Genetic Susceptibility Risk Models in Clinical Decision Making

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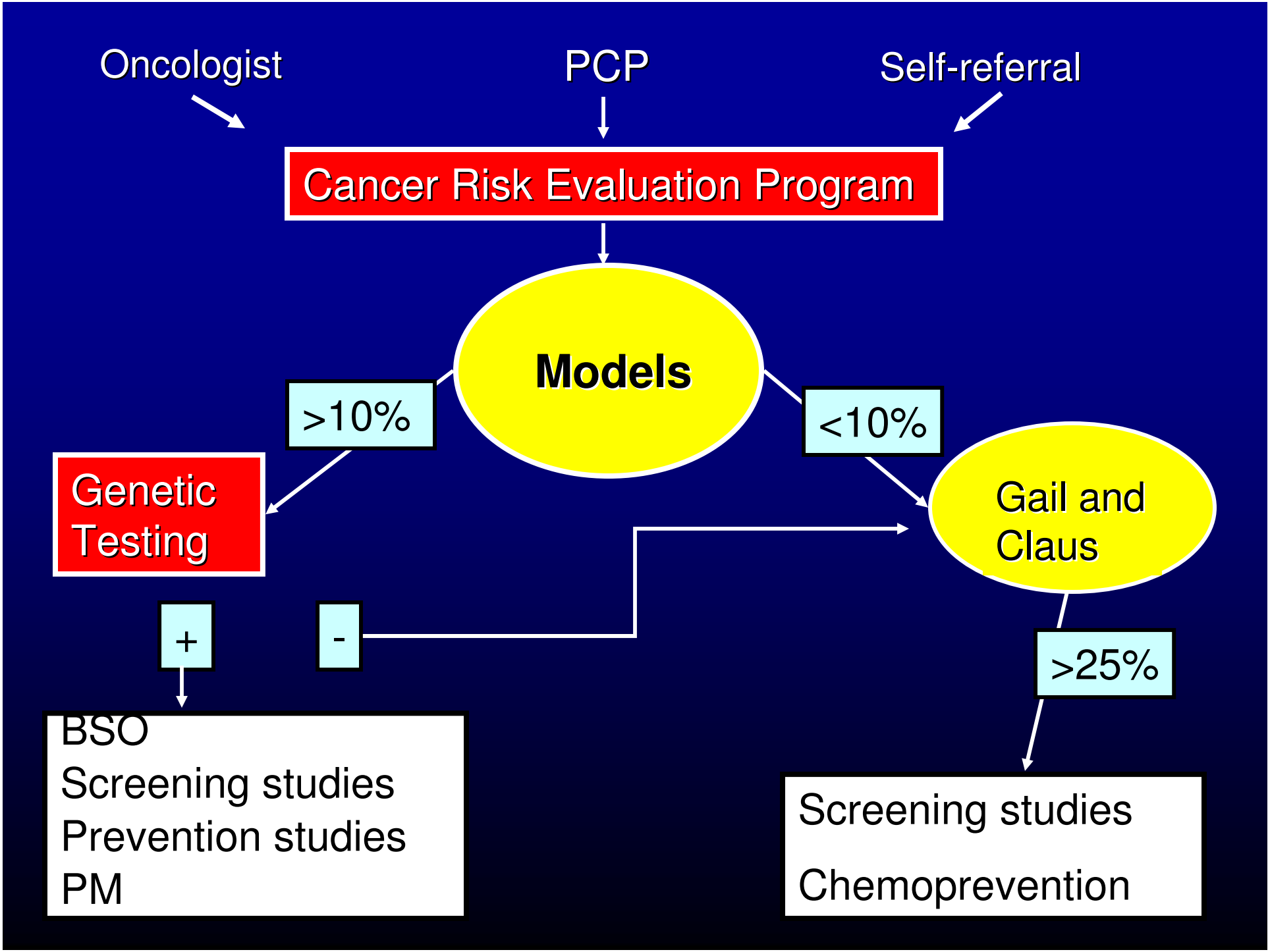

Oncologist
PCP
Self-referral
Cancer Risk Evaluation Program
Models
>10%
<10%
Genetic Testing
Gail and Claus
+
-
>25%
BSO
Screening studies
Prevention studies
PM
Screening studies
Chemoprevention

BRCA prediction models

- Logistic regression models (Couch, Shattuck-Eidens, Frank)
- Bayesian formulations (BRCAPRO)
- Empiric tables (Frank 2002)
- Prevalence tables
- Unique attributes to each model
- Consideration of testing for women with a probability of 10%

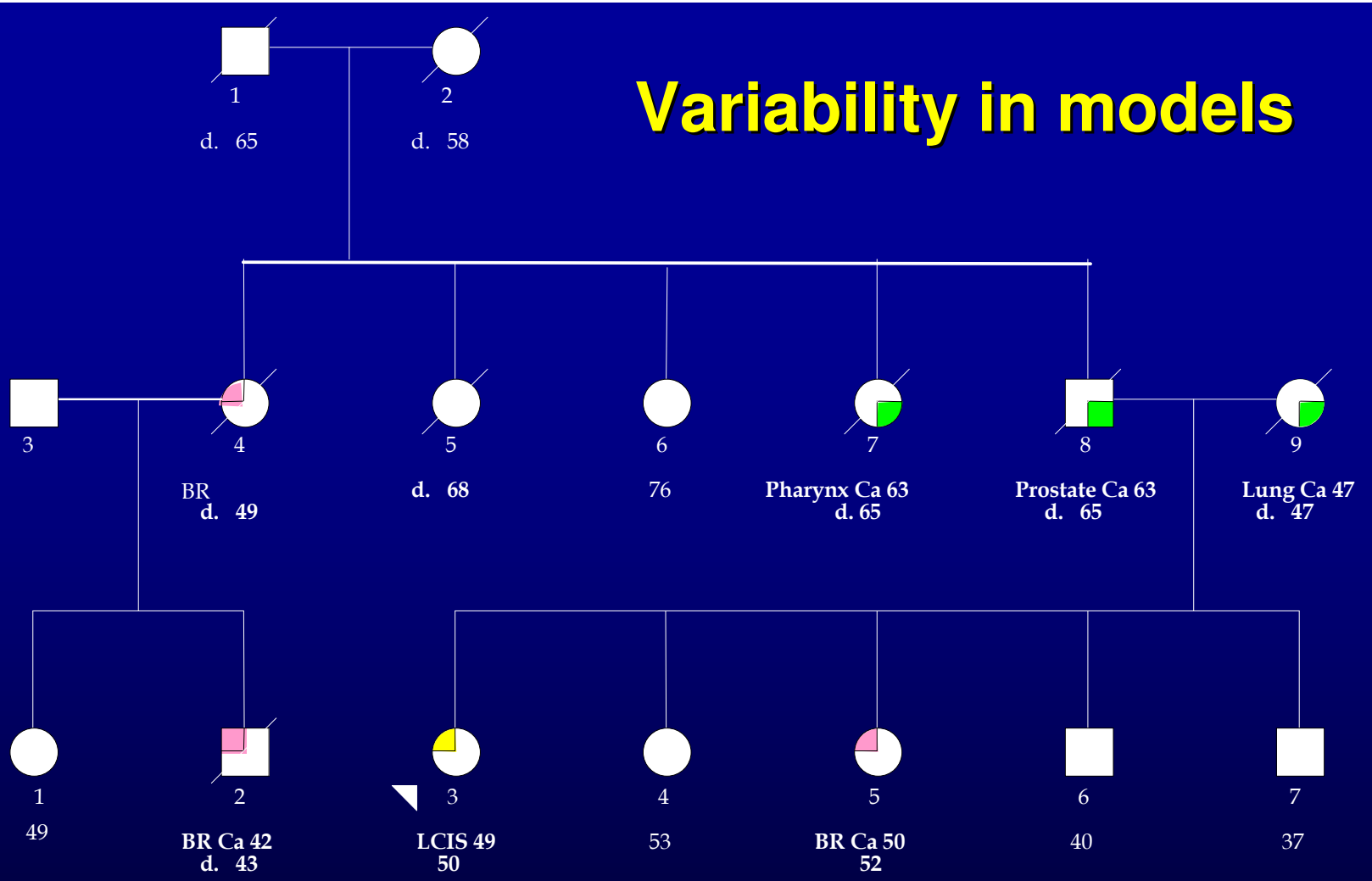
Limitations of family history

- Adoption
- Small family size, especially women
  - Prevalence tables can be very helpful
- Early deaths
- Accuracy of cancer information
  - Stomach cancer in women
  - Obtain medical records whenever possible

Limitations of all models

- Race/ethnicity data
- How to handle DCIS
- LCIS
- “Other” cancers – pancreatic cancer, melanoma, early prostate

Variability in models



Myriad Tables: 21.2% (47% in 2 <50)

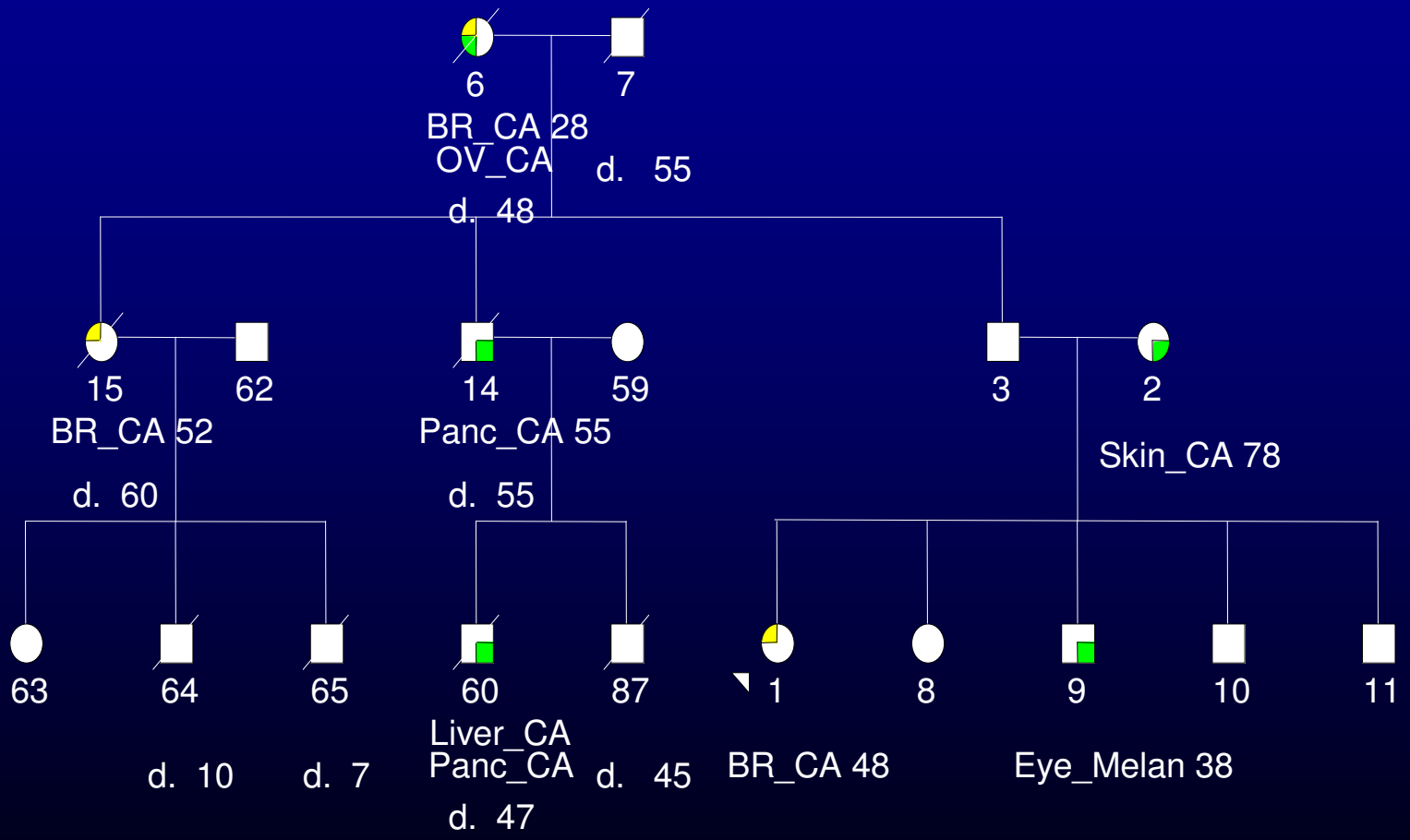
Couch: 7.7% for family

BRCAPro: Dependent on proband – 55% vs 1.6%

What is the goal of prior probability models?

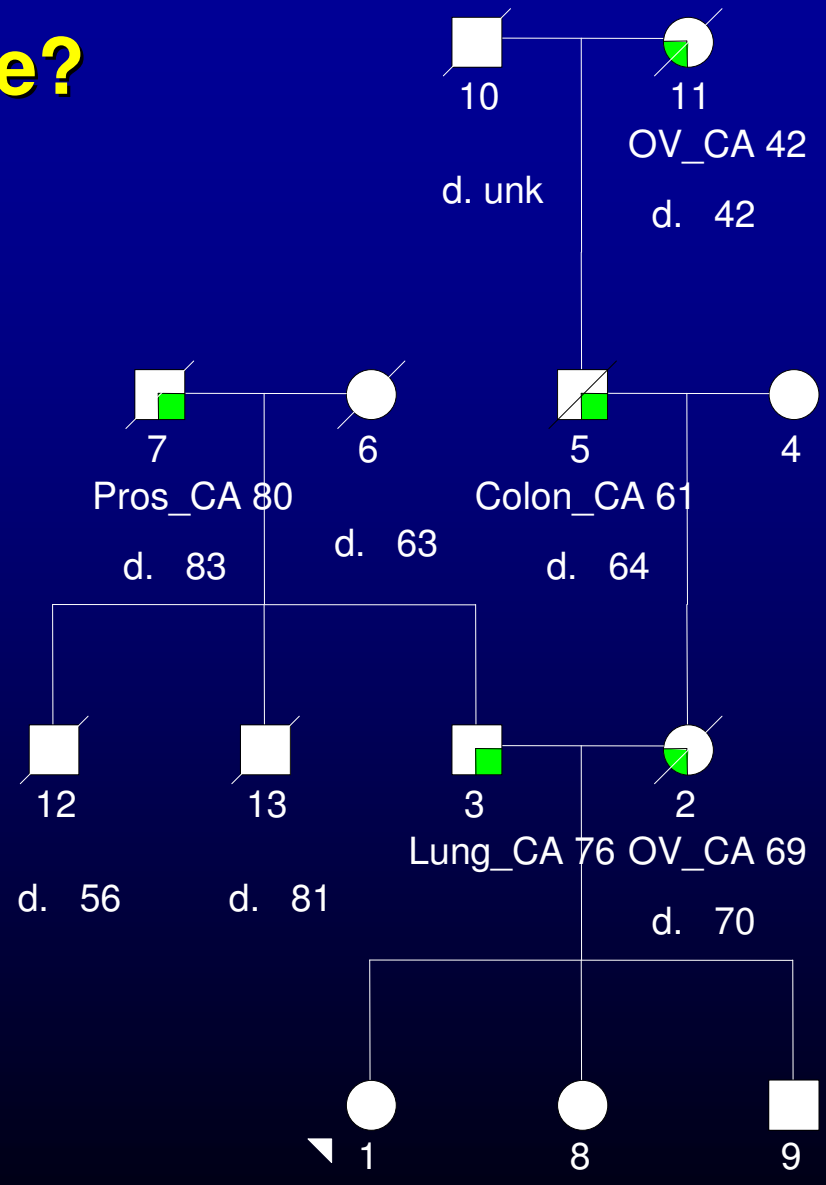
- Identify candidates for testing for BRCA1/BRCA2
  - Do we care more about sensitivity or specificity?
  - Clinically: sensitivity
  - Economically: specificity
- Stratify risk of hereditary syndromes
  - In tested negative families should we do counseling based on PP models?

“False” negative: what to counsel?



Which syndrome?

What ovarian cancer risk?



Can pathologic features help?

- BRCA1 mutation related breast cancers
  - 90% are estrogen receptor negative
  - High grade, aneuploid, “pushing margins”
  - 3% are HER2/neu positive
- BRCA2 mutation related breast cancers
  - More like sporadic tumors
  - Approximately 50% are ER positve
  - Only 3% HER2/neu positive

Probability of BRCA1 mutation by age, ER status and grade

ER positive tumors

Age	All (%)	Grade 1(%)	Grade 2 (%)	Grade 3 (%)
<30	8	1.1	1.6	2.7
30-34	5	0.8	1.2	2.0
35-39	2	0.2	0.3	0.5
40-44	1.5	0.1	0.2	0.3
45-49	1	0.1	0.1	0.2
50-59	0.3	0.03	0.04	0.07

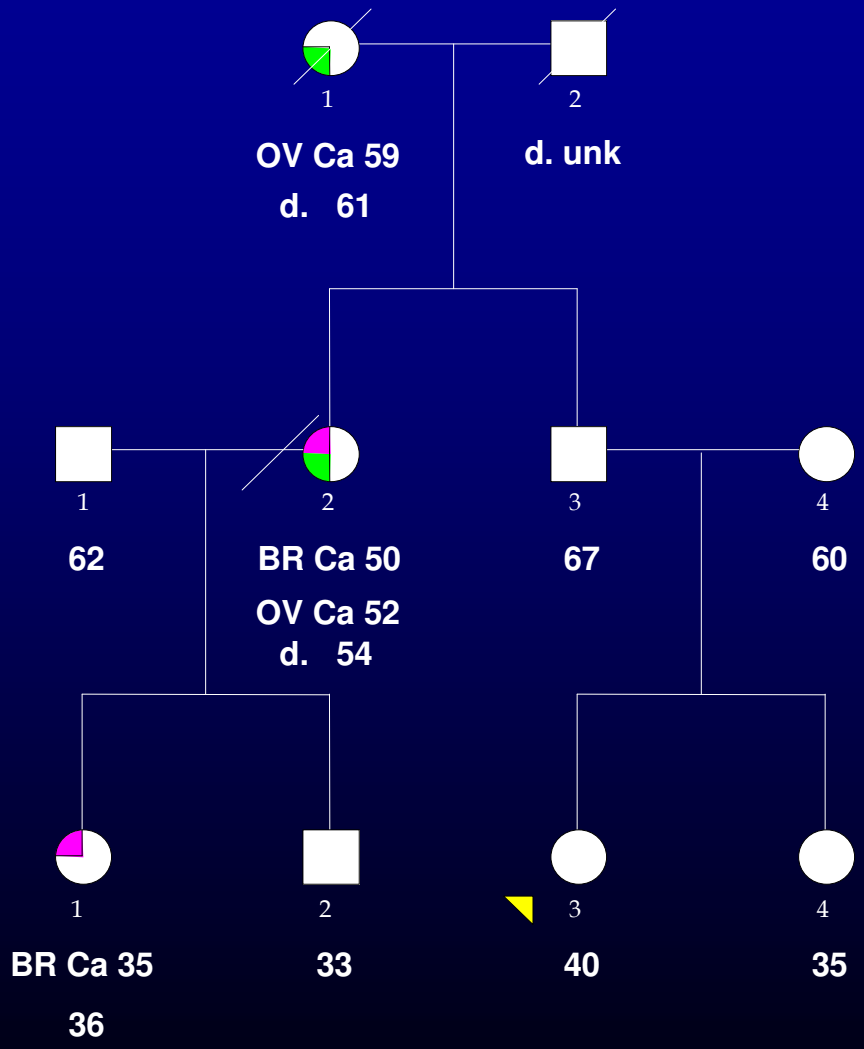
Lahkini et al, JCO 2002

Probability of BRCA1 mutation by age, ER status and grade

ER positive tumors

Age	All (%)	Grade 1(%)	Grade 2 (%)	Grade 3 (%)
<30	8	14.4	21.0	35.0
30-34	5	10.9	15.9	26.5
35-39	2	2.7	4.0	6.6
40-44	1.5	1.5	2.2	3.7
45-49	1	1.0	1.5	2.5
50-59	0.3	0.4	0.6	0.9

Claus and Gail in Hereditary Families



Issues in clinical decision making

- “Hereditary” patterns that test negative
- How to define them?
- Is breast cancer risk assessment accurate?
- What is their ovarian cancer risk?
- Risk assessment in VUS?