Hereditary Breast and Ovarian Cancer and Genetic Testing

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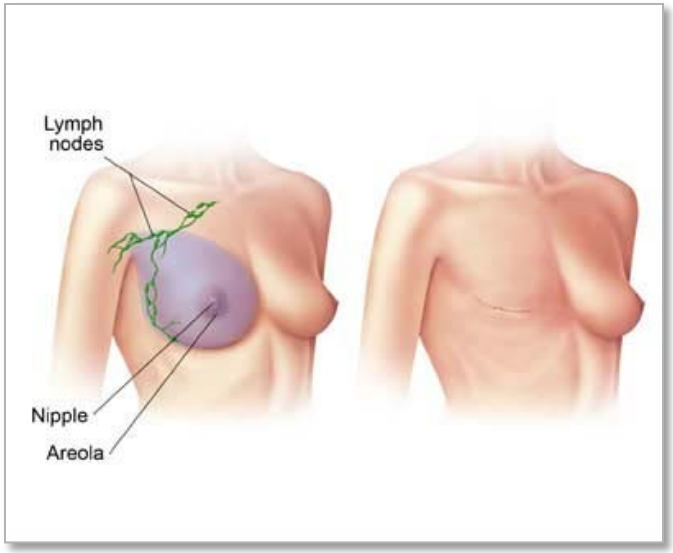
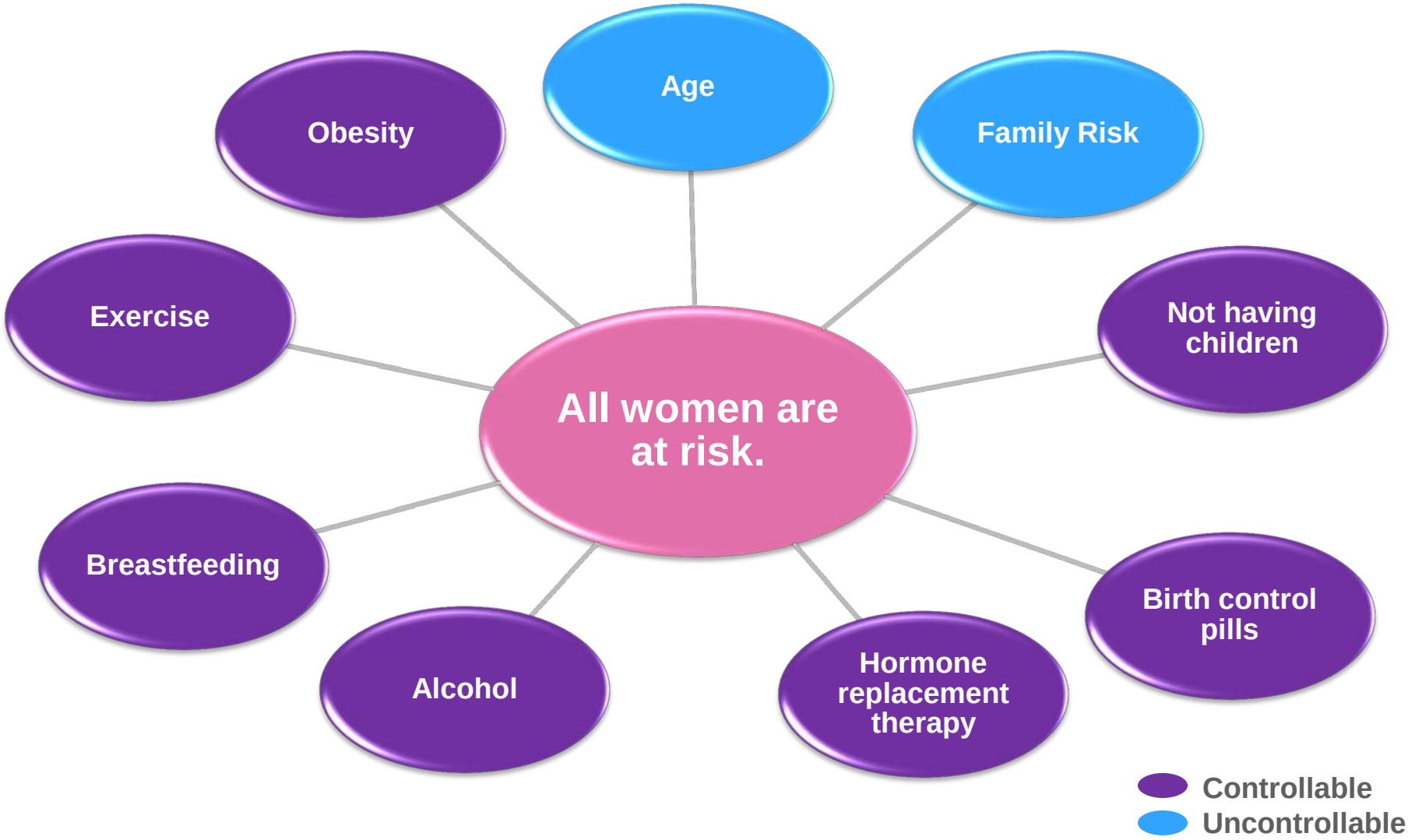
Breast Cancer

- Breast cancer is one of the most common forms of cancer among women (40,290 in 2015).
- It is second only to lung cancer as a cause of cancer deaths in American women,
- One-third of women with breast cancer die from breast cancer,
- One out of every eight women will be diagnosed with breast cancer in 2015.



Breast Cancer Risk Factors

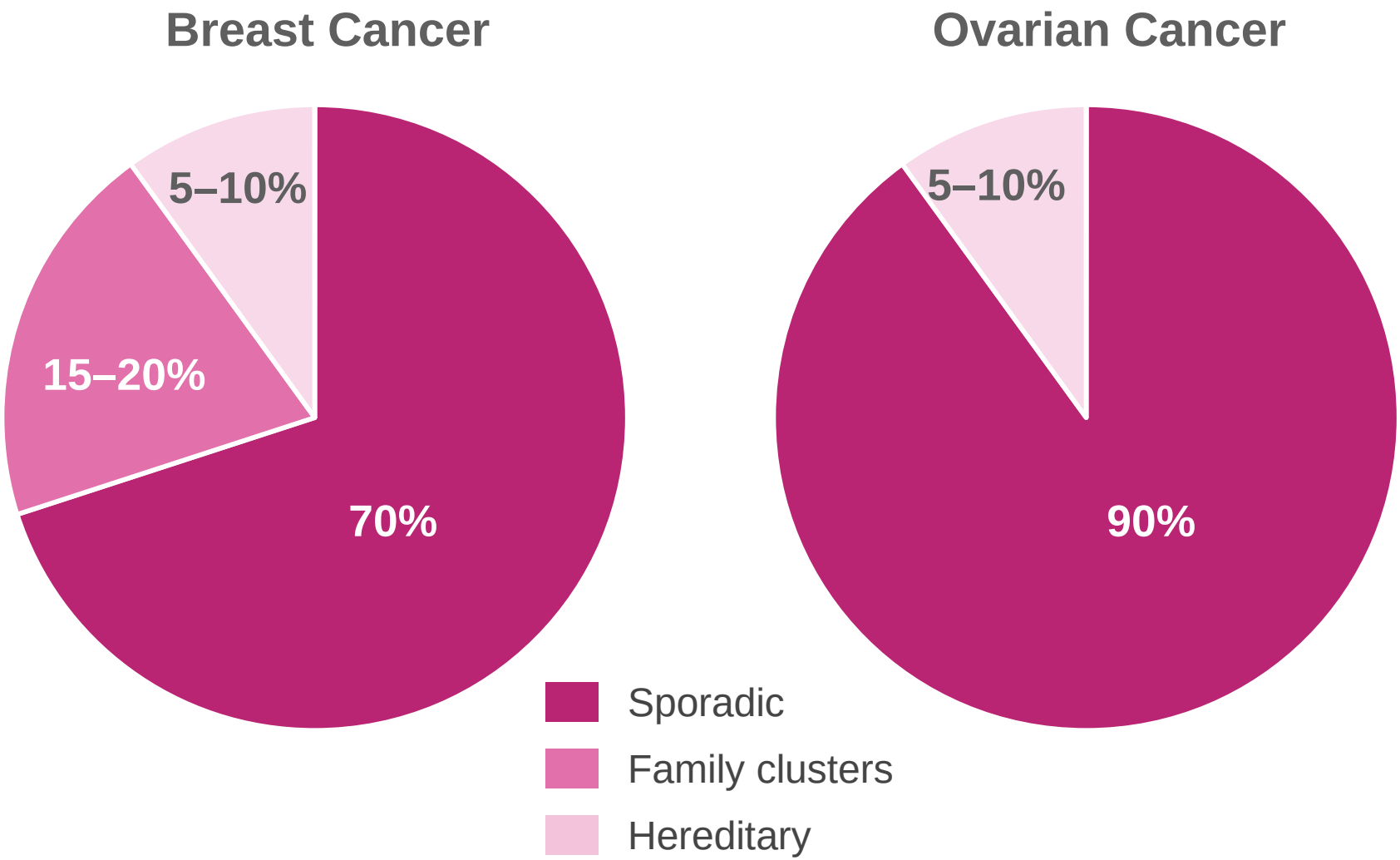


Breast Cancer Risk Factors: Age

Risk	
By age 30	1 out of 2,000
By age 40	1 out of 233
By age 50	1 out of 53
By age 60	1 out of 22
By age 70	1 out of 13
By age 80	1 out of 9
Lifetime risk	1 out of 8

NCI SEER Program. http://seer.cancer.gov/

Family History as a Risk Factor



Compare Hereditary vs. Sporadic Cancer

- A younger age at the onset of cancer
  - Generally < 50 years of age

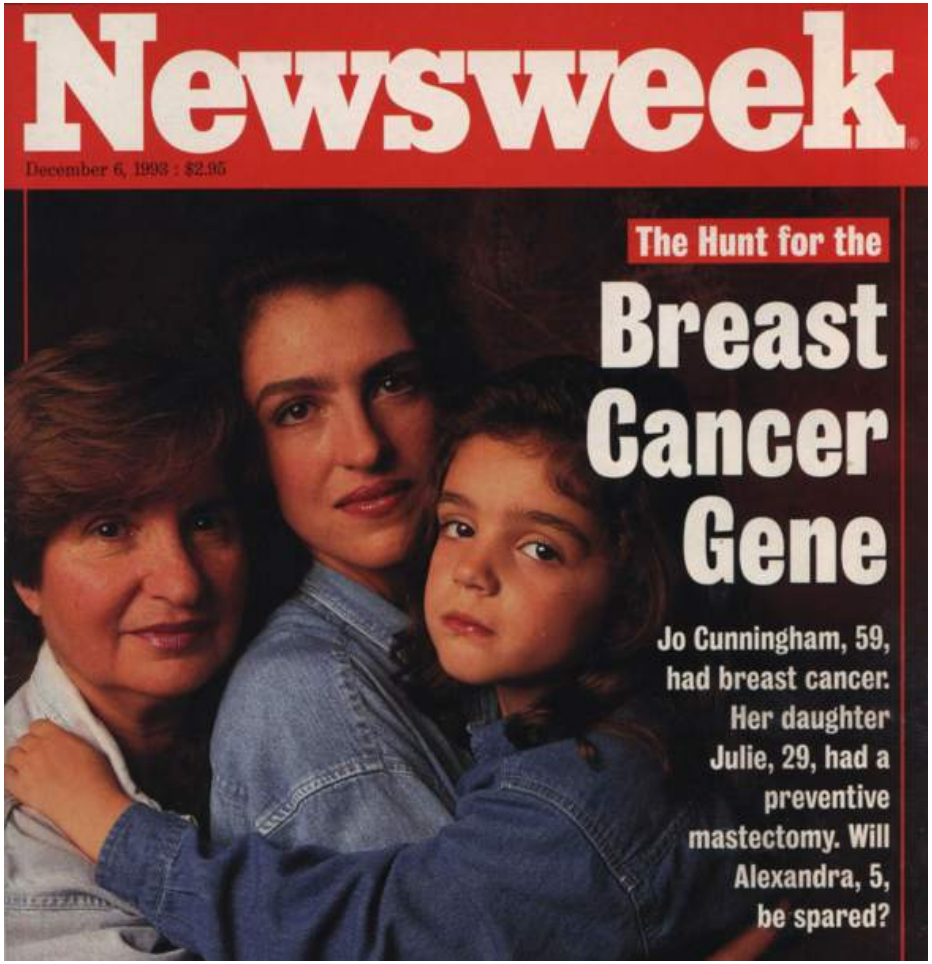
- Multiple primary cancers:
  - Breast
  - Ovarian
  - Other

Causes of Hereditary Susceptibility to Breast Cancer

5–10% of breast cancers can be attributed to inherited factors.

Gene	Contribution to Hereditary Breast Cancer
BRCA1	20–40%
BRCA2	10–30%
TP53	<1%
PTEN	<1%
Undiscovered genes	30–70%

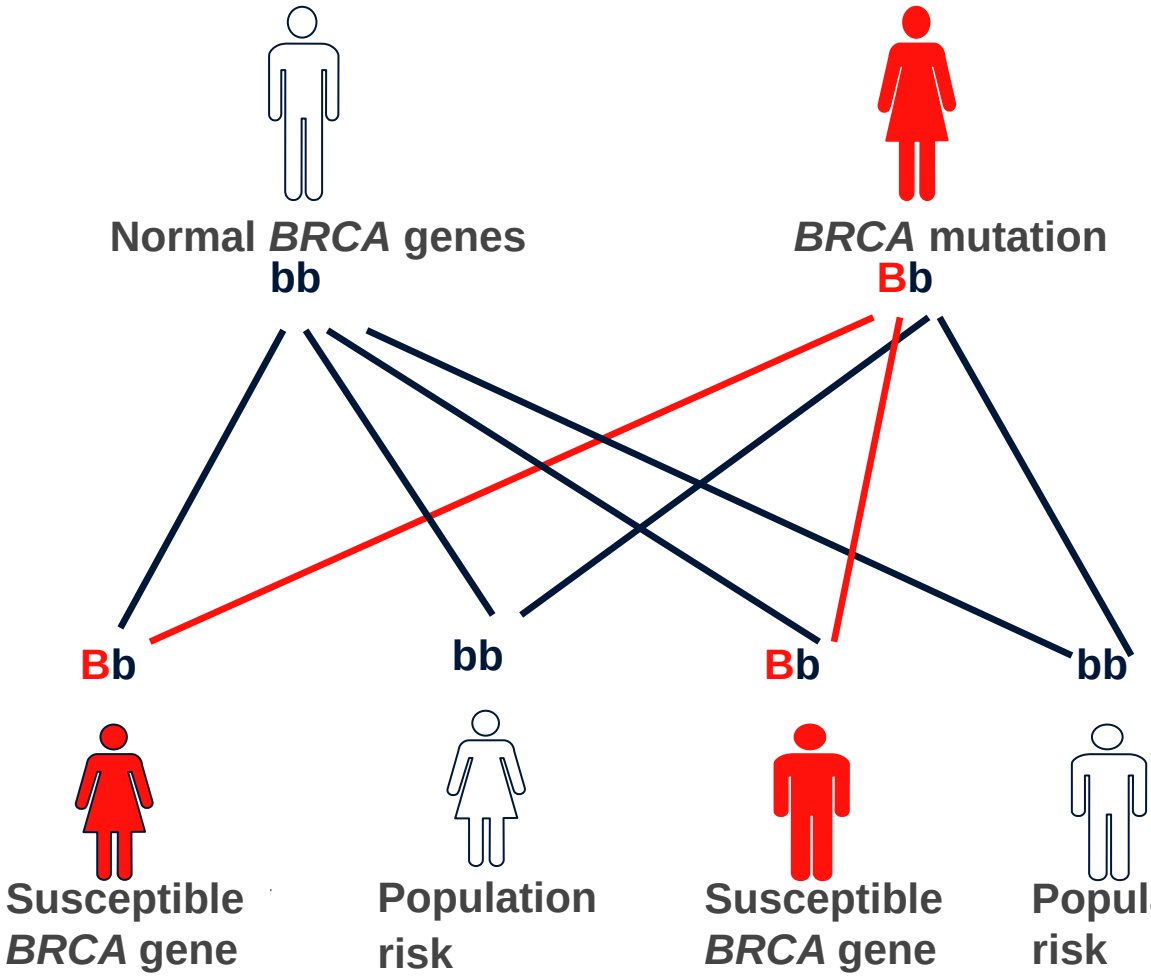
Breast Cancer Genes Found



- ***BRCA1*** (for **BR**east **CA**ncer gene 1) was described in 1990 on chromosome 17 and isolated in 1994.
- ***BRCA2*** was isolated on chromosome 13 in late 1994.

Passing on Risk: Autosomal Dominant

Each child has 50% risk of inheriting a familial mutation.



Legend

B: *BRCA* gene with mutation

b: Normal *BRCA* gene

Consequences of Having a *BRCA* Mutation

Estimated cancer risk by age 70		
	BRCA Mutation Carriers	In General Population
Breast Cancer ♀ *BRCA1 & BRCA2*	50–85%	11%
Ovarian Cancer *BRCA1*	40–60%	1–2%
Ovarian Cancer *BRCA2*	10–20%	1–2%
Breast Cancer ♂ *BRCA2*	≤6%	Rare

Other *BRCA+* Related Cancers

Slight risk for other cancers

- Shown to be increased in carriers:
  - Pancreatic
  - Melanoma
  - Stomach
  - Colon
  - Prostate
  - Male breast cancer

Who Should Be Tested?

- Multiple family members with breast cancer
- A family member with primary cancer in both breasts
  - Especially if manifested before age 50
- A family member with ovarian cancer
- A family member with male breast cancer
- A family member with an identified *BRCA1* or *BRCA2* mutation
- Jewish ancestry

BRCA1 and *BRCA2* Mutations

- ***BRCA1*: 1873 mutations**
  - Point mutations: 1574 (84%)
  - Large deletions/duplications: 299 (16%)

- ***BRCA2*: 1597 mutations**
  - Point mutations: 1523 (95%)
  - Large deletions/duplications: 74 (5%)

BRCA1 and *BRCA2* Jewish Mutations

- Three mutations in *BRCA1* and *2* account for 97% of *BRCA1* and *BRCA2* mutations in Ashkenazi Jewish individuals:
  - *BRCA1*: 185delAG, 5382insC
  - *BRCA2*: 6174delT

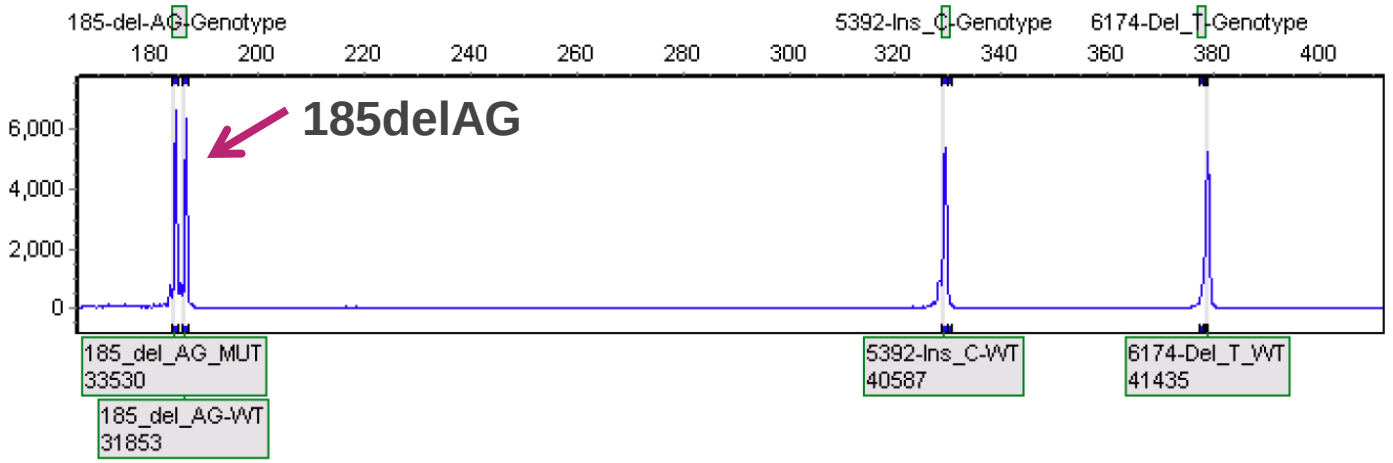
Hereditary Breast/Ovarian Cancer Testing

- Ashkenazi Jewish (*BRCA1* and *BRCA2*), 3 Mutations (2011958)
- Breast and Ovarian Hereditary Cancer Syndrome (*BRCA1* and *BRCA2*) Sequencing and Deletion/Duplication (2011949)
- Breast and Ovarian Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 20 Genes (2012026)

Test Recommendation for Jewish Ancestry

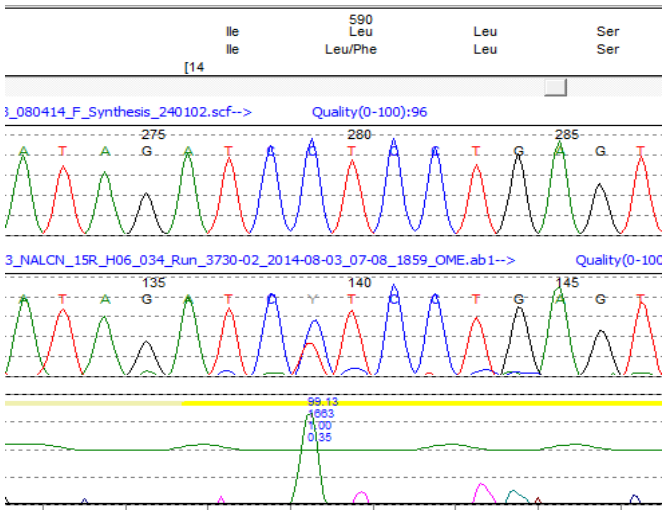
- Test with Ashkenazi Jewish (*BRCA1* and *BRCA2*), 3 Mutations (2011958): sensitivity 97% (PCR/ capillary electrophorese)

- Negative: Breast and Ovarian Hereditary Cancer Syndrome (*BRCA1* and *BRCA2*) Sequencing and Deletion/Duplication (2011949)

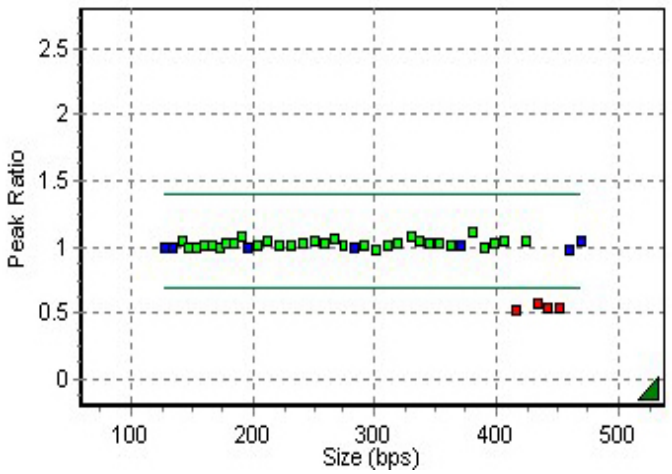


Testing for High-Risk Individuals

- Breast and Ovarian Hereditary Cancer Syndrome (*BRCA1* and *BRCA2*) Sequencing and Deletion/Duplication (2011949)
  - Sequencing *BRCA1* and *BRCA2* genes: sensitivity 80–84% and 90–95%
  - Deletion/duplication of *BRCA1* and *BRCA2* genes: sensitivity 16% and 5%



Sequencing

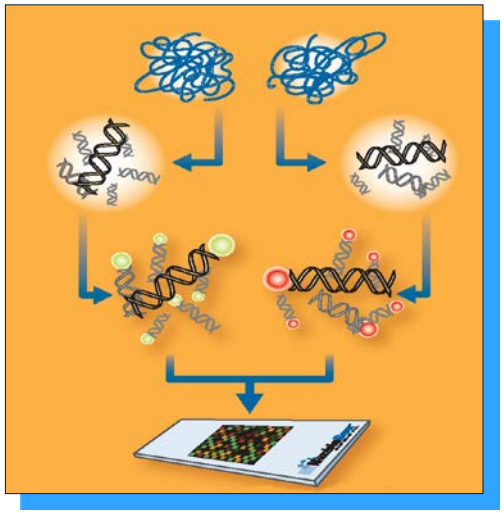


MLPA

Breast Cancer Multi-Gene Panel

- Breast and Ovarian Hereditary Cancer Panel, Sequencing and Deletion/Duplication, 20 Genes (2012026)
- 20 genes associate with increased risk of breast cancer: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53*

Next-generation sequencing



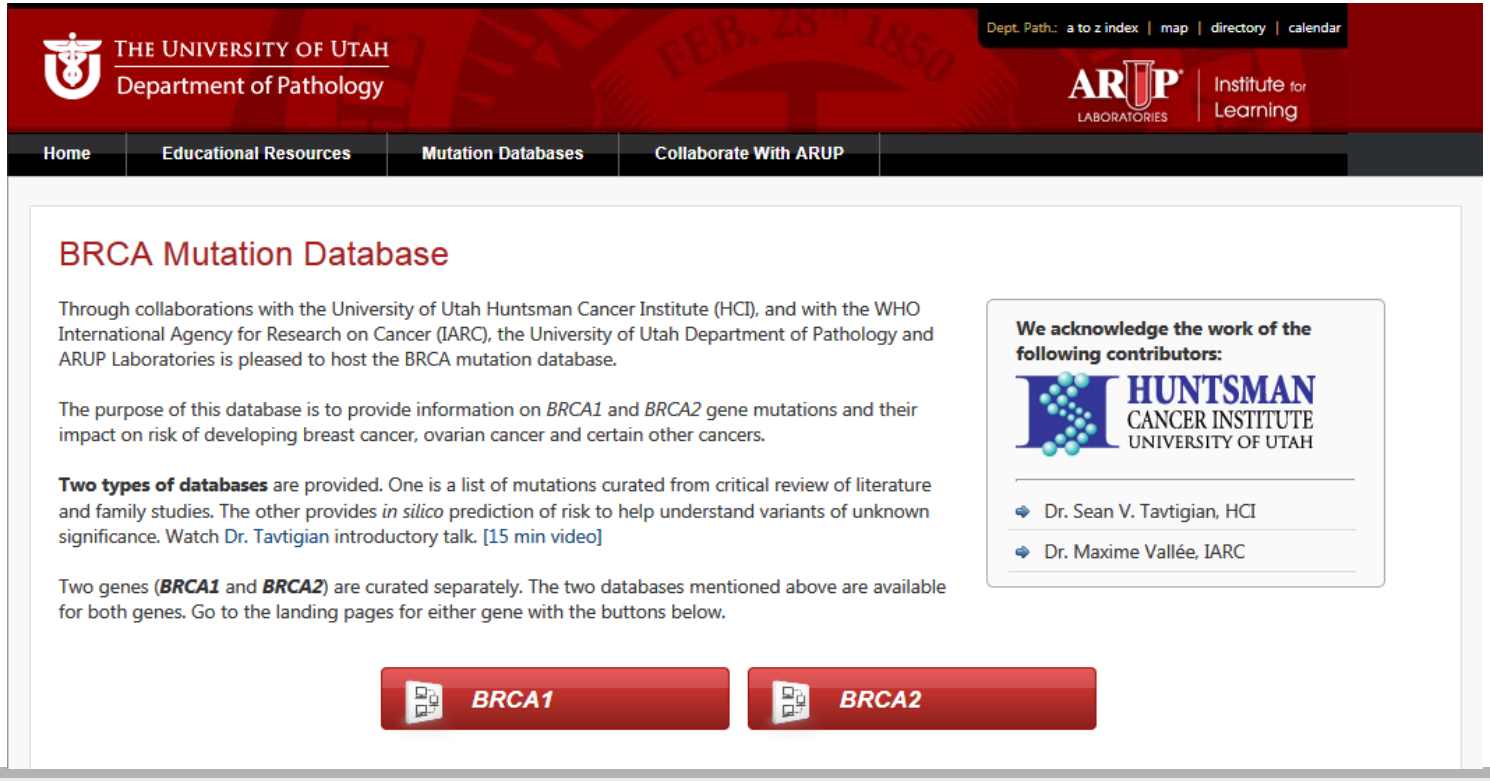
Array CGH

Is This Sequence Variant a Mutation?

M18T in *BRCA1*: Is this a mutation or benign?

Publication, computational prediction, database

http://www.arup.utah.edu/



ARUP *BRCA1* and *BRCA2* Mutation Database

1168 variants found.

Search

Location	Mutation Type	Nucleotide Change	Protein Change	Classification	Posterior Probability	Reference	Secondary Reference	Comments
Exon 2	Nonsense	c.8T>G	p.L3*	5 - Definitely pathogenic	>0.99	Keshavarzi (2012) Fam Cancer 11; 57		
Exon 2	Insertion	c.32_33insC		5 - Definitely pathogenic	>0.99	Szabo (1995) Hum Mol Genet 4; 1811		
Exon 2	Nonsense	c.34C>T	p.Q12*	5 - Definitely pathogenic	>0.99	Adem (2003) Cancer 97; 1		
Exon 2	Indel	c.38_39delATinsGGG		5 - Definitely pathogenic	>0.99	Lim (2009) J Cancer Res Clin Oncol 135; 1593		
Exon 2	Missense	c.53T>C	p.M18T	4 - Likely pathogenic	0.9840	Easton DF et al., Am J Hum Genet, 81: 873-883, 2007.	Tavtigian et al., Human Mutation 29: 1342-1354, 2008.	
Exon 2	Nonsense	c.55C>T	p.Q19*	5 - Definitely pathogenic	>0.99	Machackova (2008) BMC Cancer 8; 140		
Exon 2	Deletion	c.61delA		5 - Definitely pathogenic	>0.99	Thirthagiri (2008) Breast Cancer Res 10; R59		
Exon 2	Insertion	c.62dupT		5 - Definitely pathogenic	>0.99	Yassaee (2002) Breast Cancer Res 4; R6		

Management of *BRCA*+ Women

Prevention and Screening Options	
Prophylactic surgery	Mastectomy Oophorectomy
Chemoprevention	Tamoxifen Oral contraceptives
Screening	Mammograms MRI Ultrasound Clinical breast exams

Current Screening Recommendations for *BRCA*+ Women

- **Breast**
  - Monthly breast self-exams (begin by age 18)
  - Early clinical surveillance (begin by age 25)
    - Biannual clinical breast exams at a breast center
    - Annual mammography
    - Sonography? MRI?
- **Ovarian: no good options**
  - Transvaginal ultrasound
  - CA-125 blood levels

Conclusion:

Identifying high-risk individuals will help surveillance and prevention of breast/ovarian cancer.

Germline Pharmacogenetics in Breast Cancer

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Co-Medical Director, Pharmacogenetics

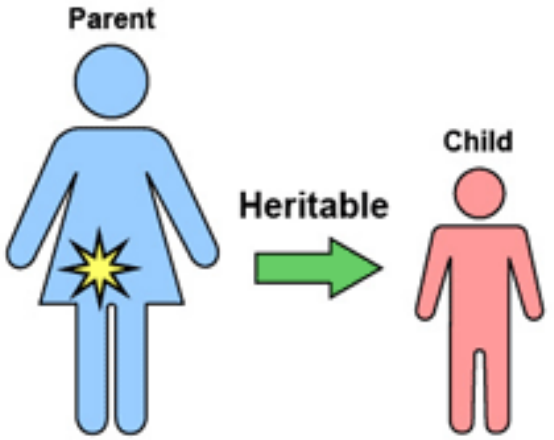
Germline vs. Somatic Genetics

Somatic mutations
- Occur in ***nongermline*** tissues
- Cannot be inherited

Nonheritable

Mutation in tumor only
(for example, breast)

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome



Mutation in
egg or sperm

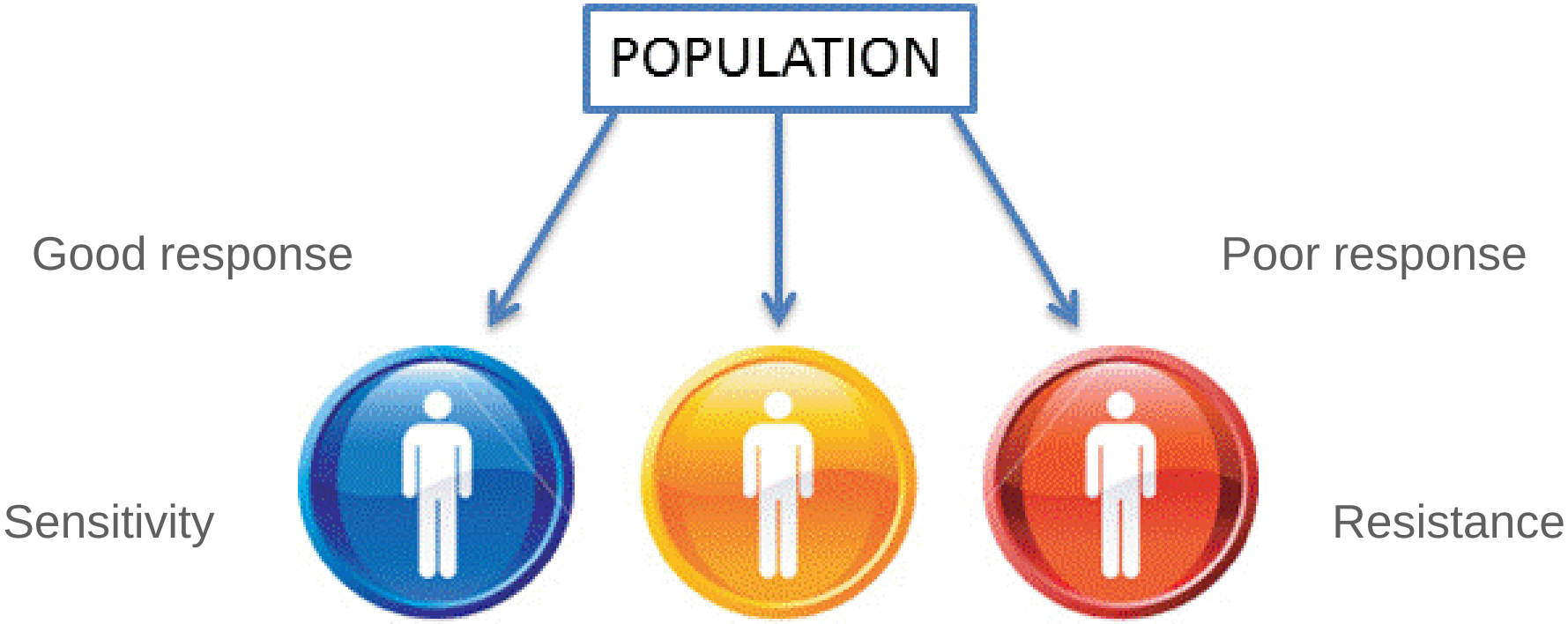
All cells
affected in
offspring

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

Germline Pharmacogenetics

Inherited genes can predict/explain if and how a person will tolerate and respond to a drug:

- Pharmacokinetics, such as **drug metabolism**
- Pharmacodynamics, such as drug response

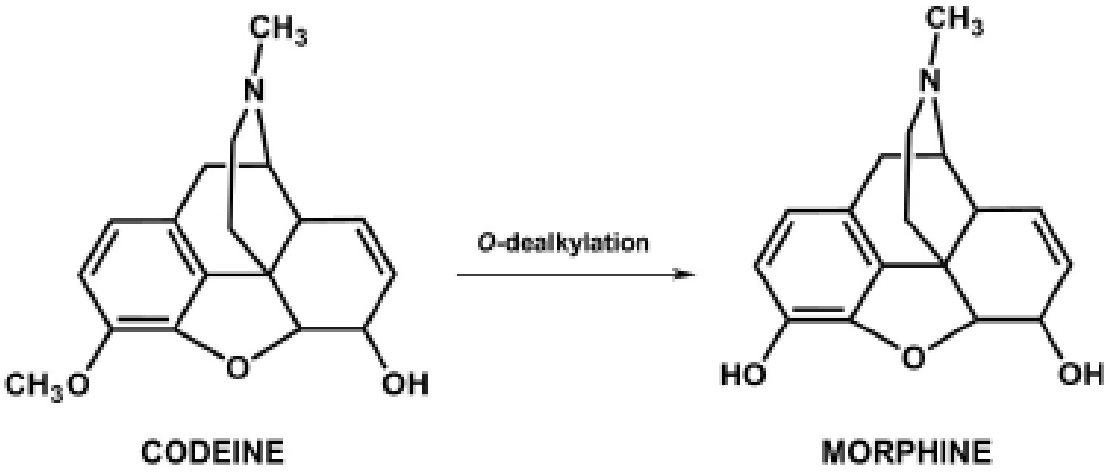


Unconventional
dose and/or dosing frequency

Drug Metabolism

- Most drugs are metabolized.

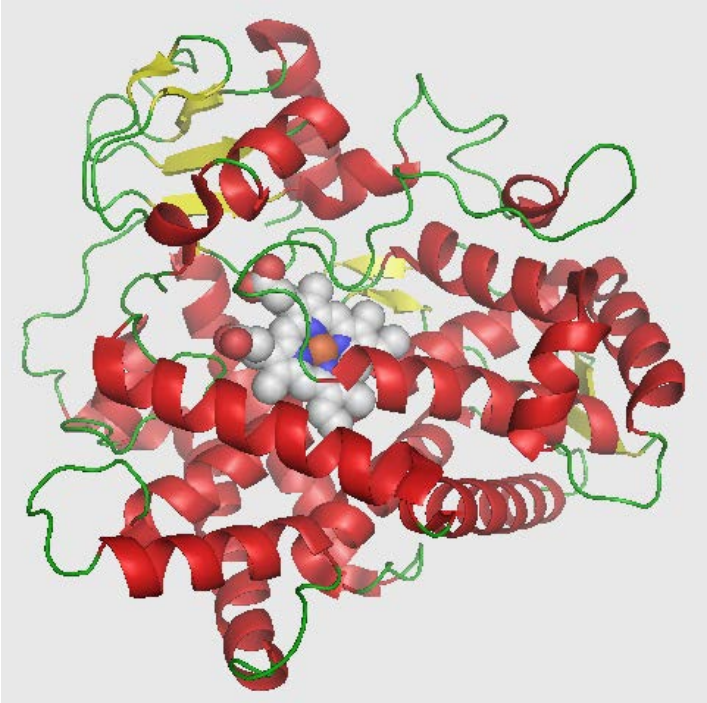
- Some drugs require metabolism to be converted to an active form (drug activation); these drugs are called “prodrugs.”



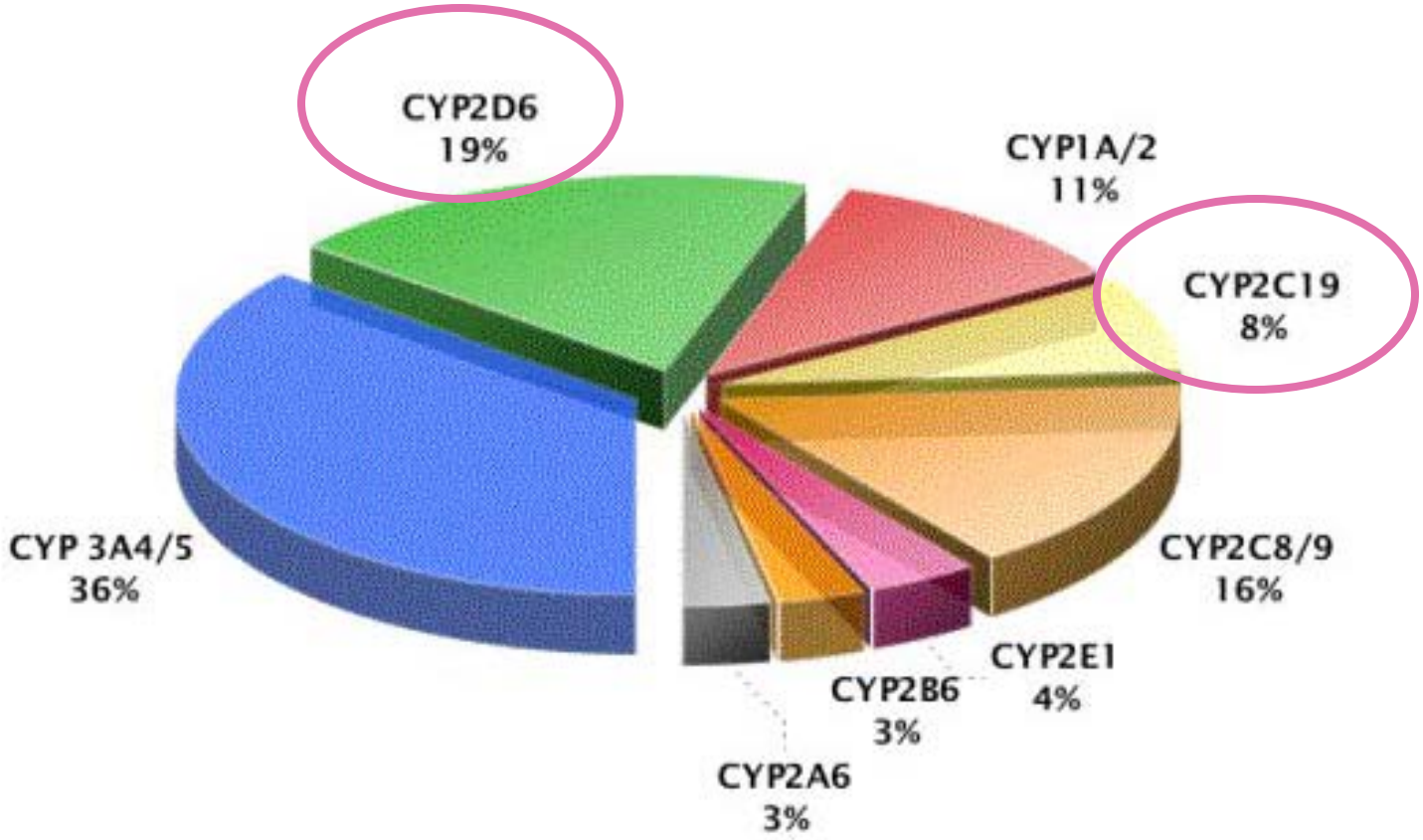
CODEINE MORPHINE

Drug Metabolism (cont.)

- Most drugs are inactivated by metabolism to promote elimination of the drug.
- Drug metabolism is mediated by enzymes; the cytochrome P450 (CYP) family is one of the most clinically significant.



Proportion of Drugs Metabolized by P450 Enzymes



Adapted from: Wrighton SA et al. Crit Review Toxicology 1992;22:1-22.
Kashuba and Bertino. Mechanisms of drug interaction. In Drug Interactions in Infections Diseases. Humana Press. 2001.

Relationship to Breast Cancer

CYP2D6

- Major enzyme responsible for ***activation*** of tamoxifen and some pain drugs
- Major enzyme responsible for ***inactivation*** of many drugs, such as antidepressants

CYP2C19

- Minor enzyme responsible for ***activation*** of tamoxifen
- Major enzyme responsible for ***inactivation*** of many drugs, such as antidepressants and gastrointestinal drugs

Genetic variants can increase, decrease, or obliterate metabolism.

Common Genetic Variants (Alleles)

CYP2D6

- *CYP2D6*4* (↓ function)
  - 1–8% of Asians
  - 6–18% of Caucasians and African-Americans
  - 8% of Middle Easterners
- *CYP2D6*1 or 2xN* (↑ function)
  - 1% of Asians
  - 2–3% of Caucasians and African Americans
  - 7% of Middle Easterners

CYP2C19

- *CYP2C19*2* (↓ function)
  - 30–35% of Asians
  - 15–20% of Caucasians and African Americans
  - 55% of Oceanians
- *CYP2C19*17* (↑ function)
  - 1–15% of Asians
  - 15–20% of Caucasians and African Americans
  - 2.5% of Oceanians

2015 CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of SSRIs –Supplemental v1.0.

Two Alleles = Genotype

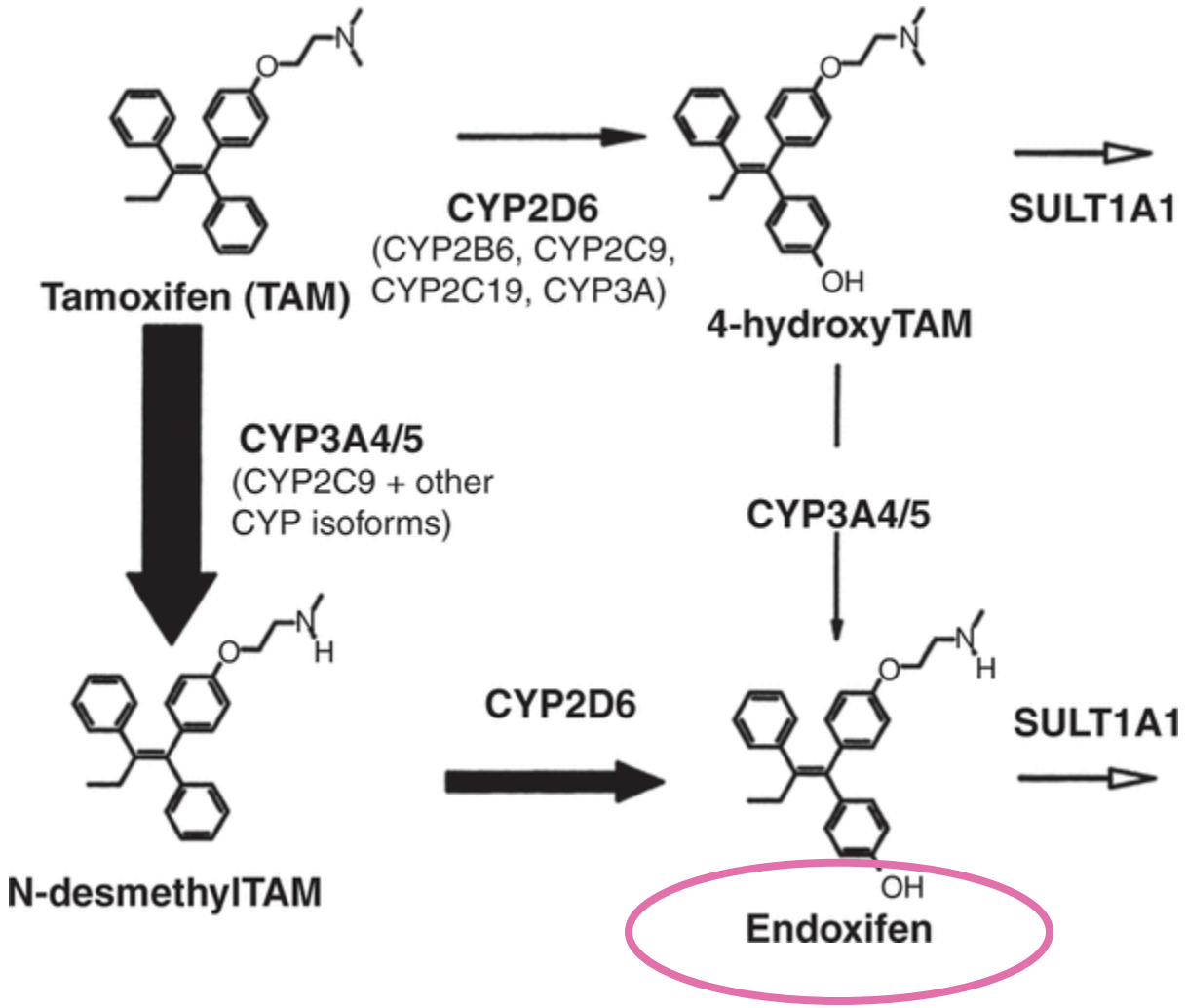
From which phenotype is predicted

- EM = extensive metabolizer = normal
- IM = intermediate = combinations of non-functional and/or reduced function alleles and/or normal alleles
- PM = poor = two non-functional alleles
- UM = ultra-rapid = duplications of functional alleles or alleles that increase expression

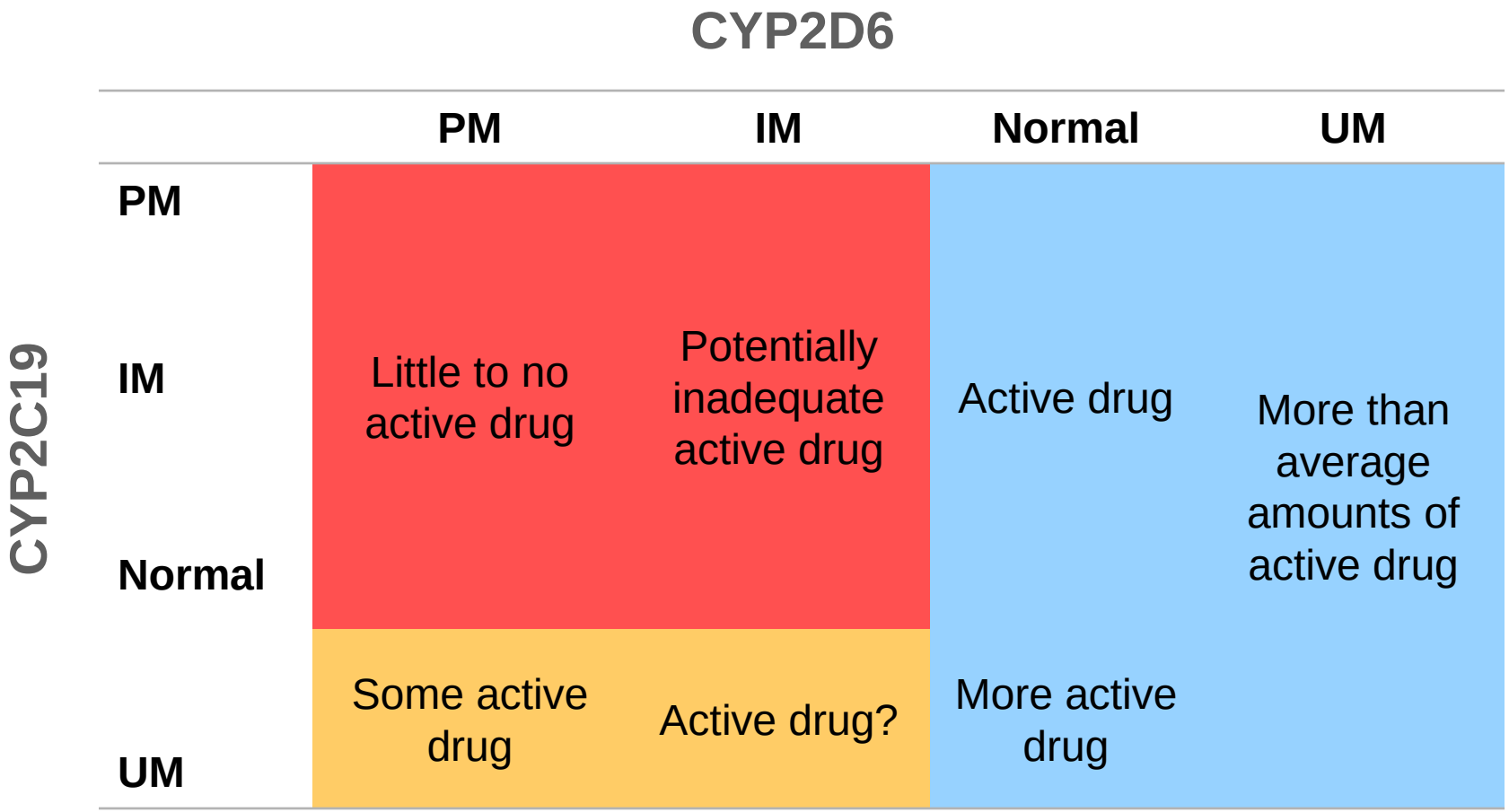
Tamoxifen

- Most commonly prescribed anti-estrogen
- Prodrug
- Used since 1971 for breast cancer treatment, adjuvant therapy, prevention, and several other indications
- Annual sales in the U.S. > $500 million
- ~35% of women do not respond

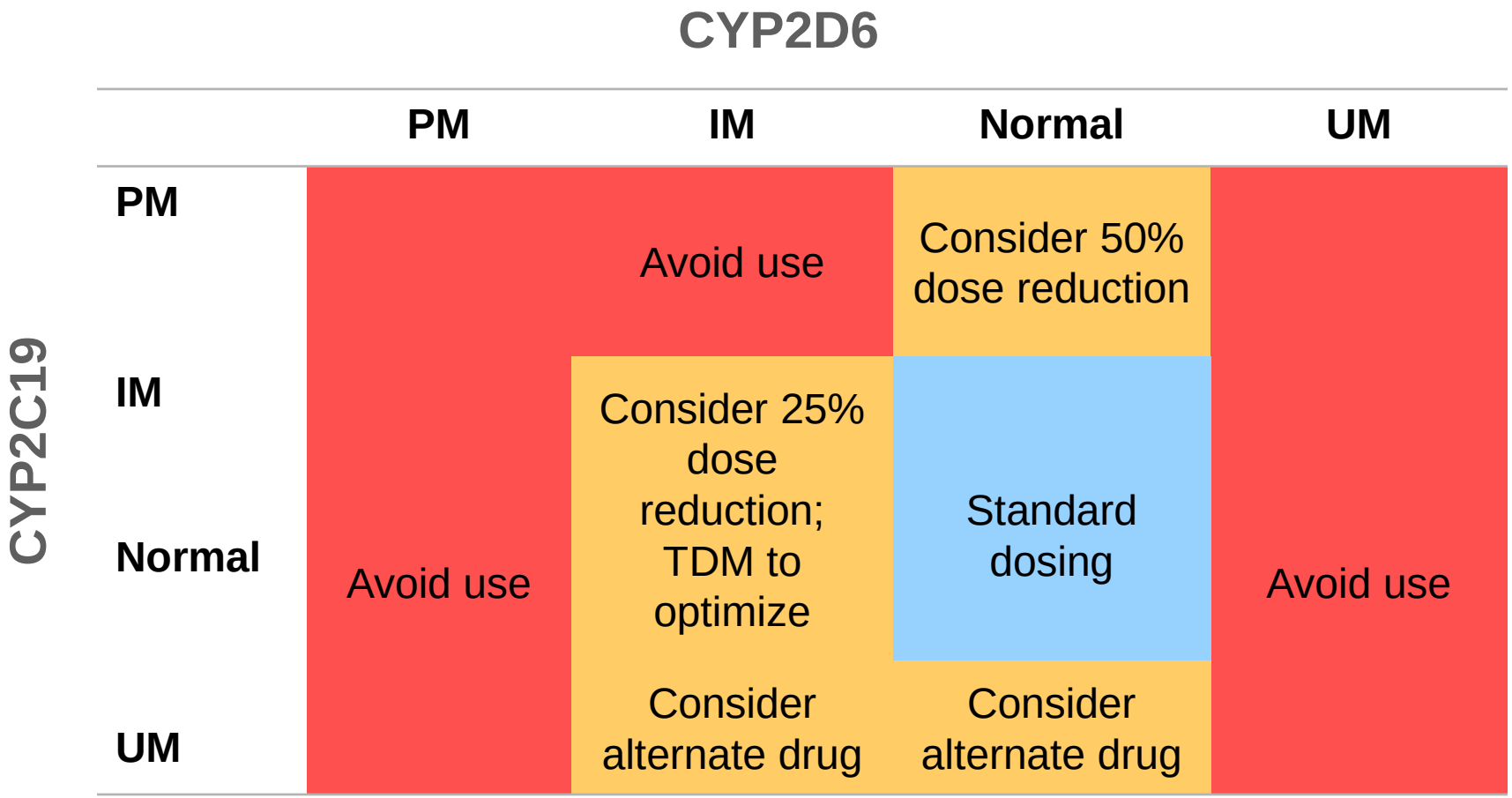
Simplified Schematic of Tamoxifen Metabolism



Theoretical Effect of CYP Phenotypes on Activation of Tamoxifen



CYP Phenotype and Amitriptyline Recommendations



https://www.pharmgkb.org/guideline/PA166105006

CYPs for Other Drugs Used in Treating Breast Cancer Patients

CYP2D6

- Antidepressants
  - Paroxetine, venlafaxine
- Other psychiatric drugs
  - Risperidone, atomoxetine
- Analgesics
  - Codeine, tramadol, oxycodone
- Cardiac drugs
  - Flecainide, propafenone

CYP2C19

- Antidepressants
  - Citalopram, sertraline
- Gastrointestinal drugs
  - Omeprazole, lansoprazole, rabeprazole
- Cardiac drugs
  - Clopidogrel
- Other misc. drugs
  - Voriconazole, clobazam

CYP Tests at ARUP

Single gene

- CYP2D6: 0051232
  - 14 variants and gene duplication/deletion
- CYP2C19: 0051104
  - 9 variants

Multi-gene DME panel

- Includes CYP2D6, CYP2C19, and CYP2C9 (test code 2008920)

Notes:

- ***CYP3A5*** will be available with the November 2015 hotline and will be added to the gene panel in 2016.
- A **saliva kit** will be available soon to promote non-invasive (not blood), outpatient collections.
- **Custom interpretation for multi-gene panel** is anticipated for 2016.

Summary and Conclusions

- Germline pharmacogenetic testing can help personalize drug therapy by predicting whether a patient will be able to metabolically activate and inactivate drugs.

- CYP genetic testing is relevant to all breast cancer patients who are prescribed drugs, particularly tamoxifen, antidepressants, and opioid analgesics.