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National Alliance for Life and Heath Sciences

Institut National du Cancer

CONSIDERATIONS FOR THE ONCOLOGIST WHEN REFERRING FOR TESTING: WHICH TESTS ARE AVAILABLE AND WHY ?

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The author has no conflict of interest to declare

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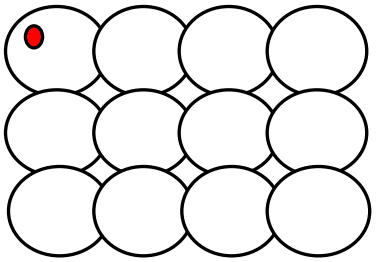
iRiB

Normandie Université

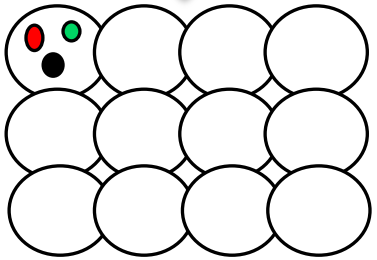
Cancéropôle Nord-Ouest

MOLECULAR BASES OF CANCER AND MEDICAL BENEFITS OF GENETIC TESTING

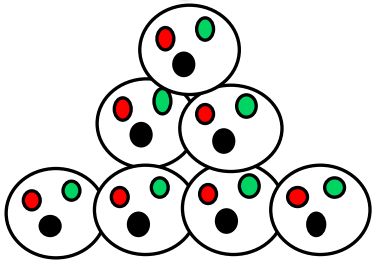
Somatic mutation



Somatic mutations

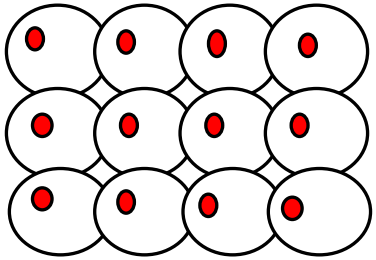


Targeted therapies

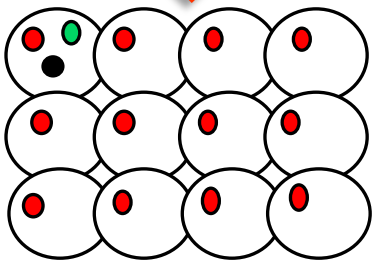


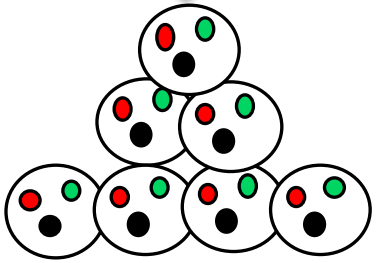
Sporadic form of cancer

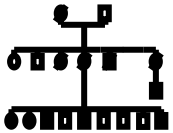
Germline mutation



Somatic mutations



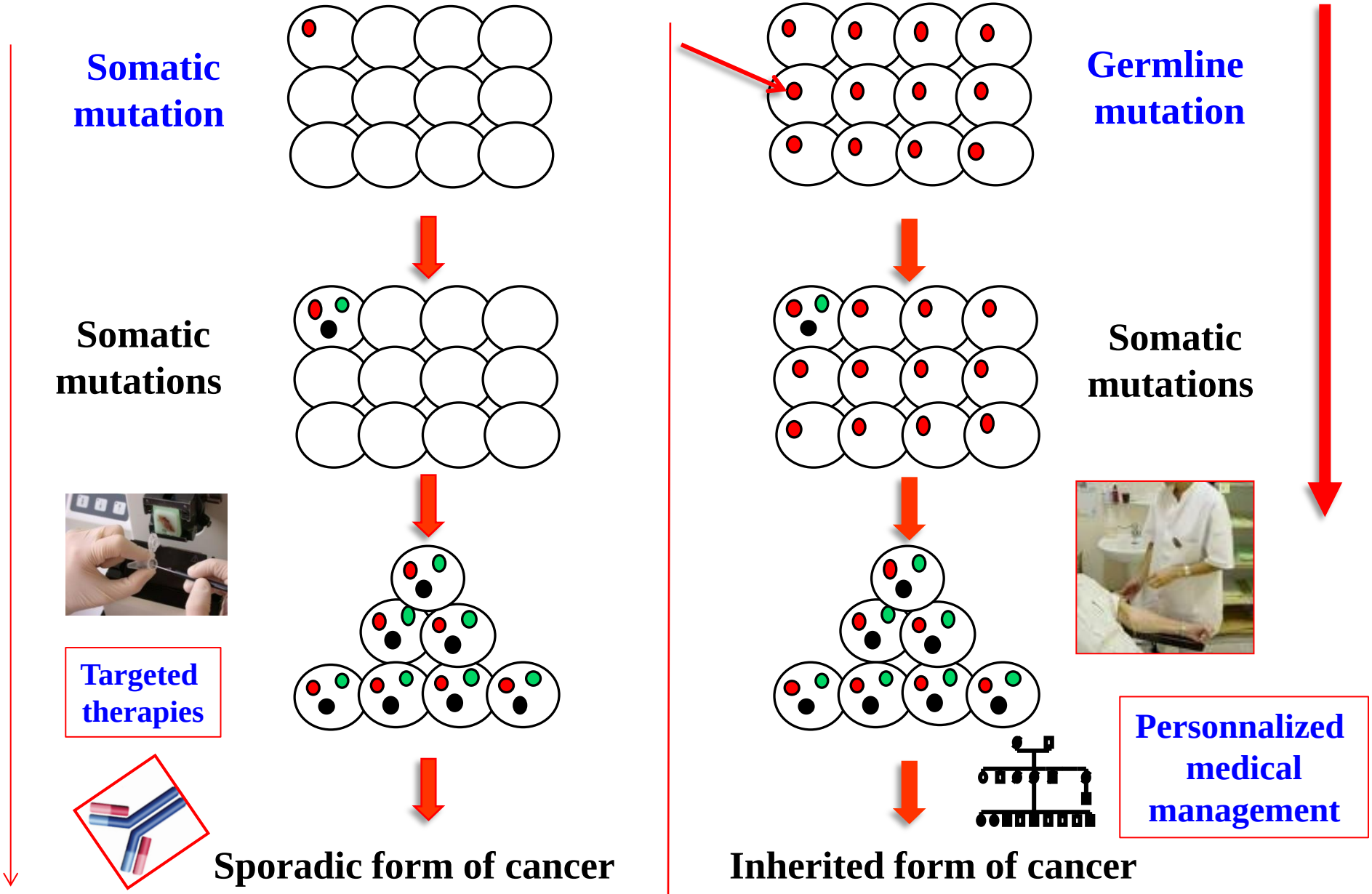




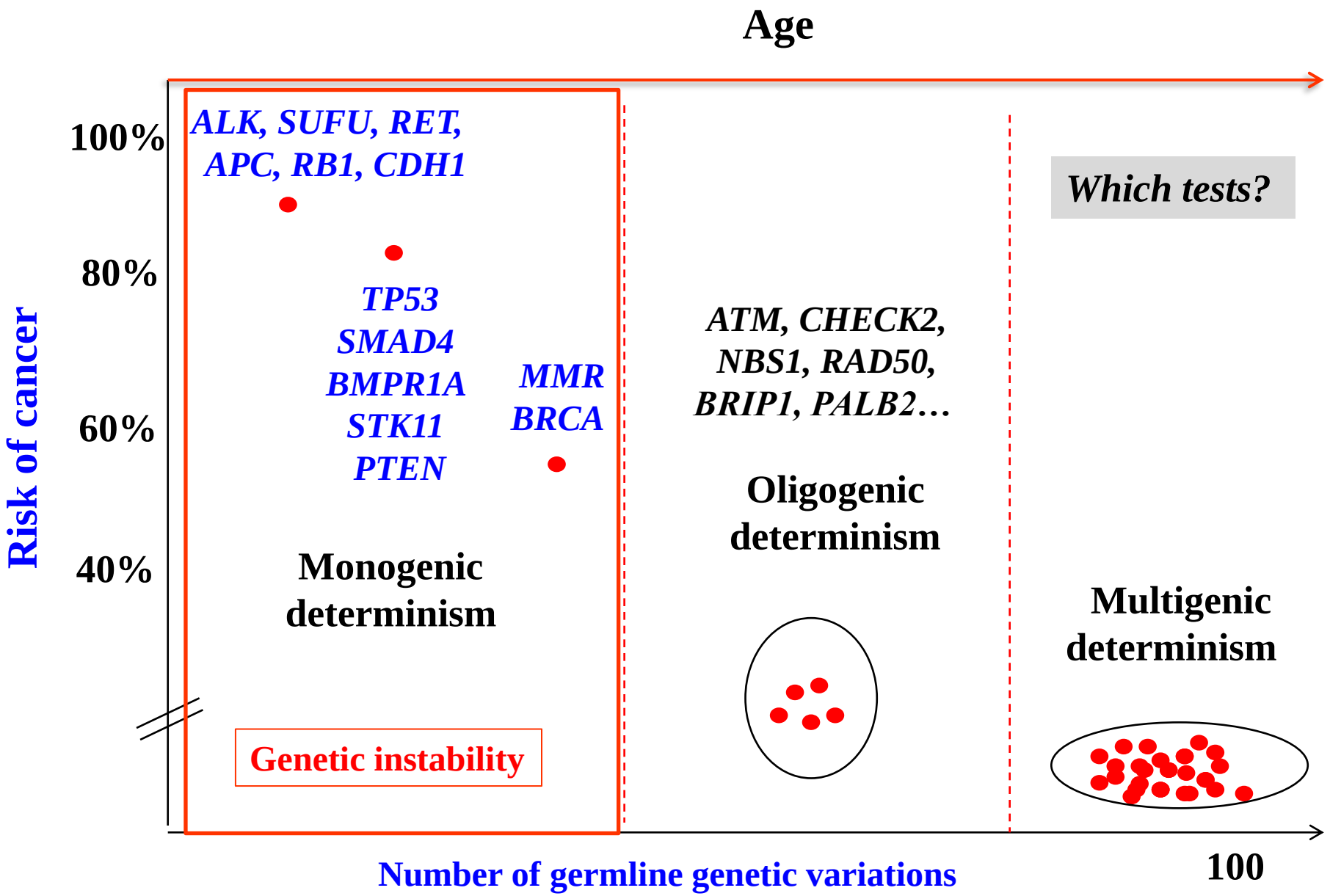
Personnalized medical management

Inherited form of cancer

MOLECULAR BASES OF CANCER AND MEDICAL BENEFITS OF GENETIC TESTING



GENETIC DETERMINISM OF CANCER



IMPACTS OF GENETIC TESTING ON CLINICAL MANAGEMENT

Why?

IMPACTS OF GENETIC TESTING ON CLINICAL MANAGEMENT

Hereditary colorectal cancer : 1/500

✓*MSH2, MLH1, MSH6, PMS2*

✓*APC, MUTYH*

✓*STK11,*

SMAD4, BMPR1A,

PTEN

Why?

IMPACTS OF GENETIC TESTING ON CLINICAL MANAGEMENT

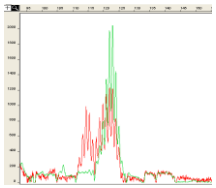
Why?

Colon cancer 62 years

Wt/ mt

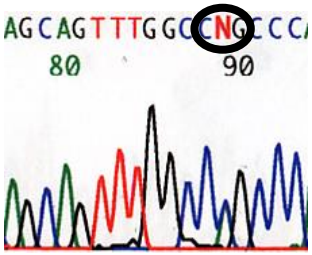
Colon cancer 32 years

Colon cancer 36 years



RER+ phenotype

MSH2



IMPACTS OF GENETIC TESTING ON CLINICAL MANAGEMENT

Why?

Colon cancer 62 years

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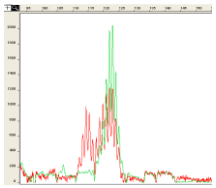
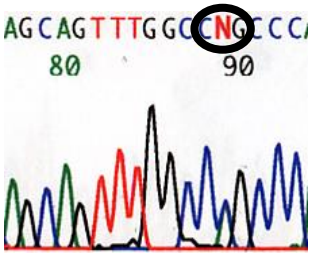


RER+ phenotype

Colonoscopy every 2 years
Hysteroscopy - Prophylactic hysterectomy

MSH2



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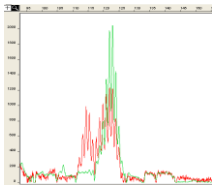
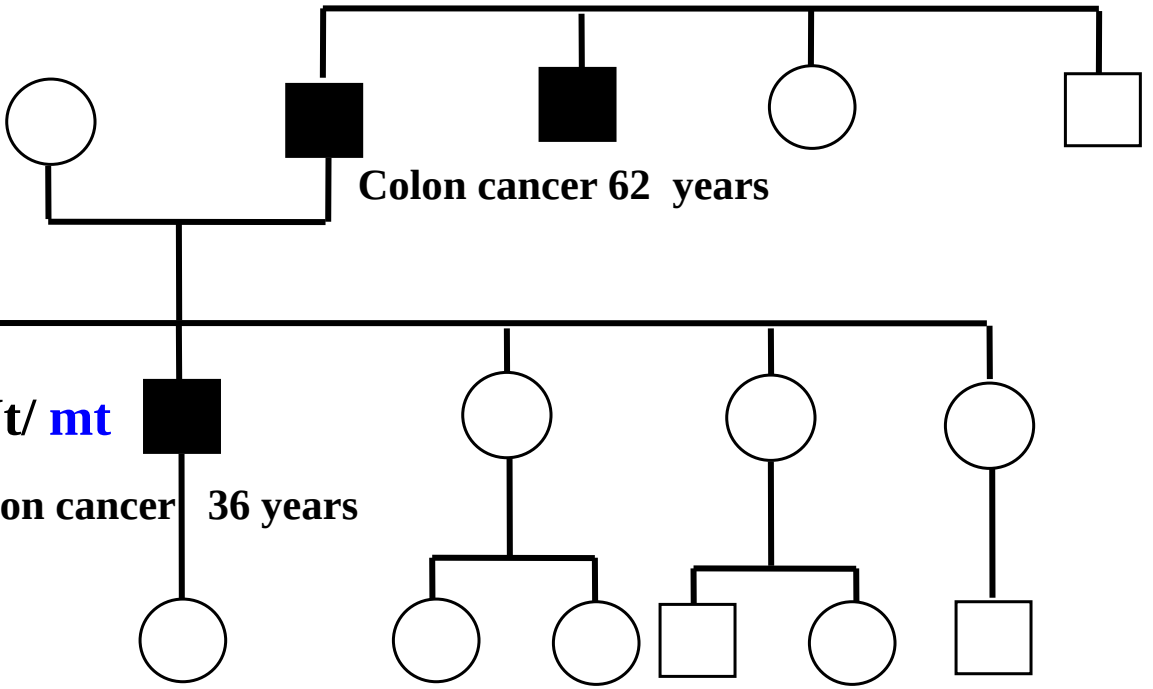
Why?

Colon cancer 32 years

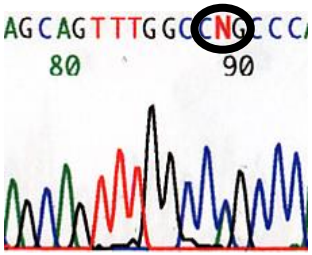


RER+ phenotype



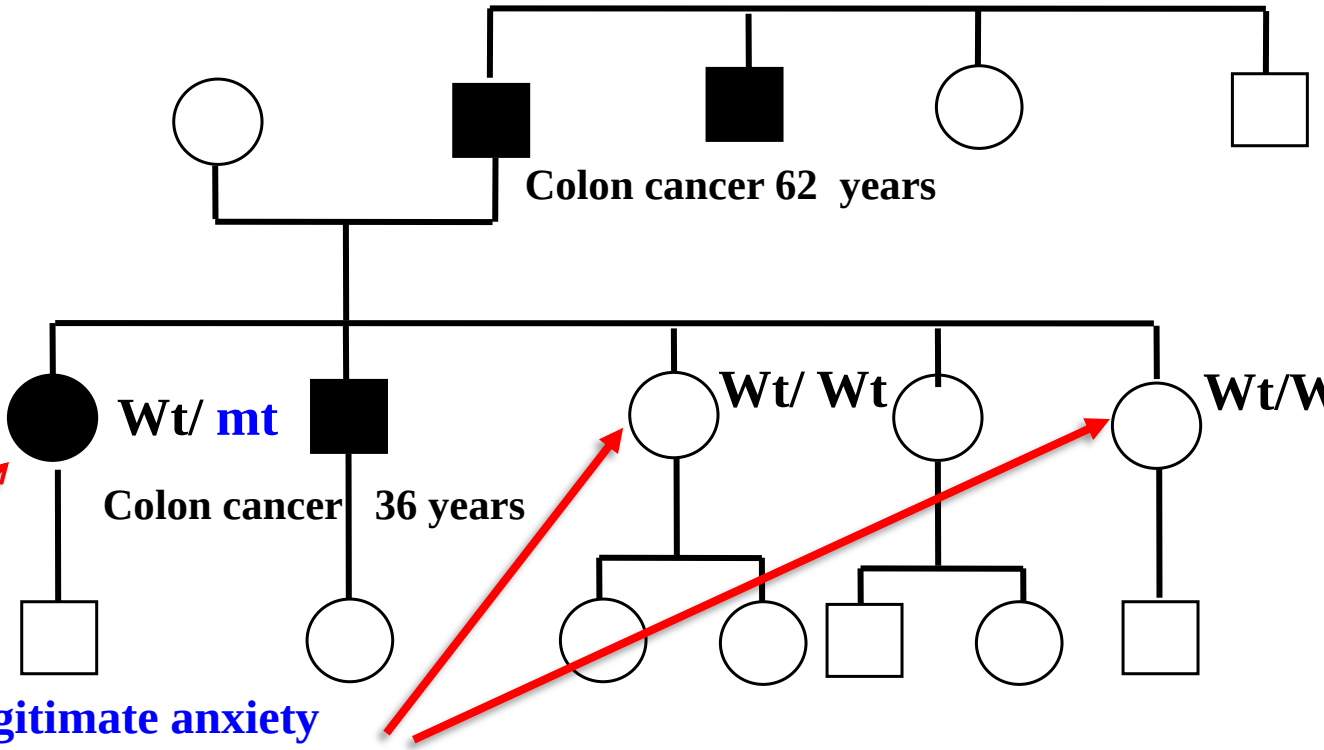
Presymptomatic testing

MSH2



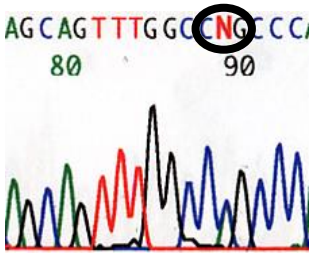
IMPACTS OF GENETIC TESTING ON CLINICAL MANAGEMENT

Why?



Suppression of an illegitimate anxiety and inappropriate medical follow-up in non mutation carriers

MSH2



IMPACTS OF GENETIC TESTING ON CLINICAL MANAGEMENT

Why?

Colon cancer 62 years

Wt/ mt

Colon cancer 32 years

Colon cancer 36 years

Wt/ Wt

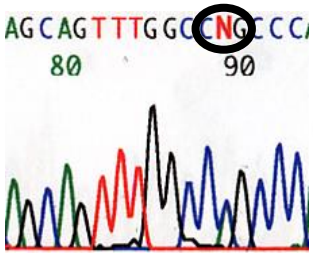
Wt/ mt

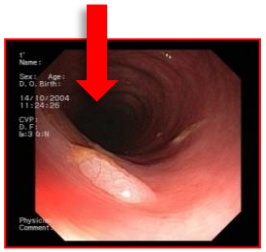
Wt/Wt

Suppression of an illegitimate anxiety and inappropriate medical follow-up in non mutation carriers

Colonoscopy since 20 years of age every 2 years

MSH2





IMPACTS OF GENETIC TESTING ON CLINICAL MANAGEMENT

Hereditary breast and ovarian cancer : 1/400
BRCA1, BRCA2

Why?

Breast cancer 35 years
Breast cancer 50 years

Breast cancer 67 years

Ovarian cancer 50 years

Breast cancer 27 years

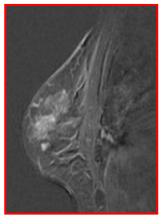
Ovarian cancer 45 years

Wt/Wt

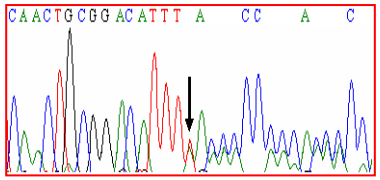
Wt/Wt

Breast cancer 34 years

Wt/Mt



✓Annual MRI
✓Prophylactic mastectomy < 40 years
✓ Prophylactic salpingo-oophorectomy > 40 years



***BRCA1* mutation**

IMPACTS OF GENETIC TESTING ON TREATMENT

Hereditary breast and ovarian cancer : 1/400

Why?

Breast cancer 35 years
Breast cancer 50 years

Breast cancer 67 years

Ovarian cancer 50 years

Breast cancer 27 years

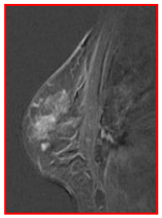
Ovarian cancer 45 years

Wt/Wt

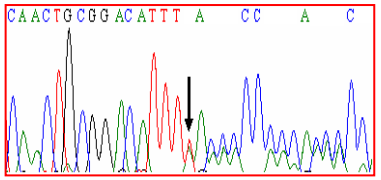
Wt/Wt

Breast cancer 34 years

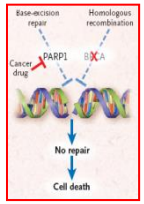
Wt/Mt



✓**Partial *versus* complete mastectomy**
✓**PARP inhibitors**

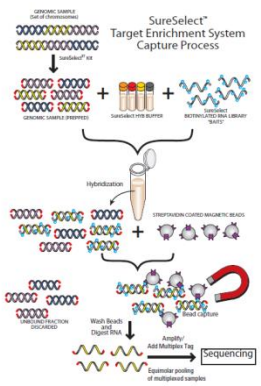


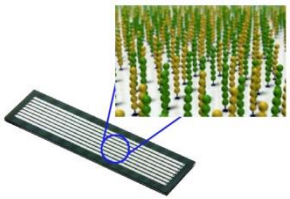
***BRCA1* mutation**

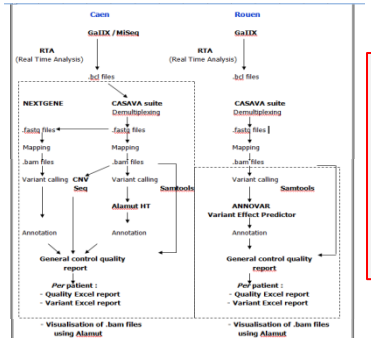


Olaparib

GENETIC TESTING USING NEXT GENERATION SEQUENCING



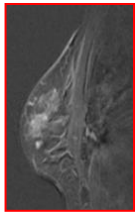




How?

✓**High throughput**
✓**Simultaneous analysis of genes**
✓ **Reduction of delay**

Breast and ovarian cancer



Not for diagnostic

Colorectal cancer

MSH2
MLH1
MSH6
PMS2
APC,
MUTYH
STK11,
SMAD4
BMPR1A
PTEN

Overlapping phenotypes

530 patients

BRCA1	PALB2
BRCA2	MRE11A
TP53	NBS1
PTEN	BARD1
ATM	CDH1
BAP1	MSH2
BARD1	MLH1
BRIP1	MSH6
CHEK2	PMS2
RAD50	PMS1
RAD51	MLH3
RAD51B	
RAD51C	

2100 patients

Genetic session

One month

Result

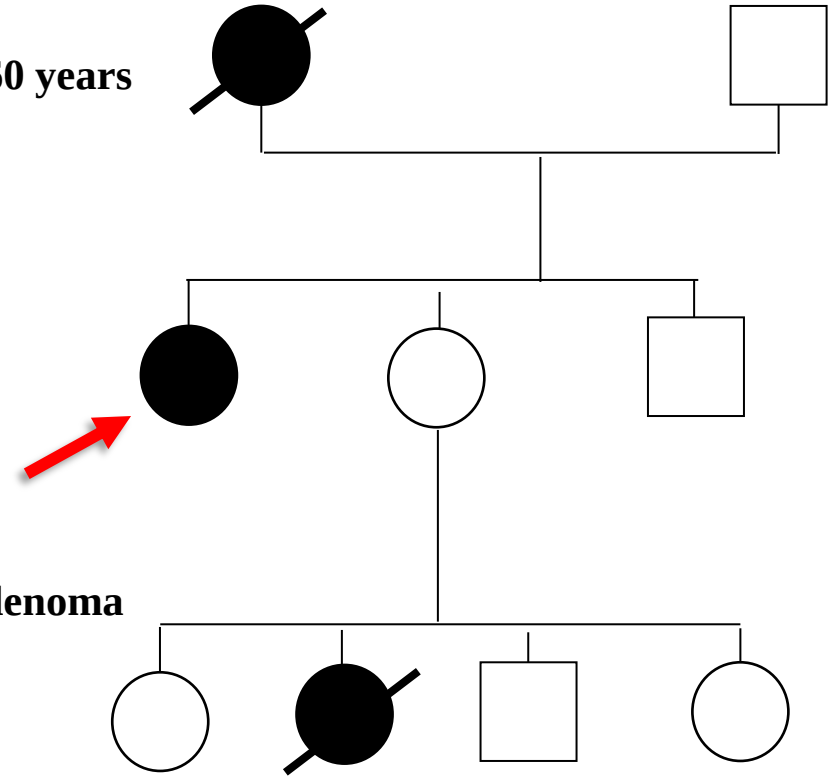
INSTITUT NATIONAL DU CANCER

Caen-Rouen Normandy NGS Center

GENETIC TESTING USING NEXT GENERATION SEQUENCING

Why?

Renal cancer 60 years



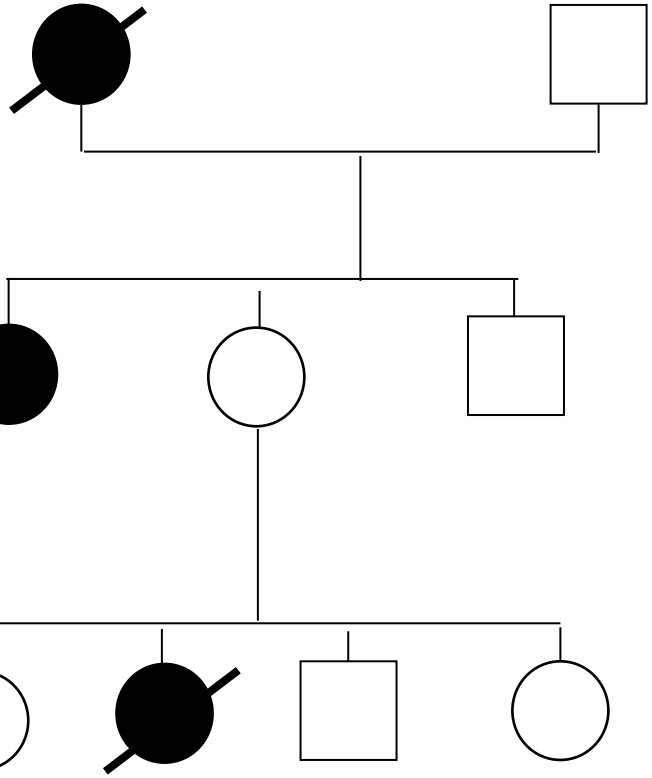
Breast cancer 48 years
Colorectal cancer 52 years
Colorectal and duodenal adenoma

Cervix carcinoma, 36 years

GENETIC TESTING USING NEXT GENERATION SEQUENCING

Why?

Renal cancer 60 years



Breast cancer 48 years
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Colorectal and duodenal adenoma

Cervix carcinoma, 36 years

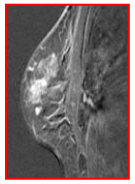
MSH2
MLH1
MSH6
PMS2
APC,
MUTYH
STK11,
SMAD4
BMPR1A
PTEN

→ ***PTEN*** **mutation** → **Cowden disease** → **Main risks:** **Breast cancer** **Thyroid cancer**

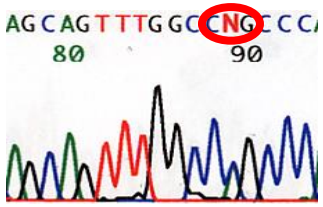
CHALLENGE OF GENETIC TESTING : INTERPRETATION OF VARIANTS OF UNKNOWN SIGNIFICANCE

How?

Breast and ovarian cancer



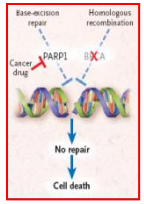
BRCA genes
(*BRCA1, BRCA2*)



Lynch syndrome
Hereditary Non Polyposis Colorectal Cancer

MMR genes
(*MLH1, MSH2, MSH6, PMS2*)

20%: Variants of unknown significance



Neutral variation?
Pathogenic mutation?

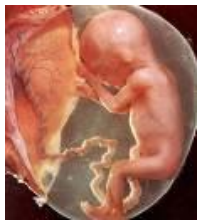
Genetic counseling

Targeted therapies
e.g.: anti-PARP for BRCA deficient patients

Appropriate clinical follow-up

MMR **: Colonoscopy, Hysteroscopy**
BRCA **: Breast MRI, Mastectomy, salpingo-oophorectomy**

HUMAN GENETICS IN THE POST-NGS ERA : THE CHALLENGE OF THE INTERPRETATION OF GERMLINE GENETIC VARIATION



***Per* exome**
34 Mb : 1.2% of the total genome

✓**20000 *Single Nucleotide Variations*** **(SNV)**
✓**500 rare (<0.1%) SNVs not present in the data bases**
✓ **1 *de novo* SNV with potential impact *per* generation**

Main medical challenge :
Interpretation of rare genetic variations

Statistical analyses

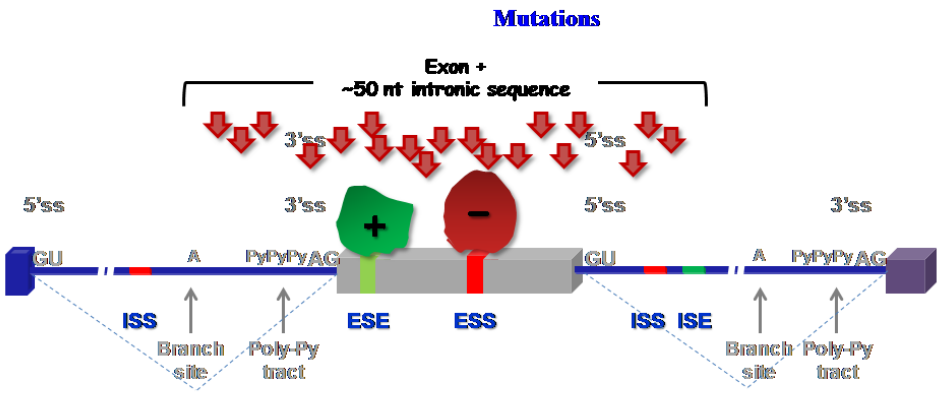
Phenotypic evaluation

Development of clinical and molecular networks

Animal models

INTERPRETATION OF VARIANTS OF UNKNOWN SIGNIFICANCE

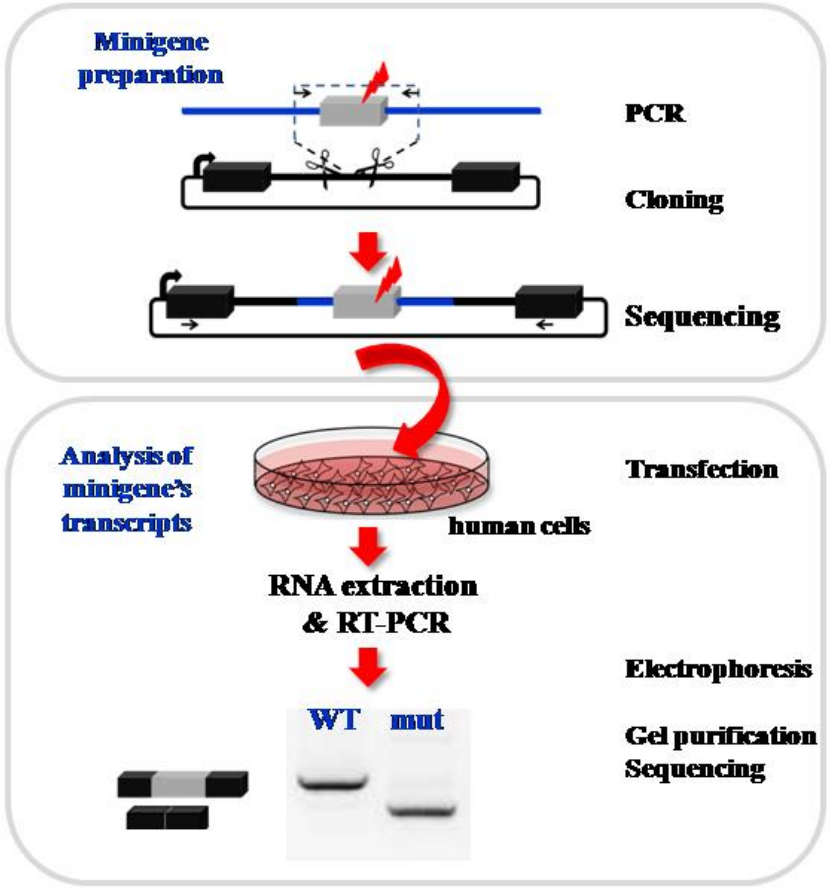
Impact of unclassified variants on splicing



Tournier et al., Hum Mutat. 2008
Bonnet et al., J Med Genet. 2008
Vezain et al., Hum Mutat. 2010
Gaildrat et al., J Med Genet. 2010
Gaildrat et al., Methods Mol Biol. 2010
Théry et al., Eur J Hum Genet. 2011
Vezain et al., Hum Mutat. 2011
Gaildrat et al., J Med Genet. 2012
Di Giacomo et al., Hum Mutat. 2013

How?

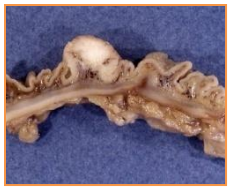
The minigene assay

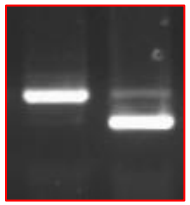


Inserm U1079

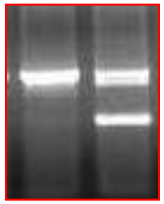
INTERPRETATION OF VARIANTS OF UNKNOWN SIGNIFICANCE

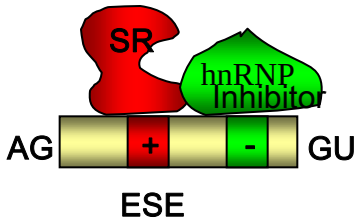
259 *MSH2*, *MLH1* and *MSH6* VUS
French cancer genetic laboratories network





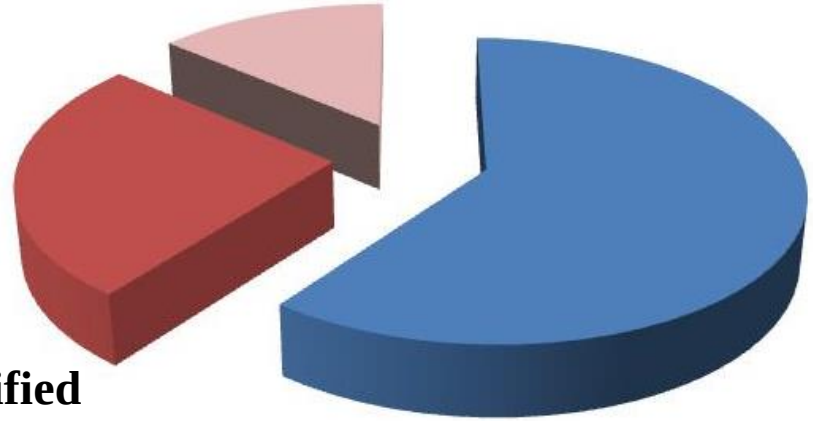
25 VUS (10%) with partial effect



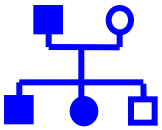


71 VUS (28%) with splicing effect

46 VUS (18%) with complete effect

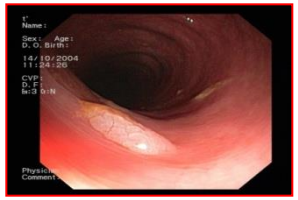


188 VUS (72%) without splicing effect



18% of VUS re-classified as deleterious splicing mutations

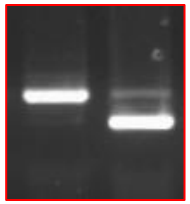
INCa MMR Data base



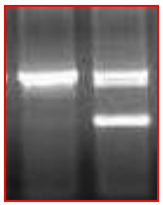
INTERPRETATION OF VARIANTS OF UNKNOWN SIGNIFICANCE

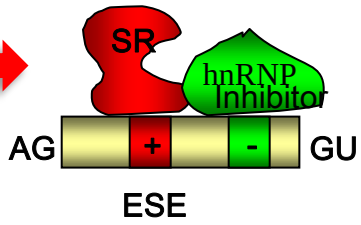
174 *BRCA1* and *BRCA2* VUS

French cancer genetic laboratories network



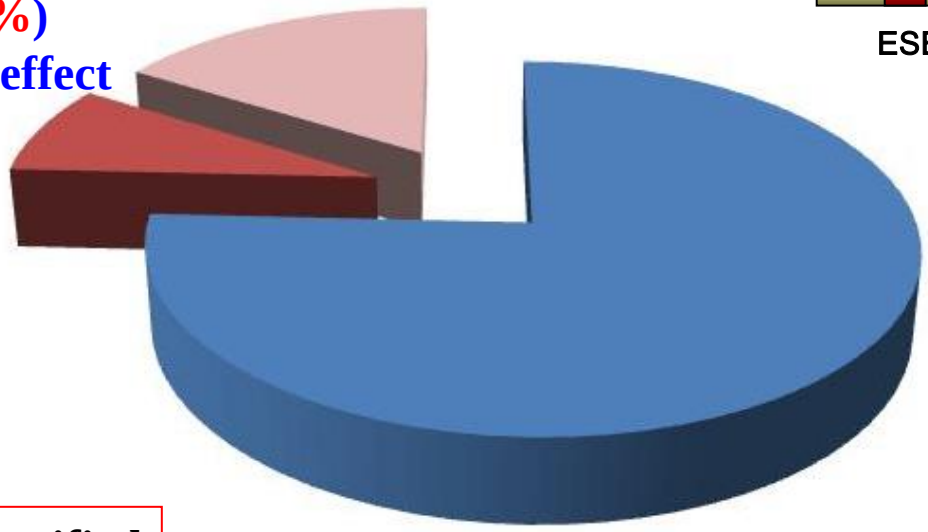
21 VUS (12%) with partial effect



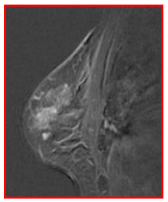


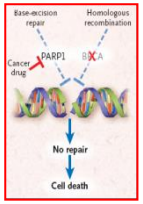
50 VUS (29%) with splicing effect

29VUS (17%) with complete effect



17% of VUS re-classified as deleterious splicing mutations



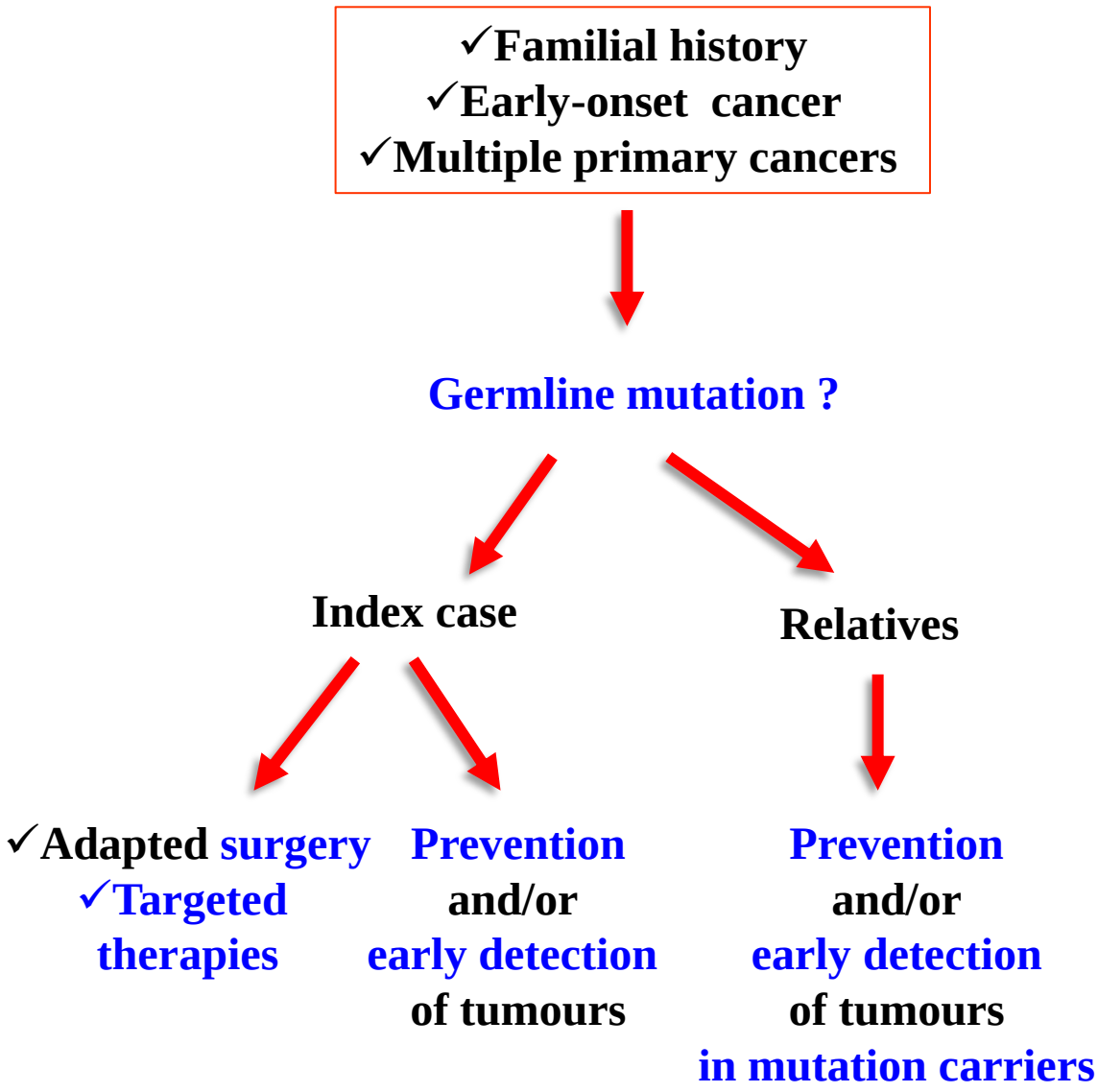


124 VUS (71%) without splicing effect

INCa *BRCA* Data base

PARP inhibitors

THE CASCADE OF GENETIC TESTING IN CANCER



THE CASCADE OF GENETIC TESTING IN CANCER

✓Familial history
✓Early-onset cancer
✓Multiple primary cancers

Germline mutation ?

Index case

✓Adapted surgery
✓Targeted therapies

Prevention and/or early detection of tumours

Relatives

Prevention and/or early detection of tumours in mutation carriers

Oncologist

Geneticist

✓Validate the indication of the test
✓Anticipate the personnal and familial consequences of mutation detection

Genetic testing of genes corresponding to the phenotype in specialized laboratories
✓ Detection and interpretation

Geneticist

Oncologist