Hereditary Cancer Update
Strengthening Linkages Workshop
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Faculty/Presenter Disclosure

- Relationships with commercial interests:
  - Consulting fees: Western Canadian Ovarian Cancer Advisory Board (Astra Zeneca), 2014/2015

Objectives

- Understand **who** and **how** to refer patients to Hereditary Cancer Clinic
- Highlight recently available multigene hereditary cancer testing in Alberta and it's implications for patients & families
- Review management for patients with hereditary breast and ovarian cancer
- Be aware of available private genetic testing options

What is Hereditary Cancer?

- Cancer predisposition syndromes are caused by inherited (germline) mutations
  - Often high risk for cancer
  - Often *young* age at diagnosis
  - Contribute to nearly all types of cancer
  - Underlie ~ 10% of all cancer diagnoses

- >100 different cancer predisposition syndromes
  - BRCA1/BRCA2 (hereditary breast and ovarian cancer syndrome) and Lynch syndrome are the most common syndromes

Hereditary Cancer Services

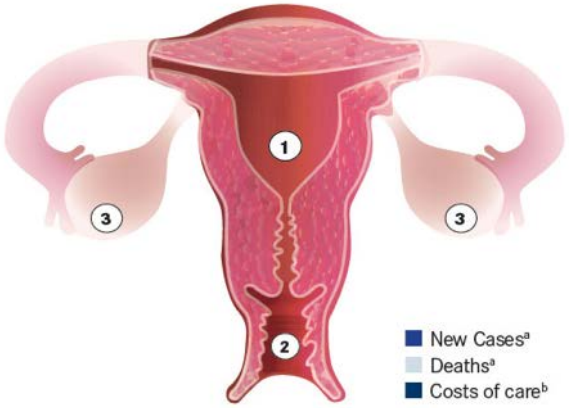
Provides genetic risk assessment, counselling & genetic testing for Albertans & their families who are affected or at risk for hereditary cancer syndromes

Goals:

- ✓ Identify patients/families at high risk of cancer due to hereditary cancer predisposition
- ✓ Recommend optimal screening & cancer prevention strategies
- ✓ Help facilitate cancer management decisions

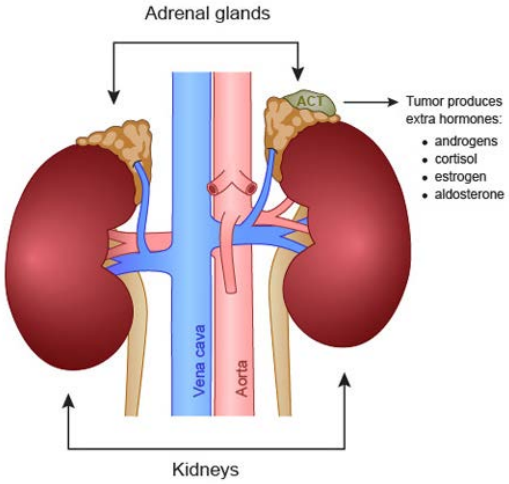
Burden of Hereditary Cancer

FIGURE 1. The annual impacts of the 3 major gynecologic cancers are shown in terms of incidence, mortality, and health care cost.[3] Numbers for new cases and deaths are estimates for 2014[1]; costs are estimates for 2010.[2]

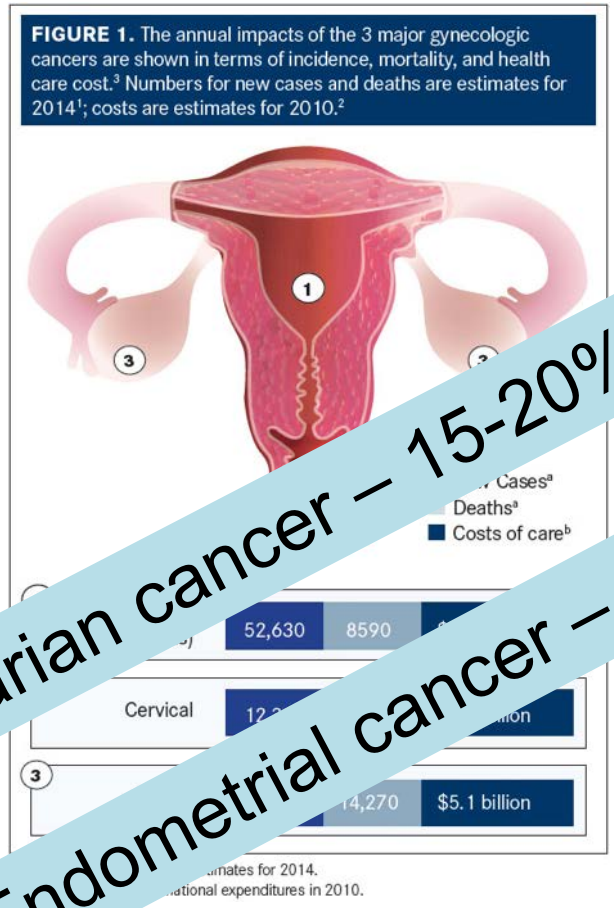


		New Cases[a]	Deaths[a]	Costs of care[b]
1	Endometrial (uterine corpus)	52,630	8590	$2.6 billion
2	Cervical	12,360	4020	$1.6 billion
3	Ovarian	21,980	14,270	$5.1 billion

[a]New cases and deaths are estimates for 2014.
[b]Costs are estimates of national expenditures in 2010.



Burden of Hereditary Cancer



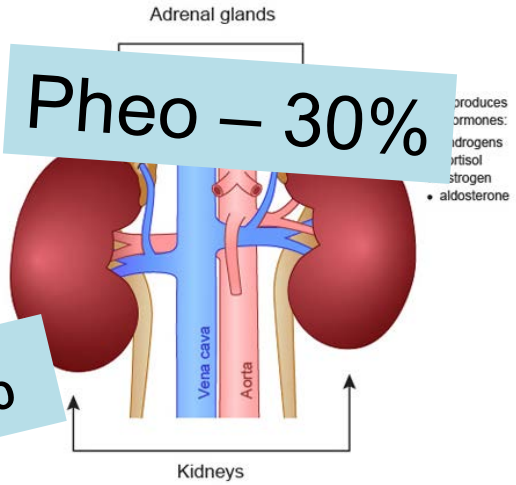
Pediatric cancer – 10%

Ovarian cancer – 15-20%

Endometrial cancer – 5%

Colon cancer – 5-10%

Pheo – 30%



Hereditary Cancer Services in Alberta

- **Clinics**:
  - Calgary (Red Deer and south) - ACH
  - Edmonton - Stollery
  - Telehealth
  - GC in Lethbridge

- **Molecular Diagnostic Laboratories**:
  - Calgary, Edmonton
  - BRCA1, BRCA2, Lynch syndrome testing
  - 2017 - expanded multigene panel testing

Referral Process

- Referrals accepted from:
  - Family physicians, surgeons, oncology, etc
  - Other genetics clinics
  - Self-referrals (if there is a known mutation in the family)
- Referral form (available on Alberta Referral directory) or by referral letter
- All patients are sent family history questionnaire
- Referrals are not usually triaged until family history questionnaire is returned

When to consider referral

- Early age at diagnosis (i.e. breast or colon cancer < 35)
- Unusual/rare cancers (i.e. medullary thyroid cancer, adrenal cortical carcinoma)
- Multiple primary cancers, or bilateral cancer
- Clustering of the same cancer in multiple family members
- Multiple generations affected
- Pattern of cancers suggestive of a specific hereditary cancer syndrome (breast & ovarian cancer, colon & endometrial cancer)

Elements of hereditary cancer risk assessment

- Collection of personal and family history
- Genetic counselling re: likelihood of hereditary cancer syndrome, options for testing
- Genetic testing (where appropriate)
- Interpretation of results
- Recommendations for cancer screening, prophylactic options
- Implications for family

What to tell your patients

- **Accurate** family history information is crucial (where available)
  - 3 generations (siblings, parents, aunts/uncles, cousins, grandparents)
  - Age at diagnosis
  - Primary cancer diagnosis (versus mets)

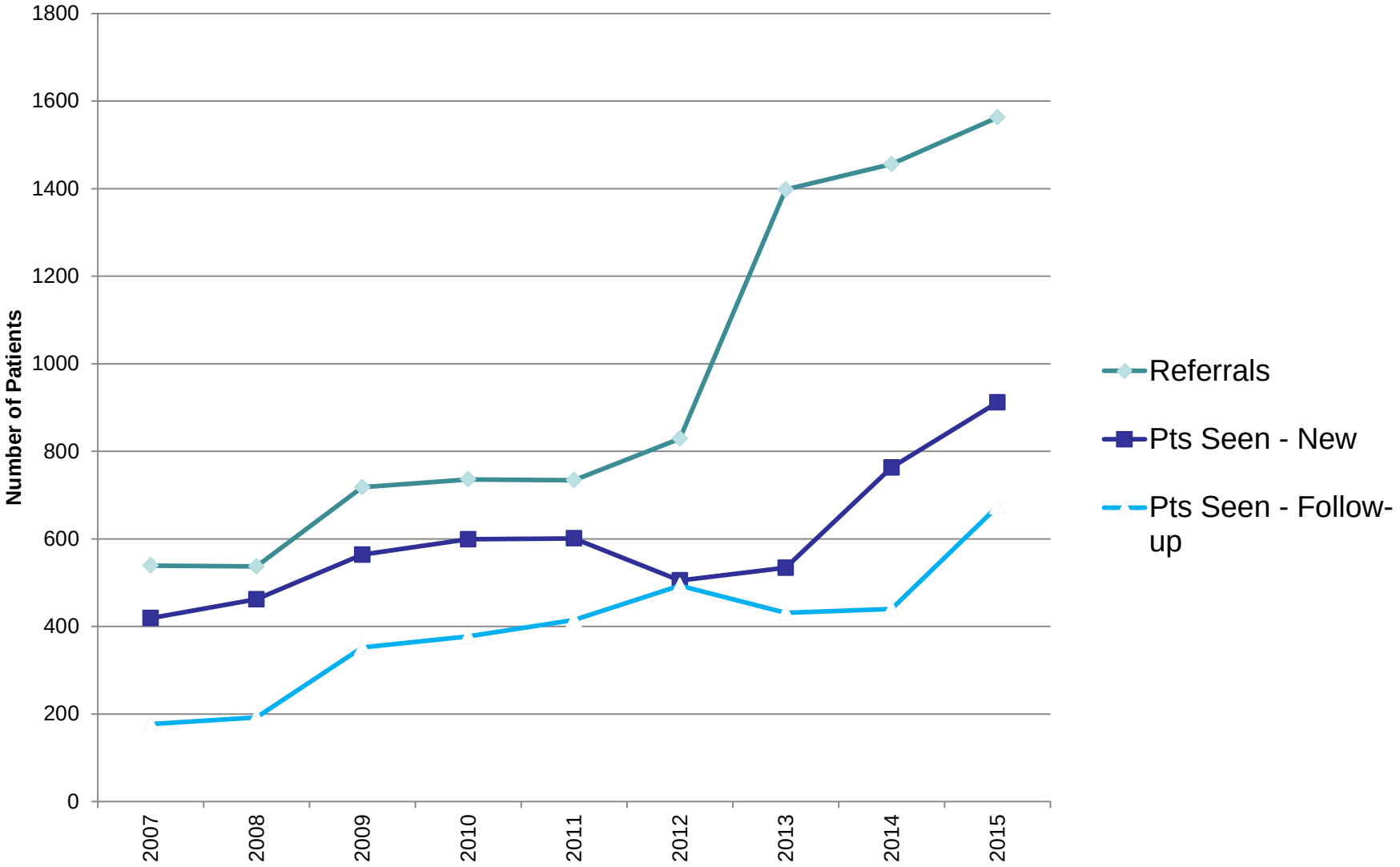
- We usually don't offer appointments to patients unless they return family history questionnaire

- Many patients are initially seen in group information sessions followed by shorter individual genetic counselling appt

- *Not all patients are offered genetic testing* (especially those without a personal history of cancer)

- Encourage your patient to talk to their affected family members about requesting a referral to a hereditary cancer clinic.

Calgary, 2007-2015




THE
ANGELINA
EFFECT
Angelina Jolie's double mastectomy puts genetic testing in the spotlight. What her choice reveals about calculating risk, cost and peace of mind
BY JEFFREY KLUGER & ALICE PARK

Num
600
400
200
0
2007
2008
2009
2010
2011
2012
2013
2014
2015
Referrals
Pts Seen - New
Pts Seen - Follow-up

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MEDICAL GENETICS
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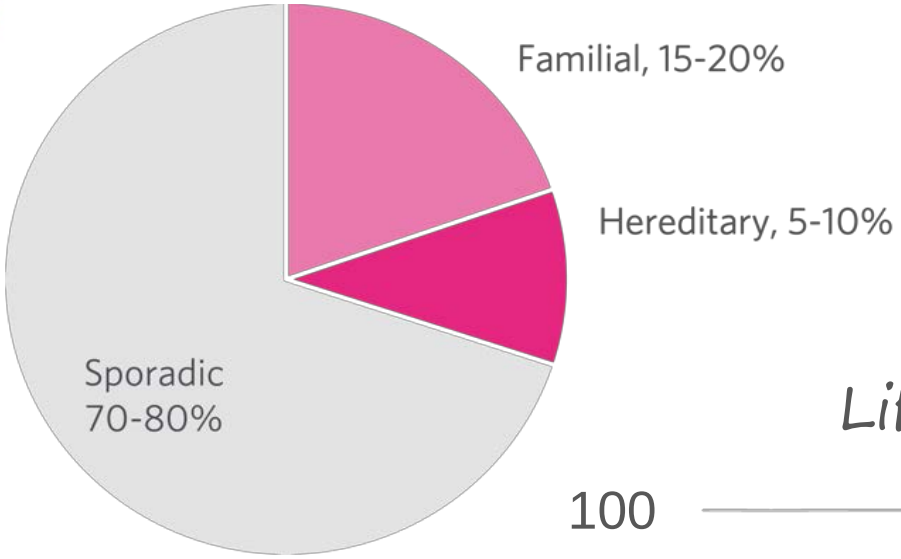
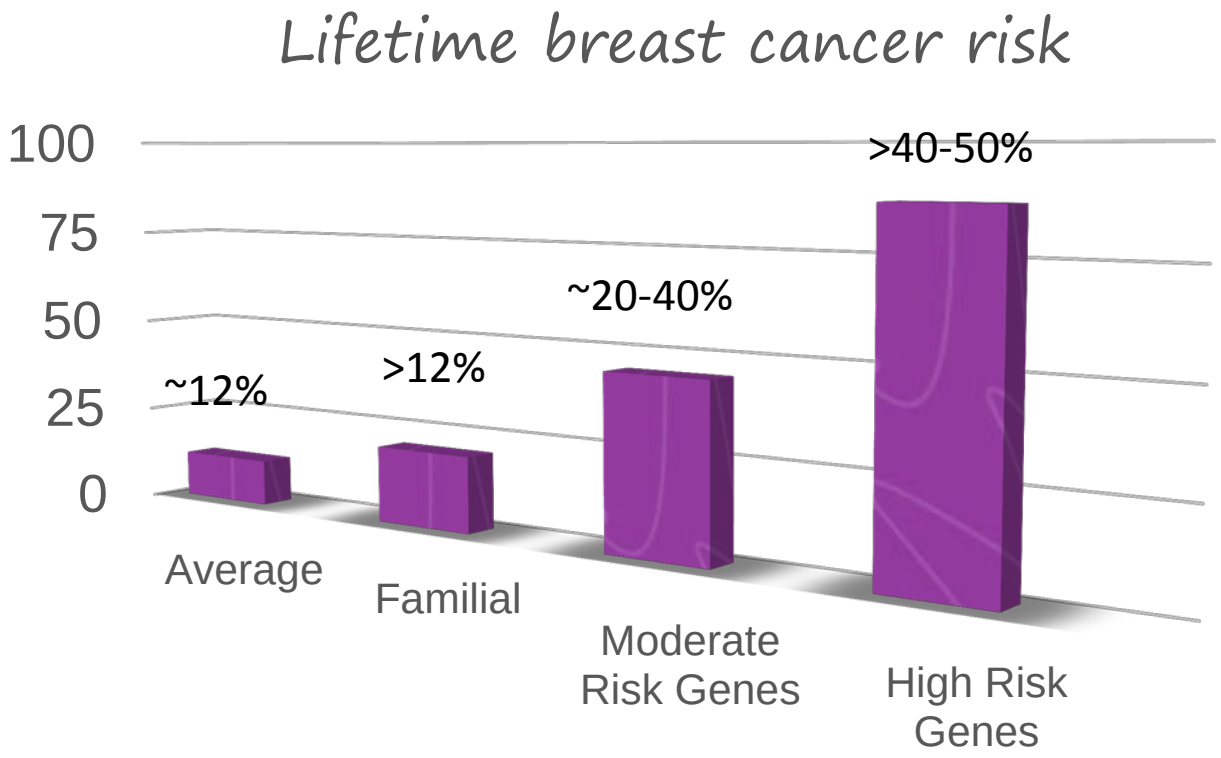
Hereditary Breast and Ovarian Cancer: BRCA and Beyond

Breast cancer susceptibility genes





HIGH Risk Breast Cancer Syndromes

- ✓ High penetrance *(= high risk for cancer)*
- ✓ Well known cancer syndromes with well defined tumor risks *(i.e. BRCA1, BRCA2)*
- ✓ *Established* screening/risk-reduction guidelines
- ✓ Straightforward implications for family members

- BRCA1/2
- Li Fraumeni sydrome
- Cowden syndrome
- Peutz Jeghers syndrome
- Hereditary Diffuse Gastric cancer

High risk genes: Management

- High risk breast cancer screening (MRI + mammogram)
- Prophylactic mastectomy *may* be appropriate
- Published surveillance & prevention guidelines for other associated cancer risks (i.e. ovarian cancer)
- Predictive testing available to at-risk relatives
  - *in some cases testing children may be appropriate*


MODERATE
RISK
AHEAD

MODERATE risk breast cancer genes

~ 20-40% lifetime risk for breast cancer

- *PALB2*
- *ATM*
- *CHEK2*
- *NBN*
- *NF1*

MEN1

MRE11

RAD50

BARD1

BRIP1

RAD51C

RAD51D

ovarian cancer

Lynch genes

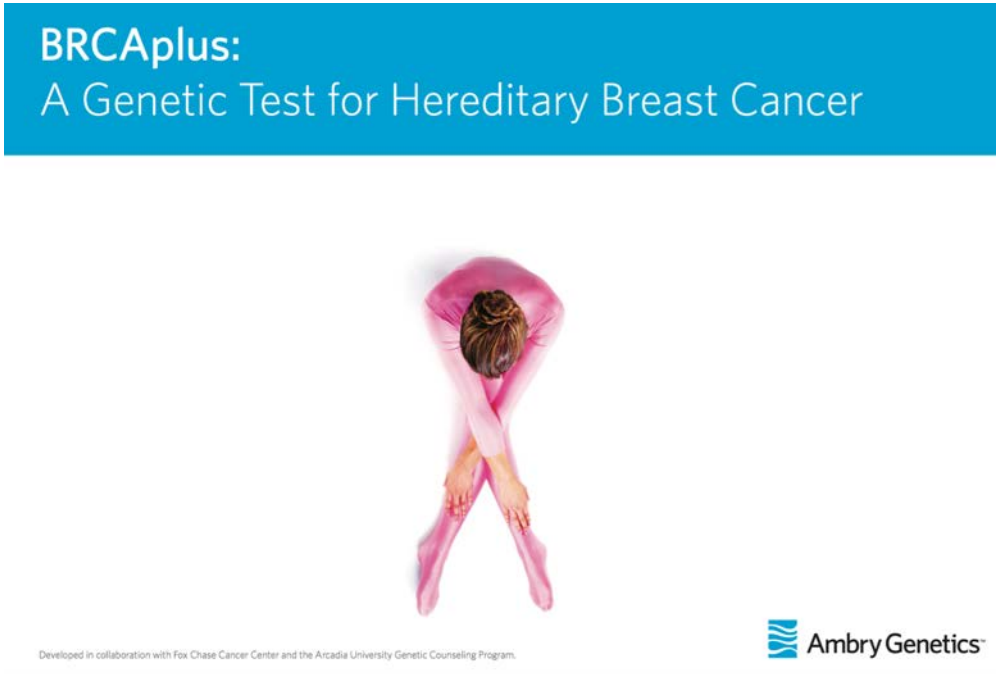
others

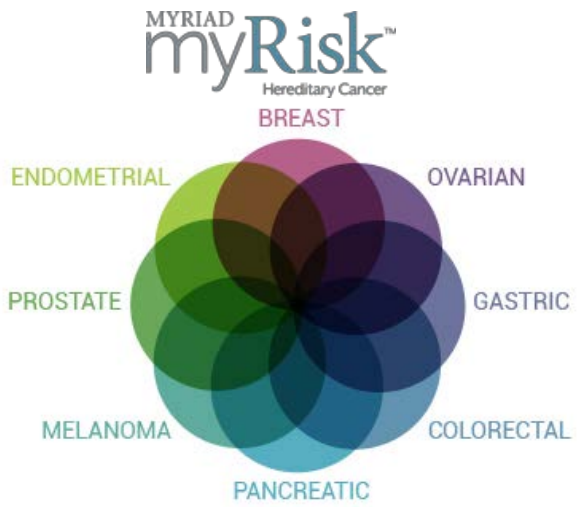
	Absolute risk (80y)	Other cancer(s)
PALB2	35-55%	? pancreas, ♂ breast
ATM	27%	? pancreas
CHEK2	30%	? CRC, ♂ breast
NBN	23%	? ovary

Easton et al. N Engl J Med. 2015

Moderate risk genes: Management

- No clearly established cancer screening guidelines
  - Generally recommend high risk breast cancer screening
  - Insufficient evidence for prophylactic mastectomy
- Less robust data re: cancer risks
  - Cancer risks may vary from family to family
  - Cancer risks may not be due to gene mutation alone → likely influence of other genetic and non-genetic modifiers
- Predictive testing of at risk relatives available but…. careful assessment of family history needed for interpretation





Multi-gene panels

Multi-gene panels: Advantages

- Cost-effective
- Time-efficient
- Increased diagnostic yield
- Allows for diagnosis of hereditary cancer predisposition in patients/families with:
  - Atypical/attenuated phenotypes
  - Limited family structure
  - Limited/inaccurate family history information
  - More than one cancer predisposing gene

Multigene Panels: Diagnostic yield

- Varies depending on cohort
- Range: **~ 3-17%** pathogenic/likely pathogenic mutations in breast cancer cohorts
- On average, 30-50% greater yield in comparison to BRCA1/2 testing alone
  - Additional yield largely due to mutations in *moderate* risk genes

15 studies (10,745 patients) → 14.1% yield

- 9.0% BRCA1/2
- 5.1% other genes

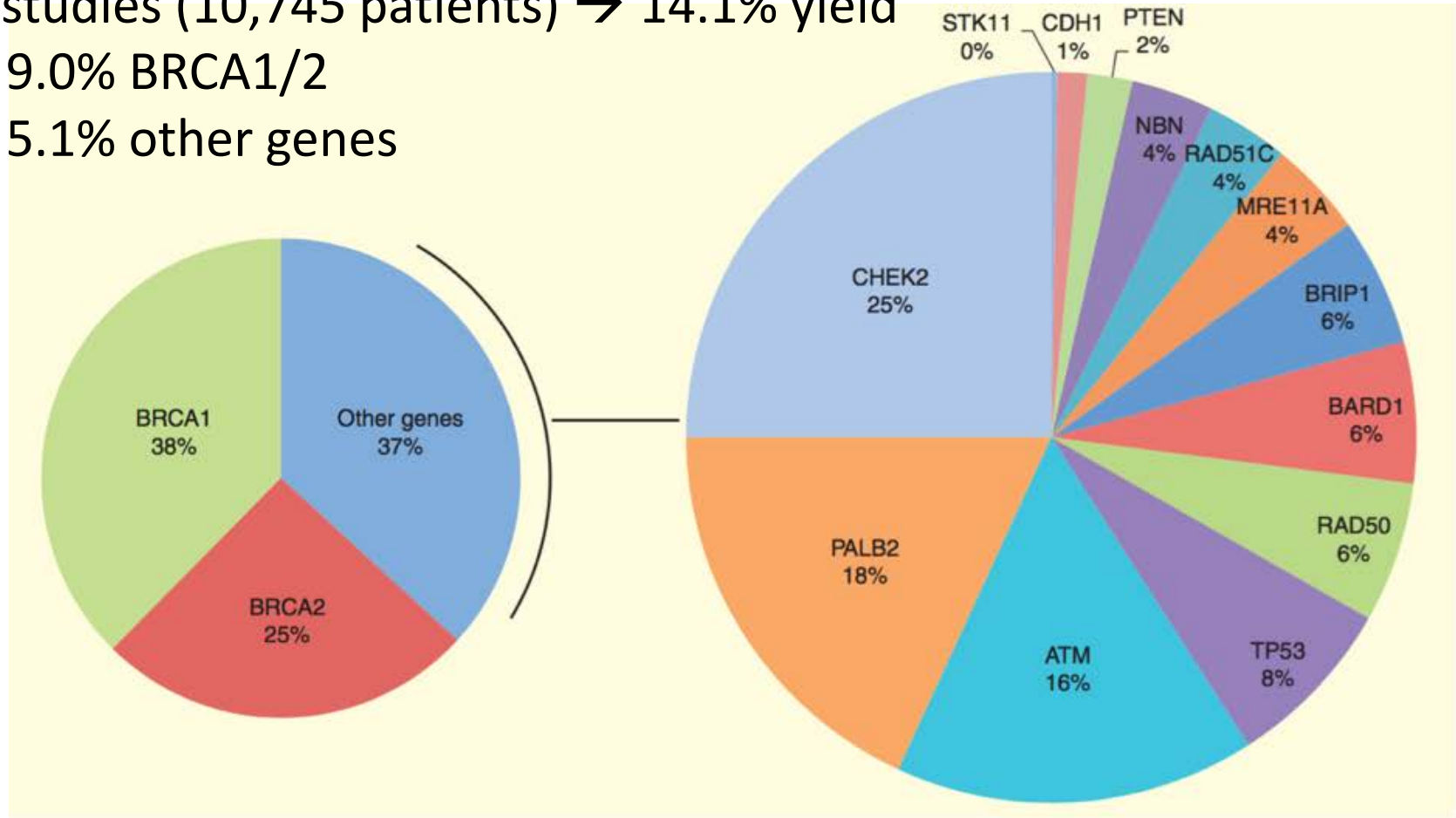


Figure 1. Proportion of pathogenic mutations detected in BRCA1, BRCA2 and 13 other genes included in the gene panel studies.

Lerner-Ellis et al. Expert Rev. Anticancer Ther. 2015

More genes, more problems?

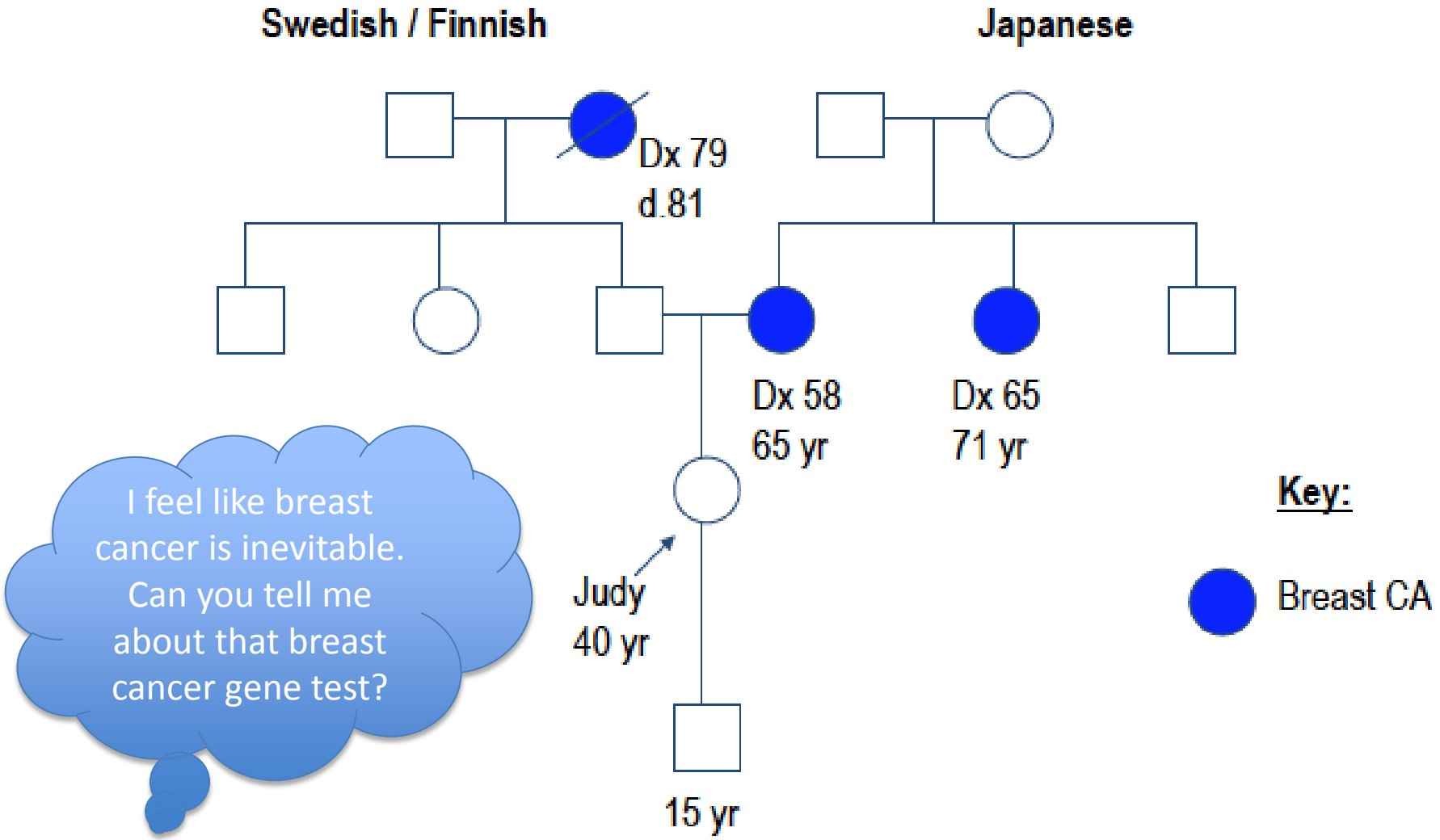
- Uncertain cancer risks
- Uncertain implications for family members
  - May not change predicted risk for family members over and above assessment based on family history alone
- Unexpected findings
- Variants of uncertain significance - *up to 20-40%*
  - Can cause patient distress, confusion, misunderstanding
- Complex counselling
- Interpretation - *Family history is still important!*

Expanded testing in Alberta

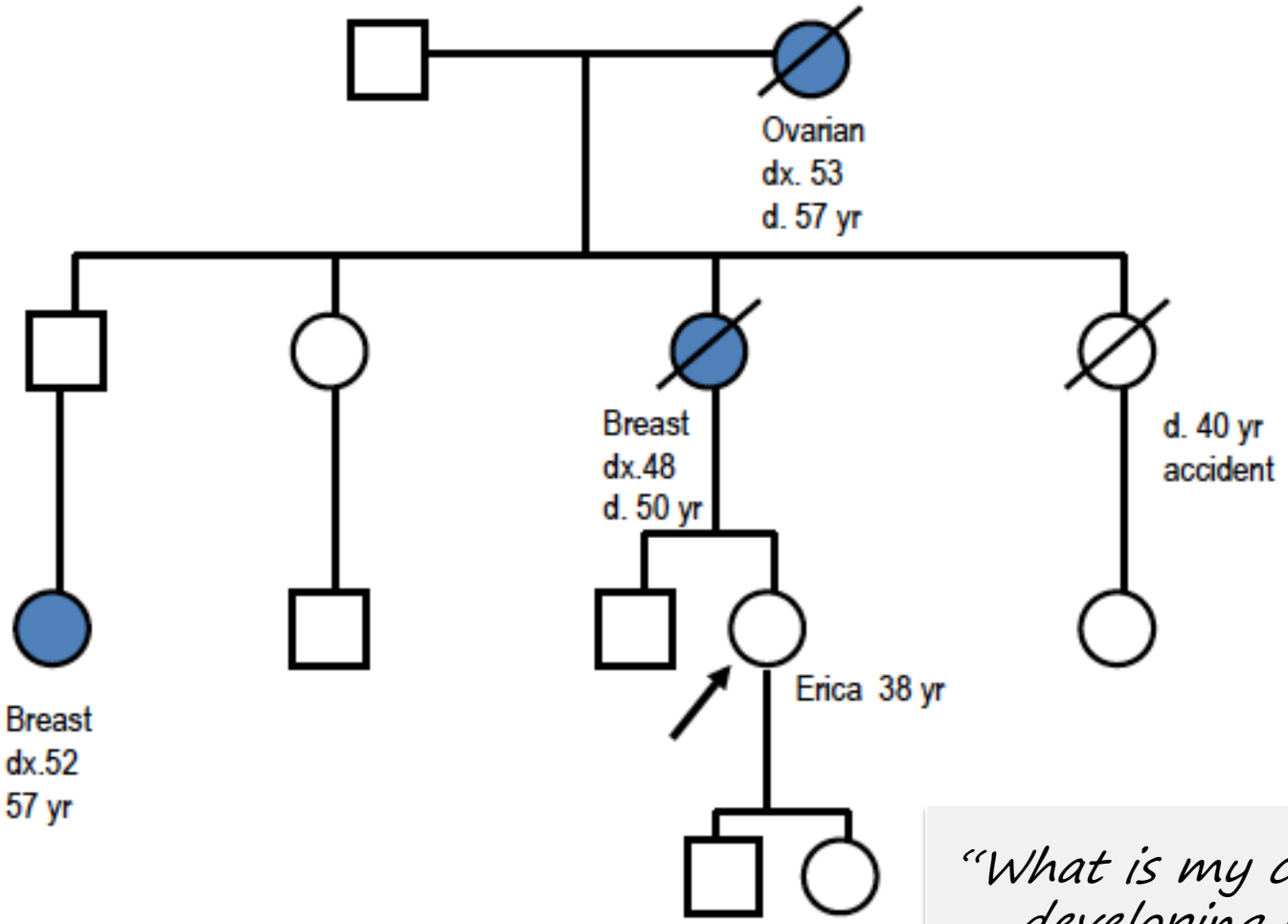
Multi-gene Panels

- ✓ Breast/ovary *(13 genes)*

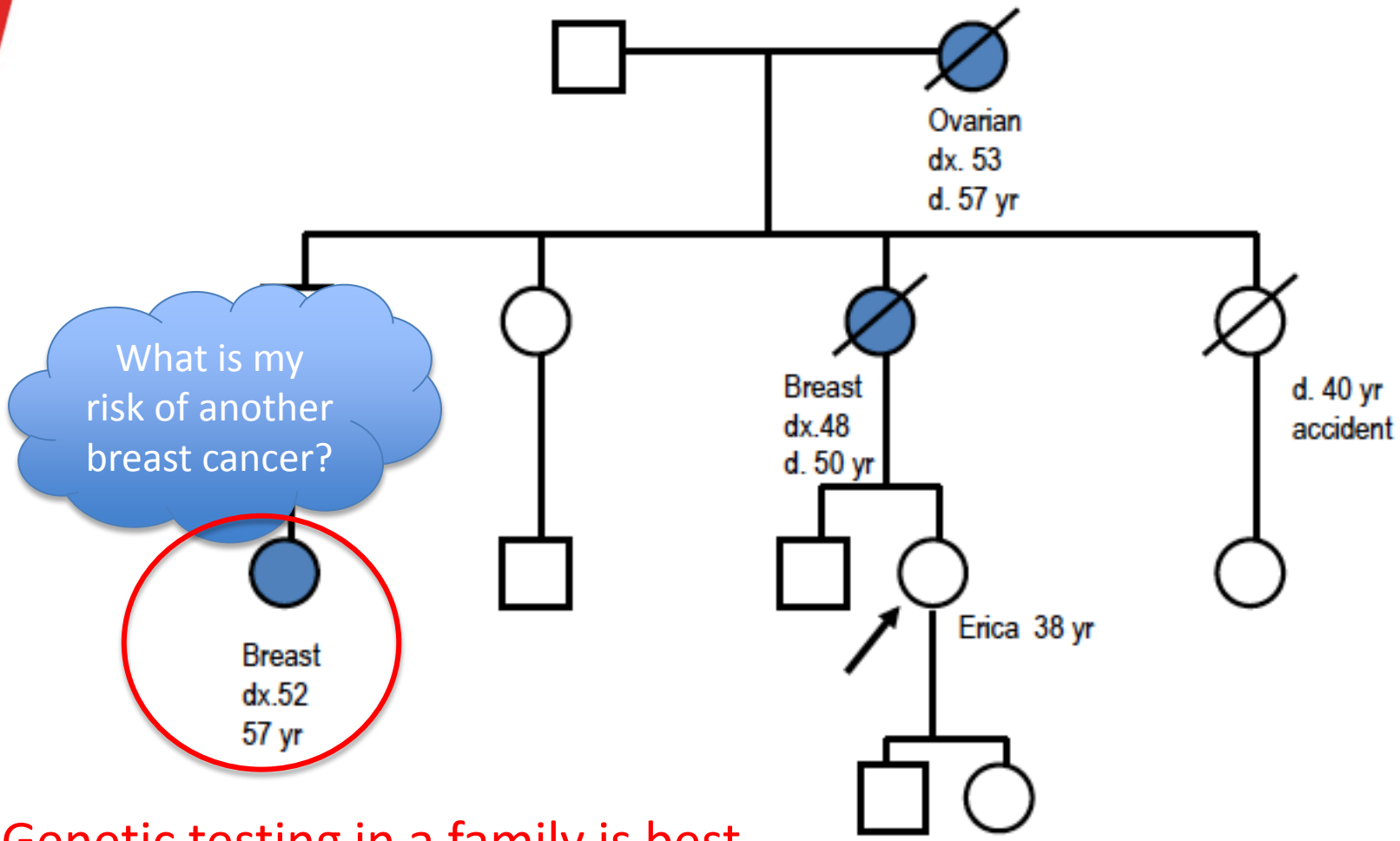
- ✓ Colon/polyposis
- ✓ Pancreatic cancer
- ✓ Renal cancer
- ✓ Melanoma/skin caner
- ✓ Endocrine cancer
- ✓ Pediatric cancer


Swedish / Finnish
Japanese
Dx 79
d.81
Dx 58
65 yr
Dx 65
71 yr
Judy
40 yr
15 yr
I feel like breast cancer is inevitable. Can you tell me about that breast cancer gene test?
Key:
Breast CA

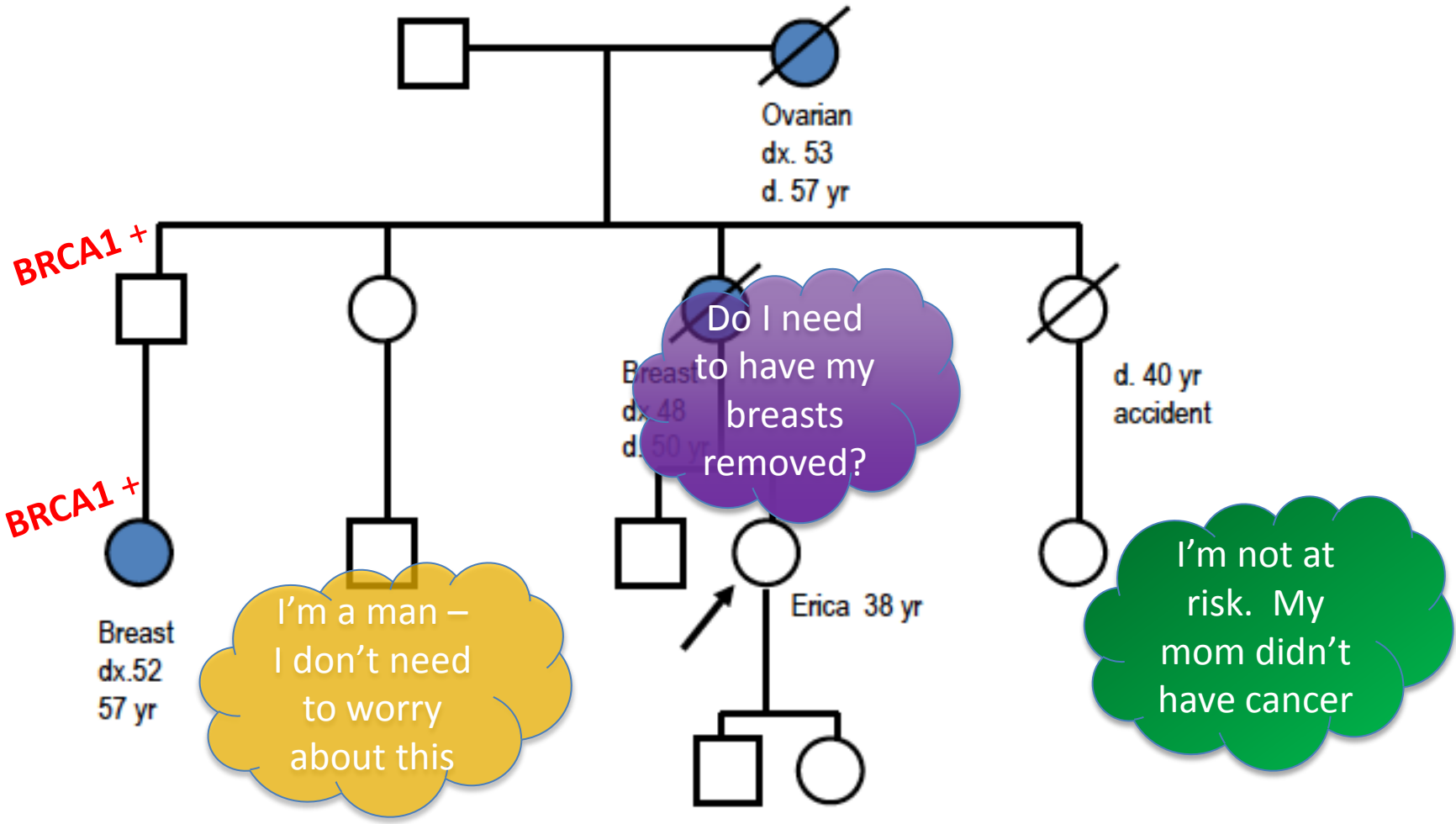
- Judy likely has a modestly increased risk of breast cancer
  - LOW risk for hereditary breast cancer
  - Referral to Genetics not indicated
- Screening recommendations: annual mammograms starting at 40
- She could chose to pursue private genetic testing (*more on this later*)



"What is my chance of developing breast cancer?"



Genetic testing in a family is best initiated in an affected relative


Ovarian
dx. 53
d. 57 yr
BRCA1 +
BRCA1 +
Breast
dx.52
57 yr
I'm a man – I don't need to worry about this
Do I need to have my breasts removed?
Erica 38 yr
d. 40 yr
accident
I'm not at risk. My mom didn't have cancer

BRCA1/2 Cancer Risks

CANCER	GENERAL POPULATION	BRCA1 CARRIER	BRCA2 CARRIER
breast cancer women	11%	47-66%	40-57%
ovarian cancer	1-2%	35-46%	13-23%
breast cancer men	0.1%	up to 6%	6%
prostate cancer	12%	increased by ~ 2-3 times	
pancreatic cancer	1%	slight increase	slight increase
other			slight increase

BRCA1/2 Management: Screening

BSE - personal preference
CBE q6 months
Mammogram yearly, starting 30
MRI yearly, 25-69 yrs (ideally alternating with mammogram)
No effective way to screen for ovarian cancer

CBE q12 months
Prostate screening, starting 40

BRCA1/2 Risk Reducing Surgery

- Mastectomy (with reconstruction)
  - Personal choice
  - Reduces breast cancer risk by 90-95%
  - No routine imaging after mastectomy/reconstruction
- Bilateral salpingo-oophorectomy
  - Recommended ~35-40 yrs
  - Reduces ovarian cancer risk by 85-95%
  - Surgical menopause!
  - Short term HRT after BSO is acceptable

Don't forget about OTHER cancers……

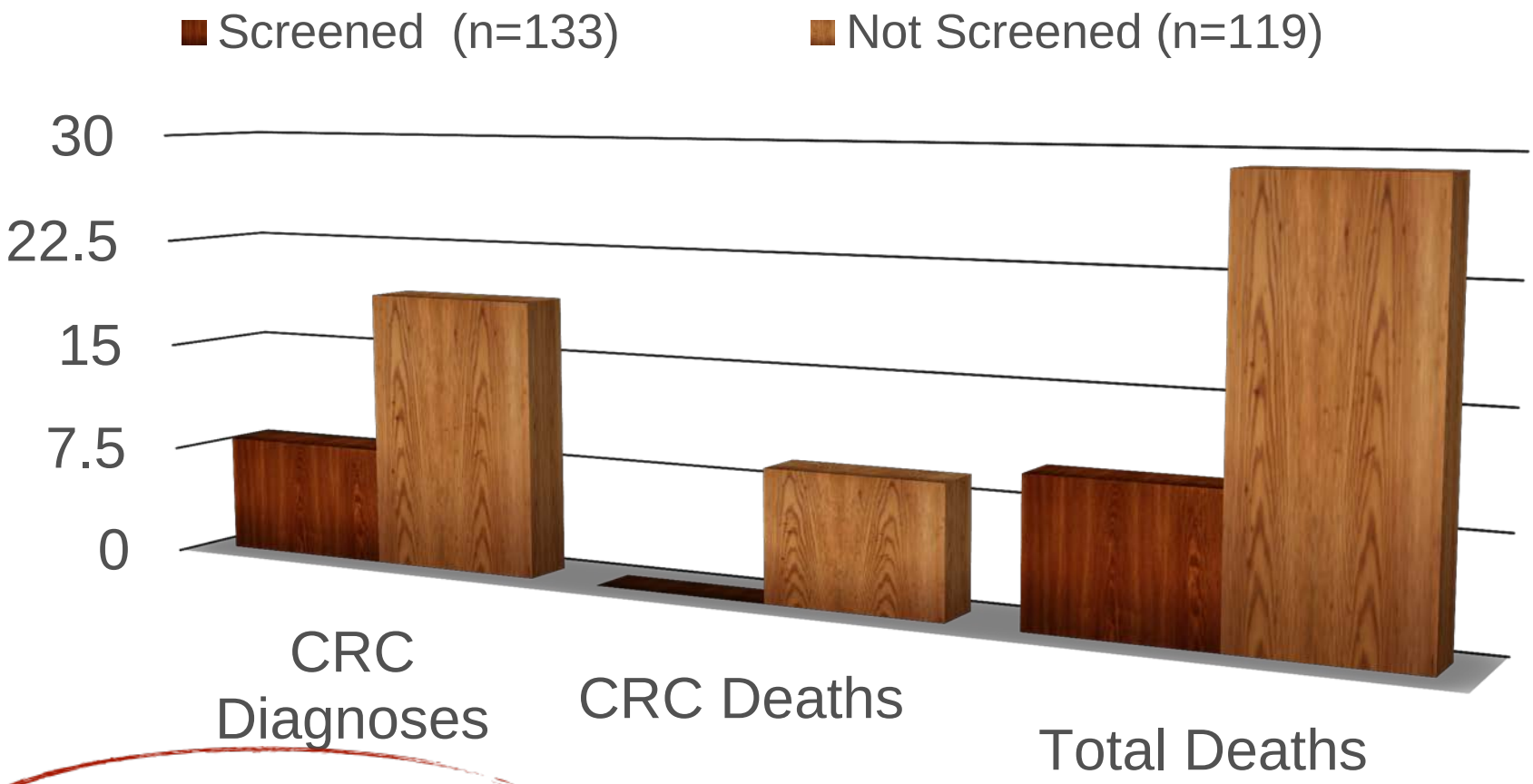
Lynch syndrome

- Accounts for:
  - 3-5% of all colon cancer
  - 3-5% of all endometrial cancer
  - 2% of all ovarian cancer
- Incidence: ~1/400 - 1/500
- Mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, *PMS2* (and *EPCAM*)

Lifetime risk of extra-colonic cancers

Endometrial cancer	27-71%
Ovarian cancer	3-13%
Gastric cancer	2-13%
Urinary tract cancer	1-12%
Brain cancer (GBM)	1-4%
Bile duct/gall bladder	2%
Small bowel cancer	4-7%

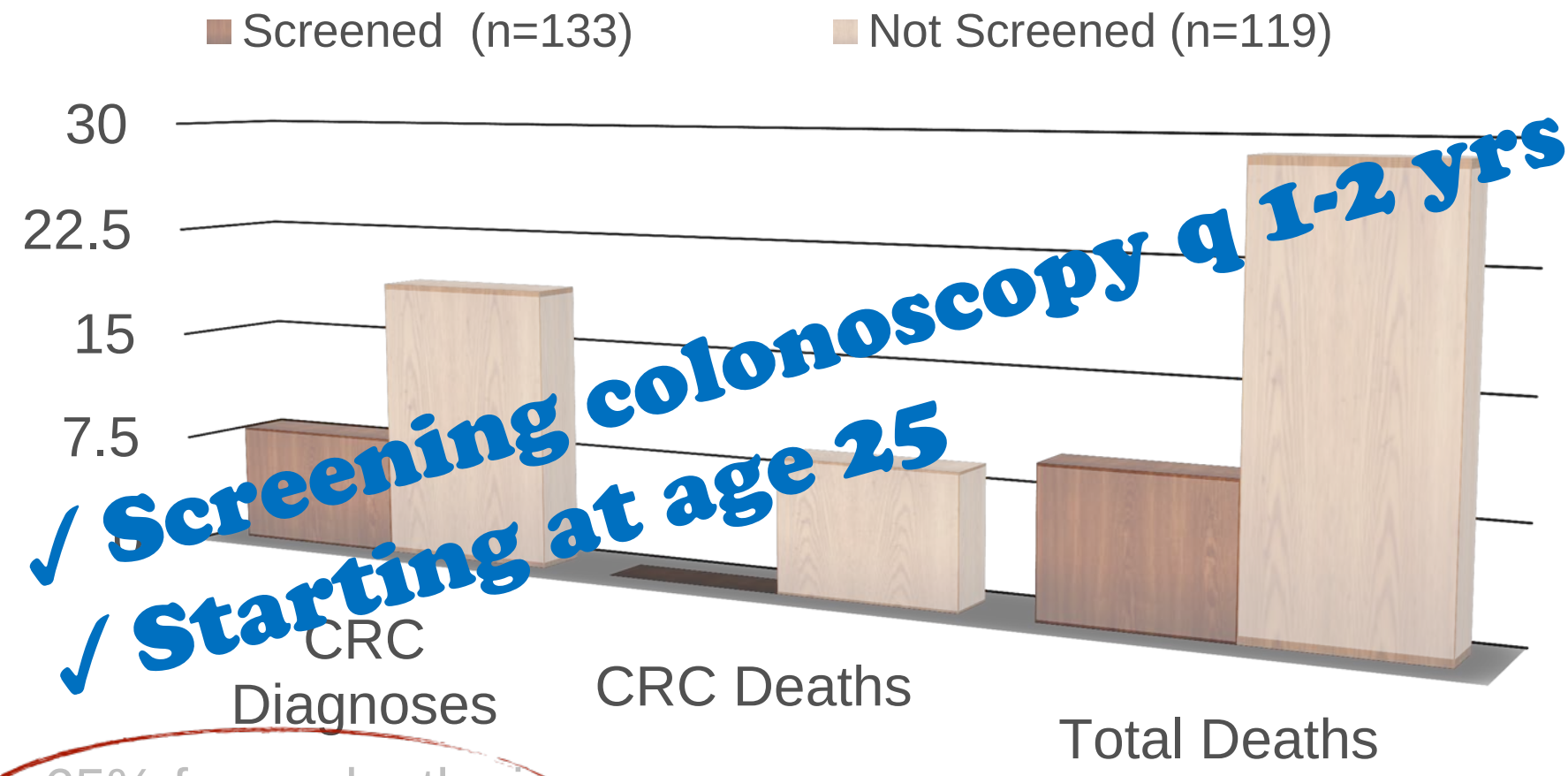
Screening colonoscopy in Lynch syndrome



65% fewer deaths in screened patients

Jarvinen et al, 1995, 2000, 2009

Screening colonoscopy in Lynch syndrome



✓ Screening colonoscopy q 1-2 yrs

✓ Starting at age 25

65% fewer deaths in screened patients

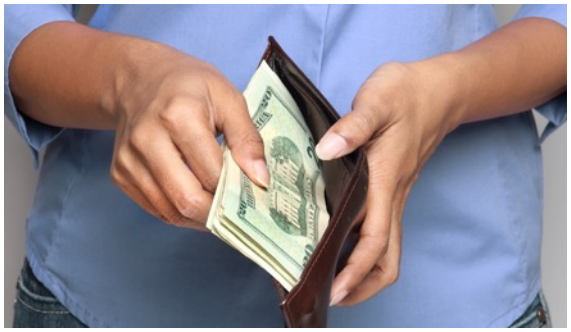
Jarvinen et al, 1995, 2000, 2009

Other Cancers

- Colon cancer < 40yrs
- Male breast cancer, triple negative breast cancer < 60yrs
- Multiple (>10 polyps (familial adenomatous polyposis)
- Ovarian cancer
  - Serous (BRCA1/2)
  - Ovarian sex cord tumor with annular tubules
  - Ovarian small cell carcinoma
- Renal cancer <40yrs
- Medullary thyroid cancer (MEN)
- Adrenocortical cancer (Li Fraumeni syndrome)
- Hemangioblastoma (Von Hippel Lindau syndrome)
- Desmoid tumors *(FAP)*
- Pheochromocytoma (MEN)

Private genetic testing options

- Many commercial labs offer hereditary genetic testing with an MD referral
- Some examples:
  - Color Genomics (www.color.com)
  - Lifelabs (www.lifelabs.com)
  - Myriad Genetics (www.myriad.com)
  - (NOT 23andMe)



- We can see patients for counselling re: results of private genetic testing
- Counselling issues….
  - Which genes or panel?, which technology?, informed consent, possible results
  - Remember that these will be low risk patients

Take home messages

- Multi-gene panels
  - Simultaneous assessment of multiple high and moderate risk cancer predisposing genes
  - ❖ With increasing diagnostic yield comes higher rates of uncertain results and increasingly complex interpretation and counselling
- The best way to assess for hereditary cancer in a family is through testing an affected relative
  - Encourage your patients to talk to their affected relatives about a referral to genetics
- When in doubt, call or us refer!

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