in our patient and their family members
- Limit psychosocial stress throughout process
- YOU CAN'T HELP THOSE WHO ARE HIGH RISK UNLESS YOU CAN FIND THEM!
- http://www.cancer.net/patient/All+About+Cancer/Genetics/What+to+Expect+When+Meeting+With+a+Genetic+Counselor

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Myths about Genetic Counseling:

- I have no family with cancer, genetics can't be involved OR my parents/siblings or others have cancer, so I must be high risk
- I don't want to go for genetic counseling because I don't want a gene test.
- I will lose my insurance if I go for GC OR my insurance won't pay
- I had a normal gene test, so I(my relatives) don't have to worry

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Myths cont.:

- I tested positive for a mutation in a cancer gene, so I WILL get cancer
- Anyone who wants to know their risk for cancer should get a gene test.
- There are only genes for breast cancer OR there is A breast cancer gene.(BRCA 1 and 2 account for at MOST half of heritable breast cancer).

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Clinical Specialty Area

CANCER

- There are more than 50 well described cancer susceptibility syndromes, many of which can result from mutations in more than one gene.

(Lindor NM et al., 2008, JNCI)

- Many common cancers (e.g. breast, colon, uterine, etc) are tumors related to 10 or more cancer susceptibility genes, making genetic risk assessment essential for cost-effective genetic testing strategies.

(Lindor NM et al., 2008, JNCI)

- Surveillance and prophylactic surgery have been shown to reduce cancer-related morbidity and mortality for several cancer susceptibility syndromes.

(Kurian AW et al., 2010, JCO; de Jong AE et al., 2006, Gastroenterology)

National Society of Genetic Counselors

Clinical Specialty Area

CANCER (continued…)

- Genetic counseling and testing shortly after cancer diagnosis can help guide patients' surgical and treatment decisions.

(Weitzel JN et al., 2003, Arch Surg; Schwartz MD et al., 2004, JCO)
(Ashworth A, 2008, JCO; Ribic CM et al., 2003, NEJM; Sargent DJ et al., 2010, JCO)

- Genetic counselors can help clarify whether a patient who tests *negative* for breast cancer susceptibility genes (such as BRCA1 and BRCA2) qualifies for breast MRI screening, using risk assessment models and ACS and NCCN breast MRI guidelines.

(Saslow D et al., 2007, CA Cancer J Clin)

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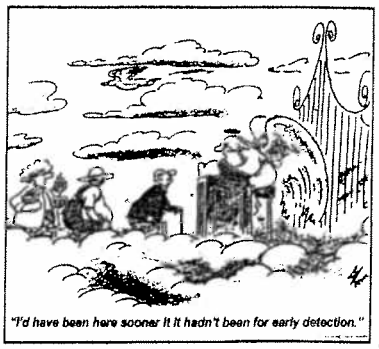

Thank you for your time!
QUESTIONS??