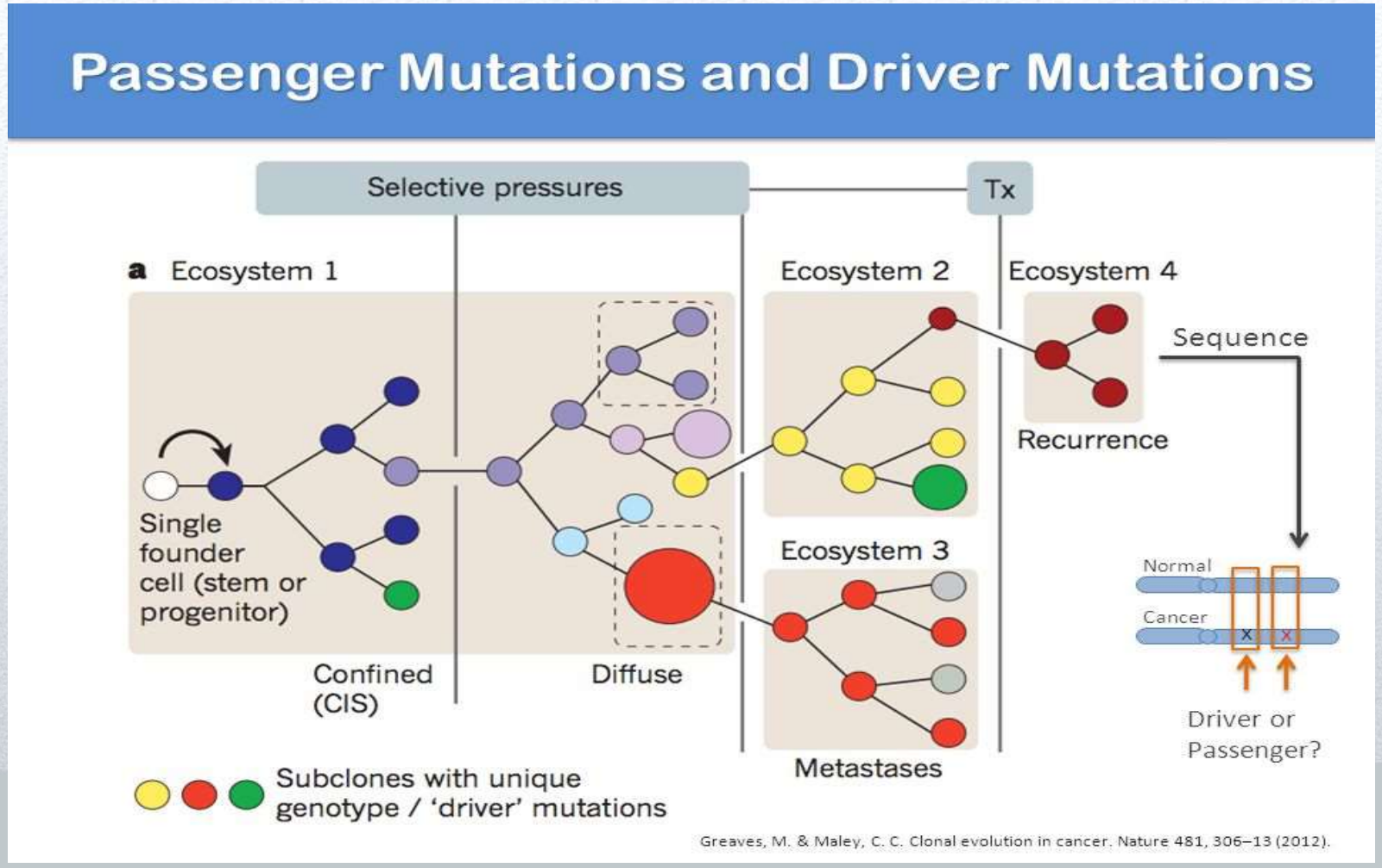
Practical Hereditary Gynecologic Cancers

Chanin Limwongse, MD



Accumulation of Driver and Passenger mutations

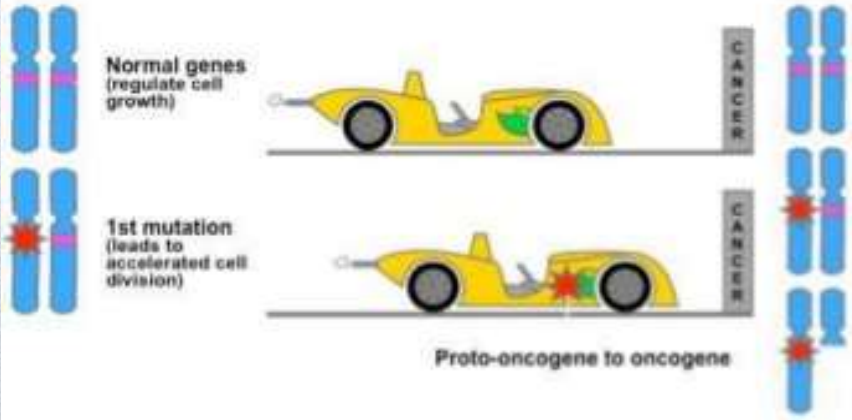
Passengers and Drivers

Driver mutations	Passenger mutations

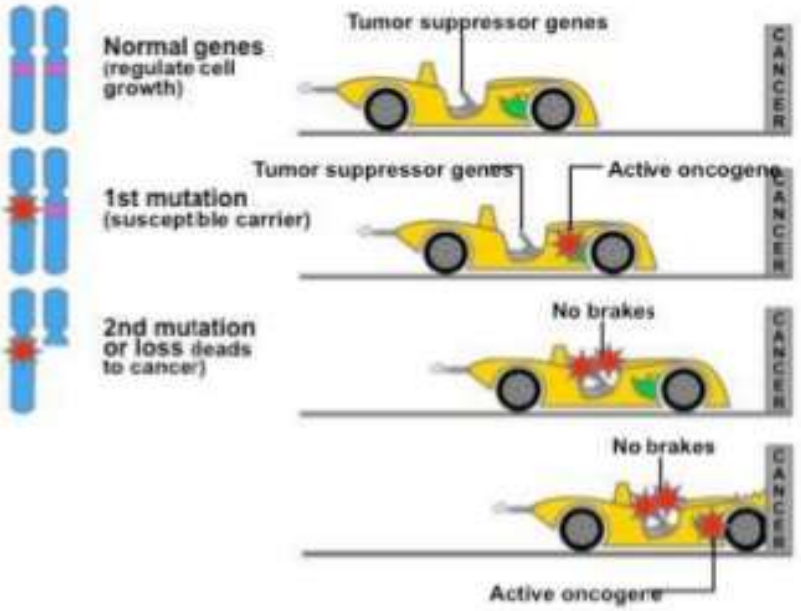
• Contribute to oncogenesis; provide growth advantage; selected for in micro-niche
• Occur in
  ◦ oncogenes (gain of function mutations) or
  ◦ tumour-suppressor genes (loss of function mutations)
	• Neutral mutations
	• Carried along for the ride
	  ◦ somatic mutations without functional consequences often occur during cell division
	• PLUS huge increase in mutation rate with loss of genome repair mechanisms

Oncogenes vs. tumor-suppressor genes

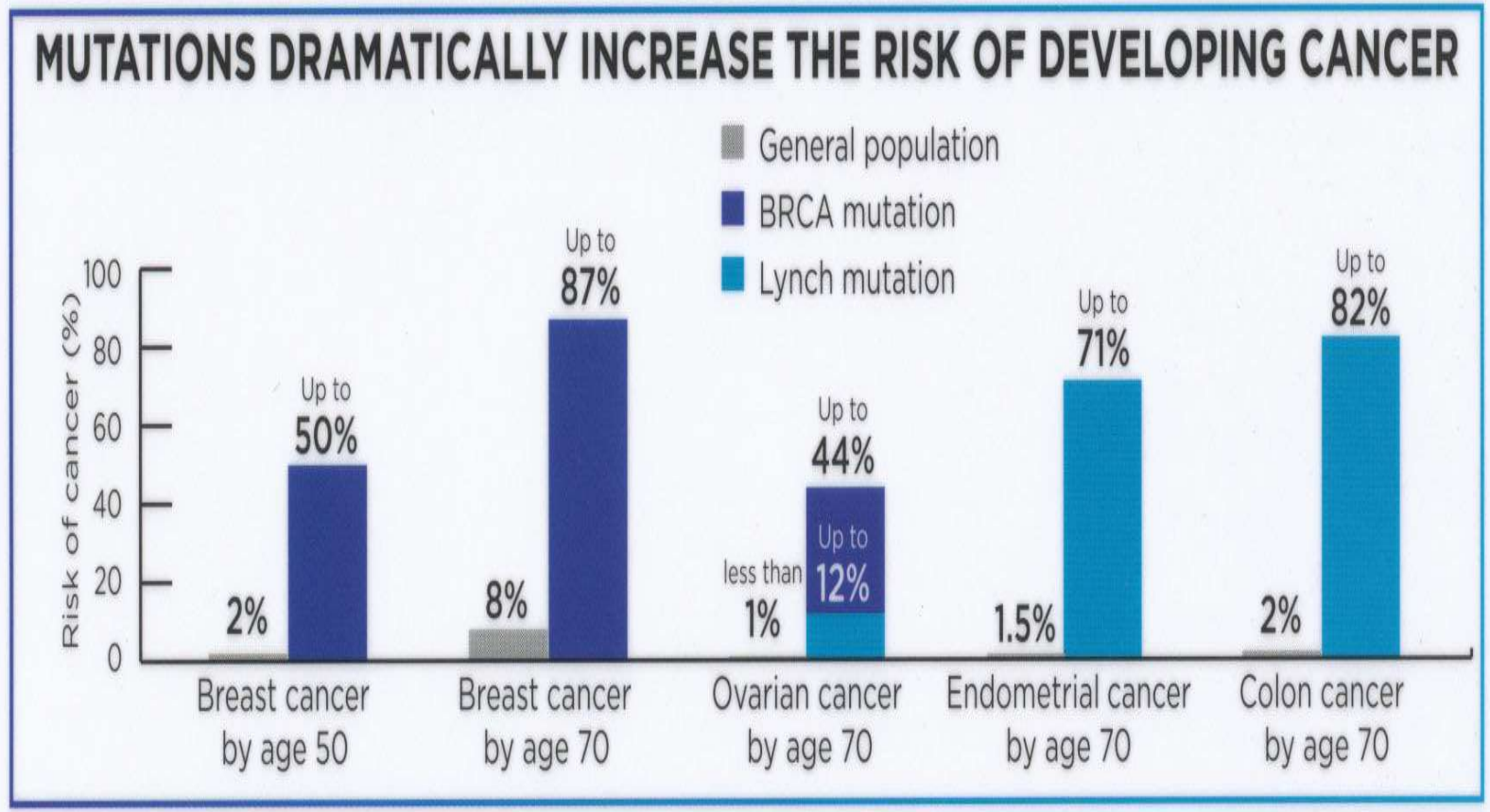
The **bad** guys, turn abnormal cell growth on **(go/gas pedal)**



The **good** guys, turn cell growth off **(stop/brake pedal)**



http://cisncancer.org/



Cancer Risk is increased

KNOW THE RED FLAGS ASSOCIATED WITH HEREDITARY CANCER

An individual with a personal or family history of **any ONE of the following:**

MULTIPLE CANCERS A combination of cancers on the same side of the family	• **2 or more:** breast / ovarian / prostate / pancreatic cancer • **2 or more:** colorectal / endometrial / ovarian / gastric / pancreatic / other cancers (i.e., ureter/renal pelvis, biliary tract, small bowel, brain, sebaceous adenomas) • **2 or more:** melanoma / pancreatic cancer
YOUNG CANCERS Any 1 of the following cancers at age **50 or younger**	• Breast cancer • Colorectal cancer • Endometrial cancer
RARE CANCERS Any 1 of these rare presentations at **any age**	• Ovarian cancer • Breast: male breast cancer or triple negative breast cancer • Colorectal cancer with abnormal MSI/IHC, MSI associated histology** • Endometrial cancer with abnormal MSI/IHC • 10 or more gastrointestinal polyps*

Certain ancestries may have greater risk for hereditary cancer syndromes (e.g., Ashkenazi Jewish ancestry)

Assessment criteria based on medical society guidelines. For these individual medical society guidelines, go to www.MyriadPro.com/guidelines.
Family members include first-, second-, and third-degree blood relatives on both your mother's and father's sides.

*Adenomatous type. **Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

Hereditary Gynecologic Cancer Syndromes

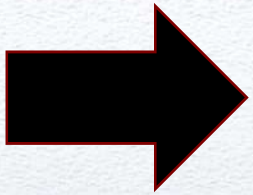
- 1. Hereditary Breast/Ovarian Cancer Syndrome (HBOC)
- 2. Hereditary Site-Specific Ovarian Cancer Syndrome
- 3. Hereditary Nonpolyposis Colon Cancer Syndrome (HNPCC or Lynch II)

- Cowden disease
- DICER1 syndrome
- Peutz-Jeghers syndrome
- Hereditary diffuse gastric cancer syndrome
- Li-Fraumeni syndrome
- Small cell CA of ovary, hypercalcemia type (SCCOHT)
- Neurofibromatosis type 1

Rare Causes of Hereditary Gynecologic Cancer

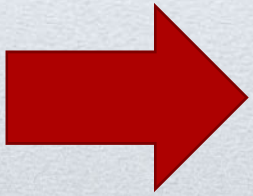
Ovarian cancer- associated cancers

- Breast cancer
- Male breast cancer
- Pancreatic cancer
- Prostate cancer
- Laryngeal cancer



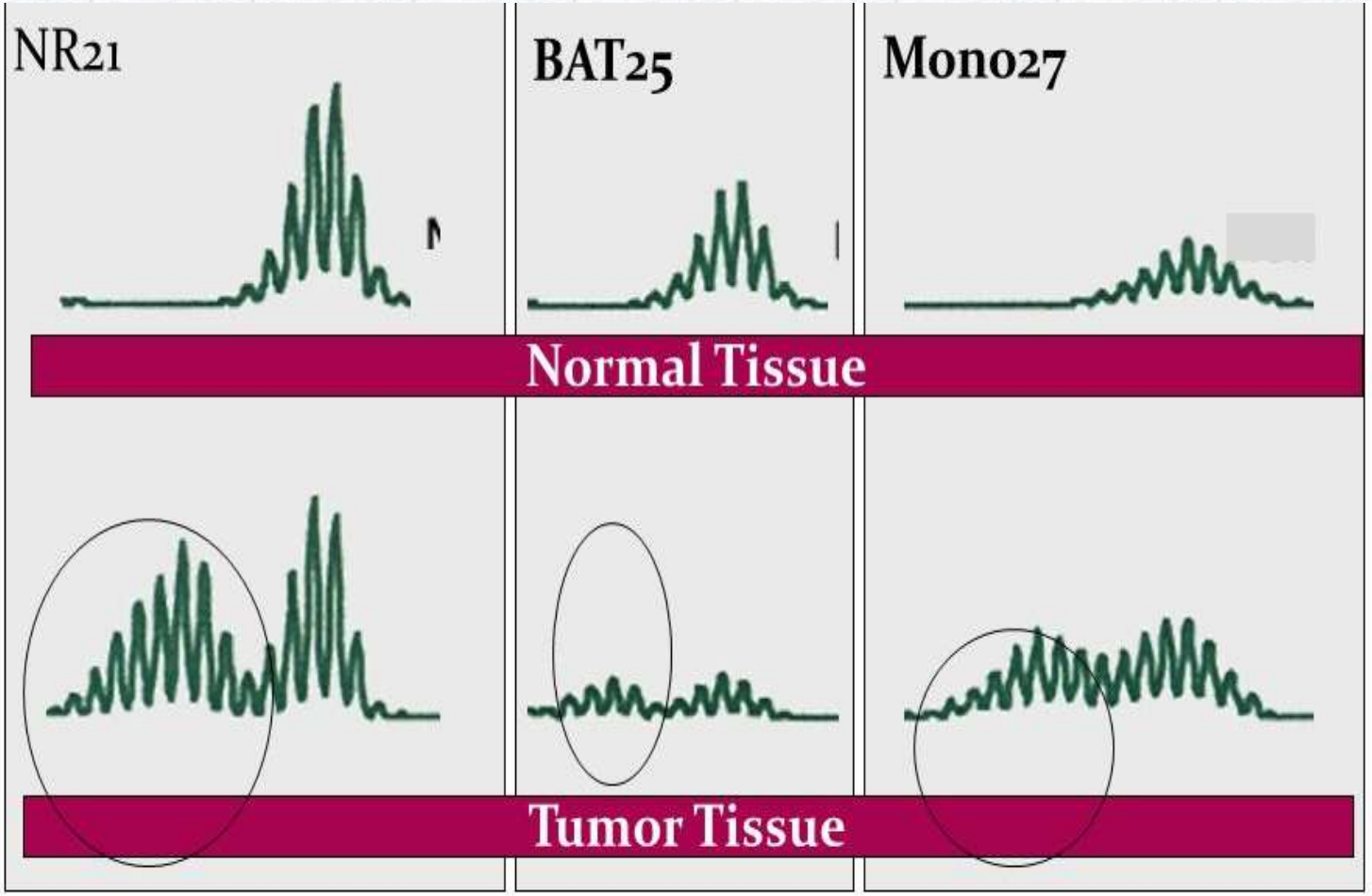
HBOC

- Colon cancer
- Endometrial cancer
- Urinary tract cancer
- GI tract cancer
- Sarcoma
- Brain cancer
- Leukemia



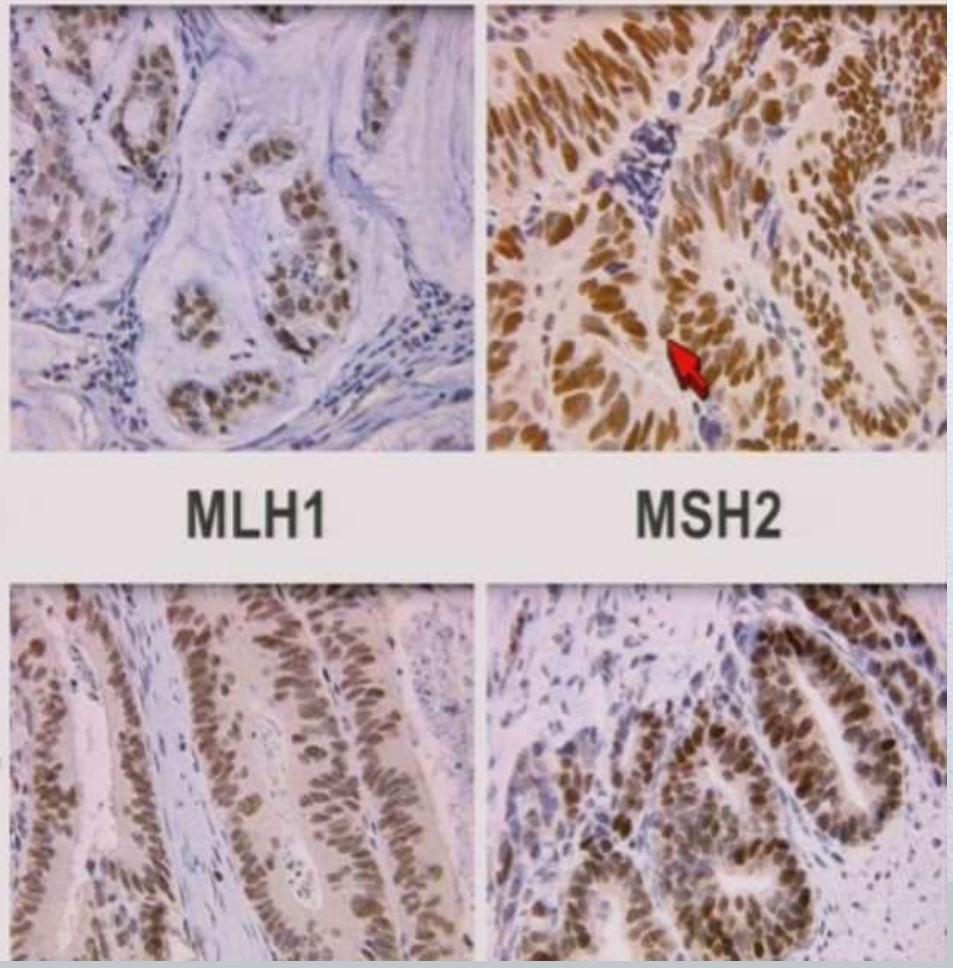
HNPCC

Cancer Type	General Population Risk	Lynch Syndrome (*MLH1* and *MSH2* heterozygotes)	
		Risk	Mean Age of Onset
Colon	5.5%	52%-82%	44-61 years
Endometrium	2.7%	25%-60%	48-62 years
Stomach	<1%	6%-13%	56 years
Ovary	1.6%	4%-12%	42.5 years
Hepatobiliary tract	<1%	1.4%-4%%	Not reported
Urinary tract	<1%	1%-4%	~55 years
Small bowel	<1%	3%-6%	49 years
Brain/central nervous system	<1%	1%-3%	~50 years
Sebaceous neoplasms	<1%	1%-9%	Not reported

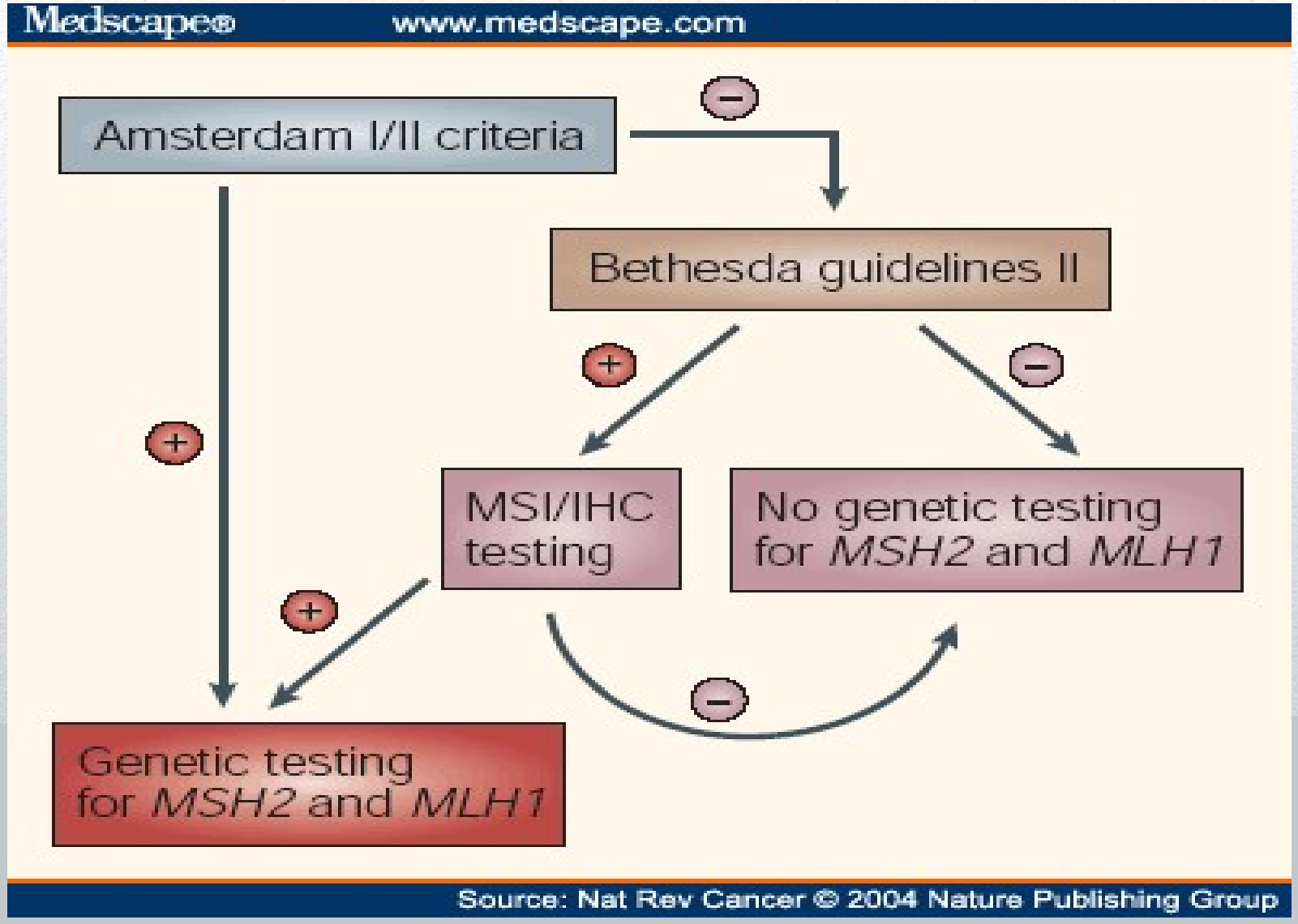


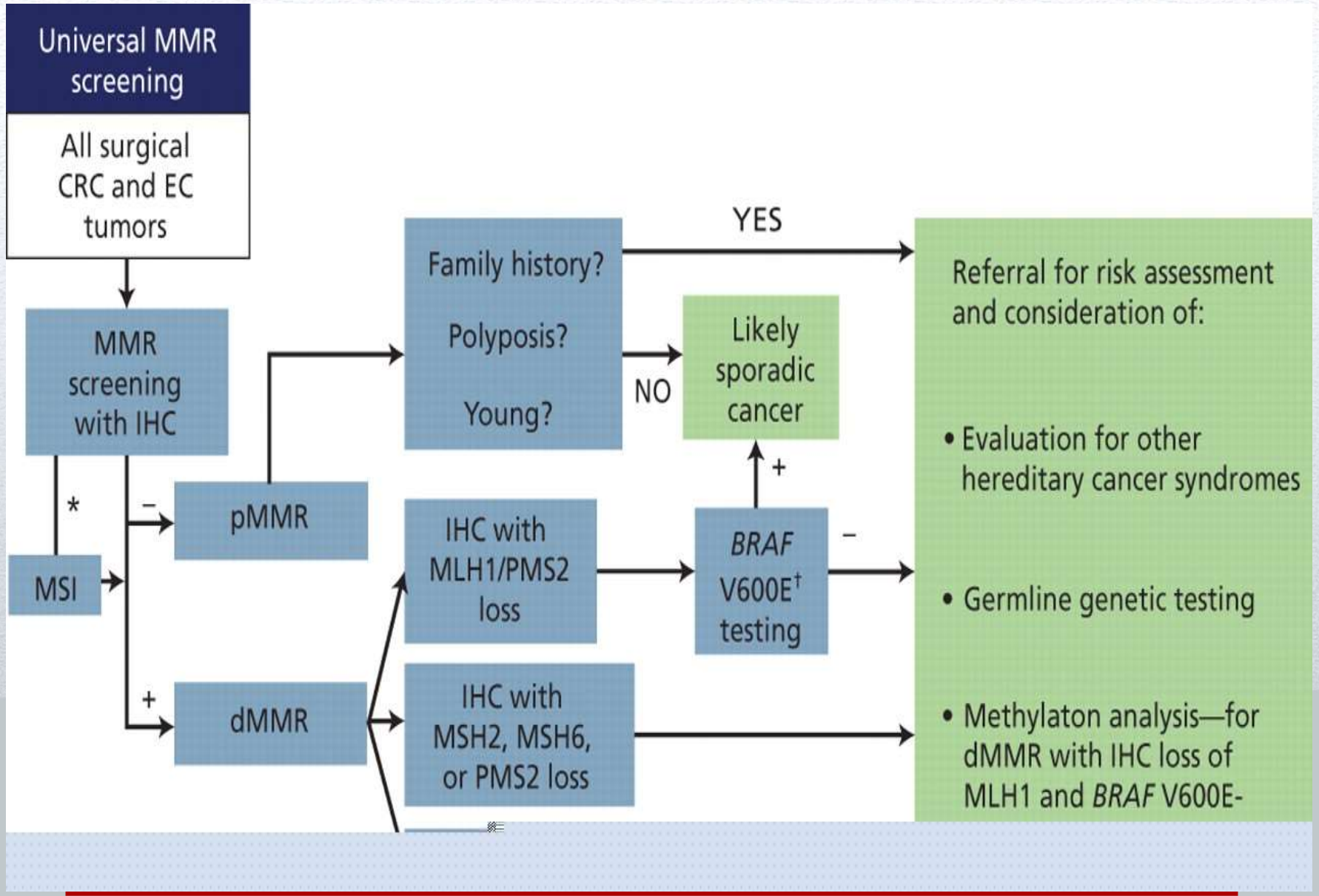
MSI TESTING

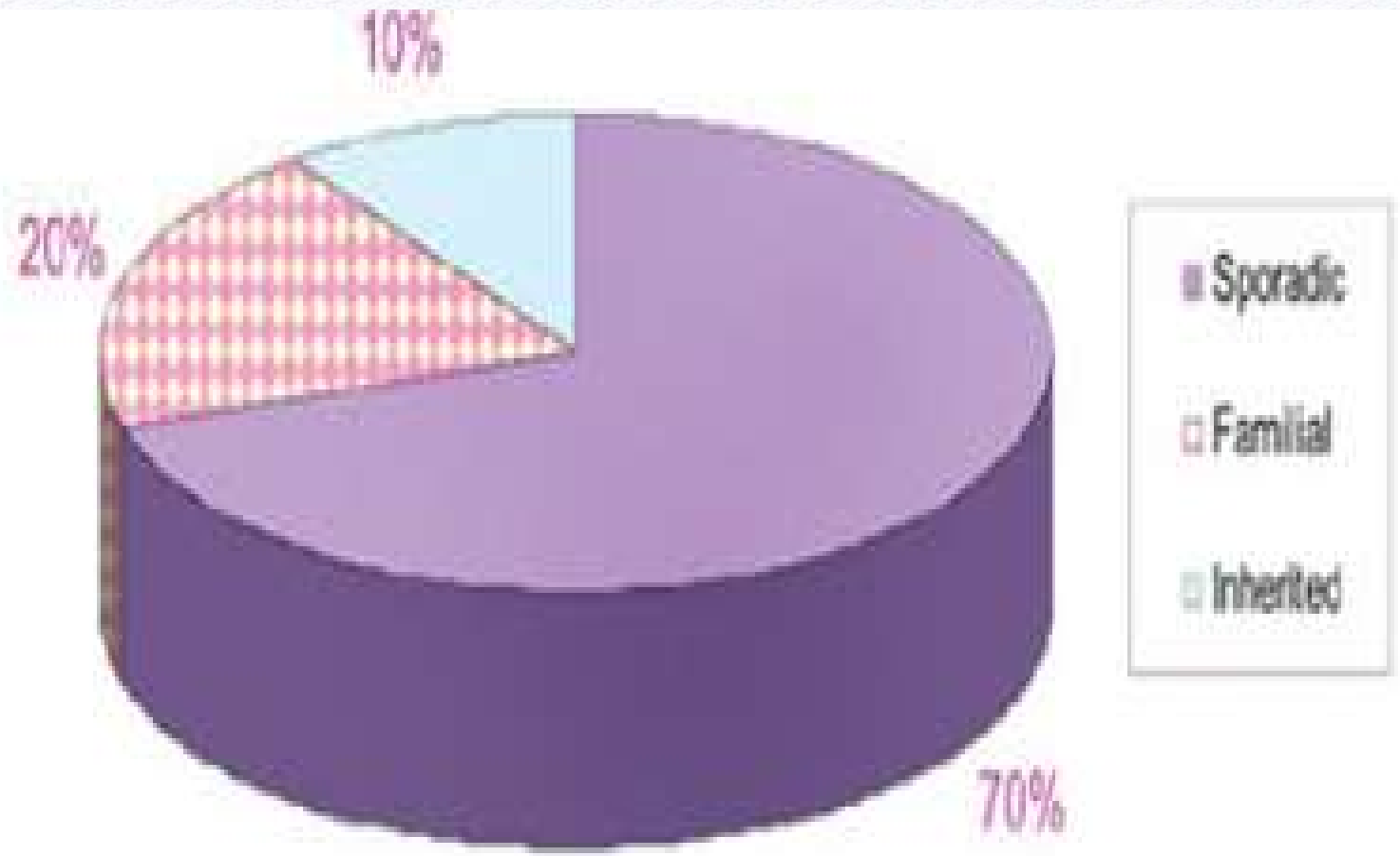
- Identify MMR proteins
- Normally present
- If protein is absent, gene is not being expressed (mutation or methylation)
- Helps direct gene testing by predicting likely involved gene
- If abnormal IHC (absent), MSI+



IHC FOR MMR PROTEIN


Medscape®
www.medscape.com
Amsterdam I/II criteria
Bethesda guidelines II
MSI/IHC testing
No genetic testing for *MSH2* and *MLH1*
Genetic testing for *MSH2* and *MLH1*
Source: Nat Rev Cancer © 2004 Nature Publishing Group


Universal MMR screening
All surgical CRC and EC tumors
MMR screening with IHC
*
MSI
–
pMMR
+
dMMR
Family history?
Polyposis?
Young?
YES
NO
Likely sporadic cancer
IHC with MLH1/PMS2 loss
IHC with MSH2, MSH6, or PMS2 loss
+
BRAF V600E† testing
–
Referral for risk assessment and consideration of:
• Evaluation for other hereditary cancer syndromes
• Germline genetic testing
• Methylaton analysis—for dMMR with IHC loss of MLH1 and BRAF V600E-

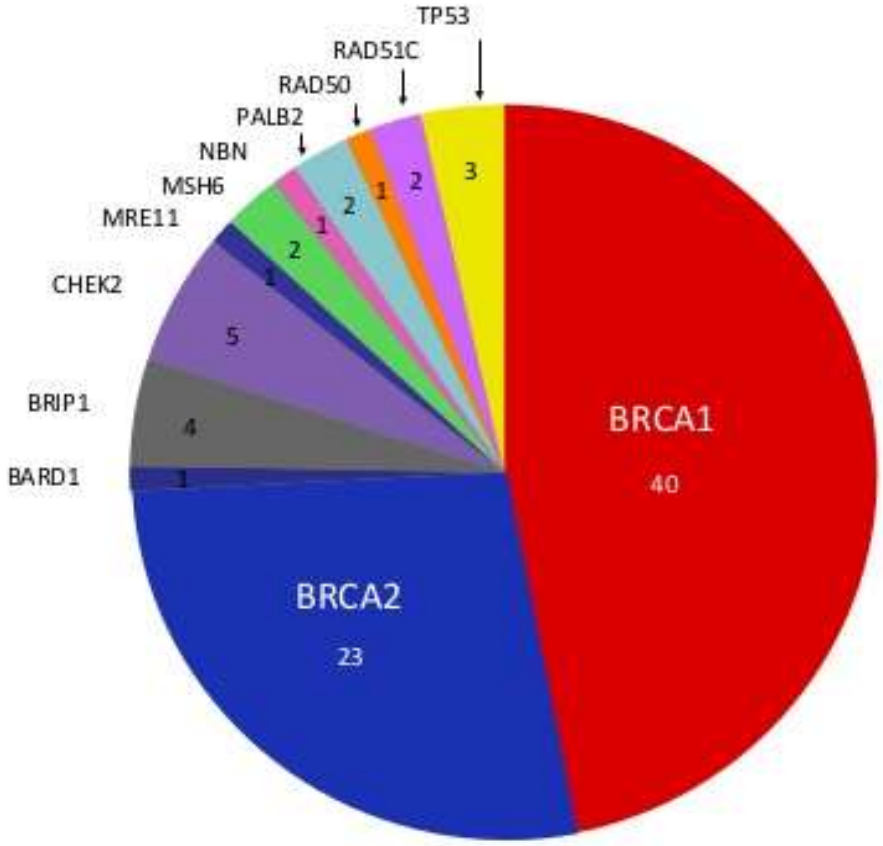


-Sporadic breast/ovarian cancer: Occurs by chance

-Familial breast/ovarian cancer: Multiple shared genes and environmental factors

BRCA1/BRCA2 mutations in ovarian cancer (UW, Seattle, USA)

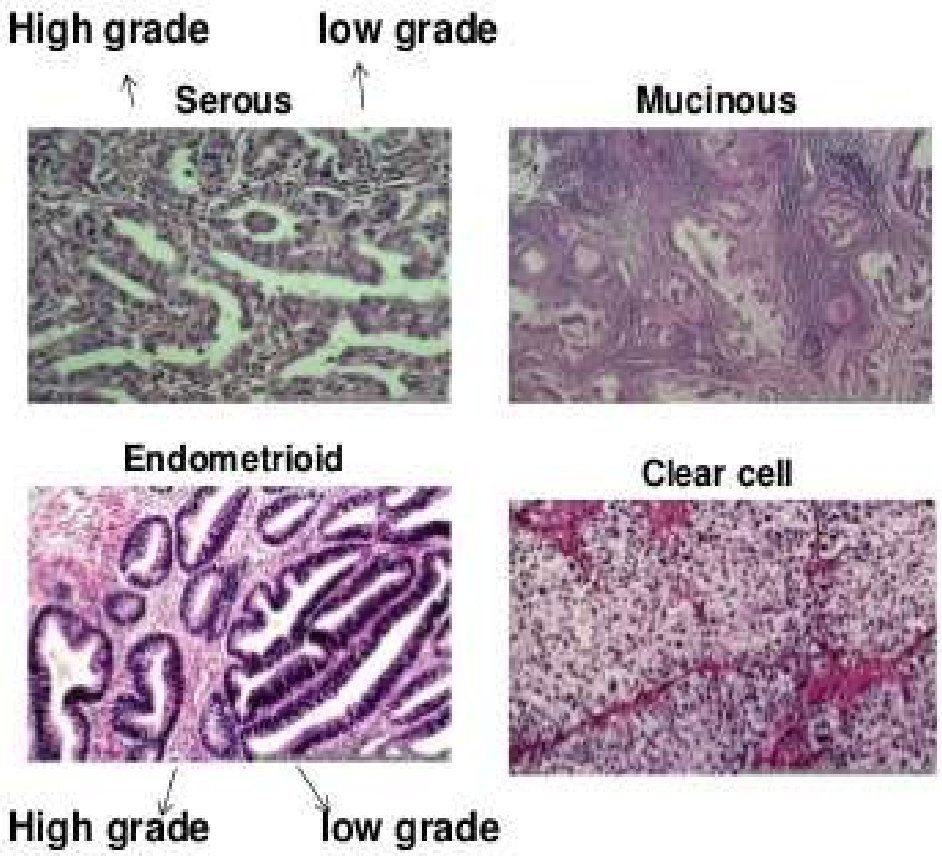
Ovarian cancer: BRCA1/BRCA2 mutations in **63/360 (18%)** patients not selected for family history or age at onset



Walsh, Swisher et al. *PNAS* 2011

Courtesy of MC King, UW

DIFFERENT HISTOLOGICAL SUBTYPES OF OVARIAN CANCER INDICATE DIFFERENT THERAPEUTIC OPPORTUNITIES



Low grade serous
KRAS

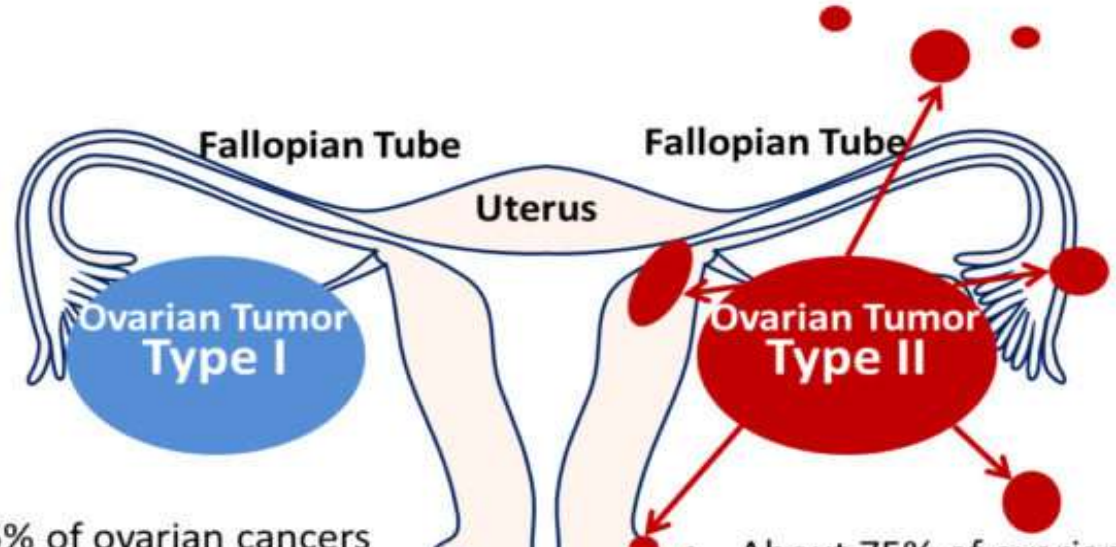
Clear Cell
PIK3CA mutations

Endometrioid
ARID1A mutation and deletion

Mucinous
Probably metastatic colon

High grade serous
p53, BRCA1/2 copy number
long tail of actionable mutations

Targeted agents
Bevaczumib
PARP inhibitors have now been FDA approved



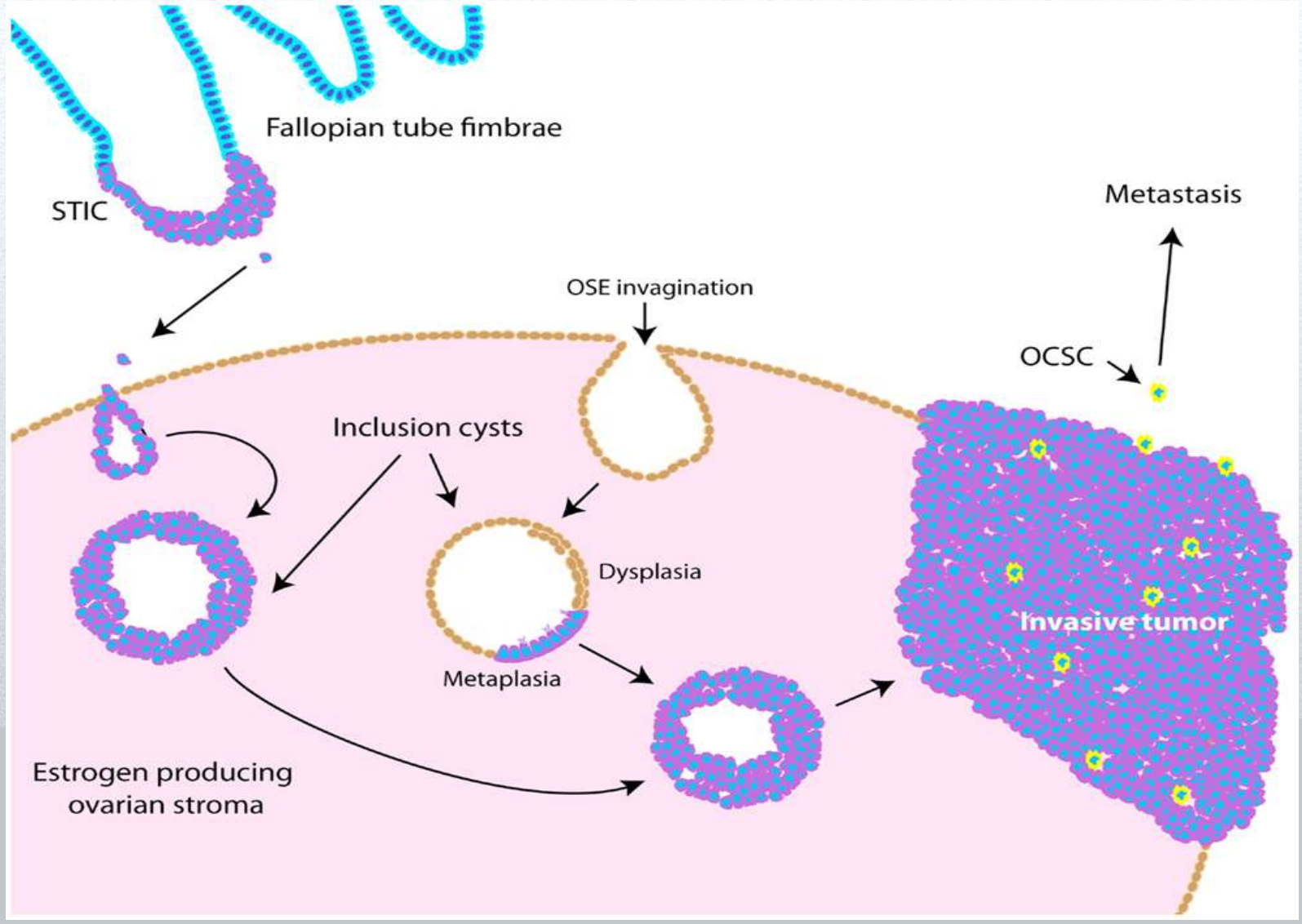
- About 25% of ovarian cancers
- Usually present at stage I (confined to ovary)
- Prognosis excellent 90% survival rate
- Slow growth
- TP53 mutations absent
- Early detection possible
- Risk factor – endometriosis in some cases

- About 75% of ovarian cancers
- Present at advanced stage Metastases beyond ovary (small red circles)
- Prognosis poor 30% survival rate
- Fast growth
- TP53 mutations present
- Early detection very difficult
- Risk factor – BRCA mutation in some cases (usually inherited)

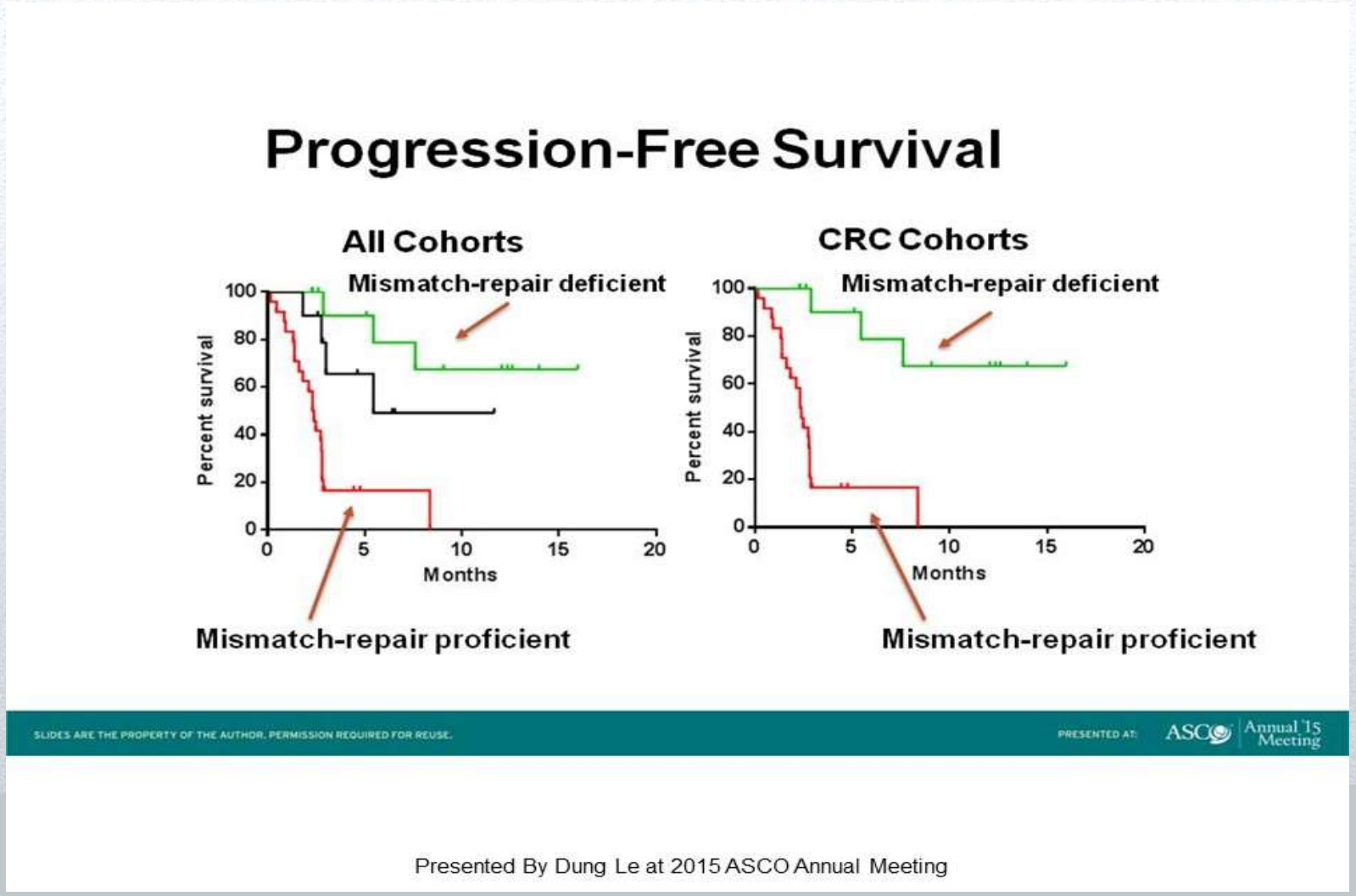
Kurman and Shih, Am J Pathol 2016

Ovarian cancer paradox

- More than 90% of BRCA carrier who became symptomatic had ovarian CA
- More than 70-80% of SO specimen from women opted for prophylaxis had FT cancer

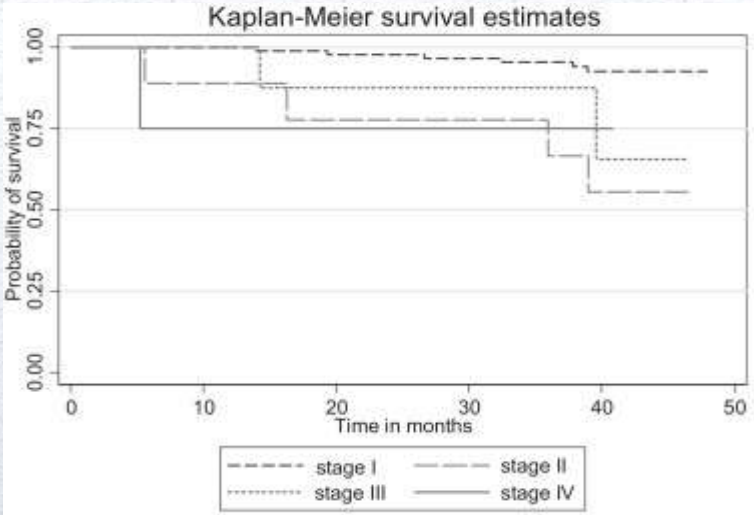

Fallopian tube fimbrae
STIC
Metastasis
OSE invagination
OCSC
Inclusion cysts
Dysplasia
Invasive tumor
Metaplasia
Estrogen producing
ovarian stroma

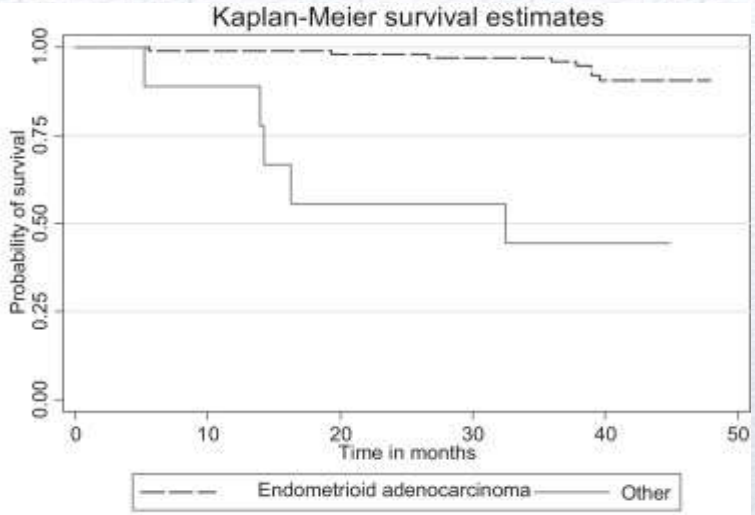
Cancer Profiling

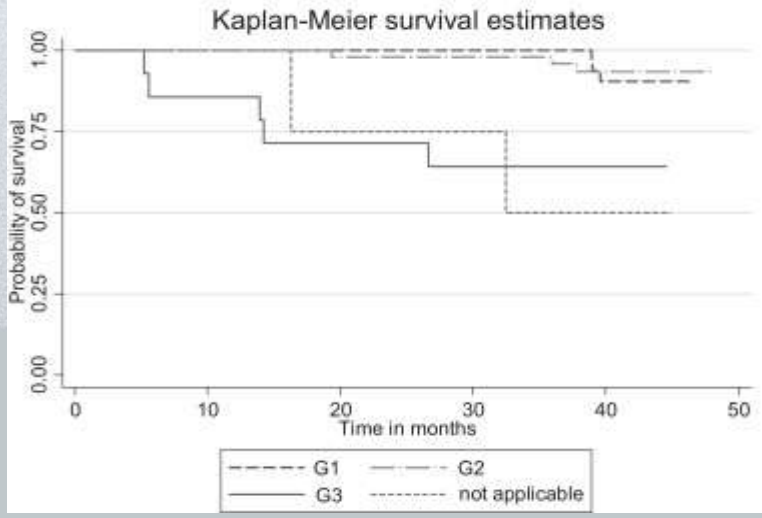


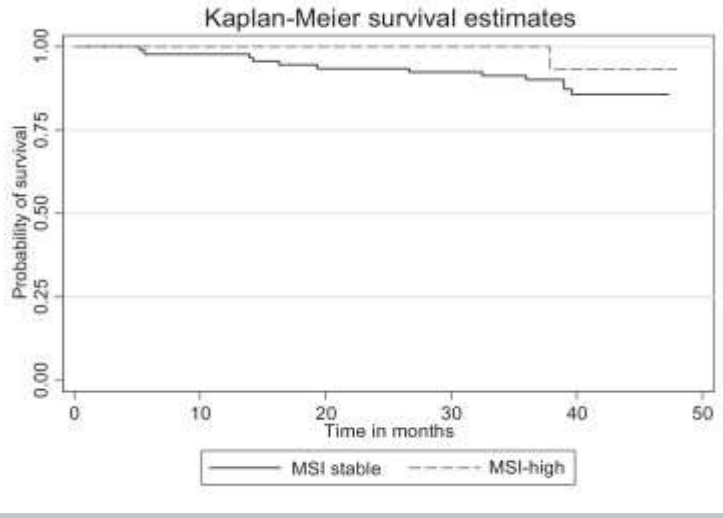
Presented By Dung Le at 2015 ASCO Annual Meeting

MSS vs MSI survival CRC



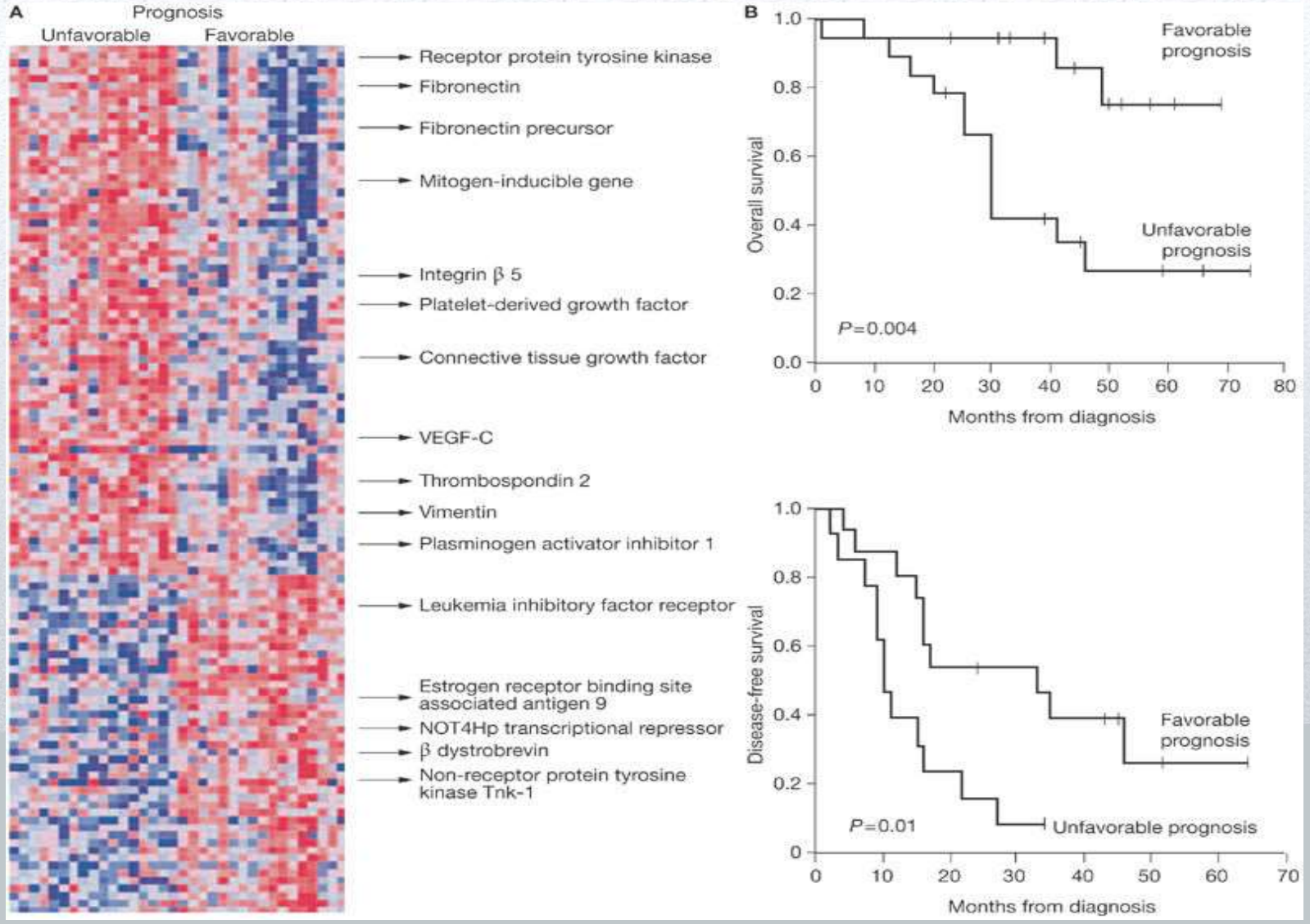




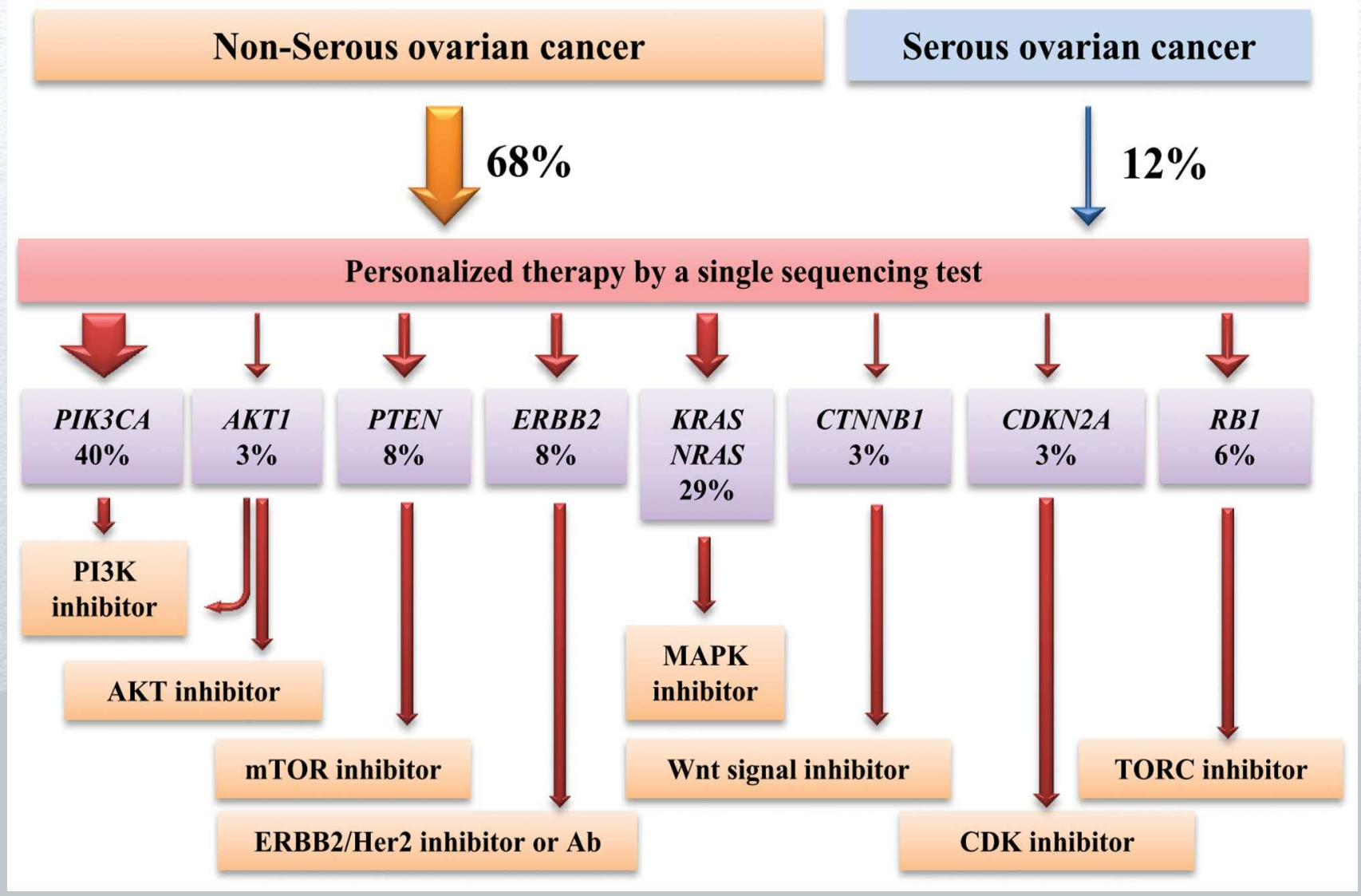


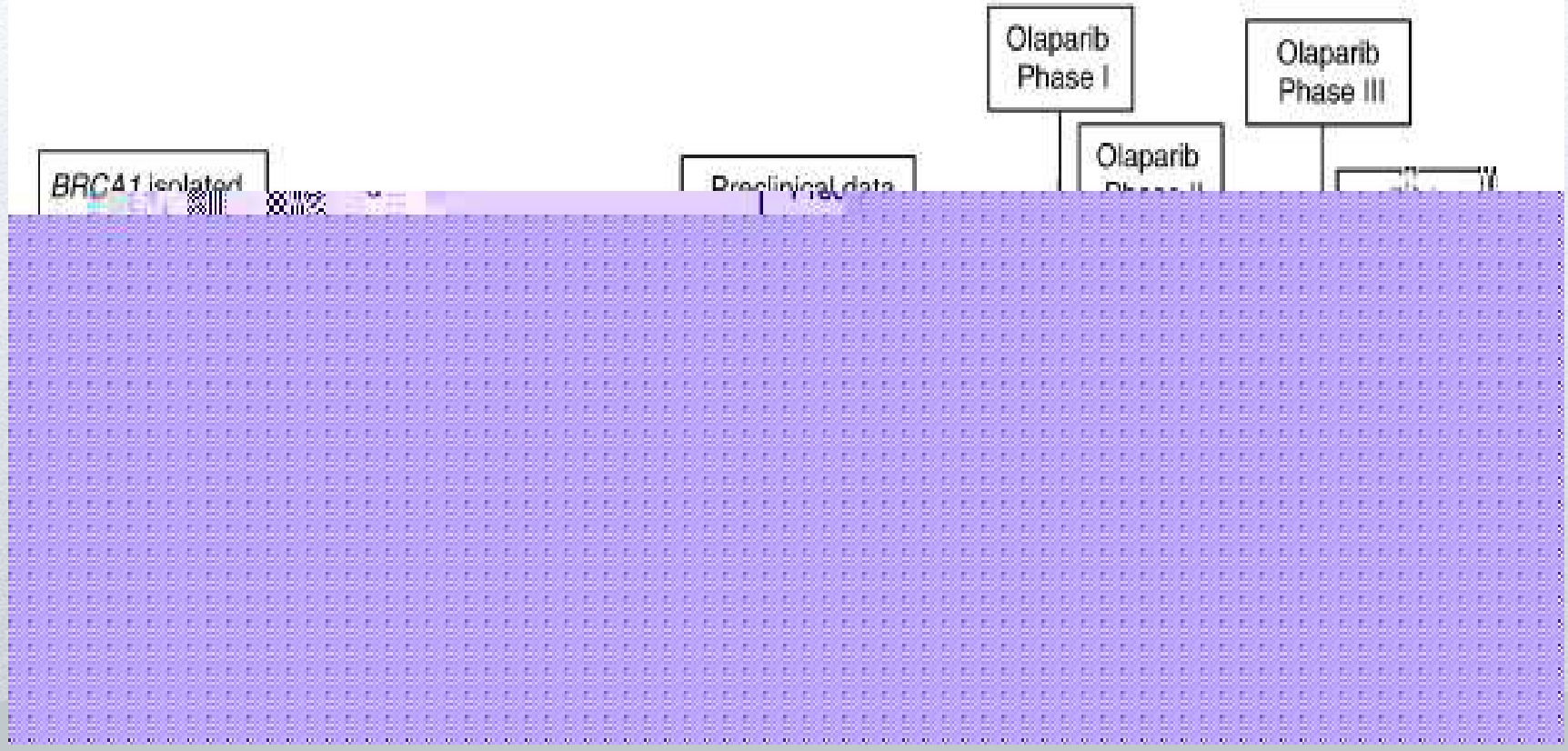
MSS vs MSI survival EC

Nature Clin Prac Oncol 2008

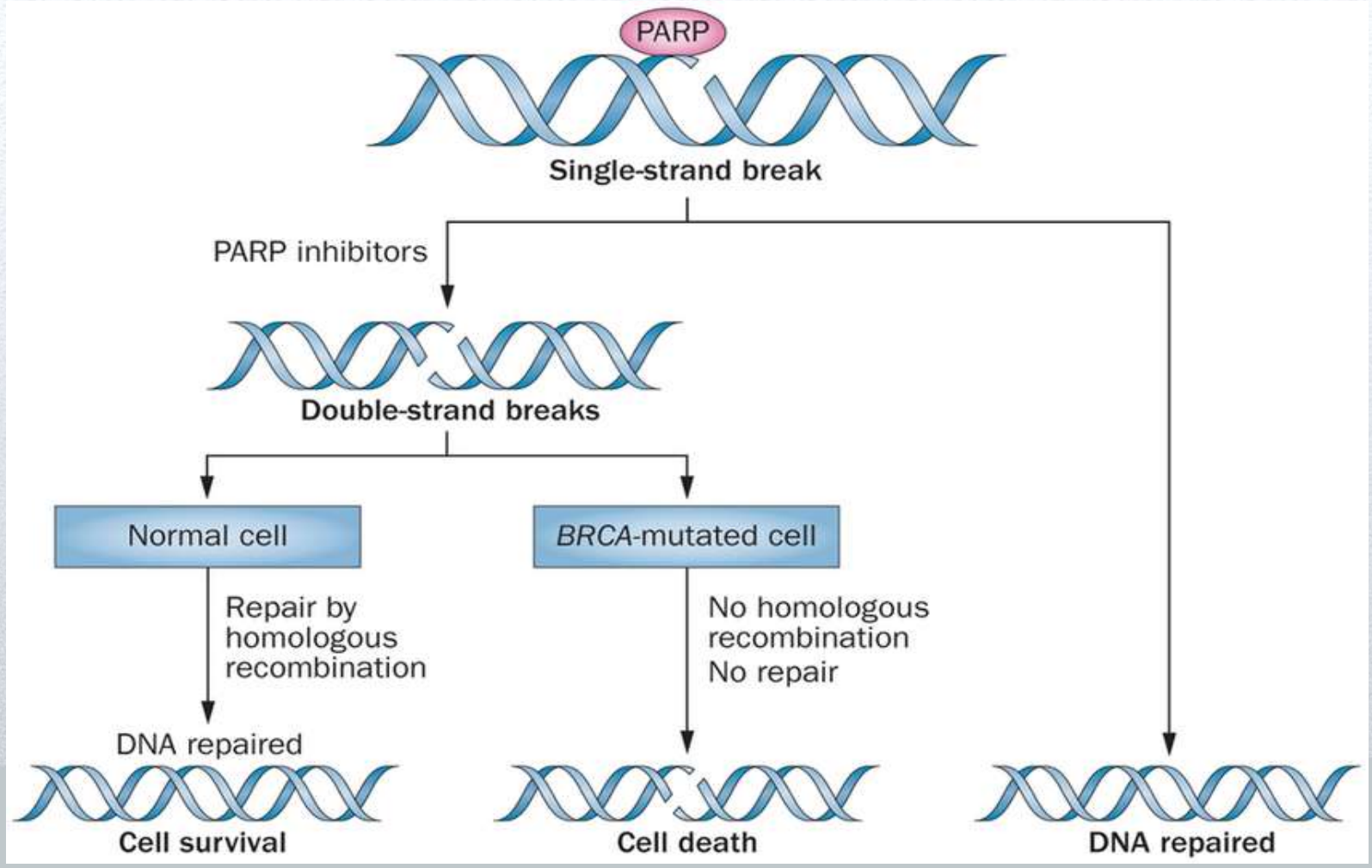


OVARIAN CANCER EXPRESSION PROFILING


Non-Serous ovarian cancer
Serous ovarian cancer
68%
12%
Personalized therapy by a single sequencing test
PIK3CA 40%
AKT1 3%
PTEN 8%
ERBB2 8%
KRAS NRAS 29%
CTNNB1 3%
CDKN2A 3%
RB1 6%
PI3K inhibitor
AKT inhibitor
mTOR inhibitor
ERBB2/Her2 inhibitor or Ab
MAPK inhibitor
Wnt signal inhibitor
CDK inhibitor
TORC inhibitor



Jarboe et al. Pathology of BRCA related ovarian cancer. 2008



Synthetic Lethality

Translating DNA test to Clinics

- To whom the test should be offered ?
- Which test to offer ?
- When and How to offer DNA test ?
- What are pros and cons of DNA testing in each patient ?
- What to do once the test result is available ?

- DIANGOSTIC TESTING IN AFFECTED MEMBER
- DIAGNOSTIC TESTING IN ASYMPTOMATIC MEMBER

The Use of Genetic Testing in Ovarian CA

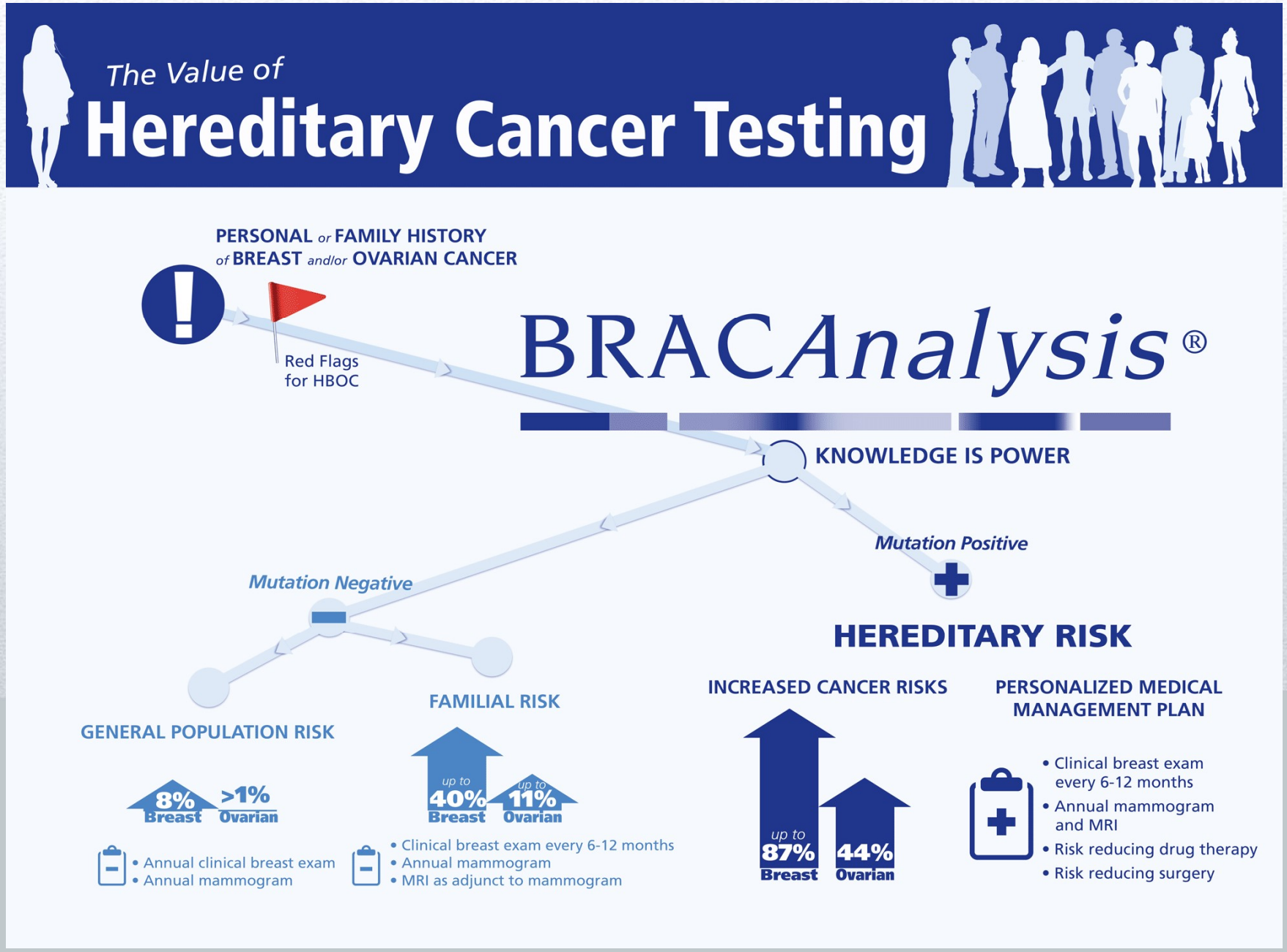
medical
genetic testing

tests in people
who are ill

predictive
genetic testing

tests in people
who are well

To whom the test should be offered ?


The Value of
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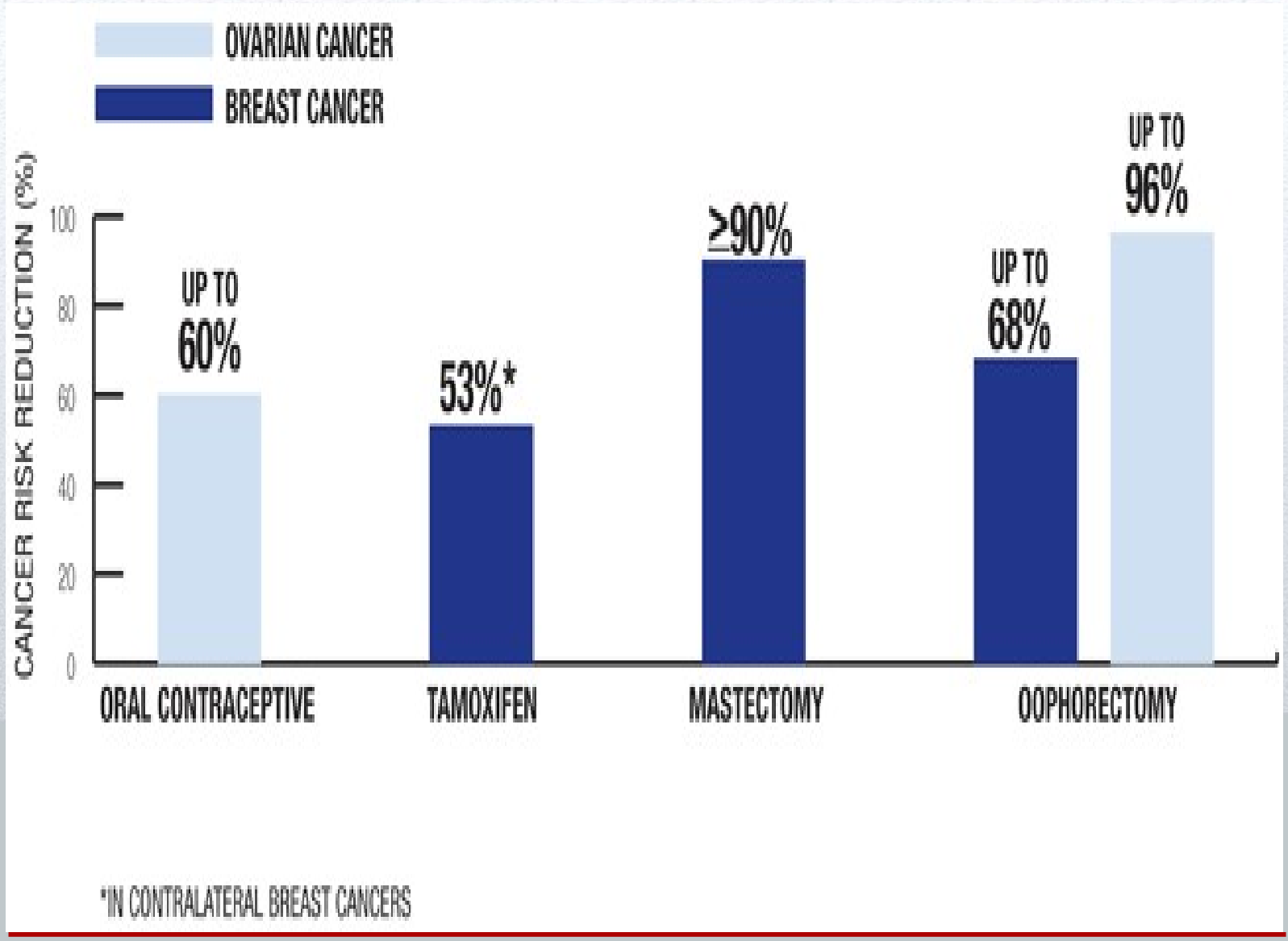
PERSONAL or FAMILY HISTORY
of BREAST and/or OVARIAN CANCER
Red Flags
for HBOC
BRACAnalysis®
KNOWLEDGE IS POWER
Mutation Positive
Mutation Negative
HEREDITARY RISK
INCREASED CANCER RISKS
PERSONALIZED MEDICAL
MANAGEMENT PLAN
FAMILIAL RISK
GENERAL POPULATION RISK
8% Breast
>1% Ovarian
up to 40% Breast
up to 11% Ovarian
up to 87% Breast
44% Ovarian
• Annual clinical breast exam
• Annual mammogram
• Clinical breast exam every 6-12 months
• Annual mammogram
• MRI as adjunct to mammogram
• Clinical breast exam every 6-12 months
• Annual mammogram and MRI
• Risk reducing drug therapy
• Risk reducing surgery



Data from Myriad Inc.

- GERMLINE MUTATION TESTING
  - SINGLE GENE TESTING
  - NGS PANEL GENE TESTING
  - FOUNDER MUTATION TESTING
- SOMATIC MUTATION TESTING
  - SINGLE GENE TESTING
  - NGS PANEL TESTING

Which Test to Offer ?

Evolution of Hereditary Cancer Risk Testing… from 2 Genes to Multi-Gene Panel Testing

Early 90's

-BRCA 1 and 2 Discovered by several scientists (Mary Claire King)

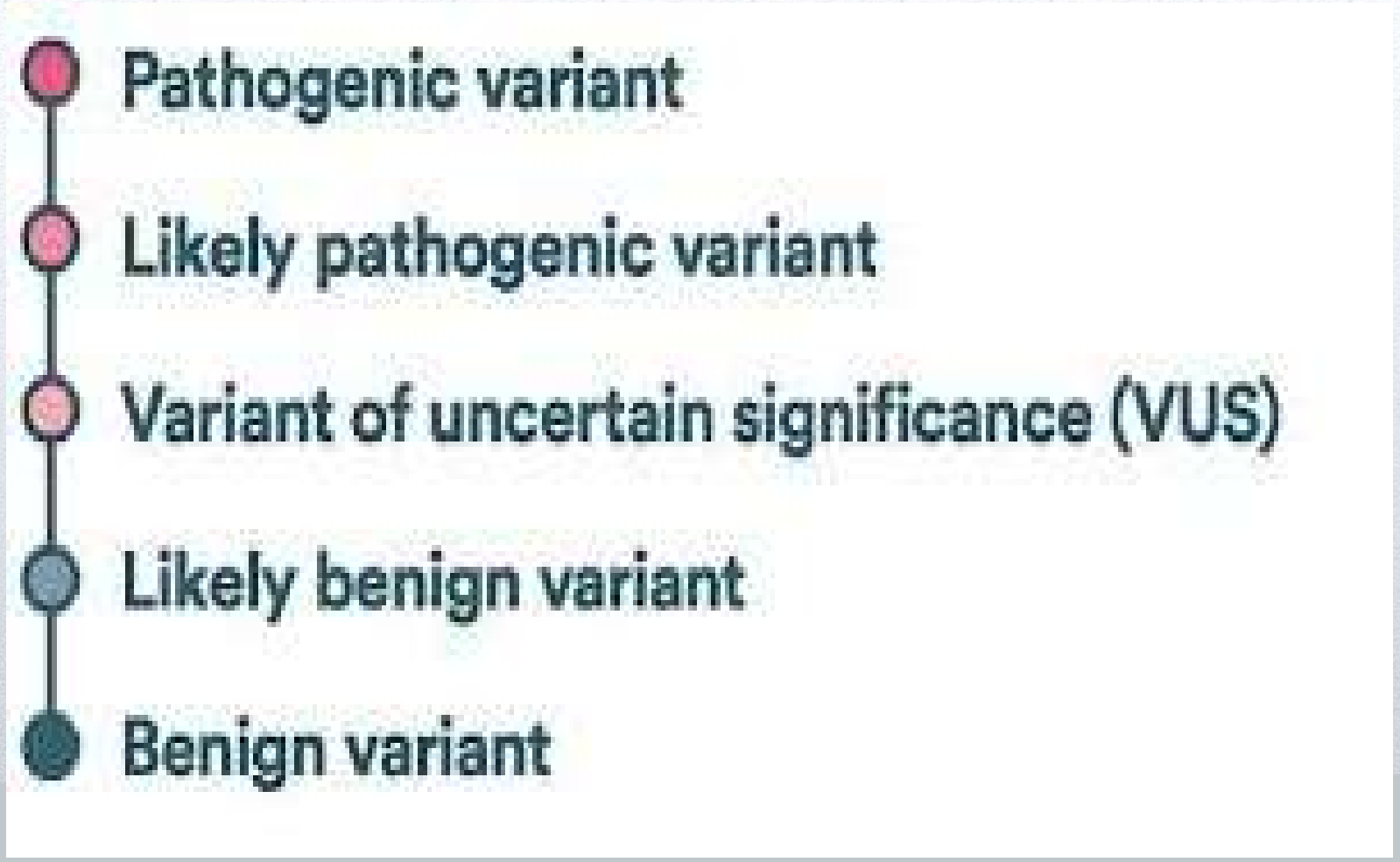
-Myriad granted a patent on the BRCA 1-2 Genes and has monopoly on market

-Myriad launched BRCAnalysis, a predictive medicine product for hereditary breast and ovarian cancer (testing BRCA 1-2) in 1996

-Supreme Court Overturns Myriad BRCA 1-2 Patent in June 2013 opening market to other labs (Ambry, GeneDx, LabCorp, Quest, etc)

-Move FROM just testing for BRCA 1&2 to Multiple Gene Testing

GeneID
The Future Today



VARIANT CLASSIFICATION RESULT

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a]

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
PALB2	**Increased risk of BC** • Screening: Annual mammogram and consider breast MRI with contrast at 30 y • RRM: Consider based on family history.	**Unknown or insufficient evidence for OC risk**	Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	**Increased risk of BC** • See Cowden Syndrome Management	**No increased risk of OC**	See Cowden Syndrome Management
RAD51C	**Unknown or insufficient evidence for BC risk**	**Increased risk of OC** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
RAD51D	**Unknown or insufficient evidence for BC risk**	**Increased risk of OC** • Consider RRSO at 45–50 y	N/A
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
STK11	**Increased risk of BC** • Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal • RRM: Evidence insufficient, manage based on family history.	**Increased risk of non-epithelial OC** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
TP53	**Increased risk of BC** • See Li-Fraumeni Syndrome Management	**No increased risk of OC**	See Li-Fraumeni Syndrome Management

[a]Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol 2016;13:581-588.

BC: Breast cancer
OC: Ovarian cancer
RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

- OF 24 DISORDERS THAT ARE DEEM TO BE APPROPRIATE FOR REPORTING INCIDENTAL VARIANT FINDING FROM EXOME SEQUENCING, 16 ARE HEREDITARY CANCER SYNDROMES
- HBOC, FAP, LFS, PJS, LS, MYHAP, VHL, MEN1, MEN2, FMTC, PTEN-HAMARTOMA TUMOR S, RETINOBLASTOMA, HEREDITARY PARAGANGLIOMA/PHEOCHROMOCYTOMA, TS, T1-WILMS TUMOR

ACMG RECOMMENDATION FOR REPORTING OF INCIDENTAL FINDING IN CLINICAL EXOME AND GENOME SEQUENCING 2013

Genetic counseling

- The process by which a counsellor provides relevant information (informative) to counselee about disease burden, etiology, and investigative and therapeutic options (advocacy) in order for the counselee to be able to make informed decision regarding his or her own health

- Valid medical evaluation and test result
- Understandable information
- Clear layout of pros ad cons of each options
- Ability of counselee to make unbiased non-directive choices
- Co-ordinated care path
- Good follow up plan

Factor influencing Successful genetic counseling

Steps of genetic counselling for ovarian cancer

- First genetic evaluation
  - Pedigree construction, Risk estimation
- Pre-test counselling
  - Pros and cons of undergoing DNA testing
- Post-test counselling
  - Result and prophylactic options

Obtaining and giving information in the first visit

- 3 generation pedigree
- History of relevant cancer : ovarian, breast, prostate, pancreatic, melanoma, colon
- Patient perception regarding the likelihood of her cancer being hereditary
- Patient readiness to discuss about genetics
- Initial opinion regarding the risk of “being hereditary”

- When and How to offer DNA test ?
- To whom the test should be offered ?
- Which test to offer ?
- What are pros and cons of DNA testing in each patient ?
- What to do once the test result is available ?

Pre-test counseling consideration

When and How to offer DNA testing ?

- When : Suspicion by family history
  Suspicion by personal history
  Indication for target therapy
  Population testing

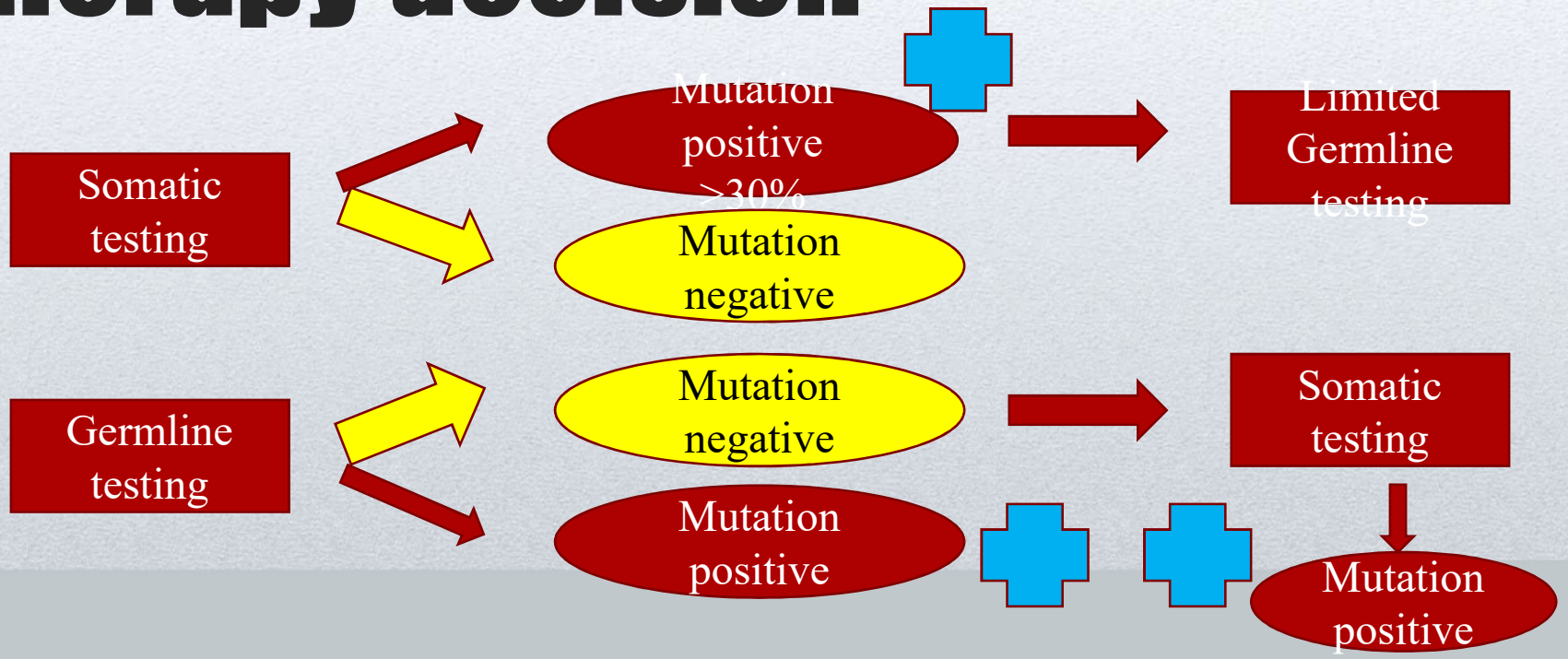
- How : By oncologist with or without detailed counseling
  By clinical geneticist/ counselor with detailed counseling

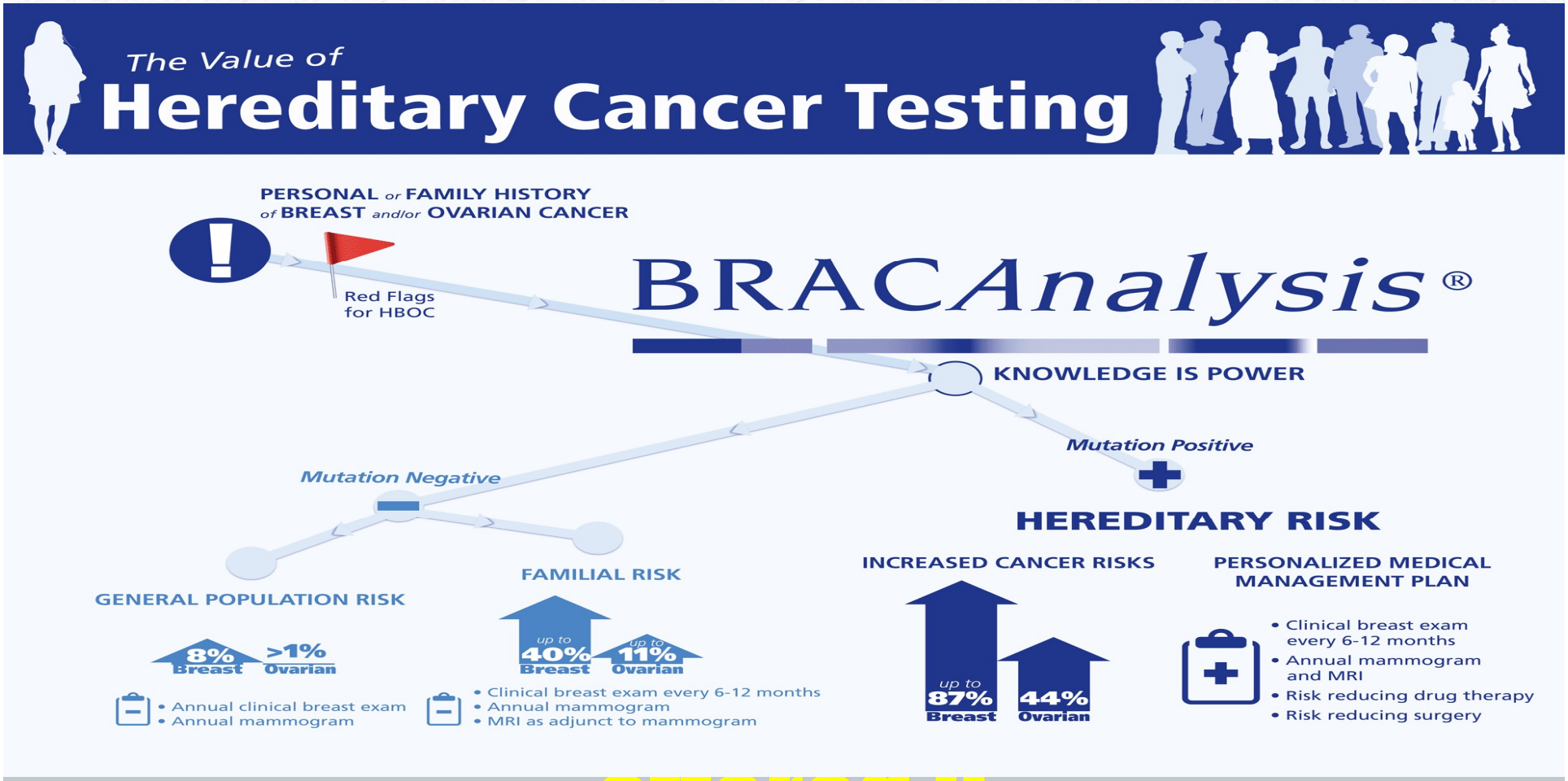
Special circumstance counseling

- DNA test guided target therapy : Olaparib
- Synthetic lethality concept
- Somatic (tumor) vs Germline (blood) testing
- Patients with positive result of somatic testing may need to undergo germline testing

- Offering somatic testing first have benefits over germline first

Testing algorithm for target therapy decision

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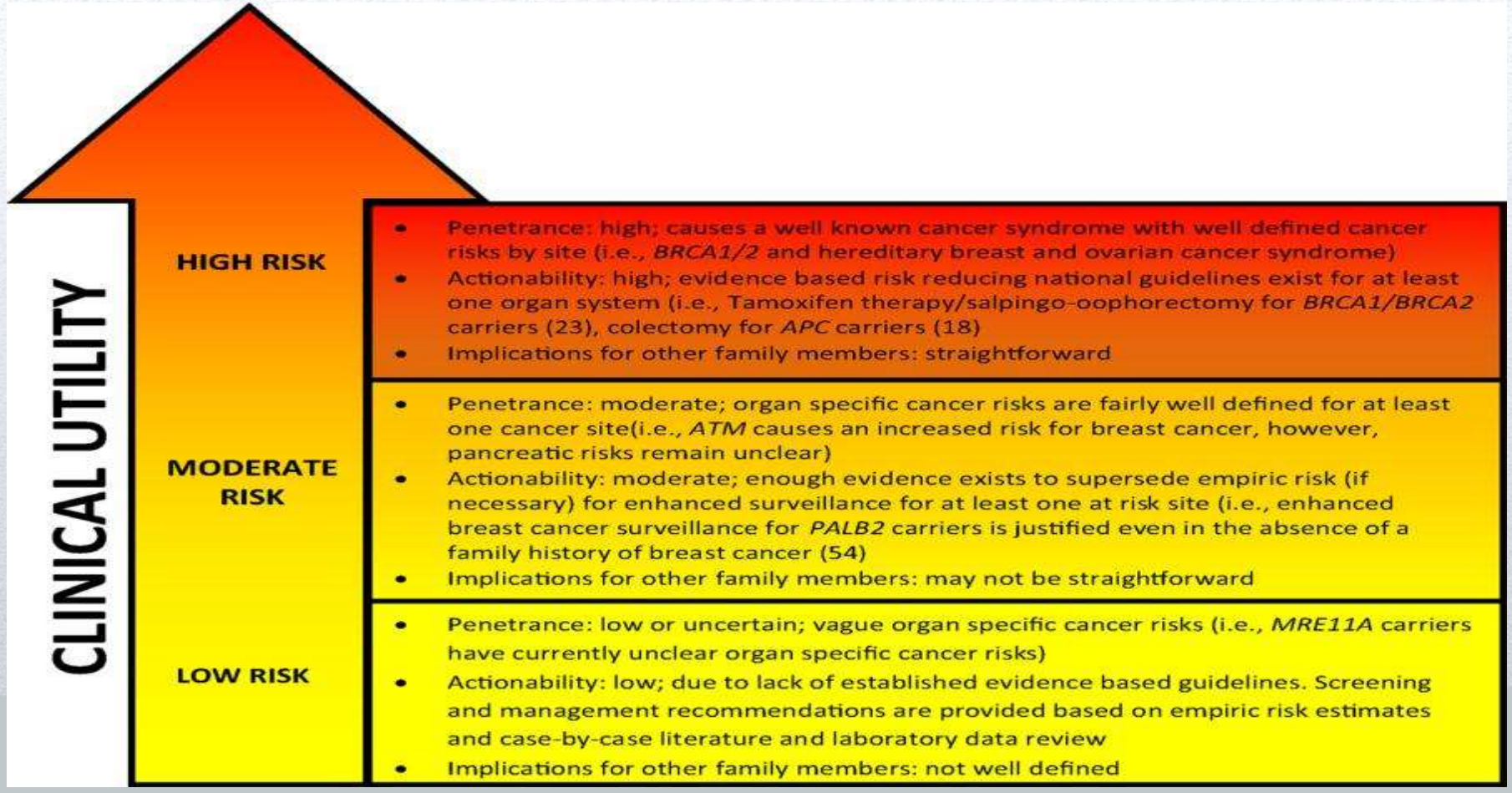
Mutation Negative
HEREDITARY RISK
INCREASED CANCER RISKS
PERSONALIZED MEDICAL
MANAGEMENT PLAN
GENERAL POPULATION RISK
8% Breast
>1% Ovarian
• Annual clinical breast exam
• Annual mammogram
FAMILIAL RISK
up to 40% Breast
up to 11% Ovarian
• Clinical breast exam every 6-12 months
• Annual mammogram
• MRI as adjunct to mammogram
up to 87% Breast
44% Ovarian
• Clinical breast exam every 6-12 months
• Annual mammogram and MRI
• Risk reducing drug therapy
• Risk reducing surgery

offered ?

Test	Use	Strengths	Limitations
Capillary (Sanger) sequencing	Sequencing of small genomic regions, e.g. individual exons	Highly accurate	Low throughput, labour intensive, expensive
Panel testing using next-generation sequencing	Simultaneous sequencing of genes causing a particular phenotype (up to several hundred genes)	Allows multipanel gene testing Useful in heterogeneous conditions	Needs adjusting when new genes are discovered, and coverage of each gene may not be as good as capillary sequencing
Array CGH	Detection of large structural chromosome rearrangements	Highly accurate, high throughput	
Exome sequencing	Simultaneous sequencing of all coding regions of the genome	Streamlines lab workflow and useful extension of the panel test	Coverage of some genes is inadequate, no information on structural rearrangements
Genome sequencing	Sequencing of the whole genome	More even coverage of all genes	Expensive, data storage and analysis costs are high, and non-coding regions hard to interpret


CLINICAL UTILITY
HIGH RISK
MODERATE RISK
LOW RISK
• Penetrance: high; causes a well known cancer syndrome with well defined cancer risks by site (i.e., *BRCA1/2* and hereditary breast and ovarian cancer syndrome)
• Actionability: high; evidence based risk reducing national guidelines exist for at least one organ system (i.e., Tamoxifen therapy/salpingo-oophorectomy for *BRCA1/BRCA2* carriers (23), colectomy for *APC* carriers (18)
• Implications for other family members: straightforward
• Penetrance: moderate; organ specific cancer risks are fairly well defined for at least one cancer site(i.e., *ATM* causes an increased risk for breast cancer, however, pancreatic risks remain unclear)
• Actionability: moderate; enough evidence exists to supersede empiric risk (if necessary) for enhanced surveillance for at least one at risk site (i.e., enhanced breast cancer surveillance for *PALB2* carriers is justified even in the absence of a family history of breast cancer (54)
• Implications for other family members: may not be straightforward
• Penetrance: low or uncertain; vague organ specific cancer risks (i.e., *MRE11A* carriers have currently unclear organ specific cancer risks)
• Actionability: low; due to lack of established evidence based guidelines. Screening and management recommendations are provided based on empiric risk estimates and case-by-case literature and laboratory data review
• Implications for other family members: not well defined

Cancer site	High risk (odds$^{\theta}$ ≥5.0)	Moderate risk (≥2.0 odds$^{\theta}$ <5.0)	Low risk (≤2.0 odds$^{\theta}$ ≥1.0 or growing evidence of association)
Breast (female)	*BRCA1* (20), *BRCA2* (20), *CDH1* (21), *PTEN* (22), *STK11* (23, 24), *TP53* (25)	*ATM* (26, 27), *BRIP1* (28), *CHEK2* (29, 30), *PALB2* (31, 32)	*BAP1* (33), *BARD1* (34, 35), *RAD50* (36, 37), *RAD51C* (38), *RAD51D* (39, 40), *MRE11A* (36), *MUTYH* (41), *NBN* (42, 43), *XRCC2* (44, 45)
Colorectal	*APC* (46), *BMPR1A* (47), $^{\Psi}$*EPCAM* (48), *MLH1* (49), *MSH2* (49), *MSH6* (49, 50), **MUTYH* (51), *PMS2* (52), *SMAD4* (47), *STK11* (53)	*CHEK2* (54, 55), *PTEN* (56), *TP53* (25)	*CDH1* (57, 58), *EXO1* (59), *GALNT12* (60, 61), *MUTYH* (62, 63), *POLD1* (64), *POLE* (64)
Ovary	*BRCA1* (65), *BRCA2* (65), *MLH1* (66), *MSH2* (66), *STK11* (24)	*MSH6* (66), *PALB2* (32, 65), *RAD51C* (65, 67), *RAD51D* (39)	*BARD1* (65, 68), *BRIP1* (65), *CHEK2* (65), *MRE11A* (65), *MUTYH* (69), *NBN* (65), *RAD50* (65), *TP53* (65)

Due to study design variation, genetic risk categorization was extrapolated from odds ratios, relative risks, cumulative, or absolute cancer risks and presented as an estimate of the generalized odds (θ) over the baseline population for organ specific cancer risk. Genes in each category are in alphabetical order. Please see individual key reference for specific risk estimate method used. When study discrepancy, or wide reported confidence intervals were reported, expert opinion was used for the final risk categorization. The list is not exhaustive for breast, colorectal, and ovarian cancer predisposition. More studies, especially on moderate and low risk category genes will be needed to better clarify the associated cancer risks and penetrance. Single nucleotide polymorphism studies, which could add hundreds of gene and locus associations to the low risk category, were not included (70). Penetrance and expressivity can widely vary with specific mutations. Asterisk (*) denotes MUTYH biallelic mutation. ($^{\Psi}$) denotes deletions only affecting transcription of MSH2.

RELATIVE RISK GENE PANEL TESTING

Pros and Cons of DNA testing

- Positive information
  - Ability to know
  - Availability of prophylaxis
  - Ability to make autonomous health choice
  - Decrease uncertainty
- Negative information
  - Increase anxiety
  - Survivor guilt
  - Potential discrimination
  - Unwanted medical certainty
  - Secondary patients in family

- Detailed upfront counseling strategy : follow set plan for personal treatment and offer pre-test presymptomatic counseling to at risk family members

- Limited upfront counseling strategy : offer detailed counseling about germline mutation status and make plan according to client's wishes

What to do once the test result is available ?

Post-test counseling

- Mutation positive : Increased risk (life time risk OvCa 50%, BrCa 70%)
  - Increased risk of recurrence
  - Prophylactic measures are available
  - Presymptomatic test is available for family members
- Mutation negative : non-familial cancer -> risk is not significantly increased
  - Familial cancer -> risk may be increased
- VUS found : risk can not be accurately quantified by test alone but may be increased by family history

Risk reduction strategy

- Ov Ca : TAH/BSO -> 90% , BSO -> 90%, BO -> no reduction
  TM -> no reduction
  OCP -> 50% (>3-5 yrs use) but increase BrCa risk
- Br Ca : TM -> 99%-100% , Nipple sparing reconstruction -> 95%
  TAH/BSO, BSO -> 50%
  Tamoxifen /Raloxifene -> 50% but increase endometrial Ca risk

Conclusion

- Molecular genetics of Ovarian Cancer is much better understood
- Causative single genes as well as risk alleles are being increasingly indentified albeit not all with actionable guidelines
- Panel gene testing is likely to be more useful than single gene testing
- Molecular profiling can lead to better individualized targeted therapy
- How to translate DNA testing into clinics needs to be carefully considered

Conclusion

- Counseling for BRCA testing must be done by oncologist or clinical geneticist familiar with benefit as well as limitation of test
- Panel gene testing is likely to be more useful than single gene testing in usual scenario with exception of target therapy decision
- Somatic tumor testing is preferred for target therapy decision and could be given in conjuction with limited genetic counseling
- Germline blood testing is preferred for familial Br/Ov cancer patients