Hereditary Cancer Update: What do GPOs need to know?



Mary McCullum, RN, MSN, CON(C)
Nurse Educator, Hereditary Cancer Program
BC Cancer Agency
October 1, 2016

Conflict of Interest Disclosure

- Nothing to disclose

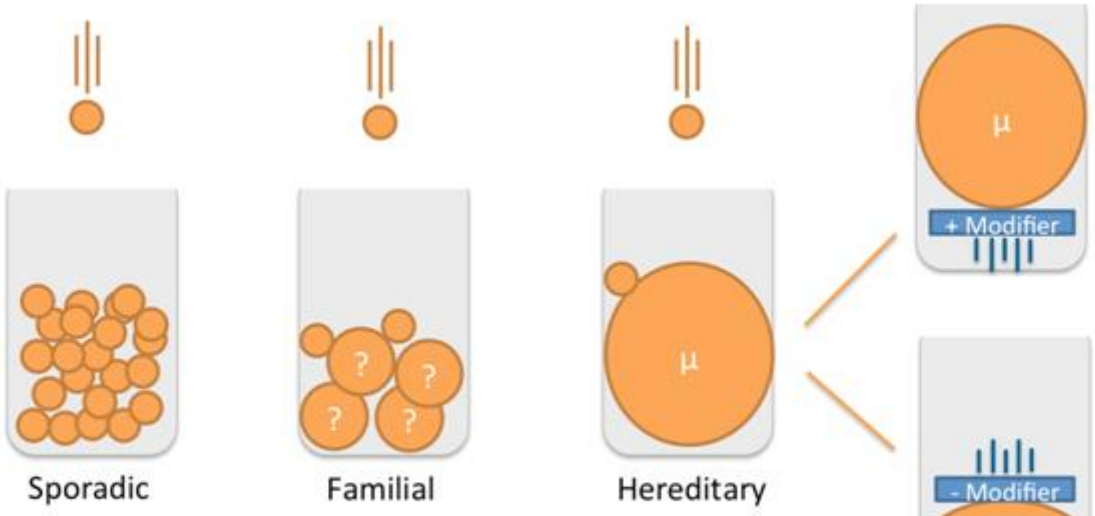
Objectives

1. Discuss the most common hereditary cancer syndromes

2. Discuss the implications of testing multi-gene panels compared to single genes

3. Discuss treatment-focused genetic testing

Sporadic, Familial & Hereditary Cancer

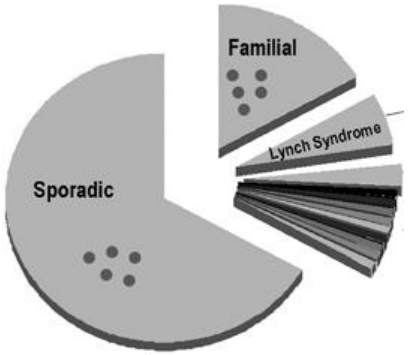


60-75% 20-25% 5-10%

When to consider hereditary cancer?

Family history may include:

- Same cancer, 2 or more close relatives (**same side of family**)
- Multiple generations affected
- Earlier age at diagnosis
- Multiple primary tumours
- Rare cancers
- Constellation of tumours consistent with specific cancer syndrome (e.g. colorectal and endometrial; breast and ovarian)



Personal history

- Pathology features
- See specific syndromes

Hereditary Cancer Syndromes (genes)

- Lynch Syndrome *(MLH1, MSH2, MSH6, PMS1, EPCAM)*
- Hereditary Breast/Ovarian Cancer Syndrome *(BRCA1, BRCA2, others)*

- less common:
  - Familial adenomatous polyposis (*APC*) and other polyposis syndromes
  - Hereditary diffuse gastric cancer (*CDH1*)
  - Li Fraumeni Syndrome (*p53*)
  - Cowden syndrome (*PTEN)*
  - Hereditary paraganglioma/pheochromocytoma (*SDHB, SDHC, SDHD,* others)
  - von Hippel Lindau
  - Multiple endocrine neoplasia – type 1 and 2
  - And others …

Cancer Genetic Counselling Session

- Personal medical history
- Review of family history
- Education
  - ✓ Review of genes, chromosomes & inheritance
  - ✓ Discussion of sporadic, familial, hereditary cancer
- Empiric risk and likelihood of specific cancer syndrome
  - ✓ Associated cancer probabilities
  - ✓ Strategies for cancer screening & risk reduction
- Genetic testing
  - ✓ Eligibility, potential harms & benefits, limitations
- Psychosocial issues, resources
- Communication with family members
- Documentation to referring provider and patient

Germline Genetic Testing

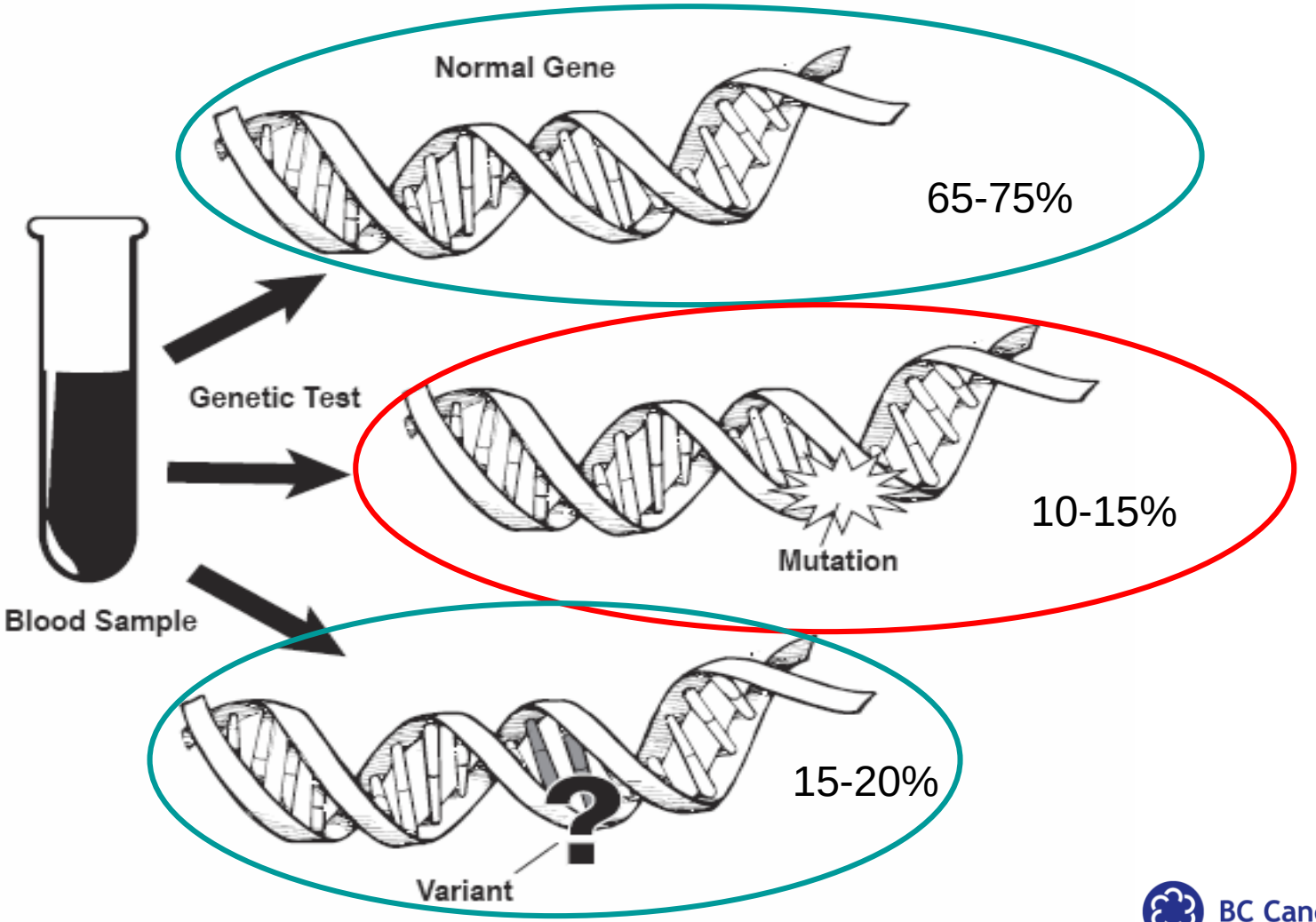
Index test:

- 1st genetic test in family
- trying to identify a specific gene mutation
- usually affected individual (relevant cancer dx)
- usually blood test; sometimes begin with tumour tissue

Carrier test:

- for specific mutation known in the family

What are the possible index results?

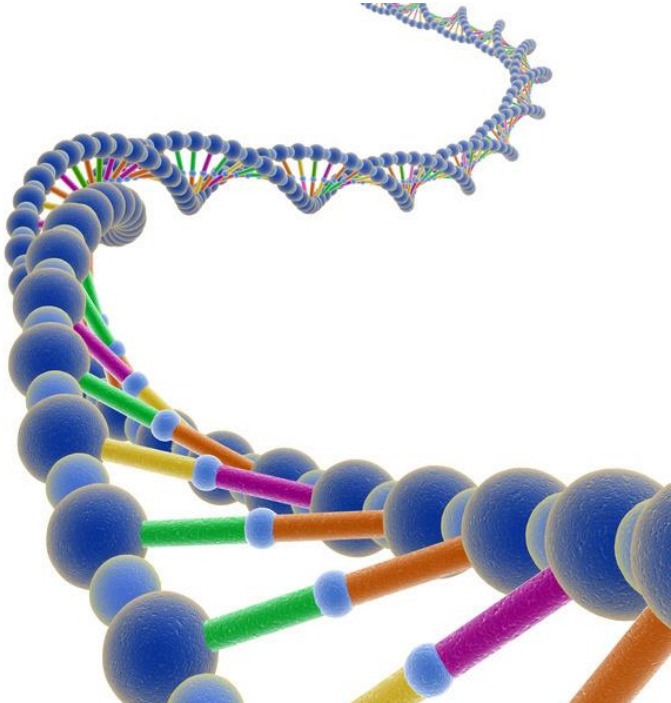


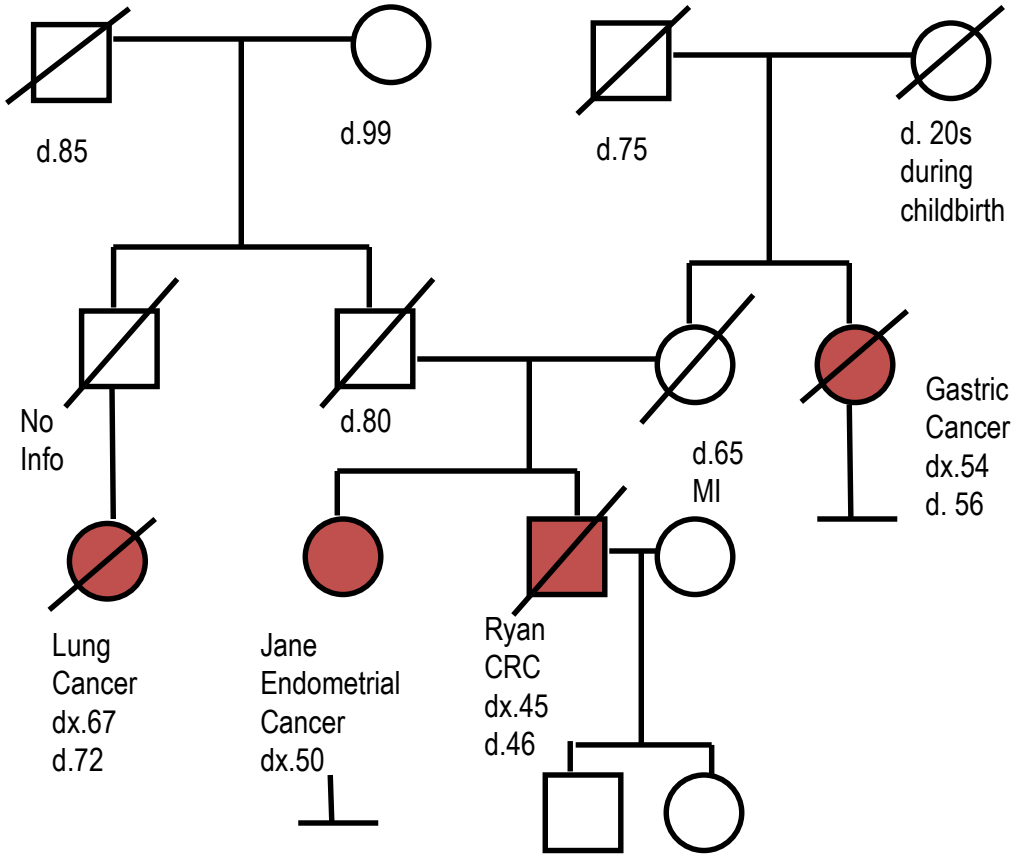
Case #1

Jane

Recently diagnosed with endometrial cancer and her brother died with colon cancer at age 45.

Surprised when her oncologist suggests she have a screening colonoscopy and genetic counselling referral.




d.85
d.99
d.75
d. 20s
during
childbirth
No
Info
d.80
d.65
MI
Gastric
Cancer
dx.54
d. 56
Lung
Cancer
dx.67
d.72
Jane
Endometrial
Cancer
dx.50
Ryan
CRC
dx.45
d.46

Lynch Syndrome (formerly known as HNPCC)

Personal history:

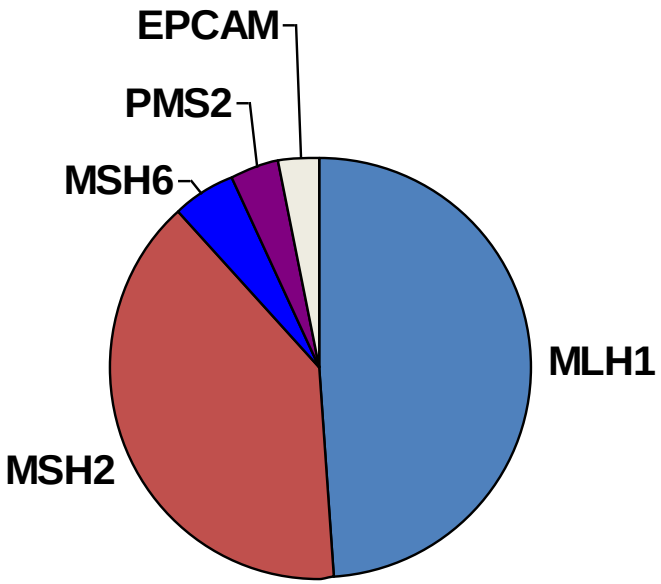
- Colorectal cancer ≤ age 40
- Lynch syndrome cancer that is IHC-deficient/MSI-H (any age)
- 2 Lynch syndrome cancers: 1st dx ≤ age 50, 1 CRC

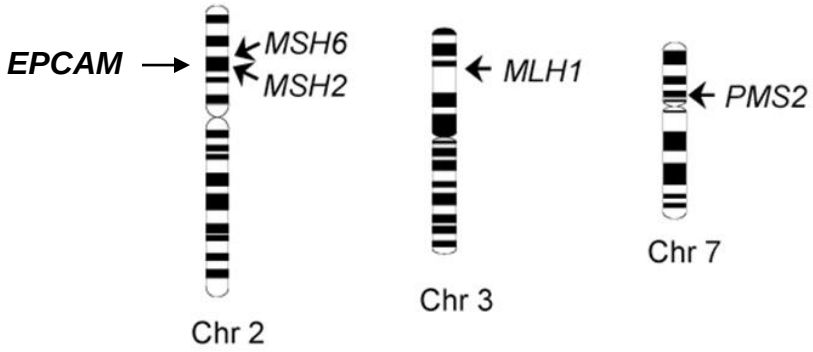
Family history:

- Confirmed *MLH1, MSH2, MSH6, PMS2* mutation
- Close relative with personal history as above
- 2 FDR with a Lynch syndrome cancer: both dx ≤ age 50 , 1 CRC
- 3 Lynch syndrome cancers: 1 dx ≤ age 50, 1 CRC, more than 1 generation

Lynch syndrome cancers: colorectal, endometrial, ovarian, gastric, small bowel, hepatobiliary, pancreatic kidney, ureter, brain; also sebaceous adenomas or colorectal adenomas ≤ age 40

What causes Lynch Syndrome?





DNA mismatch repair (MMR) genes

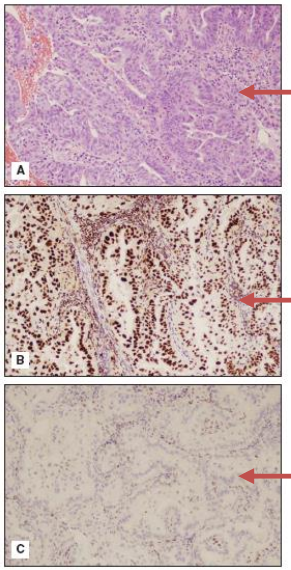
MMR complex functions as “spell-check” system to repair errors occurring in DNA replication during cell division

Loss of MMR leads to errors in short, repetitive sequences (microsatellites) leading to instability (MSI)

Lynch syndrome genetic testing begins with tumour issue

Immunohistochemistry (IHC):

- MLH1
- MSH2
- MSH6
- PMS2

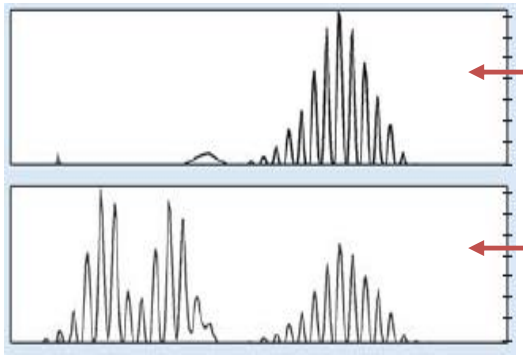


Unstained

Stained Intact

Unstained
Deficient

Microsatellite Analysis



Stable
(Normal)

Unstable
(Abnormal)

CGL tests 7 markers:
- 3 dinucleotides
- 4 mononucleotides

10-15% sporadic colorectal tumours are MSI +
Up to 95% of Lynch CRC have MSI

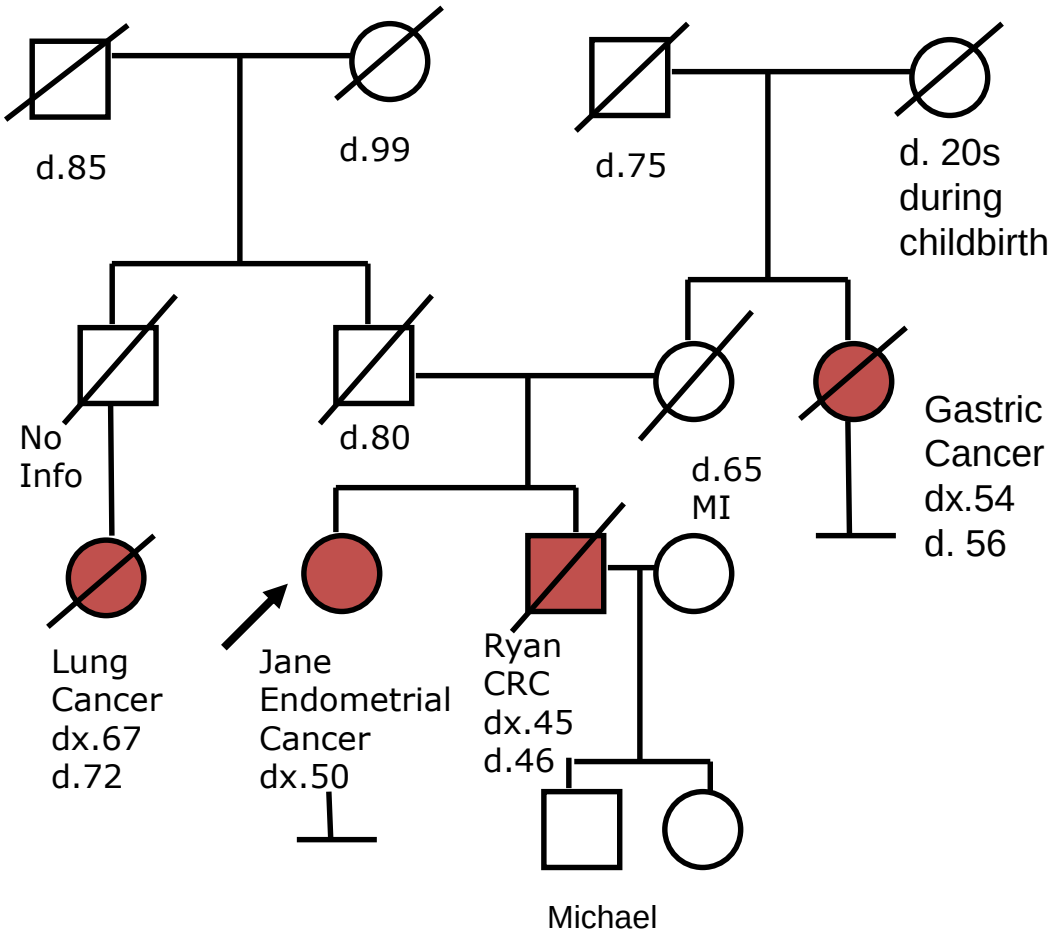
Jane's Tumour Results

Immunohistochemistry

- MLH1 – Intact
- MSH2 – Intact
- **MSH6 – Deficient**
- PMS2 - Intact

This result is suggestive of a germline *MSH6* gene mutation but does not confirm Lynch syndrome.

To whom do we offer germline genetic testing?



TYPE OF CANCER	GENERAL POPULATION RISK (Canada)	LYNCH SYNDROME RISK*	
		MLH1/MSH2	*MSH6*
Colorectal – men	7-8%	54-74%	22-42%
Colorectal – women	6%	30-52%	20-42%
Endometrial	2-3%	28-60%	20-40%
Ovarian	1-2%	6-7%	6-7%
Stomach	1%	6-9%	6-9%
Hepatobiliary tract, urinary tract (renal pelvis), small bowel, pancreas, brain/CNS	<1%	1-7%	1-7%

**Note: Cancer risks for PMS2 gene mutation carriers may be much lower than the other mismatch repair genes; however, the PMS2 research is limited at this time.*

Lynch Syndrome Screening - Colorectal Cancer*

Colonoscopy beginning at 25, or 5-10 years before the youngest age of colorectal cancer diagnosis in the family

- every 1-2 years until age 40
- every year after age 40

* Average age at diagnosis younger than in general population

* Tend to be right-sided (proximal) colon tumours

* Rapid progression from polyp to CRC

* Risk of second primary CRC up to 40%

Lynch Syndrome Screening - Endometrial Cancer

- For most women, abnormal vaginal bleeding is the first sign of endometrial cancer
  - Prompt investigation of any abnormal bleeding
- Annual endometrial biopsy & transvaginal ultrasound starting at age 25-35 is controversial

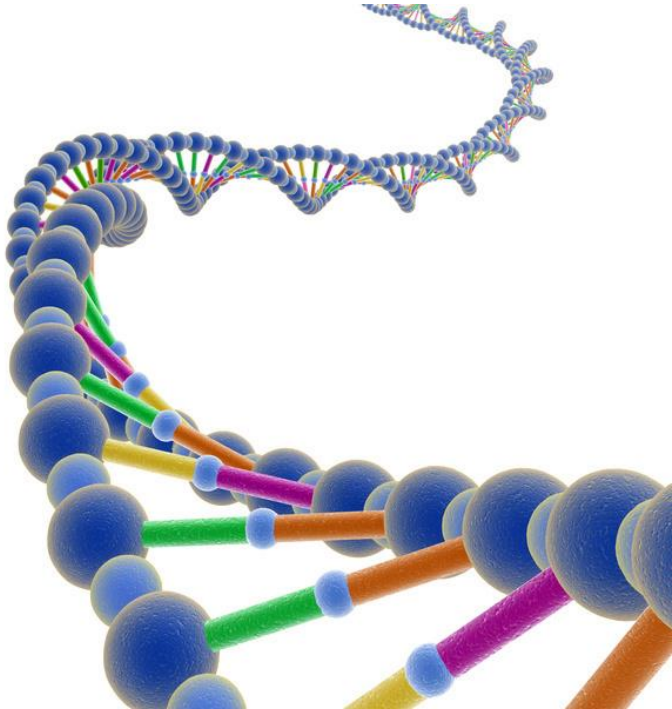
Women with Lynch syndrome may consider prophylactic hysterectomy and bilateral salpingo-oophorectomy.

Case #2

Judy

Asks her mother to have the “breast cancer gene test”. She feels that with her family history, breast cancer is inevitable.

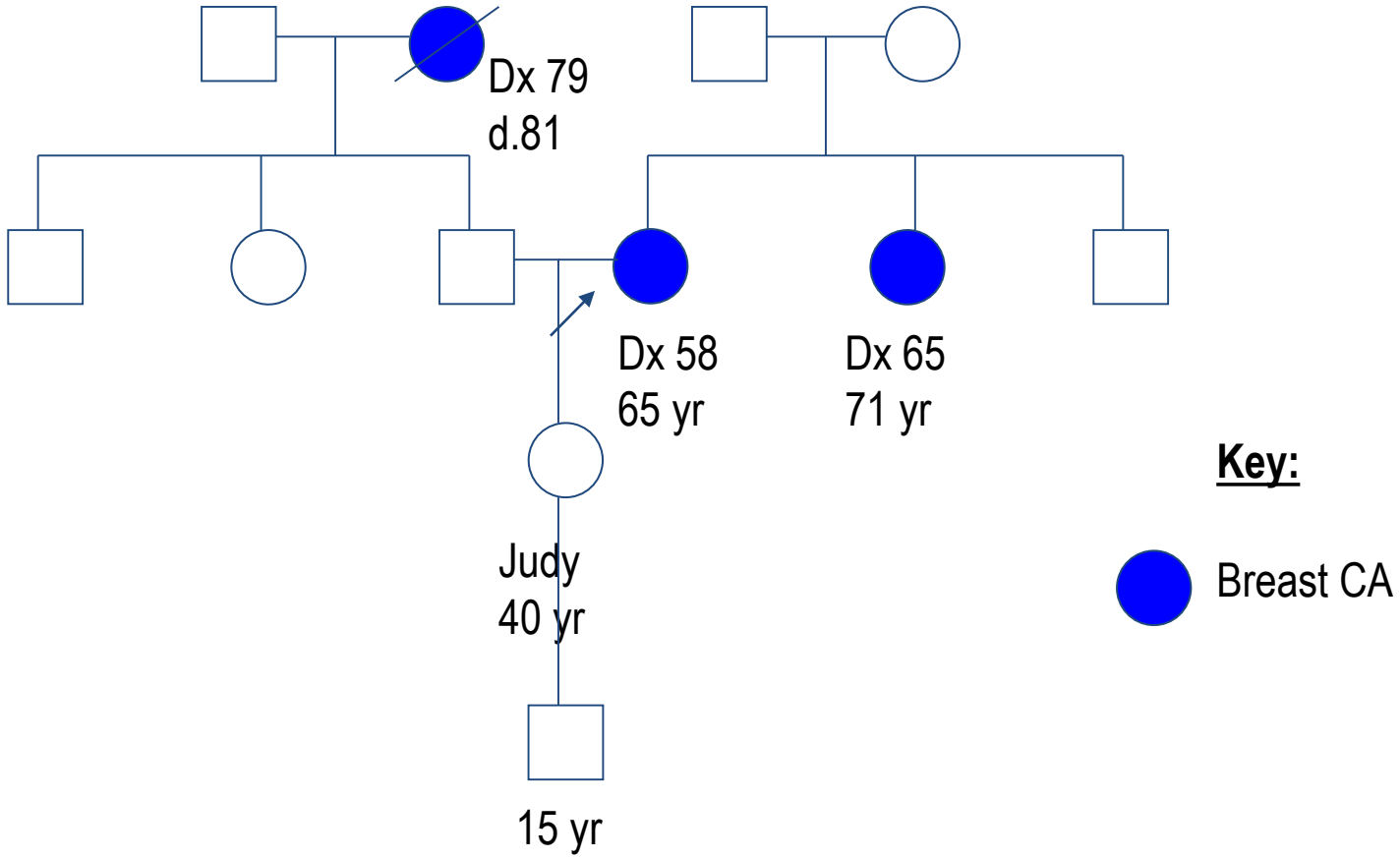
Her mother brings this request to an oncology follow-up appointment.



The “Angelina Jolie Effect”

See: Borsekowski et al., Genetics in Medicine, Dec 2013
Also: http://meetinglibrary.asco.org/content/136716-151

Swedish / Finnish **Japanese**



Hereditary Breast*/Ovarian** Cancer

Personal history:

- Breast cancer ≤ age 35
- "triple negative" breast cancer ≤ age 60
- 2 or more primary breast cancers: 1st dx ≤ age 50
- ***Ovarian cancer*** at any age (pathology required) +/- breast cancer

Family history:

- Confirmed BRCA1, BRCA2 mutation
- Close relative with personal history as above
- Ashkenazi Jewish heritage and at least 1 breast or ovarian cancer dx
- 1 breast cancer + 1 ovarian cancer dx in close relatives
- 1 male breast cancer + 1 close relative with breast or ovarian cancer
- 2 close relatives with breast cancer: both dx ≤ age 50
- 3 close relatives with breast cancer: 1 dx ≤ age 50

** ovarian cancer (epithelial non-mucinous): includes fallopian tube, primary peritoneal, "STIC"; excludes borderline/LMP tumours

* breast cancer includes DCIS (depending on age & grade); excludes LCIS

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

Assessment

- Judy's mother is not eligible for publicly funded *BRCA1/2* testing in BC

- Judy's lifetime breast cancer risk is moderately increased and she can begin annual screening mammography at age 40 in BC

Private Pay Genetic Testing

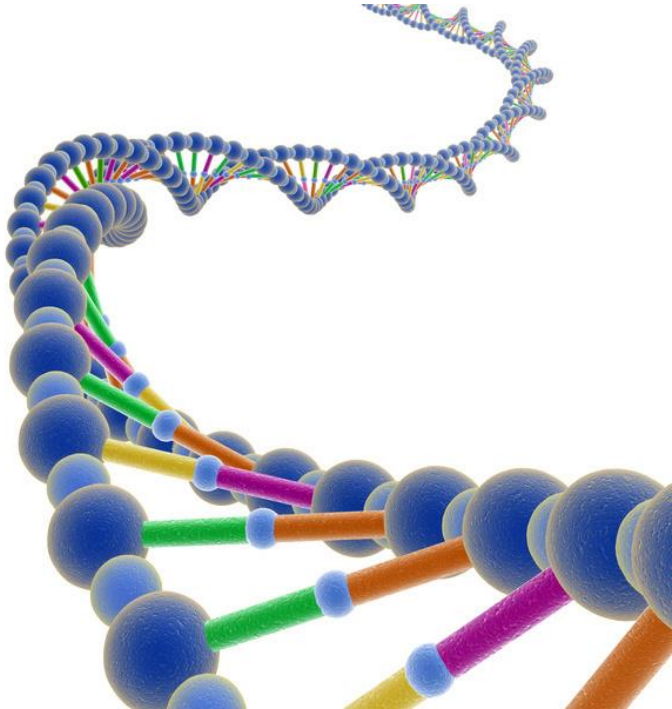
- Assessment as ineligible for publicly funded hereditary cancer genetic testing may be reassuring news for some people
- For those who still feel a genetic test would provide important information, many commercial labs now provide hereditary cancer genetic testing with MD referral
- Some examples:
  - Color Genomics (www.getcolor.com) – based in the U.S., DNA samples (saliva) sent to the US for tesitng; breast/ovarian cancer genes only; genetic counselling available on request
  - GeneDx (www.genedx.com) - based in the U.S.; DNA samples sent to the U.S. for testing; no genetic counselling offered
  - Invitae (www.invitae.com)- based in the U.S; DNA samples sent to the U.S. for testing; genetic counselling is available with genetic testing
  - LifeLabs (www.lifelabsgenetics.com) – based in Canada; DNA samples sent to Europe for testing; no genetic counselling offered
- HCP cannot endorse any specific lab; pt and provider need to investigate the options
- HCP will provide appointments about the clinical implications of the result for the tested person and their family members
- Relatives are eligible for publicly-funded genetic counselling and genetic testing when a gene mutation is confirmed in a family

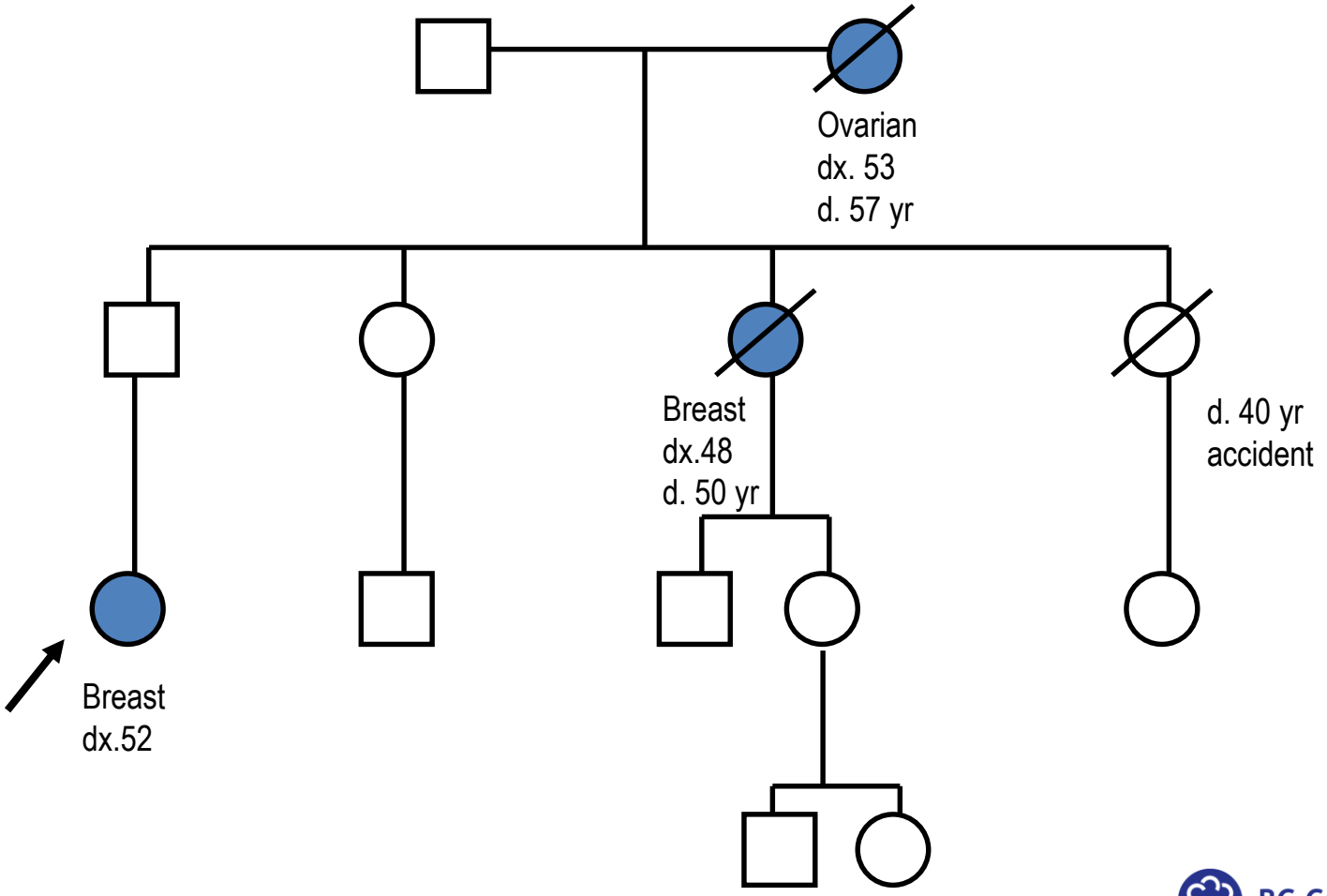
Case #3

Erica

Recently diagnosed with breast cancer.

Her physician suggests she consider genetic testing because of her personal and family history of cancer.





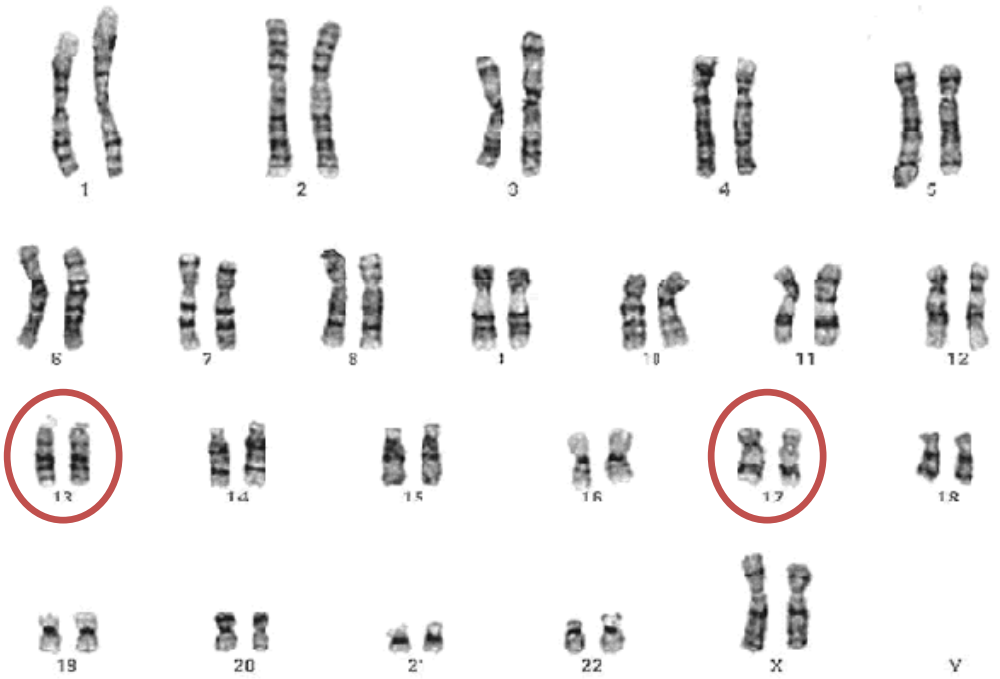
Hereditary Breast & Ovarian Cancer Syndrome

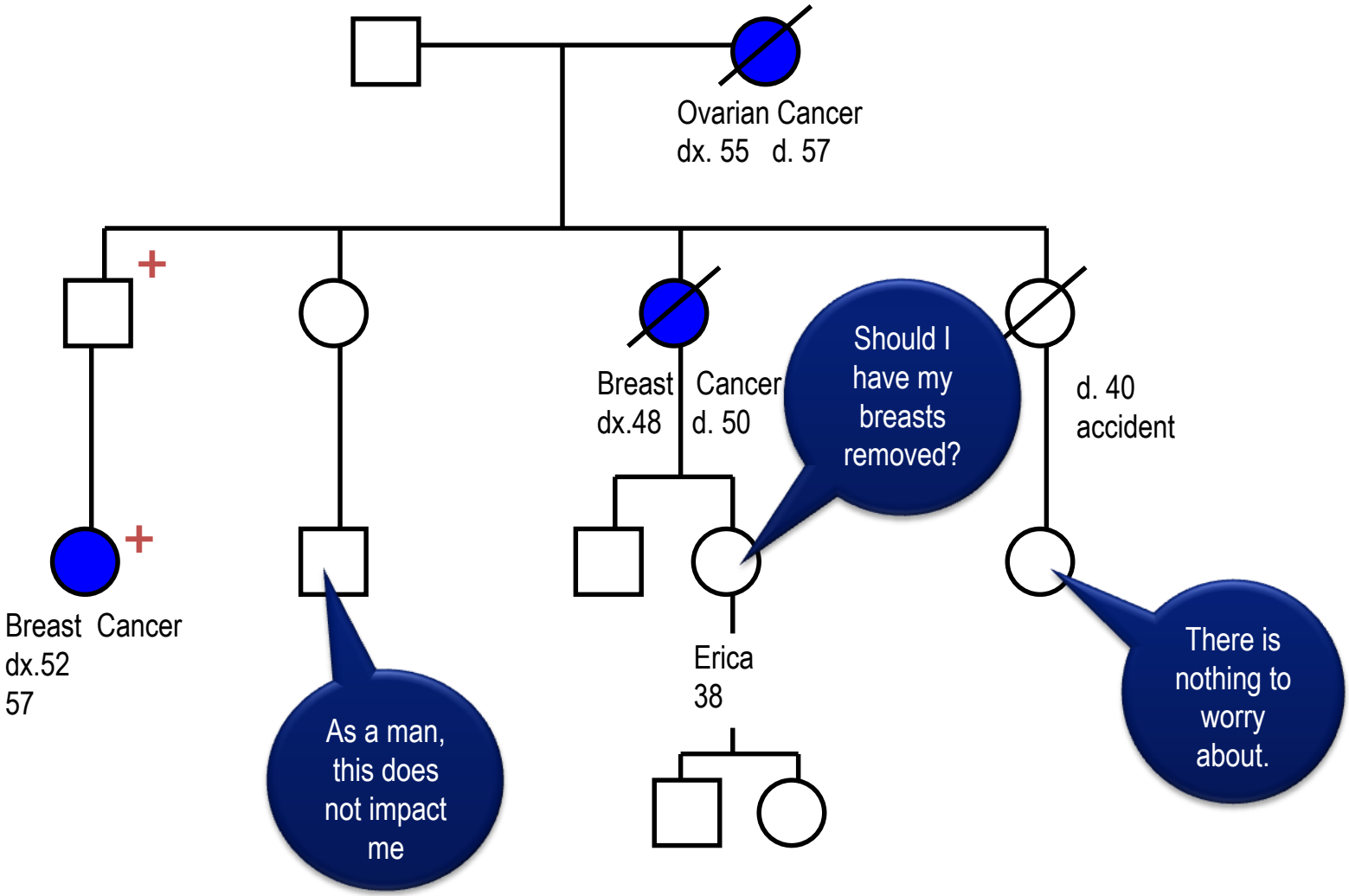
Genes
- *BRCA1* (Ch 17)
- *BRCA2* (Ch 13)

Inheritance
- Autosomal Dominant

Incidence
- General Population 1/500 to 1/800
- Ashkenazi Jewish 1/40 (3 founder mutations)

Incomplete penetrance




Ovarian Cancer
dx. 55 d. 57
+
+
Breast Cancer
dx.52
57
Breast Cancer
dx.48 d. 50
Should I have my breasts removed?
d. 40
accident
Erica
38
As a man, this does not impact me
There is nothing to worry about.

TYPE OF CANCER	RISK IN 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 approx 2-3 times	
pancreatic cancer	1%	slight increase	slight increase
other cancers	varies	—	slight increase

*2nd primary breast cancer ~20-63% (avg up to 50%)

What is recommended if you are BRCA+?

Breast screening:

♀
BSE – personal choice
CBE q6 months in conjunction with imaging
Mammography q12 months age ≥30
MRI q12 months age 25-65
Ultrasound as advised by radiologist

♂
CBE q12 months
Prostate screening from age 40

No effective way to screen for ovarian cancer

Referral to High-Risk Clinic (depends on local resources)

Canadian Hereditary Cancer Task Force, *JOGC* 2007

Risk-Reducing Surgery

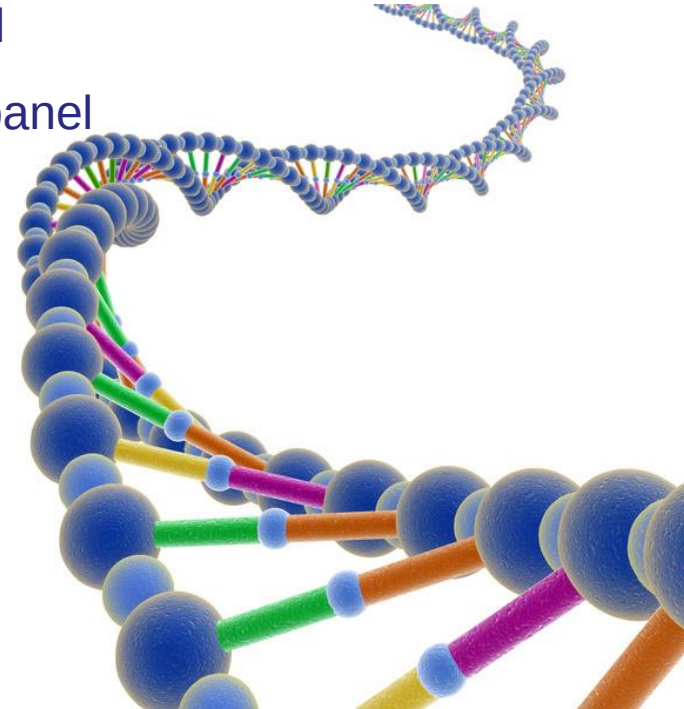
- mastectomy (with reconstruction) - personal choice
  - reduces breast cancer risk by 90-95%
  - no routine imaging of reconstructed breasts; GP follow-up for routine chest wall & regional node exam
- bilateral **salpingo**-oophorectomy
  - recommended to all *BRCA1/2*+ women by age 40
  - reduces ovarian cancer risk by 85-95% AND reduces breast cancer risk ~50% if done prior to menopause
  - attention to effects of surgical menopause
  - short term use of HRT does not negate protective effect of BSO on breast cancer risk

Canadian Hereditary Cancer Task Force, *JOGC* 2007

Multi-Gene Panel Testing

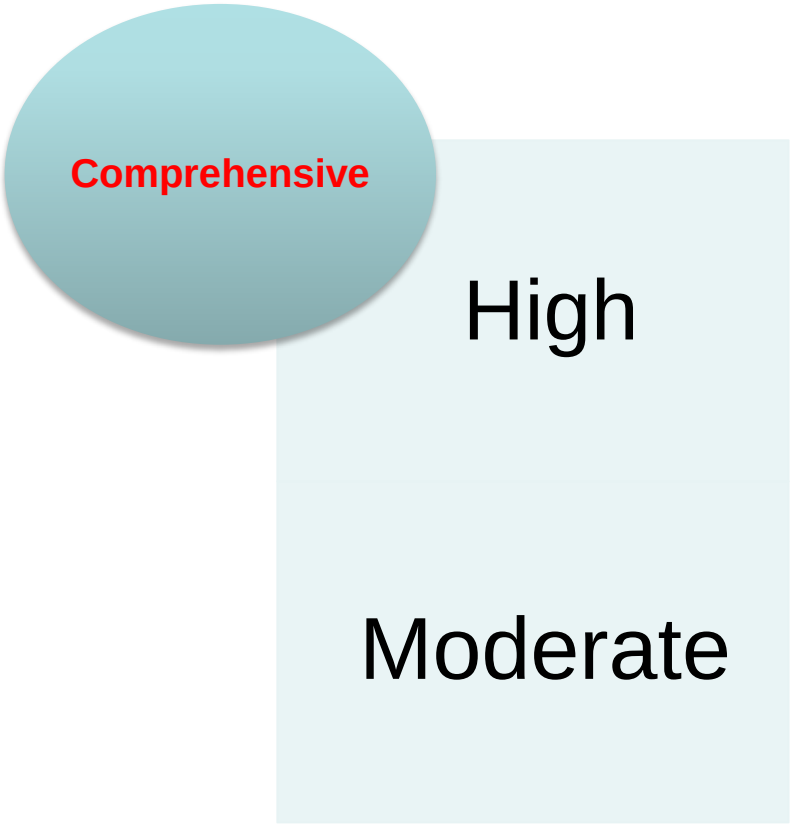
Changing landscape:

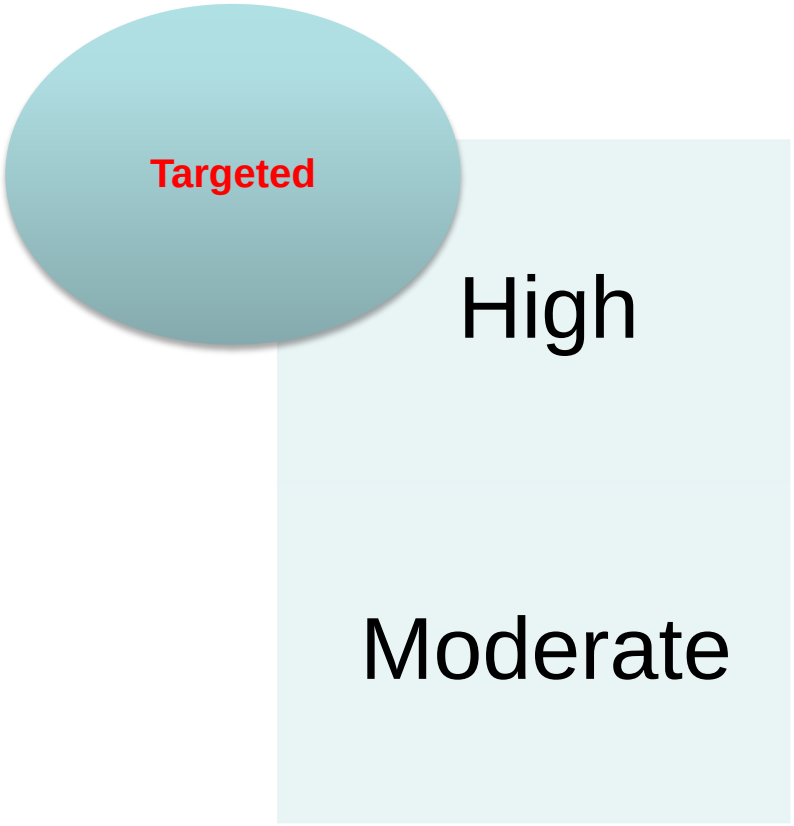
- 2008: rapid decrease in cost of genetic testing (NGS)
- Feb 2012: 1st commercial multi-gene cancer panel
- May 2013: Angelina Jolie in New York Times
- June 2013: Myriad patent on *BRCA1/2* overturned
- Oct 2014: BC Cancer Agency launches 14-gene panel
- 2016: many options now available



More = Better?

Panel Composition





Breast/Ovarian Panels

Mutation in a High Risk Gene (*BRCA1/2, TP53 & CDH1*)	Mutation in a Moderate Risk Gene (*CHEK2*)	Mutation in a Newly Characterized Gene (*NBN; RAD51C*)
• Well Studied • Most genes fit with the family history (some exceptions- CDH1) • Guidelines for screening and prevention established	• Well Studied • Increased risk for breast cancer &other cancers, although unclear • Guidelines for screening and prevention not yet established	• Not as well studied • Clear cancer risks and lifetime risks not yet determined • Guidelines for screening and prevention not yet established • Expect variants of uncertain significance in newer genes

**Includes BRCA1/2 & 19 additional genes that can increase the risk for breast cancer
**High risk gene panel-*BRCA1/2, CDH1, PTEN, STK11, TP53*

Invitae Breast and Gyn Cancers Panel

Invitae Breast Cancer Panel

Genetic testing for up to 26 genes that are associated with an increased lifetime risk of developing breast cancer, as well as other cancer types.

VIEW TEST DETAILS

GENES TESTED:

Primary Panel:

ATM	BARD1	BRCA1	BRCA2	BRIP1	CDH1	CHEK2
NBN	NF1	PALB2	PTEN*	RAD50	STK11	TP53*

*PTEN: Deletion/duplication analysis covers the promoter region.

*TP53: Deletion/duplication analysis covers the promoter region.

Limited-evidence genes for breast cancer:

AKT1	FAM175A	FANCC	MRE11A	MUTYH	PIK3CA	RAD51C
RAD51D	RINT1	SDHB	SDHD	XRCC2		

Genes with limited evidence of an association with hereditary breast cancer are available to add on to the primary panel. Some clinicians may wish to include genes that do not currently have a definitive clinical association, but which may prove to be clinically significant in the future. Visit our Limited-evidence genes page to learn more. These genes can be added at no additional charge.

Invitae Breast and Gyn Cancers Guidelines-Based Panel

Invitae Breast Cancer Guidelines-Based Panel

Invitae Breast Cancer High Risk Panel

YOUR ORDER

Your order is empty.

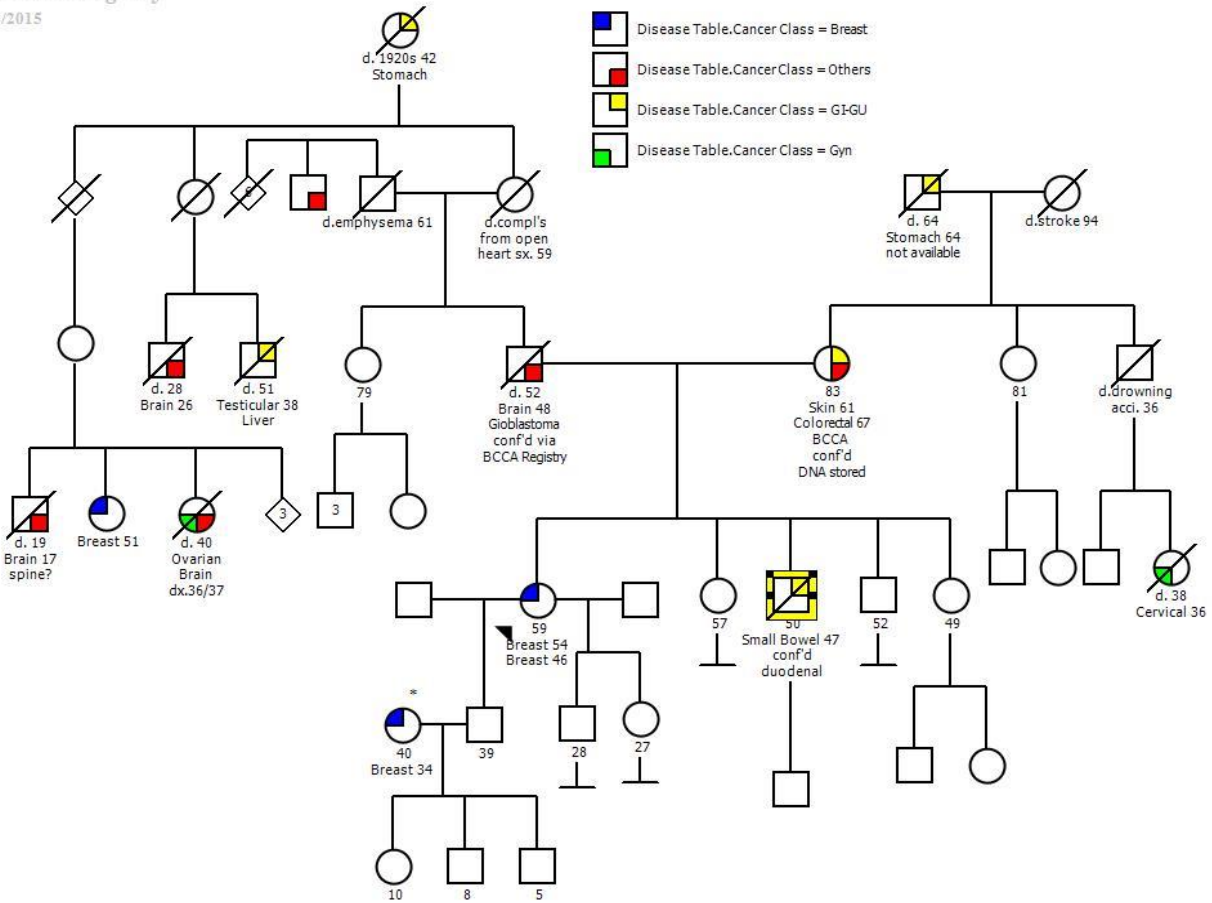
ORDER PROGRESS

NEED ASSISTANCE?

Targeted Panels

- Changing our understanding of gene prevalence and penetrance for specific tumour types
  - *ATM, CHEK2, PALB2* and *RAD51C* mutations found in breast cancer families

- May miss clinically relevant mutations due to non-traditional phenotypes


Disease Table.Cancer Class = Breast
Disease Table.Cancer Class = Others
Disease Table.Cancer Class = GI-GU
Disease Table.Cancer Class = Gyn
d. 1920s 42
Stomach
d.emphysema 61
d.compl's
from open
heart sx. 59
d. 64
Stomach 64
not available
d.stroke 94
d. 28
Brain 26
d. 51
Testicular 38
Liver
79
d. 52
Brain 48
Gioblastoma
conf'd via
BCCA Registry
83
Skin 61
Colorectal 67
BCCA
conf'd
DNA stored
81
d.drowning
acci. 36
d. 19
Brain 17
spine?
Breast 51
d. 40
Ovarian
Brain
dx.36/37
3
3
59
Breast 54
Breast 46
57
50
Small Bowel 47
conf'd
duodenal
52
49
d. 38
Cervical 36
*
40
Breast 34
39
28
27
10
8
5

Invitae Multi-Cancer Panel

Genetic testing for 79 genes that are associated with hereditary cancers across eight major organ systems: breast and gyn, gastrointestinal, endocrine, genitourinary, skin, brain/nervous system, sarcoma, and hematologic.

VIEW TEST DETAILS

GENES TESTED:

ALK	APC*	ATM	AXIN2	BAP1	BARD1	BLM
BMPR1A*	BRCA1	BRCA2	BRIP1	CASR	CDC73	CDH1
CDK4	CDKN1B	CDKN1C	CDKN2A*	CEBPA	CHEK2	DICER1
DIS3L2	EGFR*	EPCAM*	FH	FLCN	GATA2	GPC3
GREM1*	HOXB13*	HRAS	KIT	MAX	MEN1	MET
MITF*	MLH1*	MSH2*	MSH6	MUTYH	NBN	NF1
NF2	PALB2	PDGFRA	PHOX2B*	PMS2	POLD1	POLE
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					

*APC: Deletion/duplication analysis covers the 1A and 1B promoter regions.
*BMPR1A: Deletion/duplication analysis covers the promoter region.
*CDKN2A: Analysis supports interpretation of the p16 protein only
*EGFR: Analysis is limited to the NM_005228.3:c.2369C>T p.Thr790Met variant
*EPCAM: Analysis is limited to deletion/duplication analysis
*GREM1: Analysis of this gene is limited to the promoter region
*HOXB13: Analysis is limited to the NM_006361.5:c.251G>A, p.Gly84Glu variant
*MITF: Analysis is limited to the NM_000248.3:c.952G>A p.Glu318Lys variant
*MLH1: Deletion/duplication analysis covers the promoter region.

Comprehensive Panels

- Broadening our perspective of genotype-phenotype correlations

  e.g.MSH6 mutation in breast ca families

- Greater chance of variants in genes believed unrelated to phenotype
- Challenging for traditional clinical management strategies

BCCA Hereditary Ca 14 Gene Panel

Gene	Syndrome	Associated Tumours
BRCA1, BRCA2	HBOC	Breast, ovary, prostate, pancreas
TP53	Li Fraumeni	Breast (young), sarcoma, brain, adrenocortical, leukemia, others
PTEN	PTEN Hamartoma (includes Cowden)	Breast, thyroid, endometrial; benign lesions of breast, thyroid, GI tract, GU system
CDH1	Hereditary Diffuse Gastric Cancer	Diffuse gastric, (lobular) breast, colorectal
STK11	Peutz-Jegher	Breast, GI, gyne, nasal polyps
MLH1, MSH2 MSH6, PMS2	Lynch	Colorectal, endometrial, gastric, ovary, urinary tract, small bowel, hepatobiliary, pancreas, skin
MUTYH	MYH-assoc polyposis	Colorectal, GI polyposis
APC	FAP	Colorectal, small bowel, desmoids, other
SMAD4, BMPR1A	Juvenile polyposis	Colorectal, gastric, other GI (combined with hereditary hemorrhagic telangiectasia)

Multi Gene Panels

Benefits

- Increased mutation detection rate (comprehensive test)
- Cost-effective
- Less testing fatigue
- Incidental findings

Drawbacks

- Information overload
- Uncertainty if poorly understood genes are analyzed
- VUS rate
- Incidental findings

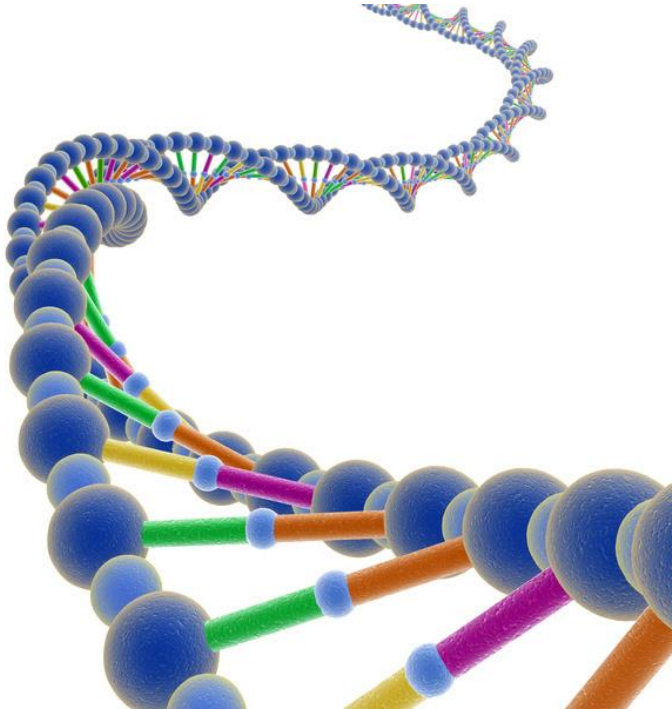
Treatment-Focused Genetic Testing

Susan

Diagnosed with recurrent high-grade serous ovarian cancer.

Brenda

Recently diagnosed with triple negative breast cancer at age 43.



When is genetic testing urgent?

- Genetic test results will impact (immediate) clinical management
  - New breast cancer dx and pending surgical decisions
  - Use of PARP inhibitors for recurrent ovarian cancer
  - Other clinical situations

- Poor health status (potential index case)
  - Storage of blood sample +/- urgent GC appt

Expedited assessment

- Timelines vary greatly across genetics clinics
  - Waiting lists for genetic counselling
  - Turnaround time for genetic test results

- Strategies
  - Integration of genetic testing into oncology clinics
    - Germline testing
    - Tumour testing
  - “Automatic” referral for genetic counselling (opt-out model)
  - Commercial labs

- Proactive case-finding
  - Identify gene mutation and share info with family

Take Home Messages

- Hereditary cancer is rare (<10%).
- Most, but not all, hereditary cancer syndromes are inherited in an autosomal dominant manner.
- Hereditary risk can come from maternal or paternal side.
- Not everyone with hereditary risk will develop cancer (incomplete penetrance).
- Options for risk reduction and/or early detection, as well as treatment implications, for confirmed mutation carriers.
- Genetic testing usually starts with an affected family member – when to consider storing a blood sample.
- Complex implications of multi-gene panels.