**BeSHG Interuniversity Course in Genetics**

**12.30-12.55** Hereditary basis of cancer – specifics for genetic counseling

DAY 5: UCLouvain
Friday 11 February 2022
Dr Anne De Leener
Centre de Génétique Humaine

Cliniques universitaires
SAINT-LUC
UCL BRUXELLES

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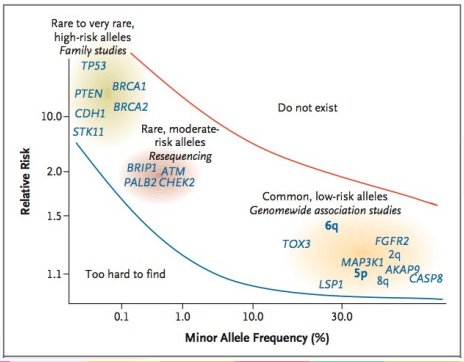
# Heredity?

It is estimated that 5-10% of the cancers are due to inherited gene mutation or deletion.

However, a much higher proportion of cancers (30-40%?) may be due to moderately penetrant cancer susceptibility gene coupled with exposure to carcinogens.




Foulkes WD, NEJM 2008



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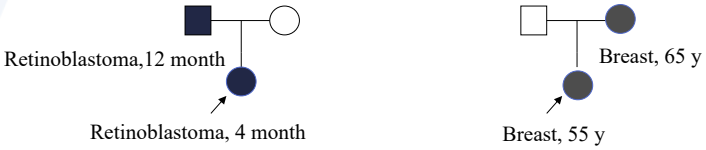
## Familial history of cancer: when do we have to think about heredity?



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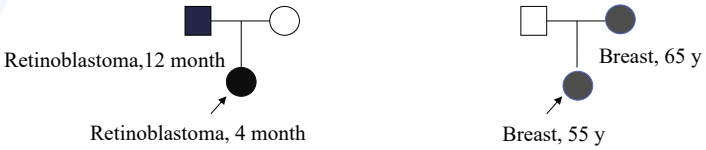
## Familial history of cancer: when do we have to think about heredity?




Retinoblastoma risk: 1/ 15000
50 new cases/year in France, and familial cases are 5 times more frequent than expected by coincidence!

Breast cancer risk: 1/10
10% of FDR will have a breast cancer < 70y
There are family histories by coincidence



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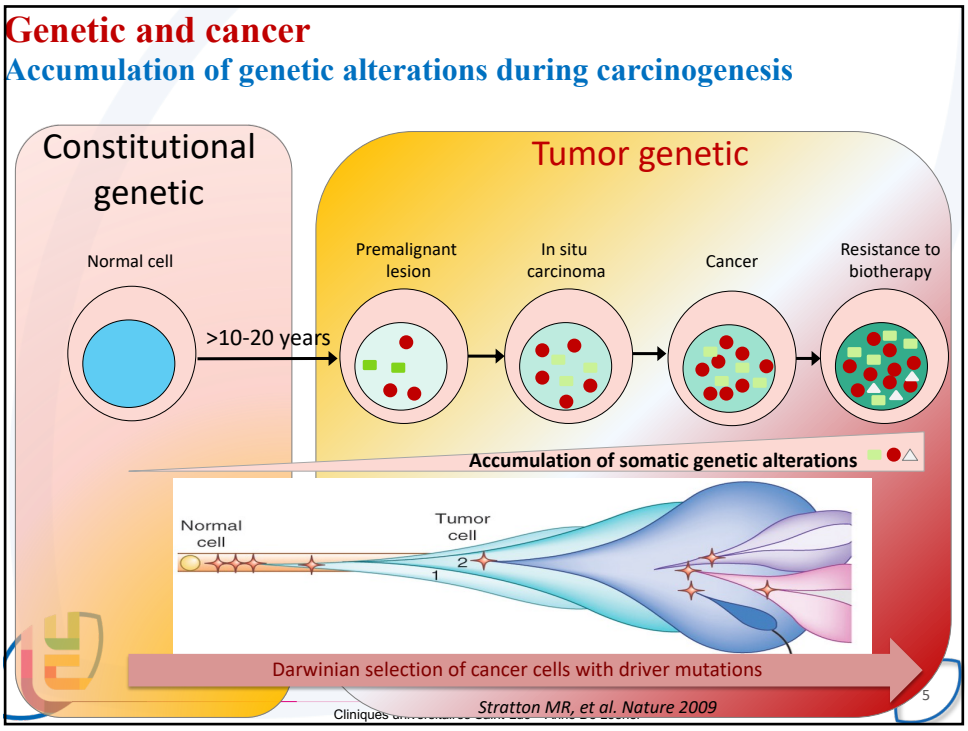
Genetic and cancer
Accumulation of genetic alterations during carcinogenesis
Constitutional genetic
Tumor genetic
Normal cell
Premalignant lesion
In situ carcinoma
Cancer
Resistance to biotherapy
>10-20 years
Accumulation of somatic genetic alterations
Normal cell
Tumor cell
1
2
Darwinian selection of cancer cells with driver mutations
Stratton MR, et al. Nature 2009
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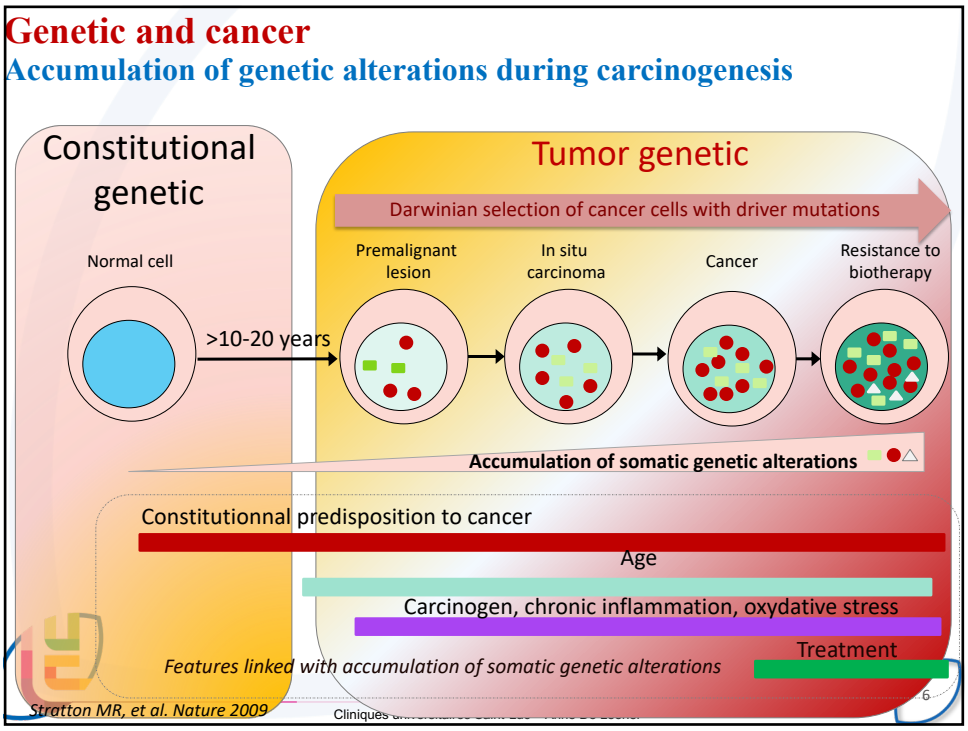
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Accumulation of somatic genetic alterations
Constitutionnal predisposition to cancer
Age
Carcinogen, chronic inflammation, oxydative stress
Treatment
Features linked with accumulation of somatic genetic alterations
Stratton MR, et al. Nature 2009
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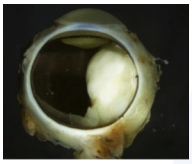
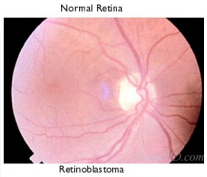
## Genetic and cancer

Retinoblastoma :
rare disease, simple genetic

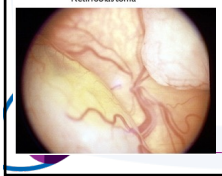


- ✓ Tumor of precursor cell of the retina
- ✓ Biallelic inactivation of a tumor suppressor gene: Rb1
- ✓ 1/15.000 to 1/20.000 children (0-8y)

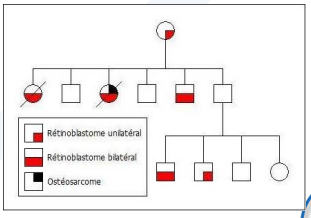



1st sign: Leukocoria

90% of cases: no familial history
- ✓ 60% unilateral
- ✓ 30% bilateral




10% of cases: familial history



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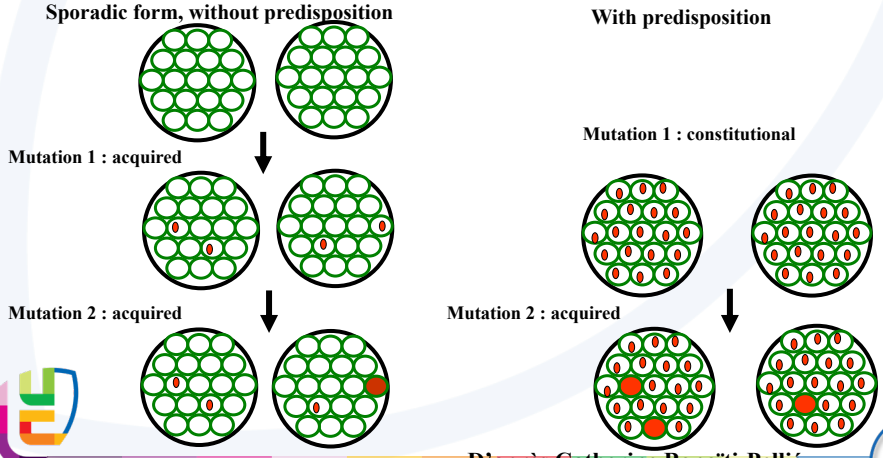
## Knudson et Comings

1971, Knudson model

- 2 genetic alterations in one cell of the retina are needed (but maybe not enough)
- In the bilateral forms: one mutation is constitutional (inherited or the novo in the early embryogenesis), the other mutation is acquired
- In the unilateral forms, both mutations are somatic

1973, Comings hypothesis

- The 2 mutations necessary for the apparition of a retinoblastoma correspond to the inactivation of both alleles of the same gene




D'après Catherine Bonaïti-Pellié



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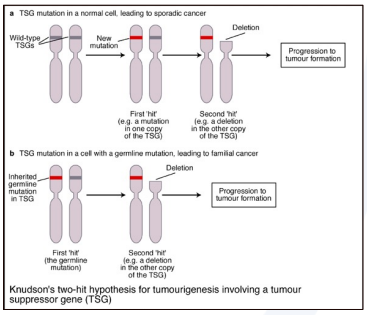
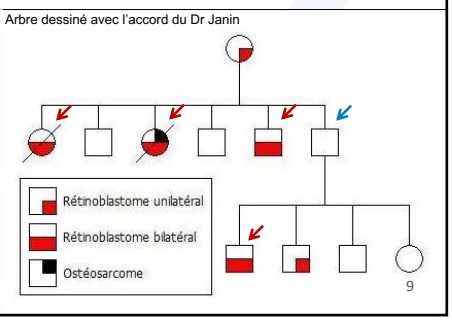
## Retinoblastoma :

- Sporadic cases (60-80%)
  - ✓ Late (80% >2yo), unilateral and unique
  - ✓ No risk for the siblings
  - ✓ No risk for other cancers
- Hereditary cases (20-40%)
  - ✓ A.D. transmission with **high** (but incomplete) penetrance (90%)
  - ✓ **Early** (90% ≤ 2yo), bilateral (25%) and/or multifocal
  - ✓ **"sporadic"** early bilateral cases are hereditary cases caused by neomutations: 15% of retinoblastomas are unique but hereditary
  - ✓ Be careful with the risk of somatic **mosaicism**
  - ✓ Increased risk of **other cancers**: osteosarcoma, soft tissues sarc., melanoma etc
  - ✓ Avoid radiations




Arbre dessiné avec l'accord du Dr Janin



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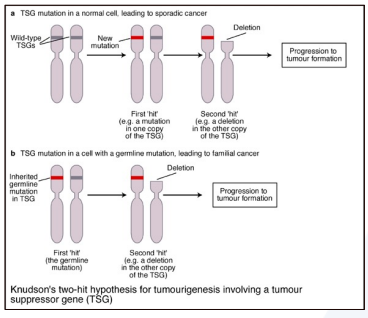
## Definitions

**Genetic predisposition to cancer :**

- ✓ Generally dominant transmission
- ✓ High penetrance but generally incomplete
- ✓ Early onset cancer development
- ✓ Multifocal or bilateral disease
- ✓ Risk to develop other types of cancers




- ✓ Risk? relative notion : corresponds to an increase in an individual's inherited risk of developing cancer(s), or a given cancer, as compared to the mean risk in the general population; this increase can be expressed as a **relative risk**

- **diagnostic genetic tests** can be offered in the case of genetic predispositions to cancer if the risk of developing a tumor has been well established, and if the there is a defined strategy for **managing** the affected individuals; the aim is to reduce the morbidity and the mortality; early surveillance is the most common approach



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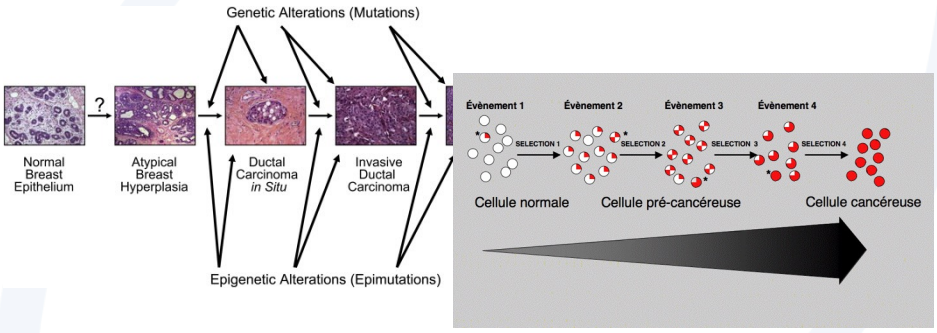
## Genes involved in inherited cancers:




- ✓ Germline inactivation of a tumor suppressor gene
- ✓ Germline activation of a proto-oncogene

} Gatekeeper

- ✓ Germline inactivation of a DNA repair gene

Caretaker

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## Genes involved in tumor processes : gatekeepers (1)
## "Loss of function" mutation
## Tumor suppressor genes

- Signal transduction:
  - *APC* (FAP)
  - *PTCH* (Gorlin syndrome)
  - *CDH1* (E. Cadherin, Gastric cancer), *NF1*
- Interaction membrane - matrix:
  - *PTEN* (Cowden)
  - *NF2*
- Cell cycle:
  - *RB1* (Retinoblastoma)
  - *CDKN2A* (Malignant melanoma)
  - *TP53* (Li Fraumeni)

1st mutation constitutional (germline)
2d mutation acquired

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## Genes involved in tumor processes : gatekeepers (2)
## « gain of function » mutation
## Oncogene

Signal transduction :

- *c.RET* (Thyroid medullar cancer, MEN2A et B)
- *c.MET* (Gastric)
- *c-Kit* (GIST)
- *Alk* (Neuroblastoma)
- *RAS,* MAP kinase pathway

The mutation itself is sufficient

Cell cycle:

- *CDK-4* (Malignant melanoma)



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## Genes involved in DNA repair : caretaker
## « Loss of function » mutations

- Recessive transmission with associated disease
  - Ataxia Telangiectasia : *ATM, MRE11*
  - Bloom : *BLM*
  - Fanconi : *FANC (A, B, C, BRCA2 (D1), D2, E, F, G, .....)*
  - Xeroderma pigmentosum : *XP-A, XP-B, XP….*
- Dominant transmission
  - LYNCH : *MLH1, MSH2, MSH6, PMS2, EPCAM*
  - HBOC : *BRCA1, BRCA2*
- Recessive transmission without associated disease !
  - Predisposition in childhood : CMMRD : biallelic mutation in MMR genes



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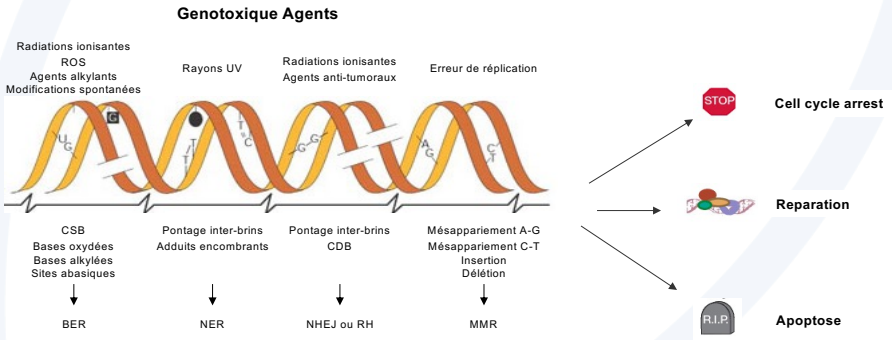
## DNA damages




*Hoeijmakers Nature 2001*

**Reparation type**

**Double strand breaks (DSB) are more toxic**
**inversions, translocations, deletions**



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## Caretaker syndromes

1. Caretakers mutations are the most frequent cause of cancer predisposition: HBOC and Lynch syndrome
2. Caretaker syndromes predispose to cancers that are frequent in the general population (breast cancers, colon cancers)
3. At risk people have a normal phenotype: You won't recognize them before they get cancer unless you got the chance to offer them predictive testing and show that they carry the responsible mutation

-> **IMPORTANT COROLLARY:** You must have identified the mutation in the family



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## Definitions

- Penetrance = the likelihood a given gene will result in disease
- High penetrance genes :
  - rare mutations
  - very high risk of disease
  - independent of other risk factors
- Low penetrance genes
  - frequent genetic variants
  - interact with exogenous factors to cause the diseases



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## Hereditary cancer syndromes

The ramification of having one of these (inherited cancer) diseases are significant for BOTH the patient and their family, with a high risk of developing a malignancy in many organs at an early age.

Clinicians should be prepared to recognize and manage these diseases. This is not as simple as it sounds.

C. Neal Ellis, 2004



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## Risk notion? …… which risk?

- Role of the geneticist: clarify the risk
- Probability of inherited syndrome?
- Risk to have a pathogenic mutation?
  - ? Criteria to refer in genetic counselling
  - ? Criteria to perform genetic analysis
  - ? Screening of predisposed patients



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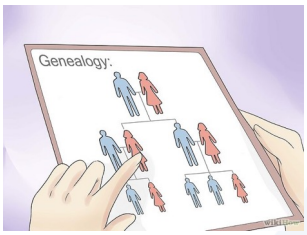
## Genetic Counseling in cancer

Usually 2 (or 3) visits (standard genetic counseling < convention):

- ✓ Risk Assessment visit
- ✓ Genetic testing visit
- ✓ Result disclosure / follow-up



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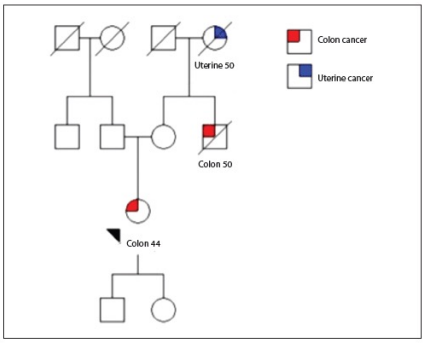
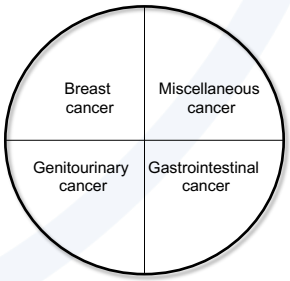
## Risk assessment: Collecting and interpreting cancer histories

Accurate and complete family history: systematic series of questions to gather relevant personal and family medical information.

Definition and purpose of the pedigree



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## Collecting and interpreting cancer histories

- Identify a cancer syndrome
- Determine the need for genetic testing
- Assist with management recommendation
- Uncover other syndromes
- Identify the disorder's inheritance pattern and other relatives at risk
- Ethnic background
- **The pedigree is an important clinical record**, it is crucial for pedigrees to reflect the most accurate information that is possible:
  - ✓ Pathology report
  - ✓ Physician note
  - ✓ Genetic test result
- Prior permission from the relative in question is needed



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# Anamnesis

Autosomal dominant transmission (most frequently) :

1. Cancers in ≥ 2 generations / One branch of family
2. Risk transmission = 50% for men and for women
3. Beware of incomplete penetrance and/or sex-related expressivity

Tumor risk is very often restricted to one or to a few tissues (spectrum –> syndrome)

People getting cancer in high risk families

- are often younger than people in sporadic cases
- often develop a 2nd cancer within the same tissue or in another tissue



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# Ways to classify family history of cancer

- Hereditary cancer syndrome
  - ✓ Mostly dominant pattern
  - ✓ 3 individuals with similar or related cancers
  - ✓ 2 generations of cancer cases and
  - ✓ 1 person diagnosed at an unusually young age
- Familial Cluster of Cancer
  - ✓ 2 or more relatives who have developed similar cancers but the family does not have any features suggestive of an hereditary cancer syndrome
- Sporadic forms of cancer
  - ✓ Most cases of cancer occur randomly without an obvious underlying risk factor.
- Environmentally caused cluster of cancer



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**Determine the likelihood that the family could have a hereditary predisposition to cancer.**

HIGH risk:

Strong evidence (Retinoblastoma)

Pattern consistent with a specific hereditary cancer syndrome.

MODERATE Risk:

Some features suggestive of cancer syndrome but may not meet criteria for the syndrome.

LOW Risk:

Negative or noncontributory history of cancer: although there are several cases of cancer in the family, the cancer types are ones that frequently occur among older individuals



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**Guidelines for genetic testing (www.beshg.be)**

Informed consent is mandatory

Discuss about the possible test results, limitations, risk and benefits, logistics of testing, including any cost associated with the testing process. Discuss about information to the family.

Discuss about how the results will be transmitted (follow-up visit, phone, etc), and the TAT.



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## Result disclosure

Cancer genetic test results are mainly disclosed in a counseling visit. It can be disclosed by phone but the mode of result disclosure has to be announced in the pretest visit.

Disclose the result early in the conversation (anxiety for the patient)

Use direct and clear language.

Allow patient time to react.

Discuss about cancer risk management for the patient/the family -> predictive testing available?

Counseling about cancer.
Katherine A. Schneider.



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## Diagnostic test, presymptomatic test & Predictive test

- Diagnostic test confirms or exclude a genetic disorder in an individual who had malignancy and features of hereditary cancer syndrome.
  - ✓ There is a good likelihood that the genetic test results will come negative.
  - ✓ The cancer syndrome may be caused by alteration in more than one gene.
- When a mutation (class IV or V) is available in the family, presymptomatic or predictive testing has to be offered in at risk asymptomatic individuals. No predictive testing in case of variant of unknown signification (VUS)
- Presymptomatic test determines if an asymptomatic individual carries a gene mutation that is associated with an absolute likelihood of cancer (or other syndromic features). APC gene for example.
- Predictive test determines if an asymptomatic individual carries a gene mutation that is associated with an increased but not absolute risk of cancer or other syndromic features. BRCA for example.



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## 5 steps procedure

- ✓ Importance of the pretest counseling: discuss about the potential risk and benefits of testing.
- ✓ Psychological assessment (before and after genetic testing).
- ✓ Genetic testing (2 blood samples, not the same day)
- ✓ Result disclosure.
- ✓ Follow-up (medical, psychological, …)