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

Department of Genetics, University Hospital
Inserm U1079, Faculty of Medicine
Institute for Research and Innovation in Biomedicine (IRIB)
Normandy University
Frebourg@chu-rouen.fr

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MOLECULAR BASES OF CANCER
AND MEDICAL BENEFITS OF GENETIC TESTING

Somatic mutation

Somatic mutations

Targeted therapies

Sporadic form of cancer

Germline mutation

Germline mutation

Somatic mutations

Personnalized medical management

Inherited form of cancer
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GENETIC DETERMINISM OF CANCER

Risk of cancer

Number of germline genetic variations

Monogenic determinism

Genetic instability

Oligogenic determinism

Multigenic determinism

Which tests?

ALK, SUFU, RET, APC, RB1, CDH1

TP53, SMAD4, BMPR1A, STK11, BRCA, MMR, PTEN

ATM, CHECK2, NBS1, RAD50, BRIP1, PALB2...

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?

Colonoscopy every 2 years
Hysteroscopy - Prophylactic hysterectomy

RER+ phenotype

Colon cancer 32 years

Colon cancer 62 years

Colon cancer 36 years

Wt/ mt

Colon cancer 32 years

Colon cancer 62 years

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

Presymptomatic testing

MSH2
Suppression of an illegitimate anxiety and inappropriate medical follow-up in non mutation carriers.
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

\(BRCA1, BRCA2\)

Breast cancer 67 years

Breast cancer 35 years

Breast cancer 50 years

Ovarian cancer 50 years

Breast cancer 27 years

Ovarian cancer 45 years

Wt/Wt

Wt/Wt

Wt/Mt

Why?

\(BRCA1\) mutation

✓ Annual MRI
✓ Prophylactic mastectomy < 40 years
✓ Prophylactic salpingo-oophorectomy > 40 years
Breast cancer 67 years

Breast cancer 27 years

Breast cancer 35 years
Breast cancer 50 years

Ovarian cancer 50 years

Ovarian cancer 45 years

Wt/Wt

Wt/Wt

Wt/Mt

Partial versus complete mastectomy
PARP inhibitors

BRCA1 mutation

Olaparib

Why?

Hereditary breast and ovarian cancer: 1/400

IMPACTS OF GENETIC TESTING ON TREATMENT
GENETIC TESTING USING NEXT GENERATION SEQUENCING

- High throughput
- Simultaneous analysis of genes
- Reduction of delay

How?

Breast and ovarian cancer

Not for diagnostic

Genetic session

One month

Result

Overlapping phenotypes

Colorectal cancer

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

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

Caen-Rouen Normandy NGS Center

530 patients

2100 patients
Breast cancer 48 years
Colorectal cancer 52 years
Colorectal and duodenal adenoma

Renal cancer 60 years

Cervix carcinoma, 36 years

Why?
Breast cancer 48 years
Colorectal cancer 52 years
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Cervix carcinoma, 36 years

**Why?**

PTEN mutation

Cowden disease

Main risks:
Breast cancer
Thyroid cancer

| MSH2 | MLH1 | MSH6 | PMS2 | APC, MUTYH | STK11, SMAD4 | BMPR1A | PTEN |
CHALLENGE OF GENETIC TESTING: INTERPRETATION OF VARIANTS OF UNKNOWN SIGNIFICANCE

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

Appropriate clinical follow-up

\(MMR\) : Colonoscopy, Hysteroscopy
\(BRCA\) : Breast MRI, Mastectomy, salpingo-oophorectomy

Targeted therapies
\(\text{e.g.}:\) anti-PARP for BRCA deficient patients

How?
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
- Animal models

Development of clinical and molecular networks
Impact of unclassified variants on splicing

The minigene assay

**How?**

- Minigene preparation
- PCR
- Cloning
- Sequencing
- Transfection
- Electrophoresis
- Gel purification
- Sequencing

**Analysis of minigene’s transcripts**

**RNA extraction & RT-PCR**

**WT** **mut**

**Inserm U1079**

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

71 VUS (28%) with splicing effect

46 VUS (18%) with complete effect

18% of VUS re-classified as deleterious splicing mutations
INCa MMR Data base

25 VUS (10%) with partial 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

- **50 VUS (29%)** with splicing effect
- **29 VUS (17%)** with complete effect
- **21 VUS (12%)** with partial effect
- **17% of VUS re-classified as deleterious splicing mutations**
- **124 VUS (71%)** without splicing effect

INCa *BRCA* Data base

INTERPRETATION OF VARIANTS OF UNKNOWN SIGNIFICANCE

PARP inhibitors
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
THE CASCADE OF GENETIC TESTING IN CANCER

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Prevention and/or early detection of tumours

Relatives

Prevention and/or early detection of tumours in mutation carriers

Oncologist

- Validate the indication of the test
- Anticipate the personal and familial consequences of mutation detection

Geneticist

Genetic testing of genes corresponding to the phenotype in specialized laboratories

- Detection and interpretation

Geneticist

Oncologist