Senology diploma
genetics – Module 1 – part 1

Hereditary Breast cancer

Which patient to test ?

Liesthal – 21 january 2021

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Hereditary breast cancer

- What is a cancer predisposing gene ?
- Is this patient a BRCA1-2 mutation carrier ?
  - *The SAKK (Swiss) criteria*
- Some examples of pedigree

Genetics in Senology
early breast cancer (unicentric)

- What is a cancer predisposing gene ?
- Is this patient a BRCA1-2 mutation carrier ?
  - *The SAKK (Swiss) criteria*
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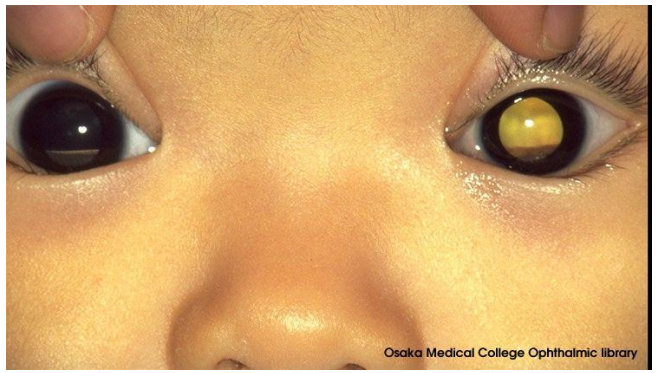
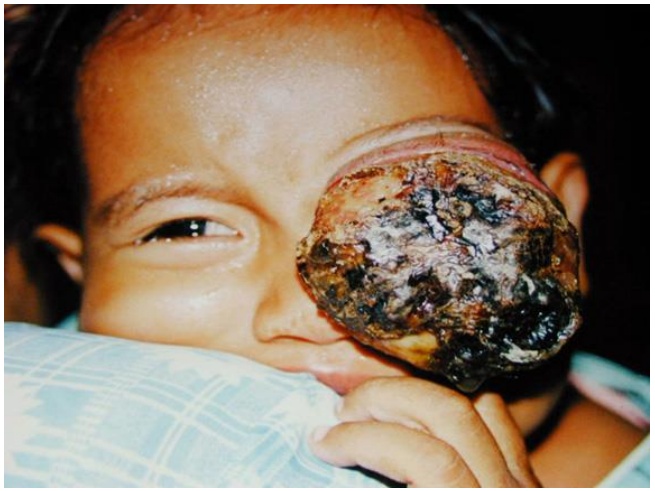
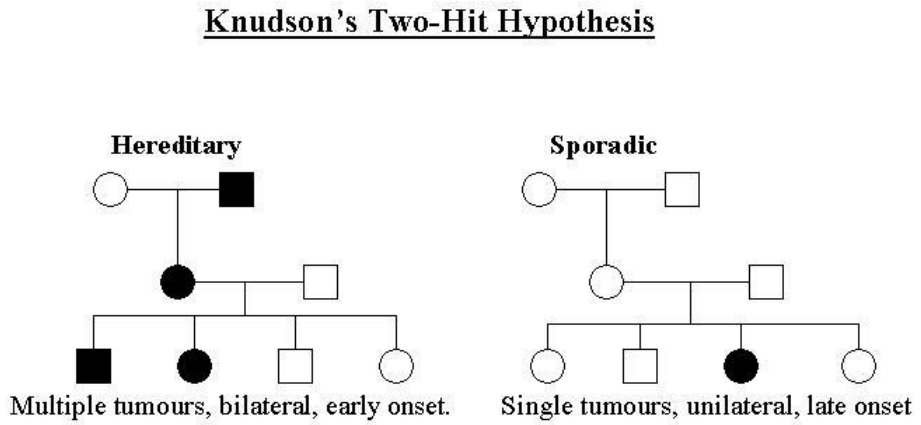
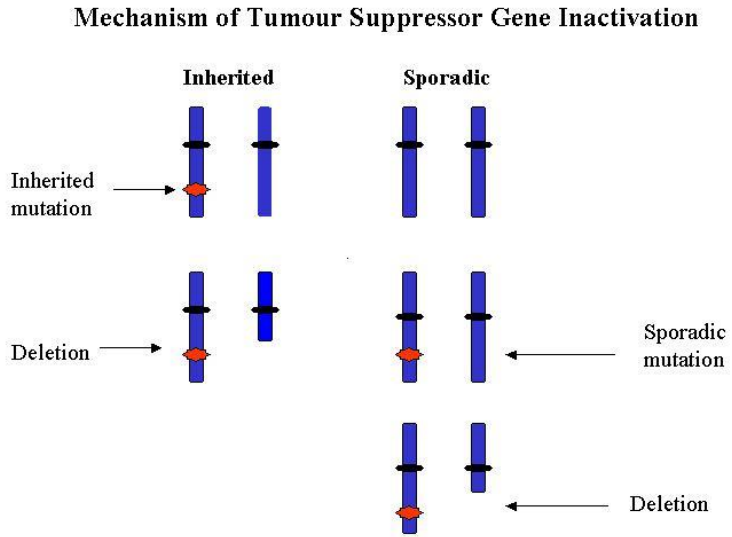
The case of retinoblastoma
The second hit hypothesis (Knudson)

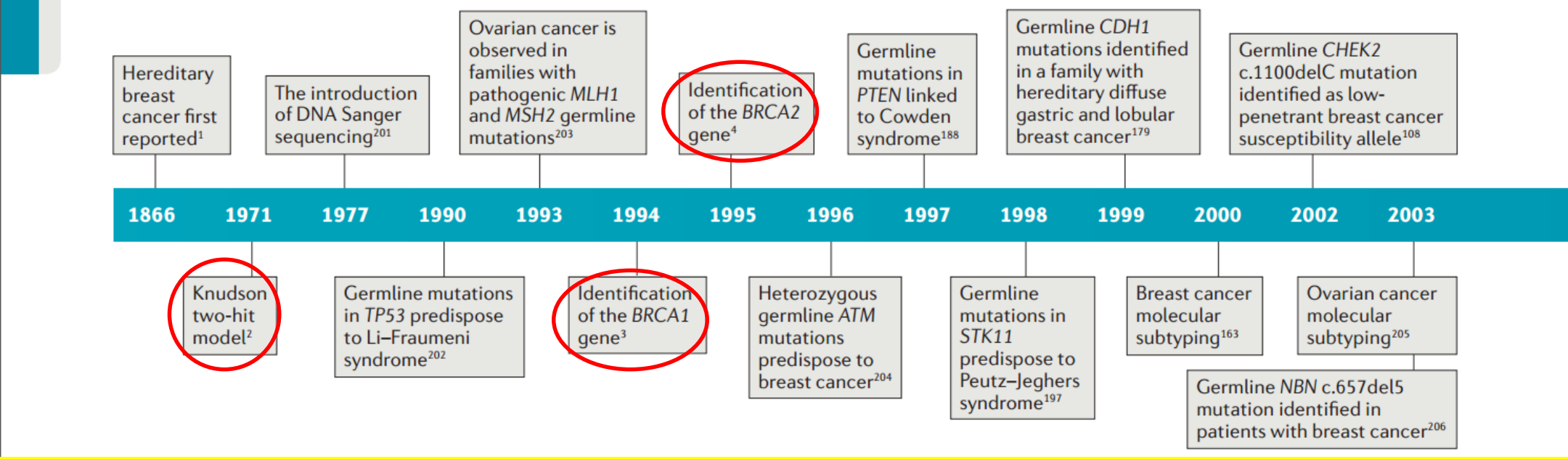




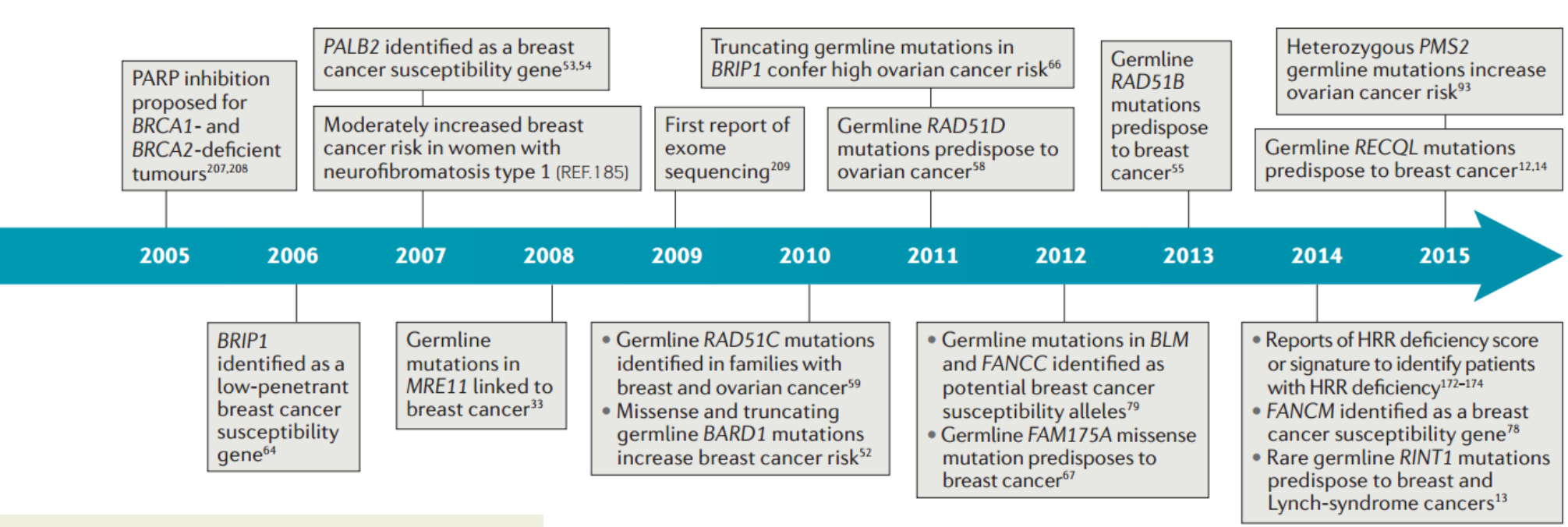




Knudson – PNAS 1971; 68:820



Timeline of events in HBOC discovery and identification of predisposing HBOC genes



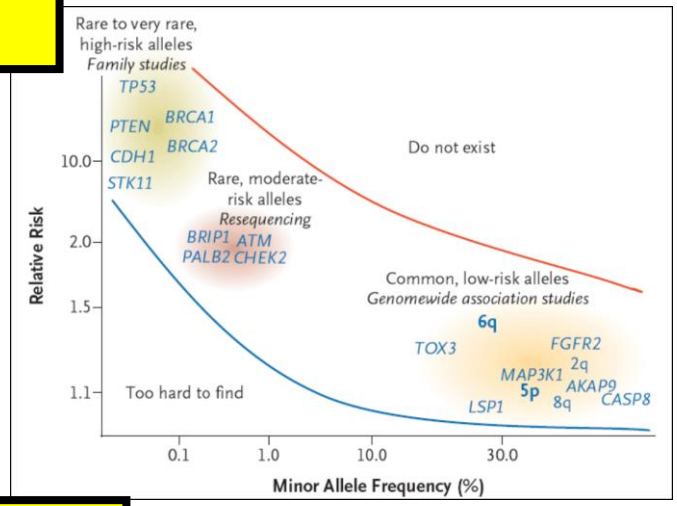
Nielsen – Nature reviews cancer 2016:16,599

Breast and ovarian cancer risk associated with established and emerging HBOC predisposing genes

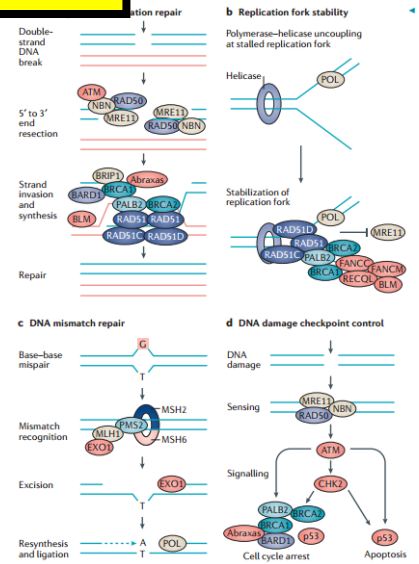
Gene	Breast cancer estimated lifetime risk (age in years)	Ovarian cancer estimated lifetime risk (age in years)	Refs
ATM	60% by age 80	Unknown	38
BARD1	Unknown	Low or none	37
BLM	Unknown	Low or none	80
BRCA1	57–65% by age 70	39–44% by age 70	5–7
BRCA2	45–55% by age 70	11–18% by age 70	5–7
BRIP1	OR: <2.0	~6% by age 80	37,64,65
CDH1	42% by age 80	Low or none	180
CHEK2	37% by age 70	Unknown	210
FAM175A	Unknown	Unknown	–
FANCC	Unknown	Unknown	–
FANCM	Unknown	Unknown	–
MLH1	~19% by age 70	20% by age 70	90,92
MRE11	Unknown	Unknown	–
MSH2	~11% by age 70	24% by age 70	90,92
NBN	OR: 3.0	Low or none	34,35,37
NF1	6.5-fold increase in women aged 30–39	Unknown	186
PALB2	35% by age 70	Low or none	37,211
PMS2	SIR: 3.8	SIR: 12.0	93
PTEN	85% by age 70	Low or none	190,212
RAD51B	Unknown	Low or none	56
RAD51C	Unknown	9% by age 80	213
RAD51D	Unknown	OR: 12	56
RECQL	Unknown	Unknown	–
RINT1	Unknown	Unknown	–
STK11	32% by age 60	Gynaecological*: 13% by age 60	199
TP53	25% by age 70	Unknown	214

Nielsen – Nature reviews cancer 2016:16,599

By risk



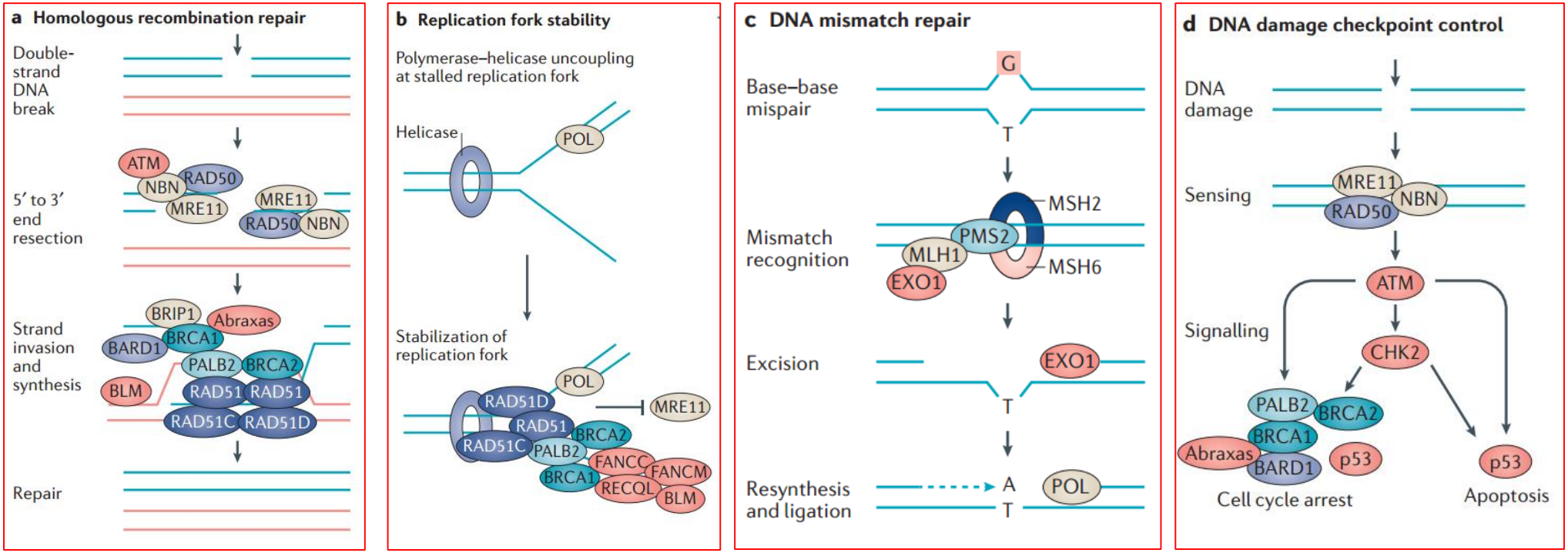
By function



Genome stability pathways and genes in HBOC (and Lynch syndromes)

By function

Genome stability pathways (> 90% of the genes)

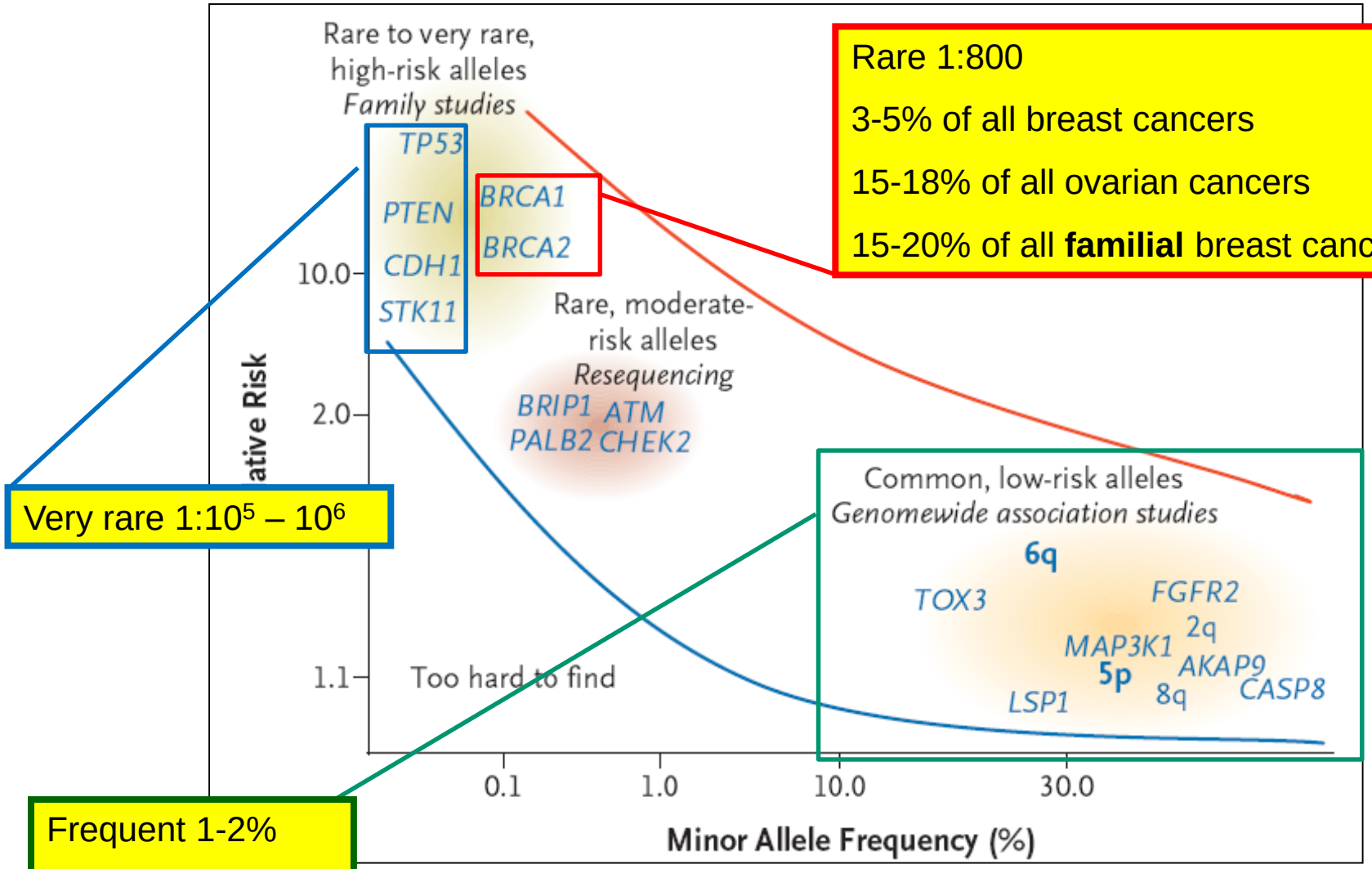


Other genes

CDH1, NF1, PTEN, STK11,APC,…

Nielsen – Nature reviews cancer 2016:16,599

The breast cancer predisposing genes



Rare 1:800

3-5% of all breast cancers

15-18% of all ovarian cancers

15-20% of all **familial** breast cancer

Very rare 1:10^5 – 10^6

Frequent 1-2%

Polygenic model

Foulkes - N Engl J Med 2008;359:2143-53.

Genetics in Senology
early breast cancer (unicentric)

- What is a cancer predisposing gene ?
- Is this patient a BRCA1-2 mutation carrier ?
  - *The SAKK (Swiss) criteria*
- Some examples of pedigree

Swiss guidelines for counselling and testing
Genetic predisposition to breast and ovarian cancer

A new version is on a working process…

Genetic predisposition to breast and ovarian cancer

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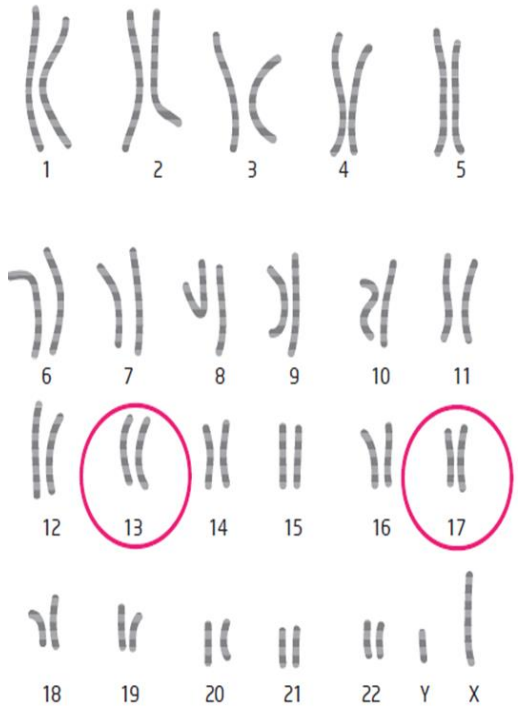
*these authors contributed equally to this publication

These guidelines have been approved by the SAKK Breast Cancer Project Group and the Gynecological Cancers Working Group. This document reflects clinical and scientific advances as of the date of publication and is subject to change.

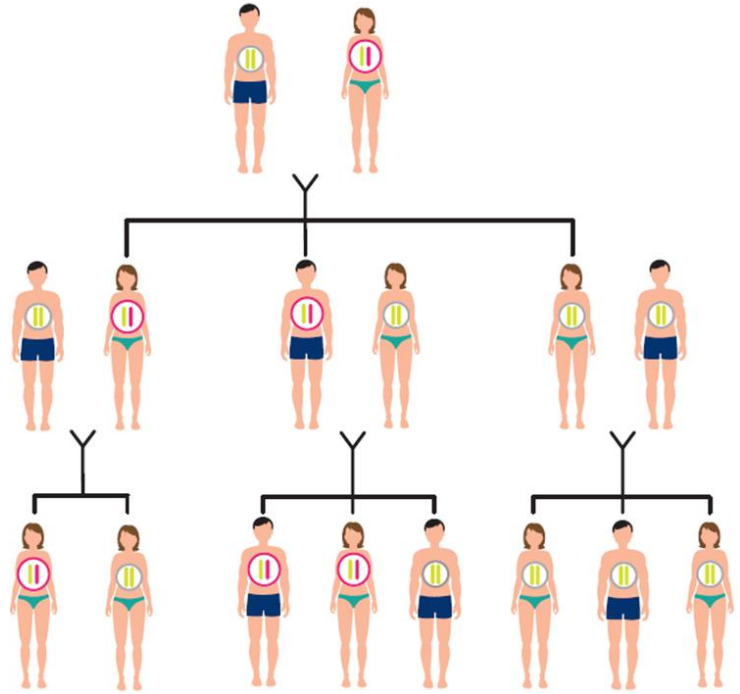
Swiss guidelines for counselling and testing
Genetic predisposition to breast and ovarian cancer

I. Individuals with a close relative[1] with a known pathogenic variant in *BRCA1* or *BRCA2*, or in another gene conferring high risk for breast and ovarian cancer.

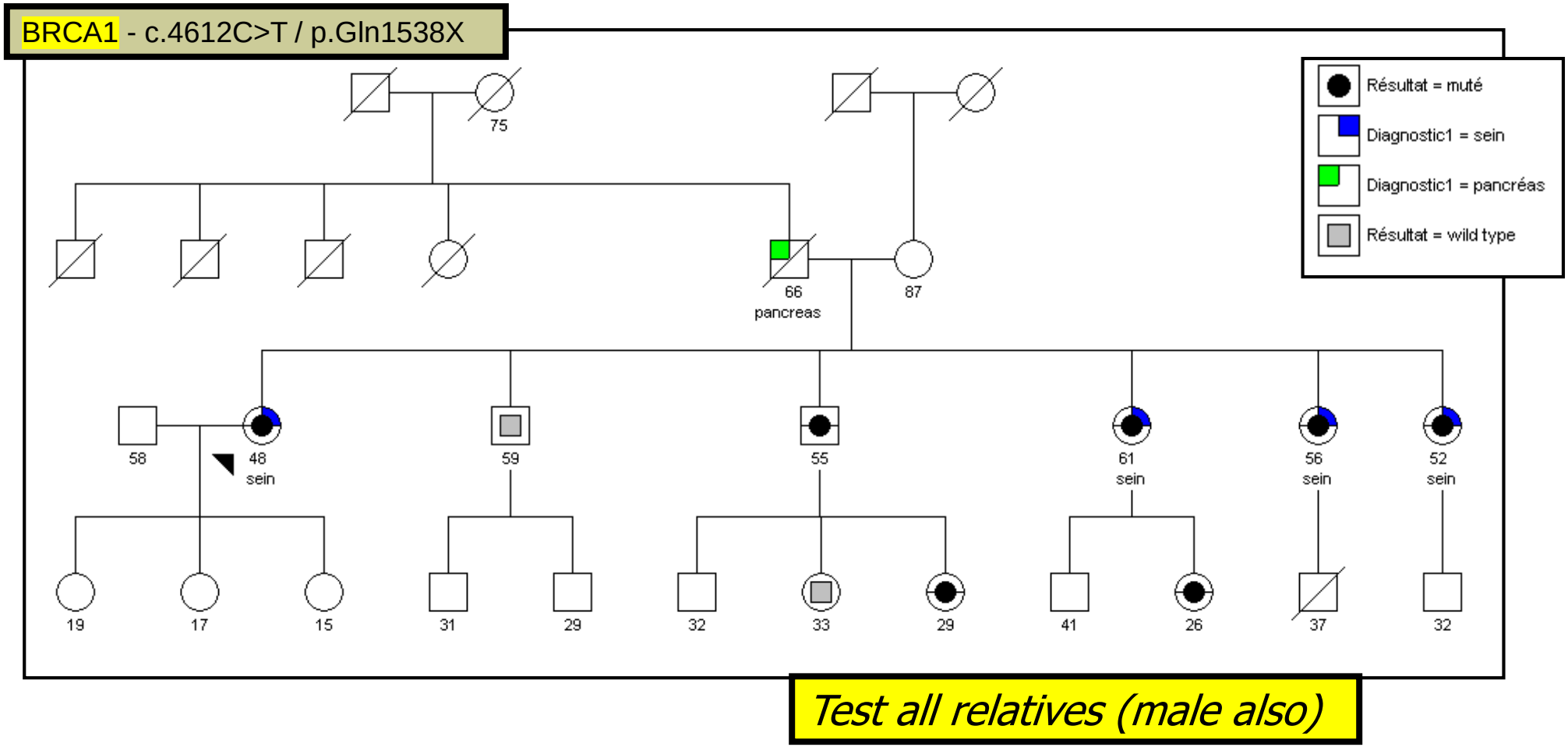
BRCA1 on chr 17; BRCA1 on chr 13



Autosomal dominant pattern



Swiss guidelines for counselling and testing
Genetic predisposition to breast and ovarian cancer



Swiss guidelines for counselling and testing
Genetic predisposition to breast and ovarian cancer

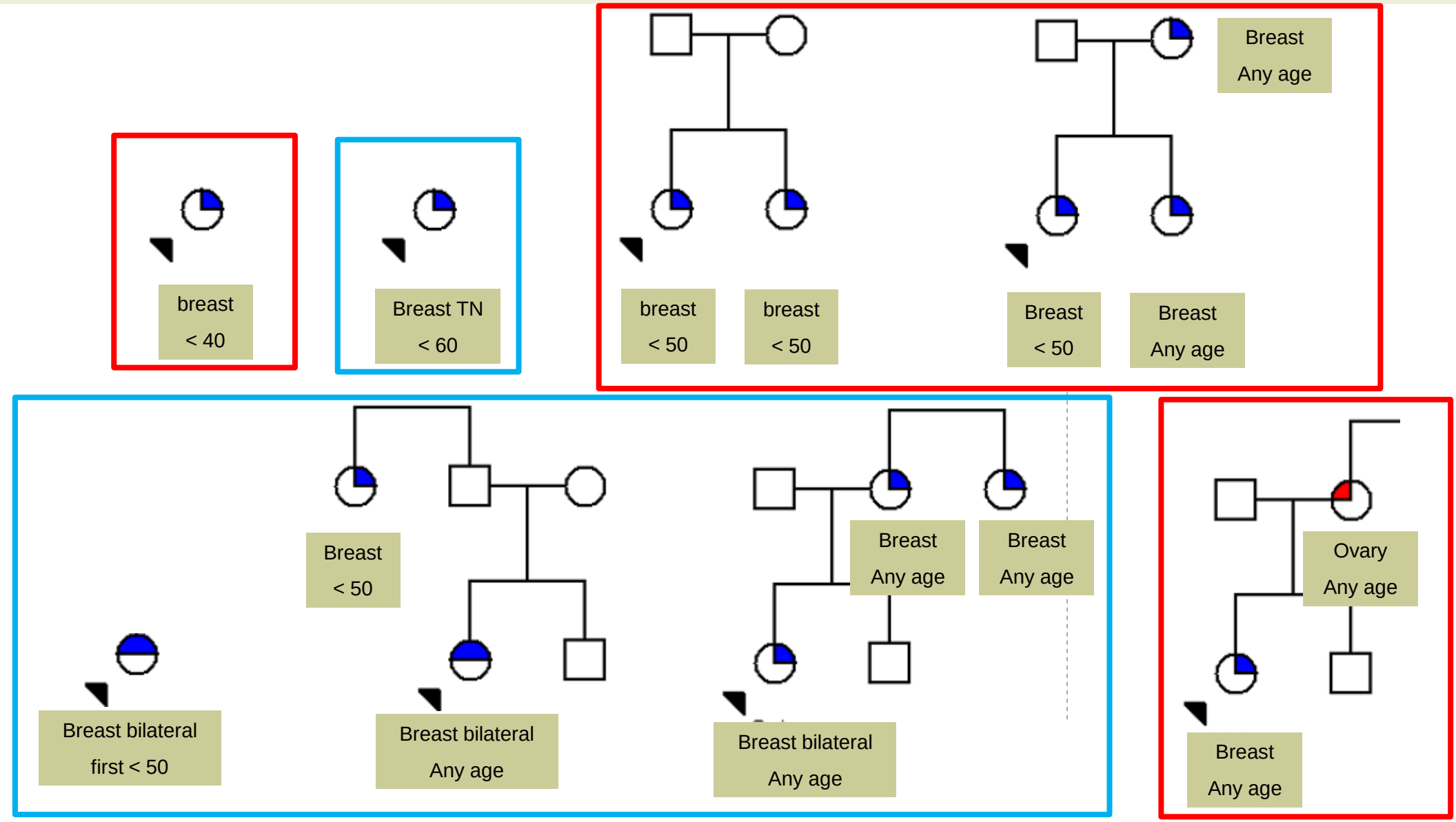
II. WOMEN with a personal history of BREAST CANCER *and* one of the following:

- Age at diagnosis <40 years;
- Triple negative (oestrogen receptor, progesterone receptor and HER2 negative) breast cancer ≤60 years;
- Age at diagnosis ≤50 years, with ≥2 close relatives[1] with breast cancer at any age or with only 1 close relative[1] with breast cancer ≤50 years;
- Bilateral breast cancer, if the first cancer was diagnosed ≤50 years;
- Bilateral breast cancer at any age, with ≥1 close relative[1] with breast cancer [if only one relative affected, then age at diagnosis ≤50 years];
- Diagnosed at any age, with ≥1 close relative[1] with ovarian[2] cancer at any age;

• See pedigrees next slide

Swiss guidelines for counselling and testing

Genetic predisposition to breast and ovarian cancer



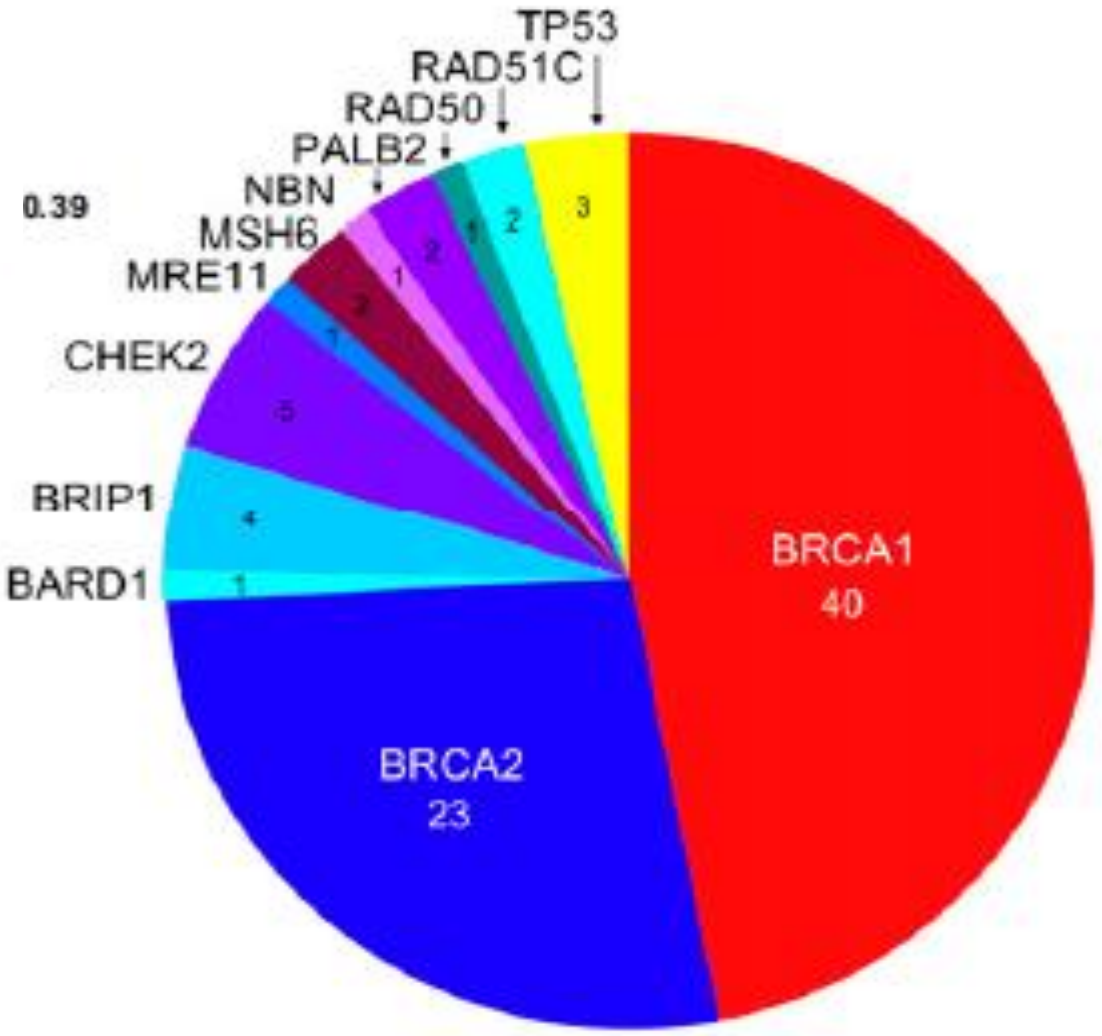
Swiss guidelines for counselling and testing
Genetic predisposition to breast and ovarian cancer

III. Women with a personal history of OVARIAN[2] CANCER *and* one of the following:

– Non-mucinous epithelial subtypes, particularly high grade serous histology, at any age;

Or any ovarian cancer in the pedigree

Ovarian cancer predisposing genes next generation sequencing



Proof of concept !

Germline mutations: 24%

85 germline mutations
12 genes identified
24% of all ovarian cancers
>30% with familial history
>35% at age < 65 y.

BRCA1 - 2 = 18%

«BRCA 3» = 6%

Walsch - PNAS 2011; 108: 18032

Swiss guidelines for counselling and testing
Genetic predisposition to breast and ovarian cancer

IV. MEN with a personal history of BREAST CANCER:

- Particularly, if one or more close male relatives[1] with breast cancer;
- Particularly, if one or more close female relatives[1] with breast or ovarian[2] cancer;

About 20% of male breast cancer are related to a BRCA mutation (most of them BRCA2)

Swiss guidelines for counselling and testing
Genetic predisposition to breast and ovarian cancer

V. Ashkenazi Jewish heritage:

Search for the 3 founder *BRCA1* and *BRCA2* pathogenic variants[3] regardless of personal or family history;

Or some other founder mutations…

But not in CH…

SPECIAL ARTICLE

WILEY HGVS HUMAN GENOME VARIATION SOCIETY

Mutational spectrum in a worldwide study of 29,700 families with *BRCA1* or *BRCA2* mutations

Europe	Austria	391	115	c.181T > G(51)	c.5266dup(46)	c.3018_3021del(35)
	Belgium	166	41	c.2359dup(40)	c.212+3A > G(26)	c.3661G > T(12)
	Bosnia	1	1	c.4158_4162del(1)		
	Czech Rep.	208	42	c.5266dup(87)	c.3700_3704del(25)	c.181T > G(20)
	Denmark	667	101	c.2475del(91)	c.3319G > T(81)	c.5266dup(41)
	Finland	57	31	c.3485del(8)	c.4097-2A > G (5)	c 5266dup(4)
	France	1,522	418	c.5266dup(118)	c.3481_3491del(70)	c.68_69del(63)
	Germany	2,287	381	c.5266dup(411)	c.181T > G(196)	c.4689C > G(63)
	Greece	208	41	c.5266dup(47)	c.5212G > A(29)	c.5406+644_*8273del(24)
	Hungary	235	47	c.5266dup(78)	c.181T > G(60)	c.68_69del(22)
	Iceland	3	1	c.5074G > A(3)		
	Ireland	2	2	c.547+1G > T(1)	c.427G > T(1)	

Rebbeck – The CIMBA consortium - Human Mutation. 2018;1–28.

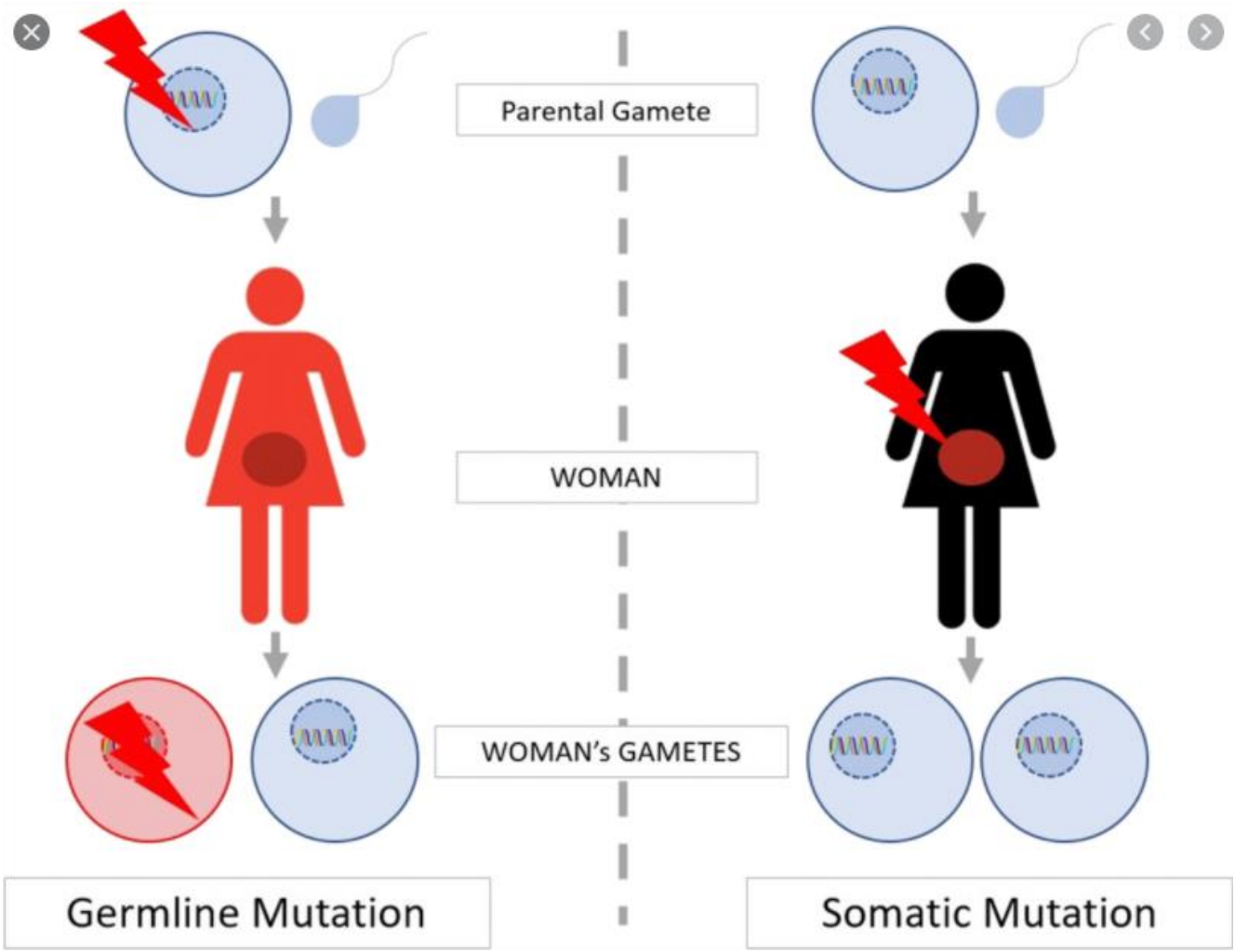
Swiss guidelines for counselling and testing
Genetic predisposition to breast and ovarian cancer

VI. Family history only (i.e. unaffected individuals):

One or more close relatives[1] with breast or ovarian[2] cancer fulfilling one of the above criteria (points II–IV).

E.G : all patients with cancer are dead…

Swiss guidelines for counselling and testing
Genetic predisposition to breast and ovarian cancer



*Test needed for the **PARPi** therapy*

*Genetic **somatic** testing in the tumor is not « limited by the insurances !*

*Confirmatory genetic **germline** testing is required for the genetic counseling*

Genetics in Senology
early breast cancer (unicentric)

- What is a cancer predisposing gene ?
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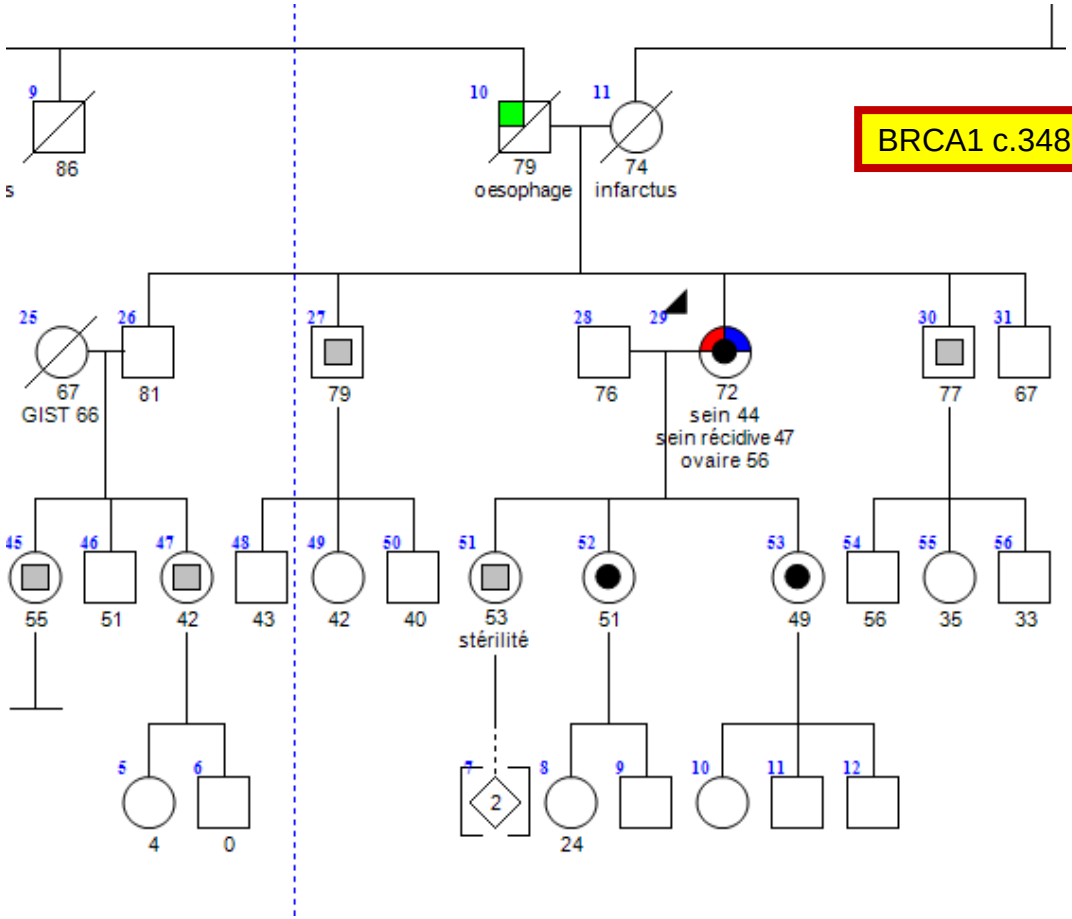
Some pedigrees to discuss a germline mutation is known

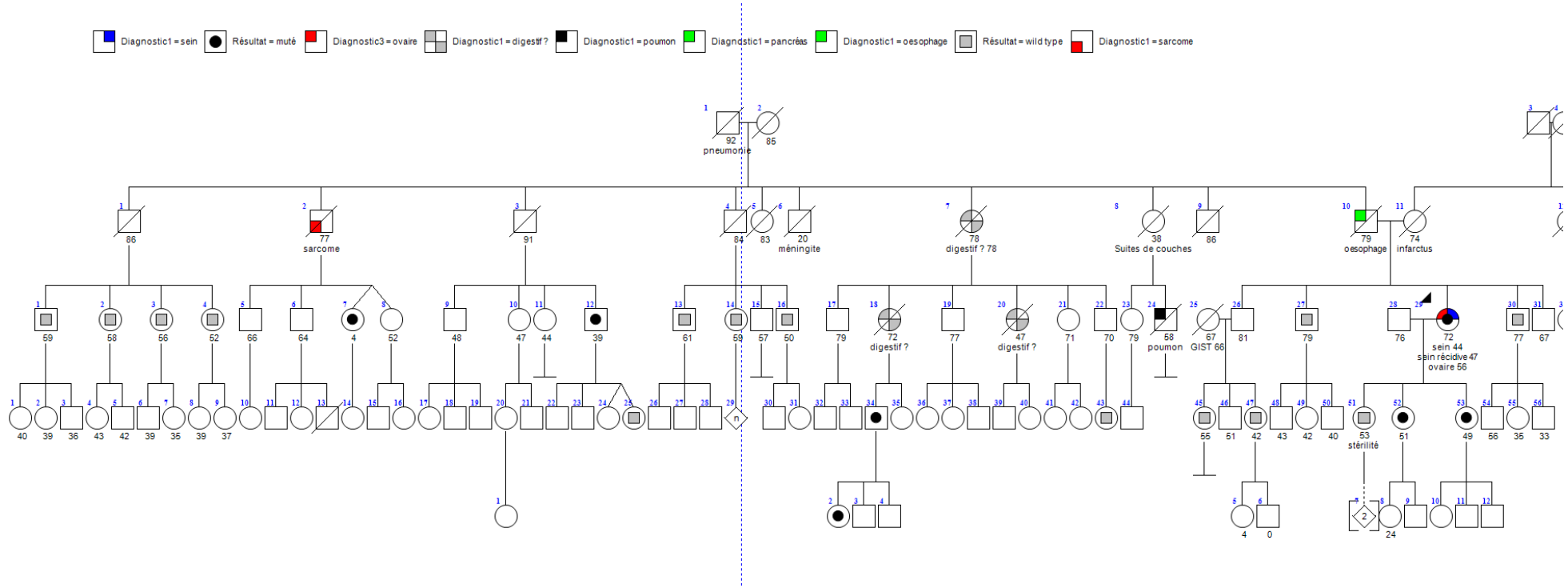
- The « cascade » screening…how « wide » ?



Some pedigrees to discuss a germline mutation is known

- The « cascade » screening…be « obstinate »

BRCA1 c.3481_3491del (p.Glu1161PhefsX3)



Some pedigrees to discuss a germline variant is known…

- **39 years old patient with a lump in the left breast in 2009**
- **Carcinome canalaire invasif du sein droit, cT2, pN0 (0/3) sn cM0G3, ER négatif, PR négatif, HER2 négatif. ypT0, 1 diagnostic : 05/09**
- 04.06.2009 : excision de 3 ganglions sentinelles indemnes de tumeur. **pN0**
- 06/09 – 09/09 : 6 cures de chimiothérapie néoadjuvante par schéma TAC (Taxotère, Adriamycin, cyclophosphamide) avec rémission pathologique complète.
- 29.10.2009 : quadrantectomie du sein droit. Histologie pathologie Bâle : tissu mammaire sans tumeur, **ypT0.**
- 01-02/10 : radiothérapie adjuvante du sein droit avec 50 Gy et 16 Gy de boost.

- **Examen oncogénétique en 2011**
- Pas de mutation pathogène BRCA1 1 ou 2,
- Mise en évidence de **variant BRCA1 5309 G>C / p.Gly1770Ala.**

No prophylactic surgeries

Some pedigrees to discuss a germline variant is known…

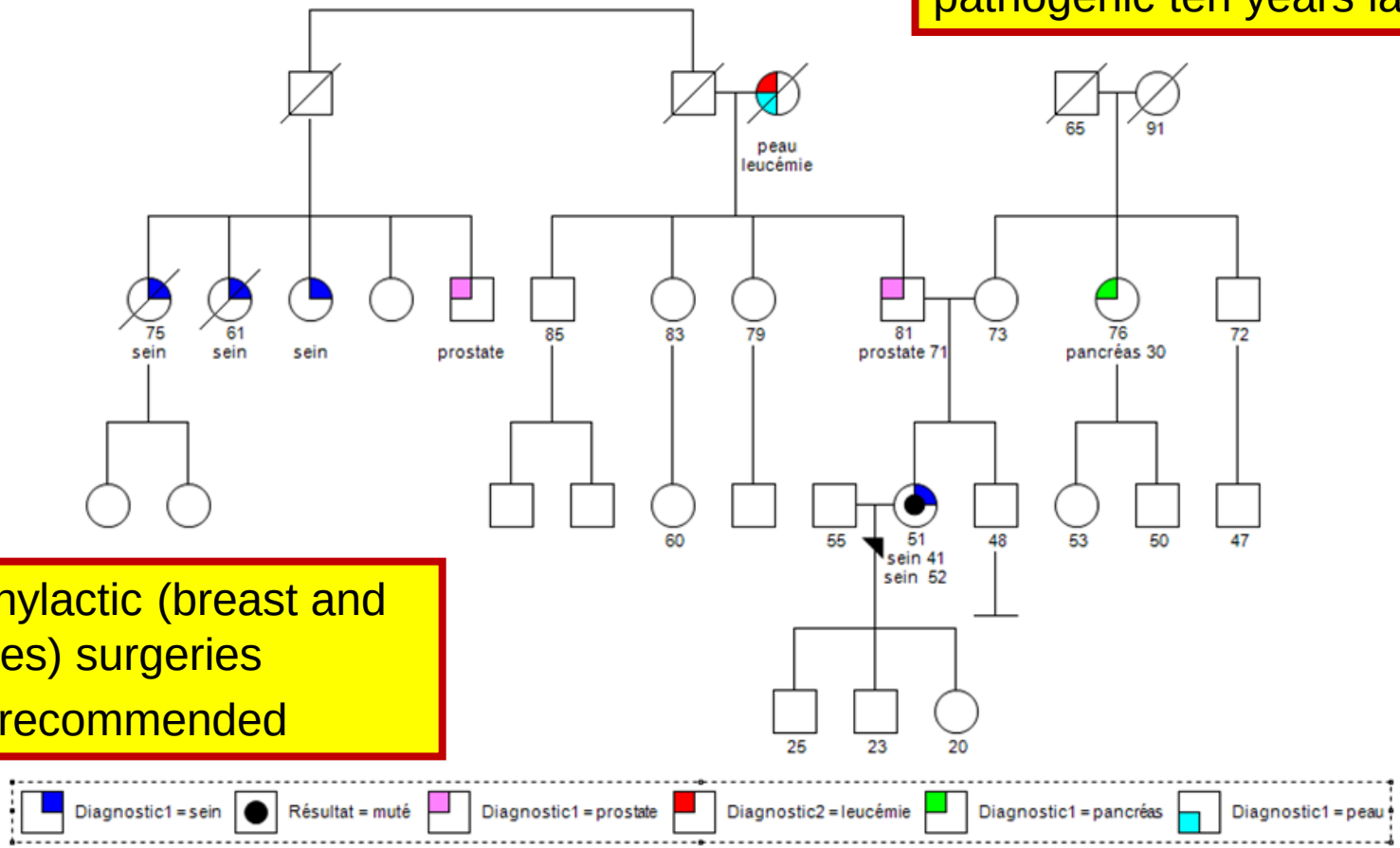
- **The same yet 50 years old patient with a lump in the left breast in 2020**
- **Récidive d'un carcinome canalaire invasif du sein droit cT1, cN0, cM0, triple négatif.**
- **Dès 29.11.19** : chimiothérapie néoadjuvante par Taxotère 75 mg/m² et Carboplatine AUC 6, toutes les trois semaines pour 6 cures.
- **2eme consultation oncogénétique**.

What about this BRCA1 variant 5309 G>C / p.Gly1770Ala ?

Some pedigrees to discuss a germline variant is known…

- **The same yet 50 years old patient with a lump in the left breast in 2020**
- **2eme consultation oncogénétique**.

Variant reclassified as pathogenic ten years later



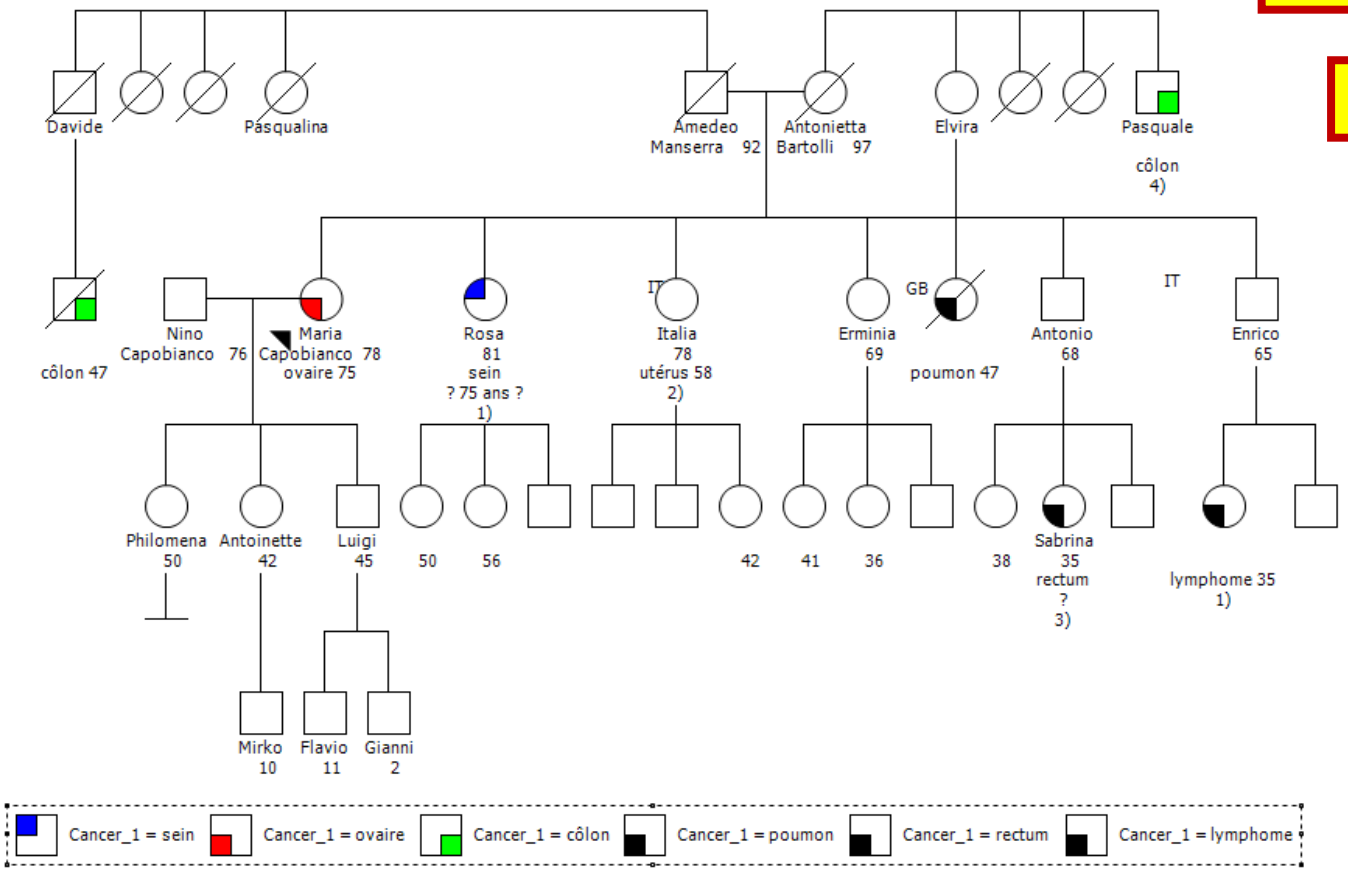
prophylactic (breast and ovaries) surgeries now recommended

Some pedigrees to discuss a somatic mutation is known

- **Carcinome séropapillaire (ER+ 80%, PR+ 20%, BRCA2 muté) de la trompe droite de stade pT3c, pN1b (12/14), FIGO IIIC.**
- Mutation somatique de BRCA2 référencé R2336P

Do you test the patient ?

Why ?



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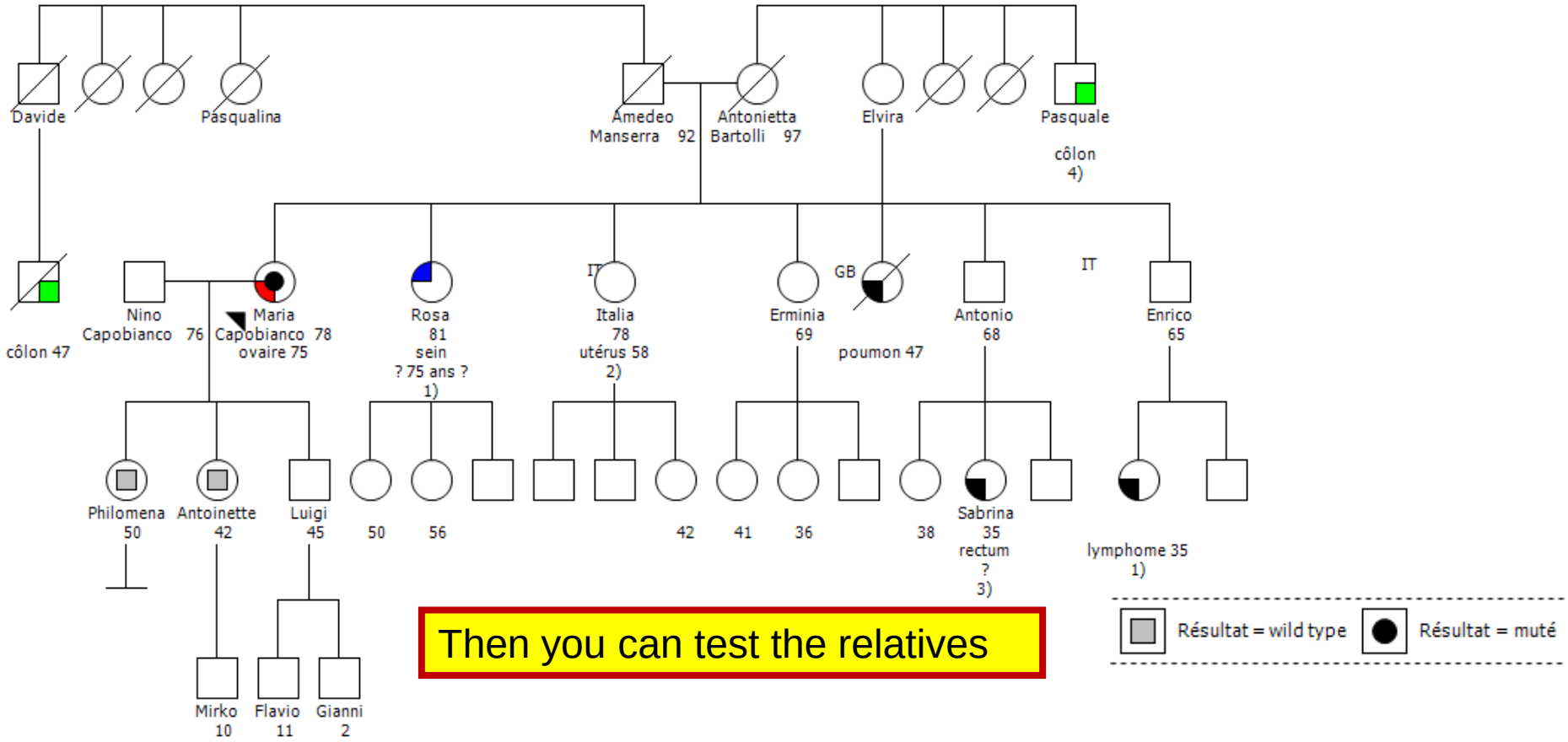
- Mutation somatique de BRCA2 référencé R2336P

BRCA2 c.7007 G>C / p.Arg2336Pro



Some pedigrees to discuss a somatic mutation is known

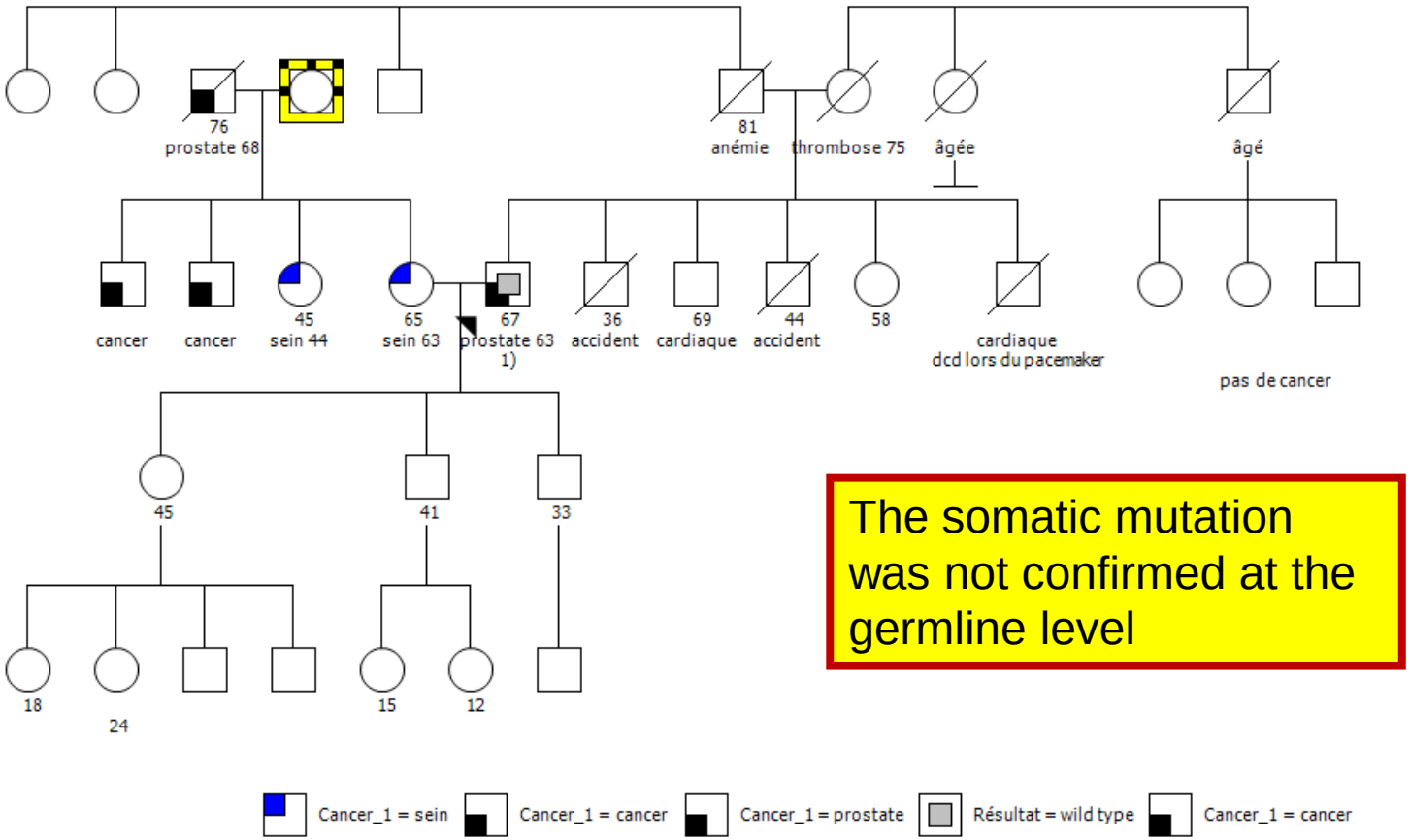
- **Diagnostics Adénocarcinome prostatique T1c, Nx, M1b, Gleason 4+5 = 9**
- 08.01.2016 Biopsie de la prostate Gleason 9 (4+5), prolifération haute
- Dès 09.02.2016 Traitement contra-sexuel par Zoladex 10.8 mg sc tous les trois mois
- 3/19 traitement antihormonal par Xtandi 160 mg/j et Xgeva 120 mg sc
- 25.3-5/1919 Docetaxel 50 mg/m2 toutes les 2 semaines

BRCA analysis for PARPi treatment

- **29.06.19 Biopsie de moelle osseuse : Infiltration par l'adénocarcinome de**
- **la prostate**
- **Mutation somatique de BRCA2 c.82dupA / p.S28Kfs*3**
- **Dès 10/19 Lynparza (Olaparib) 150 mg 2-0-2 (Inhibiteur de PARP)**

Some pedigrees to discuss a somatic mutation is known

- **Diagnostics Adénocarcinome prostatique T1c, Nx, M1b, Gleason 4+5 = 9**
- **Mutation somatique de BRCA2 c.82dupA / p.S28Kfs*3**



The somatic mutation was not confirmed at the germline level

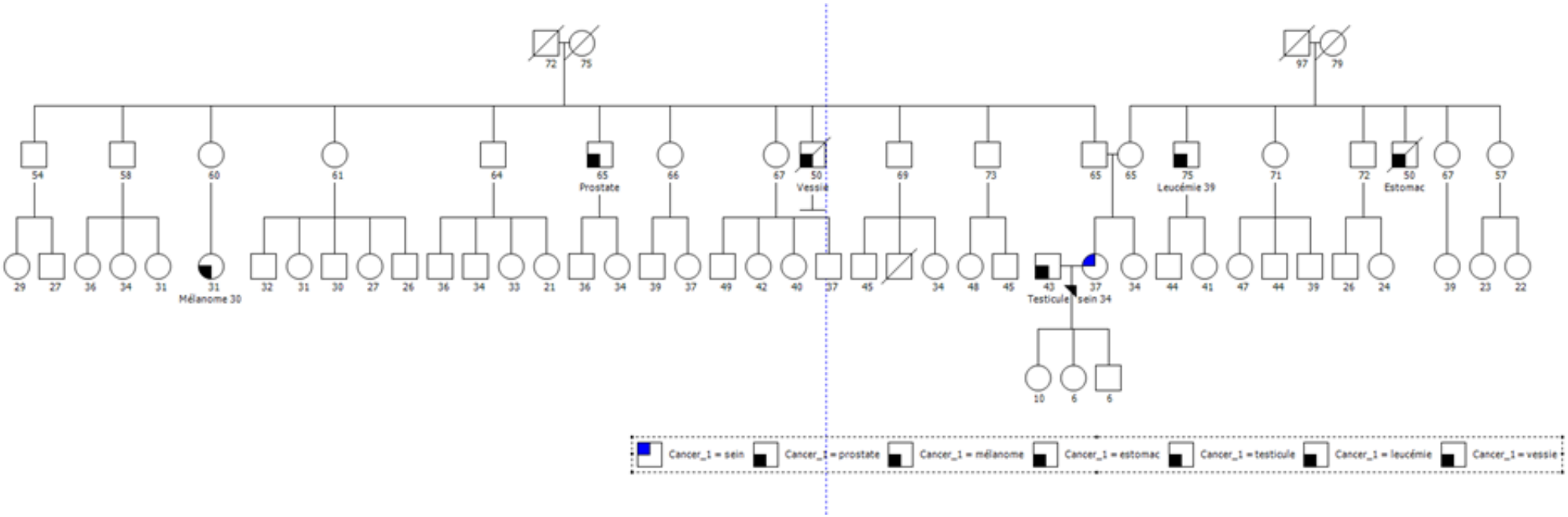
Some pedigrees to discuss
The young patient ….

- **31 years old patient with a lump in the left breast**
- **Carcinome canalaire invasif de type HER2 like (G2, ER+ 80%, PR+ 100%, HER2 3+, Ki-67, 30%) avec carcinome in situ G2, du quadrant supéro-externe du sein gauche de stade,cT2, cN1 (biopsie négative) , M0.**
- 22.05.17 : mammographie, IRM mammaire, biopsie du ganglion axillaire et clip nodal et
- tumoral. : microcalcifications étendues
- 23.05.2017 : mise en place du Port-à-cath.
- 24.05.2017 : PET-CT : pas de métastases
- 24.05.2017 : Zoladex (prévention de la fertilité)
- Du 24.05.2017 au 13.09.2017 : chimiothérapie néo-adjuvante par **6** cycles de **Taxotère**,
- **Carboplatine**, **Herceptin** dont 4 cycles avec **Perjeta**.

Genetic testing done during the neo-adjuvant chemotherapy

Breast gene panel, including BRCA1, BRCA2 , TP53…

Some pedigrees to discuss
The young patient ….



Breast gene panel, including BRCA1, BRCA2 , TP53…

Why is TP53 testing done here ?

Some pedigrees to discuss
The young patient ….

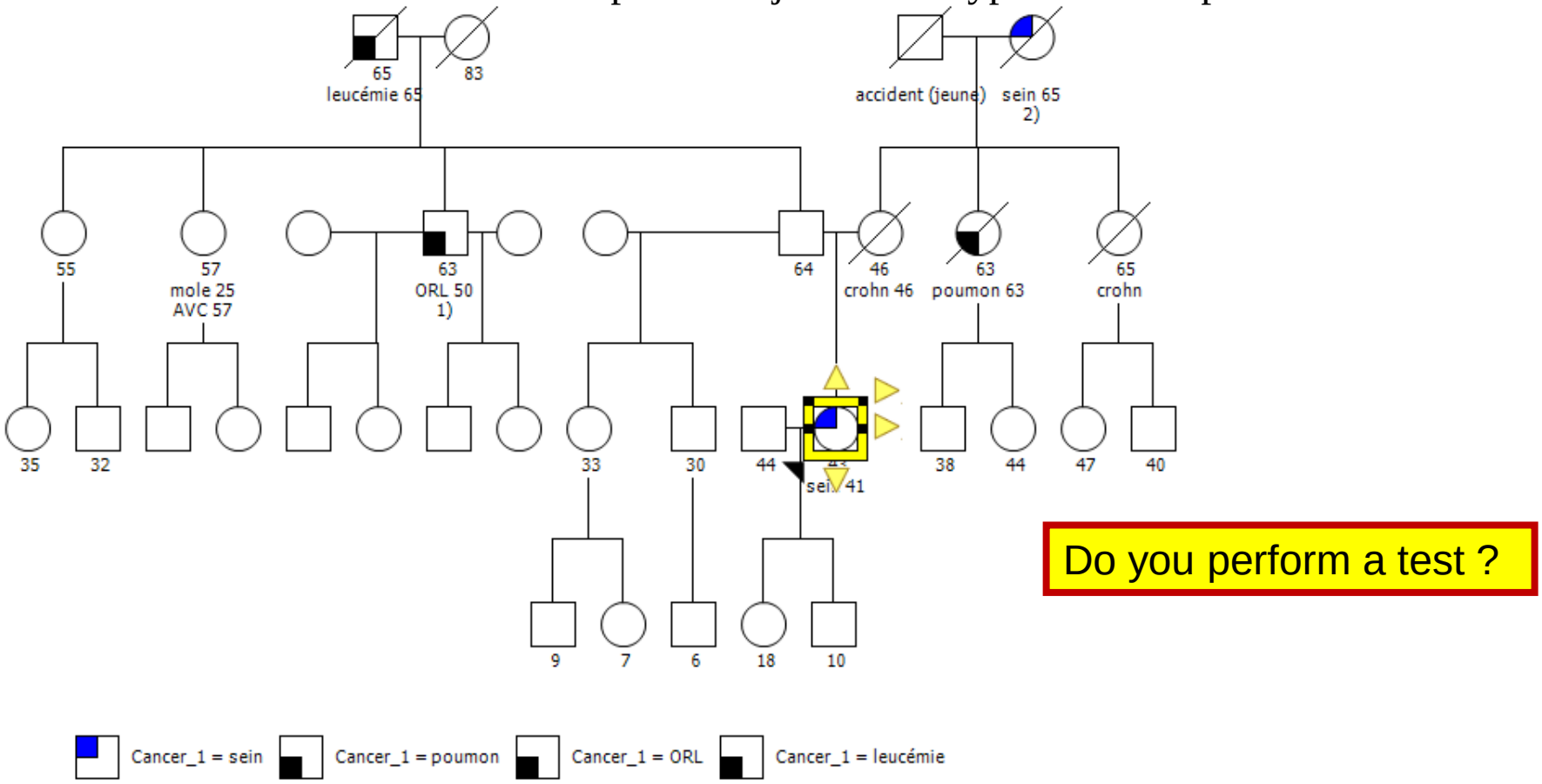
- 20.10.2017 : skin-sparing mastectomy avec reconstruction immédiate par DIEP (USB), **ypT2**
- **ypN0** (0/3)
- 3.11.2017 : Tumoroard : introduction de aromasin et poursuite du Zoladex pour 5 ans,
- poursuite de l'Herceptin pour un an (sans perjeta) et RT du sein et des aires ganglionnaires.
- Décembre 2017 à janvier 2018 : radiothérapie de la reconstruction gauche et des aires
- ganglionnaires (USB, rapport en attente)
- 18.04.2018 : opération du mamelon et ablation du PAC.
- **At a follow-up of 3 years, the patient is doing well**

Breast gene panel, including BRCA1, BRCA2 , TP53…fully negative

TP53 tips !
Li-Fraumeni syndrome is very rare
In very young patient
Assiciated with HER2 positive breast cancer
One third of the cases are neo-mutation (CAVE the negative family history)

Some pedigrees to discuss the neo-adjuvant opportunity

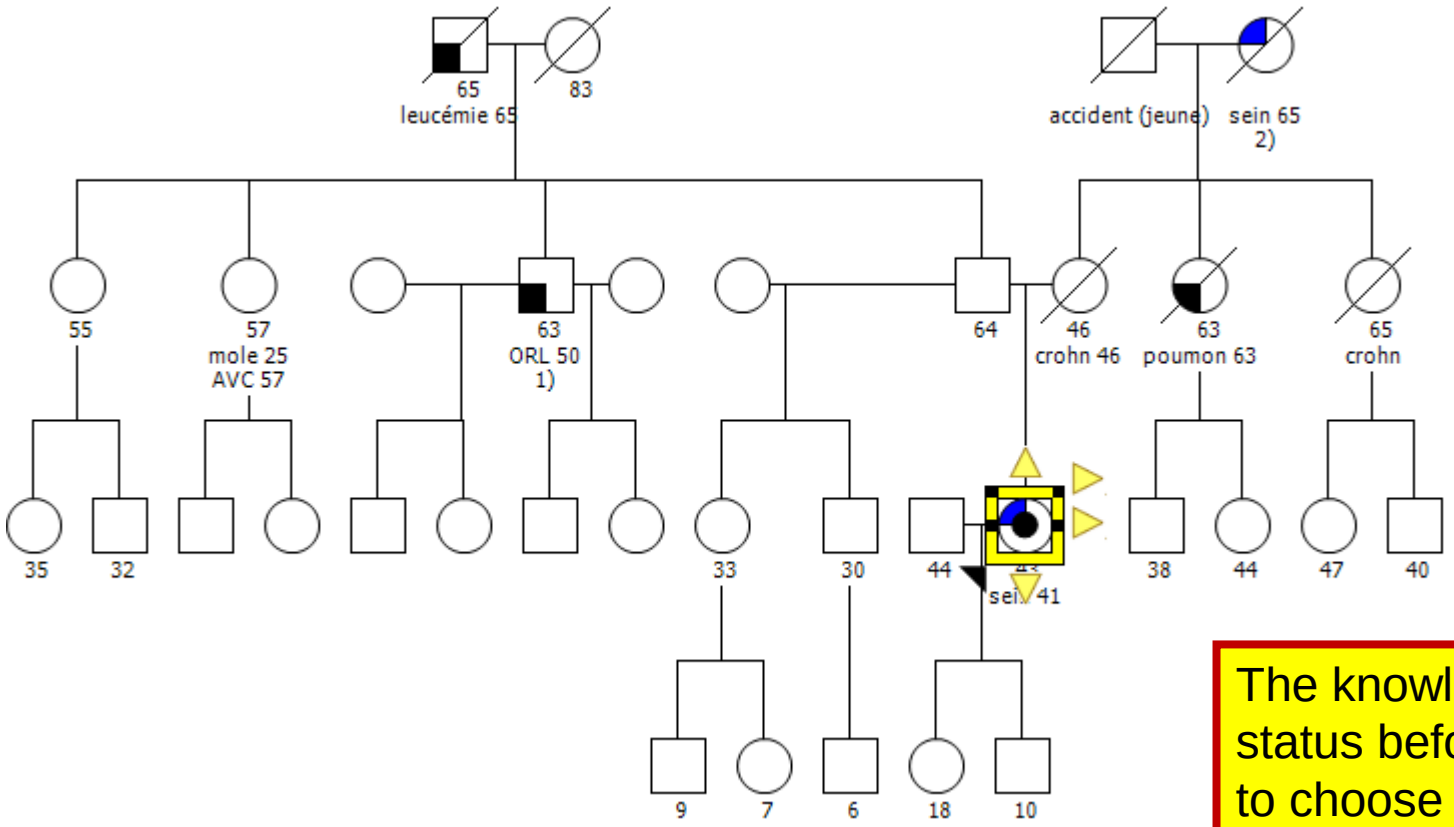
- **Carcinome canalaire invasif de type luminal B (G3, ER+ 90%, PR+90%, Her2 2+ (FISH négatif), Ki-67 25%, p53 négatif) du sein gauche de stade cT2, cN1, M0.**
- Dès le 21.12.2017 hormonothérapie par le **Zoladex LA** (protection ovarienne)
- 5.1.2018 au 28.5.2018: Chimiothérapie néoadjuvante de type **4 dd-AC** puis **12 Taxol**



Do you perform a test ?

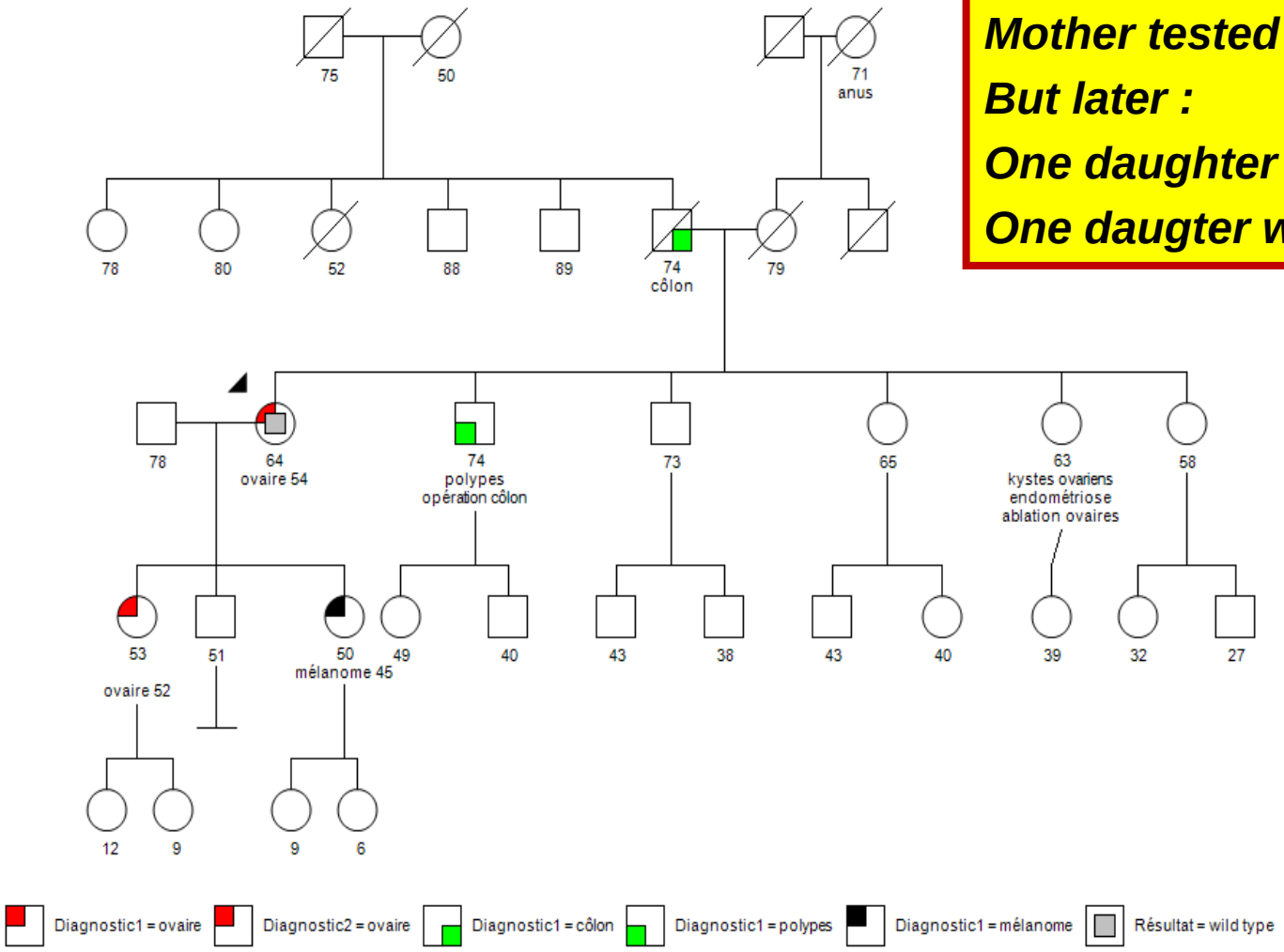
Some pedigrees to discuss the neo-adjuvant opportunity

- **Mutation pathogène de BRCA1 c.1687 C>T /p.Gln563X**
- 21.6.2018 mastectomie bilatérale avec reconstruction immédiate (Engeried, Dr. Berclaz)
- 30.10.2018 Hystérectomie et ovariectomie préventive
- Hormonothérapie par exemestane



The knowledge of the mutational status before surgery is the key to choose the right treatment

Some pedigrees to discuss
A tricky ovarian family…



A BRCA negative family

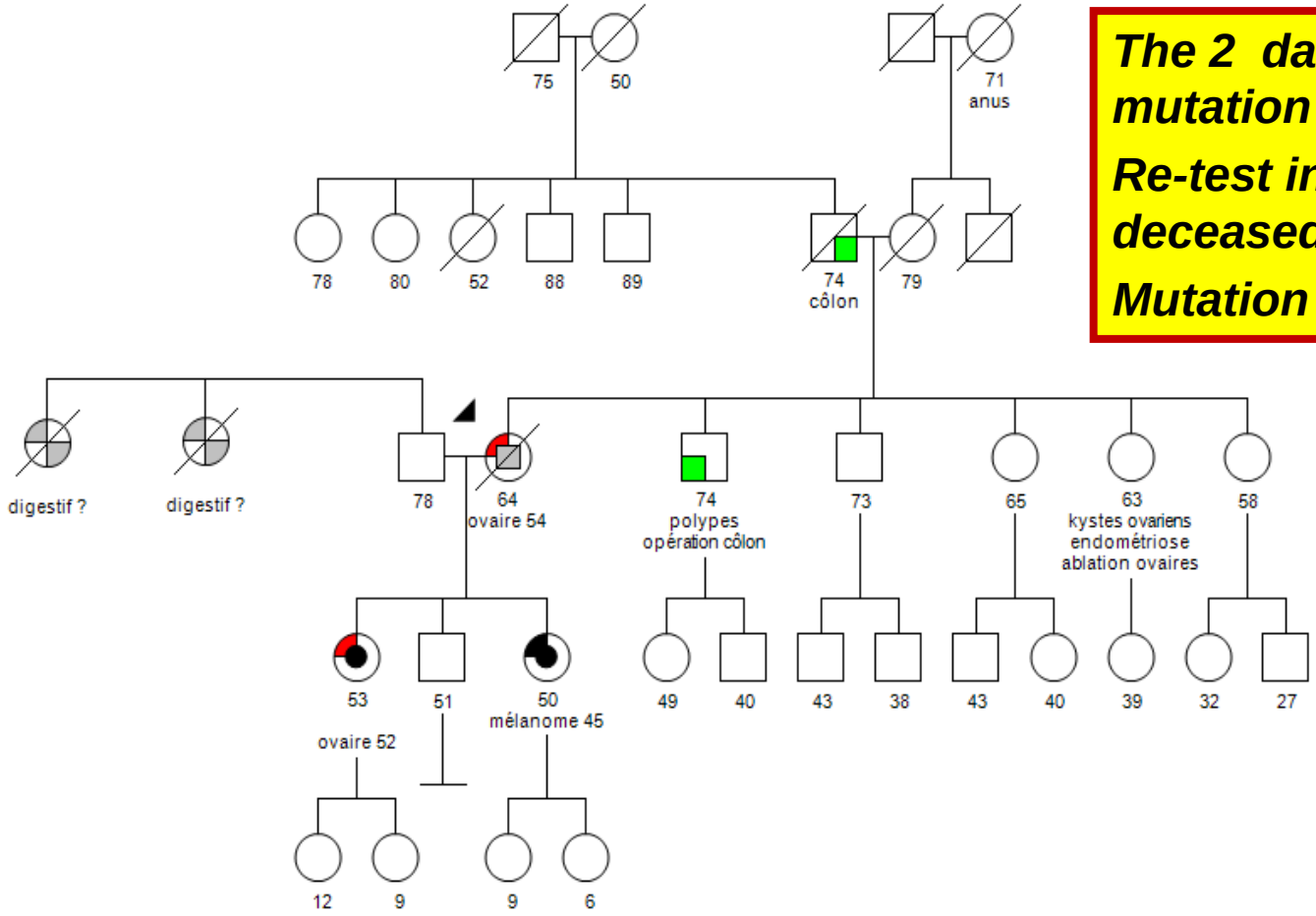
Mother tested negative

But later :

One daughter with melanoma

One daugter with ovarian cancer

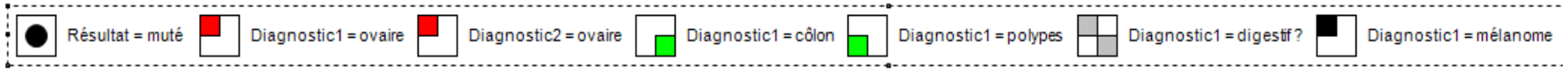
Some pedigrees to discuss
A tricky ovarian family…



The 2 daughters with a BRCA2 mutation

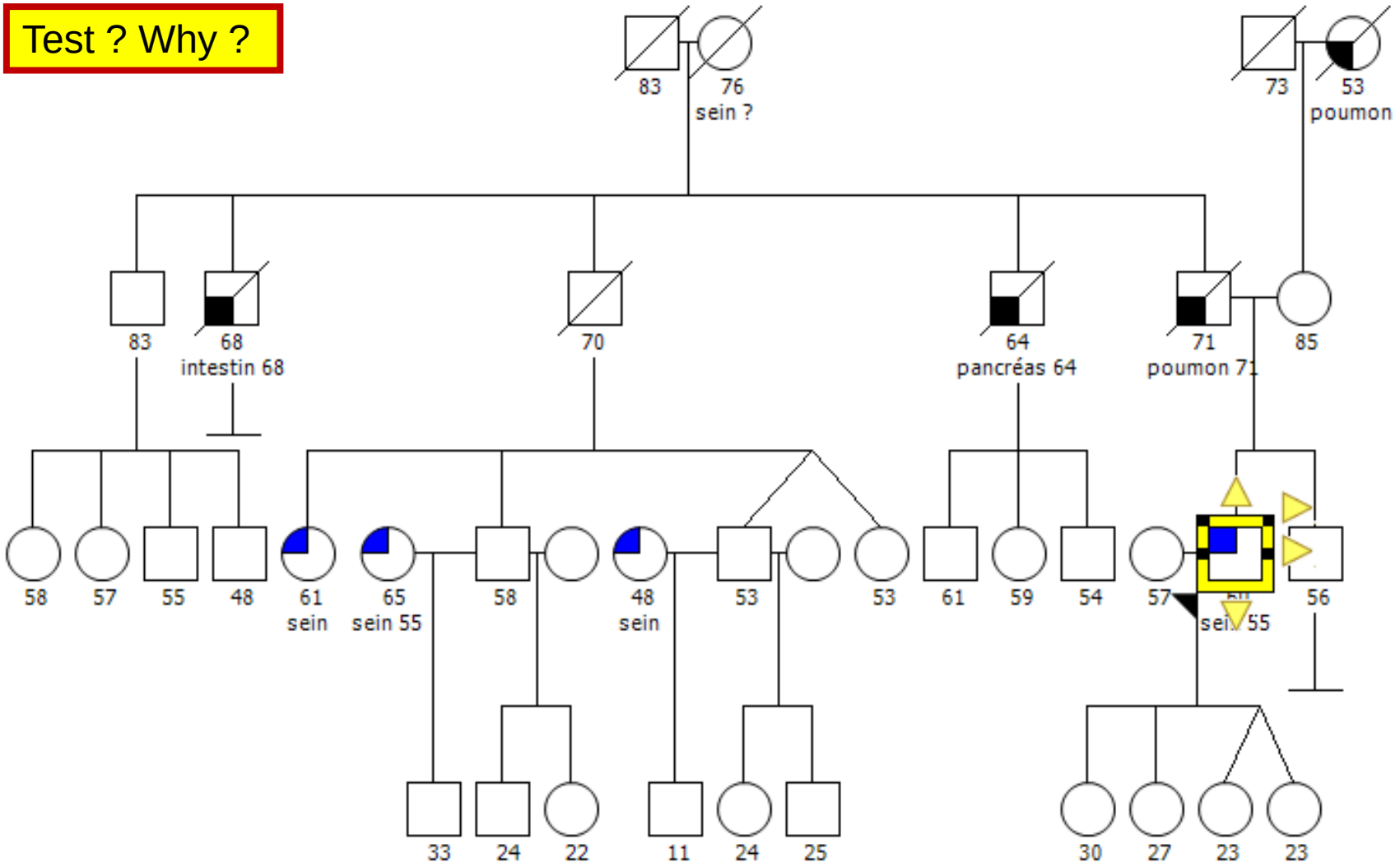
Re-test in the DNA of the deceased mother negative

Mutation probably in the father…

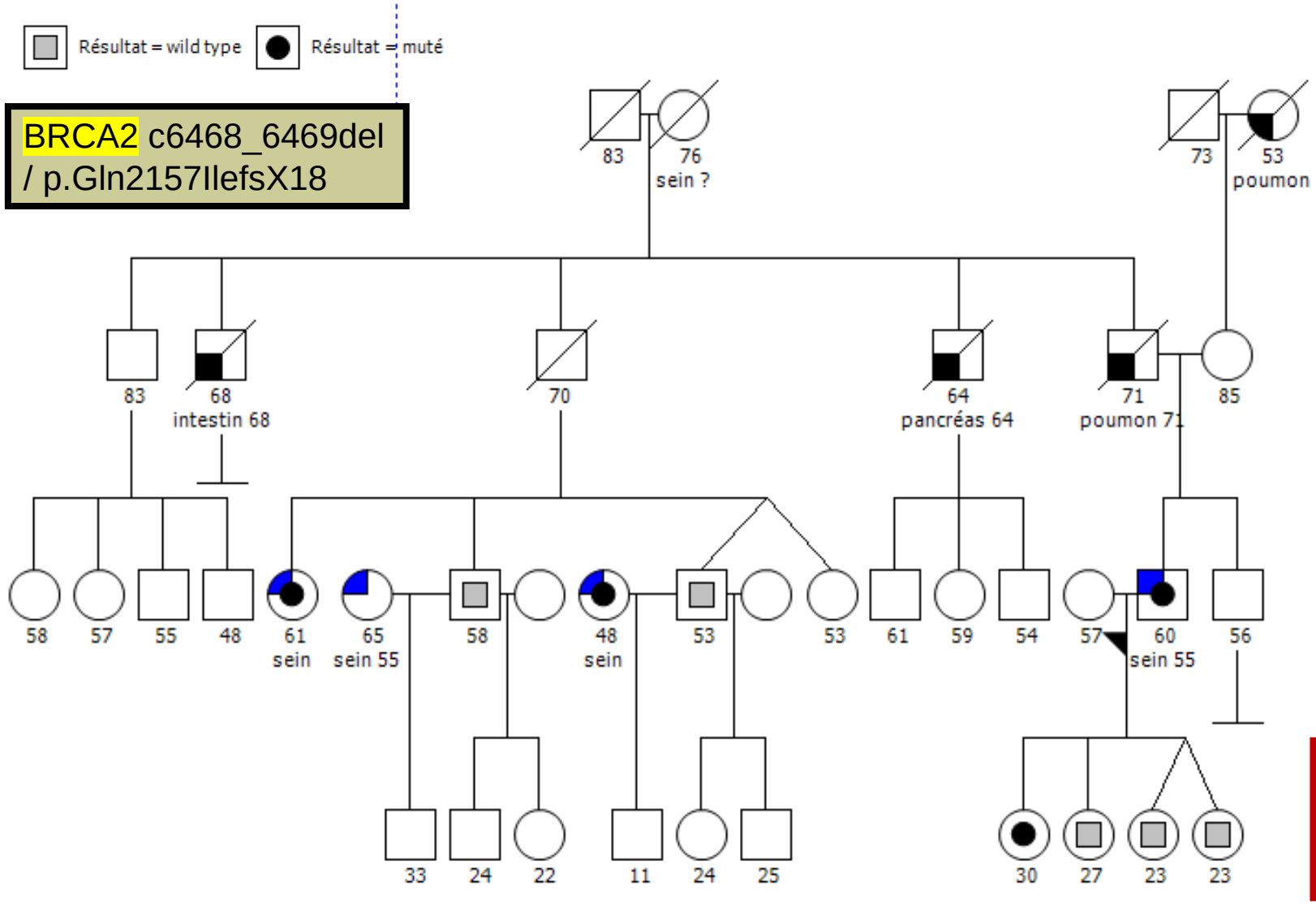


Some pedigrees to discuss the male patient…

Test ? Why ?

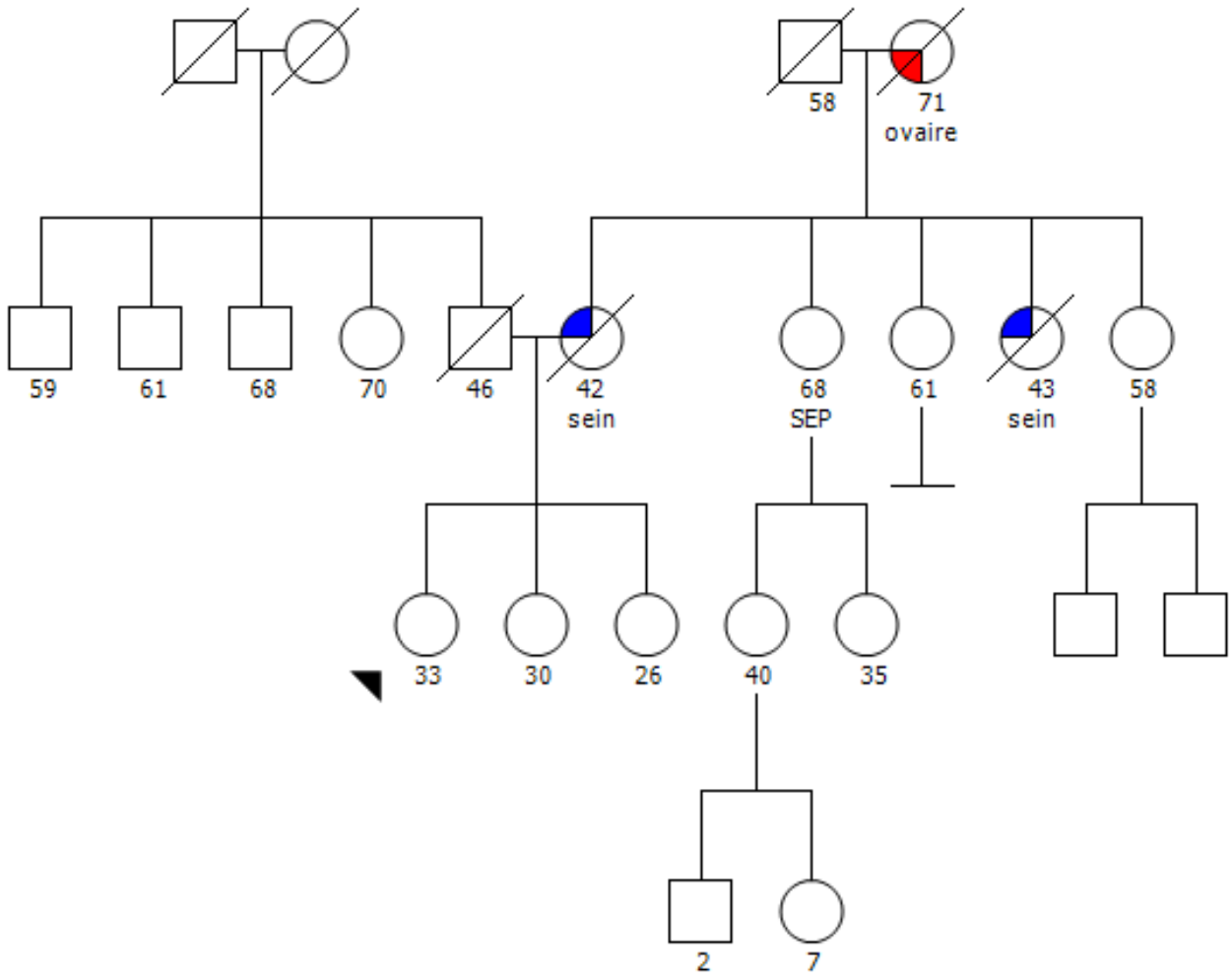


Some pedigrees to discuss the male patient…



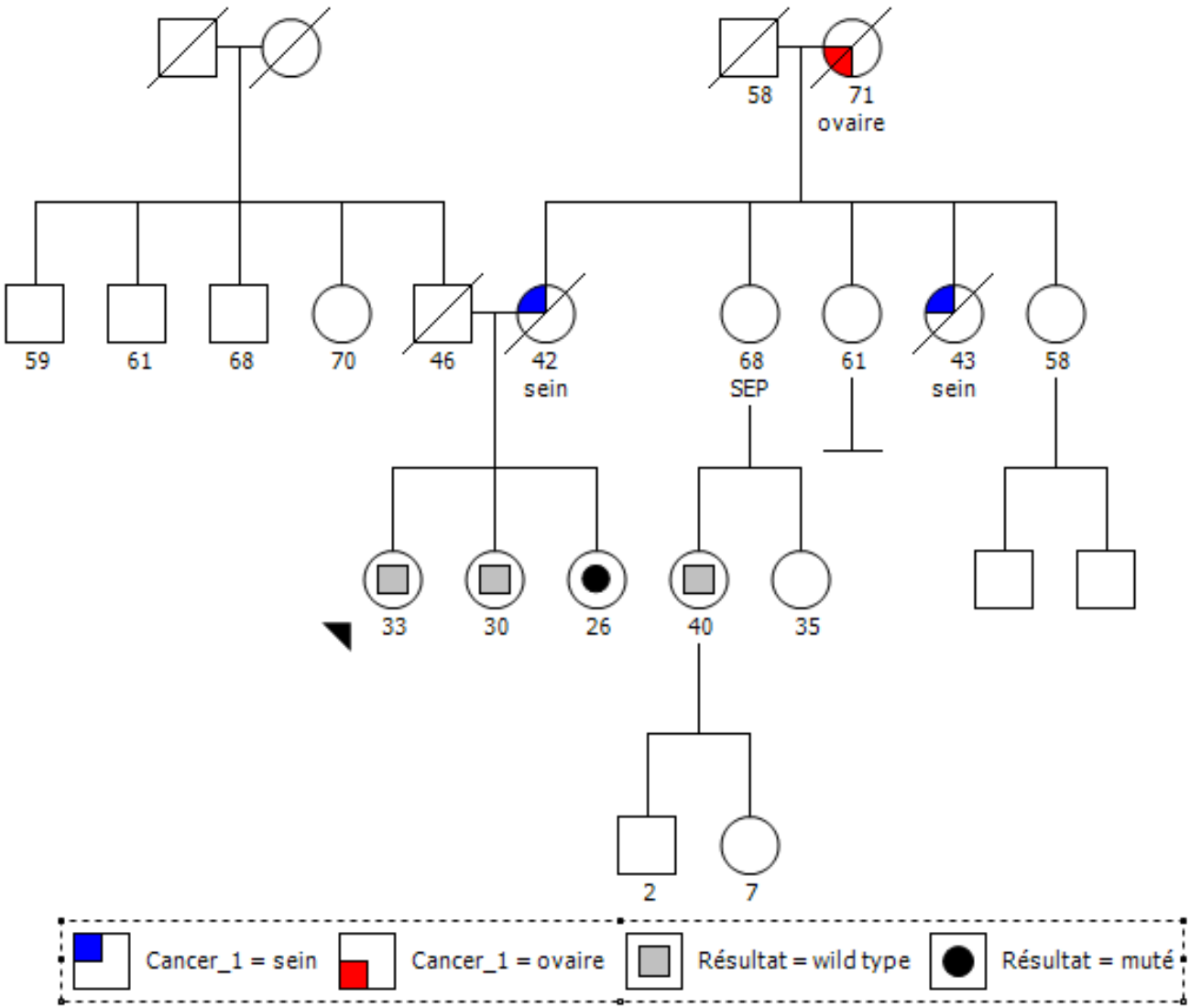
Informative testing for the 4 daughters

Some pedigrees to discuss the family history…



Test ? Who ? Why ?

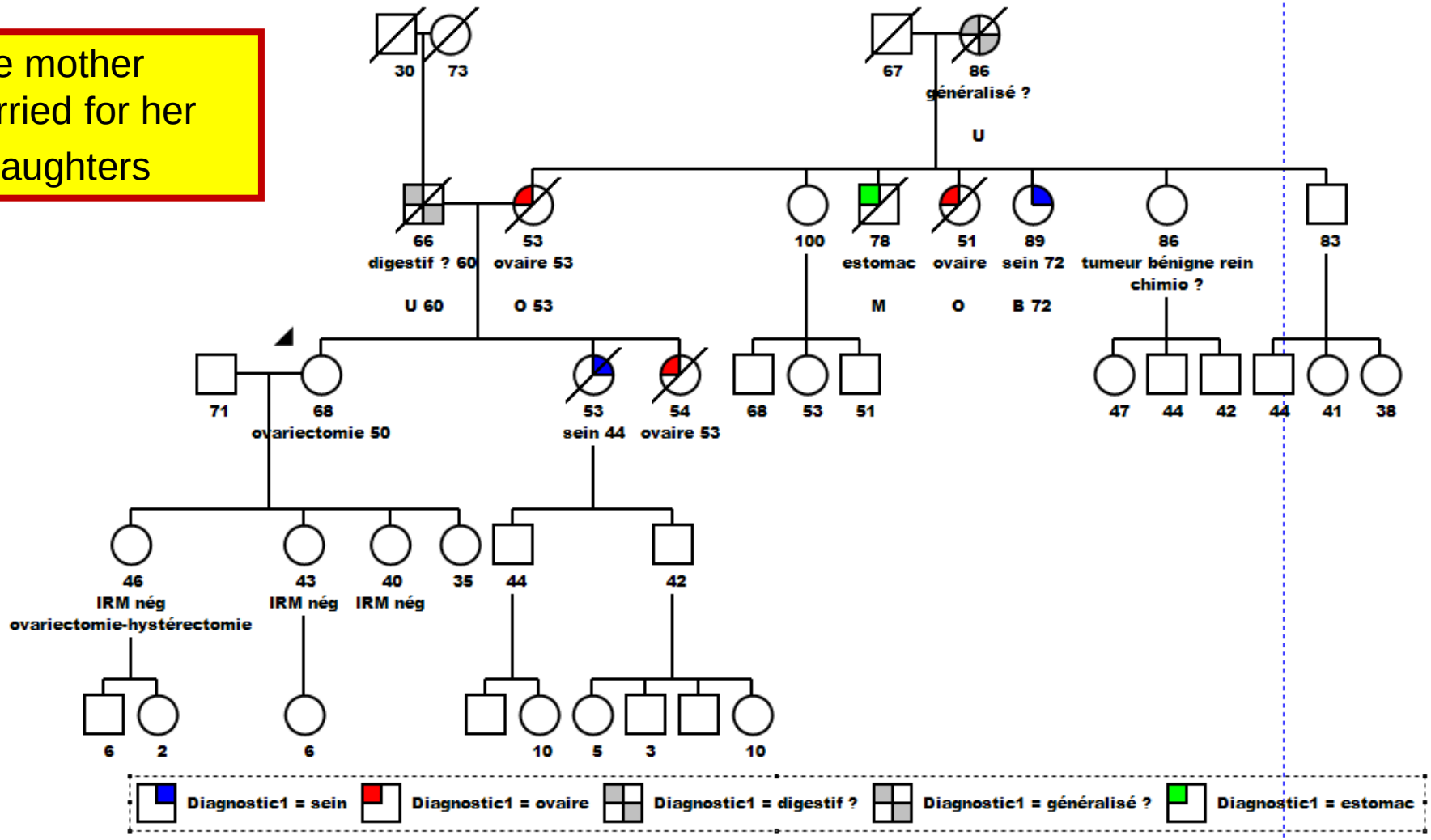
Some pedigrees to discuss the family history…



informative testing, because one mutation has been identified

Some pedigrees to discuss
The challenging pedigree…

The mother worried for her 4 daughters

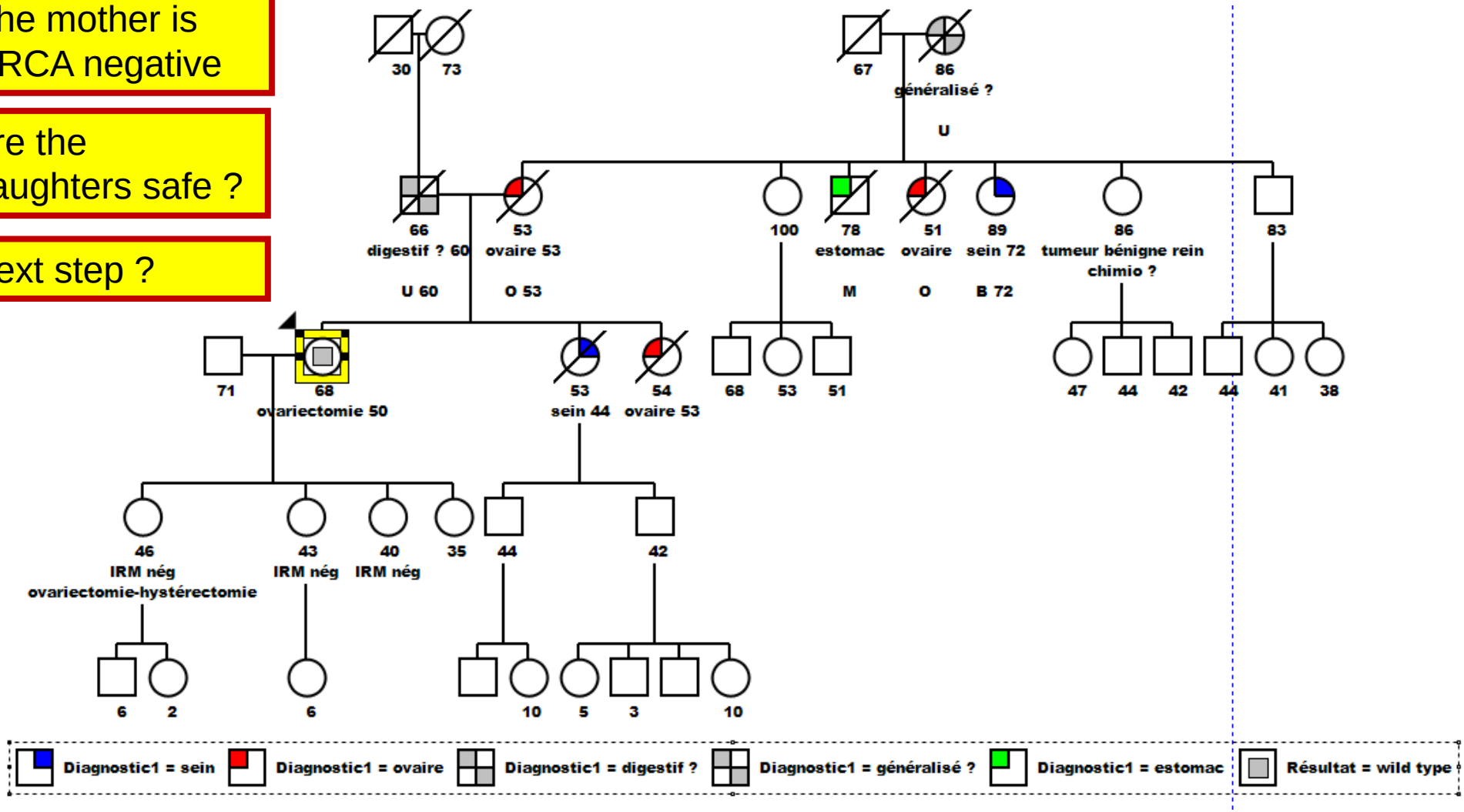


Some pedigrees to discuss
The challenging pedigree…

The mother is BRCA negative

Are the daughters safe ?

Next step ?

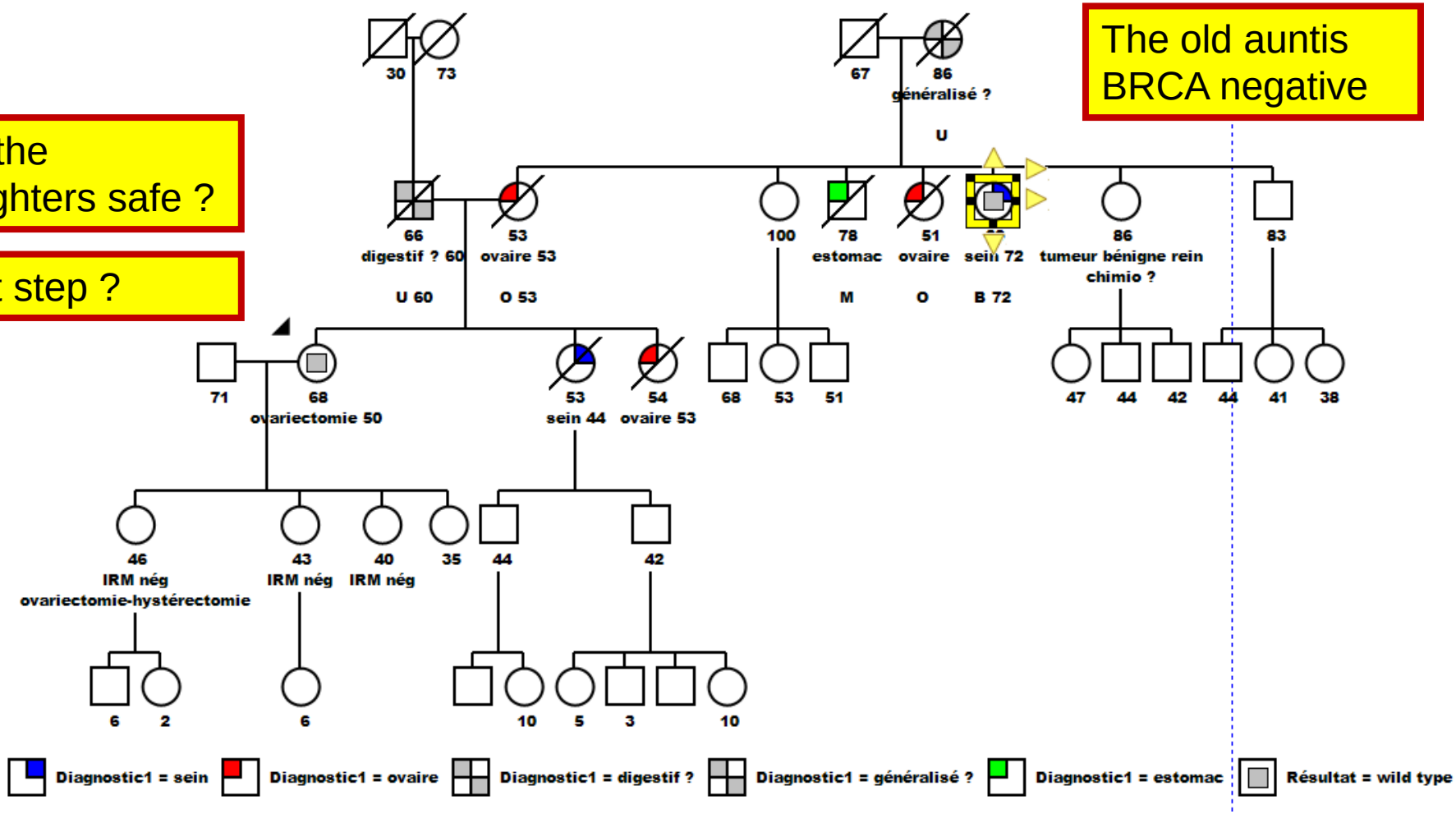


Some pedigrees to discuss
The challenging pedigree…

Are the daughters safe ?

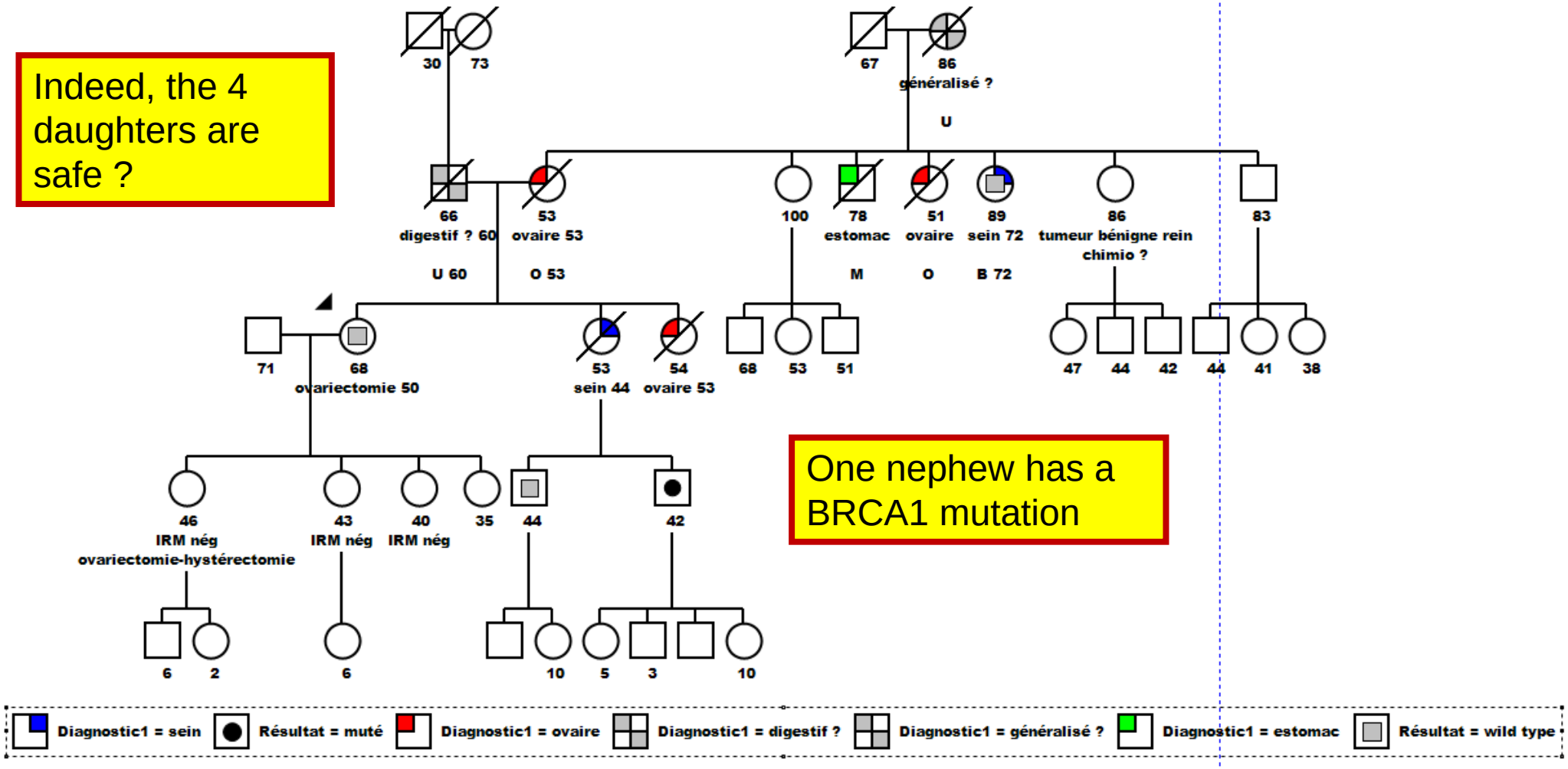
Next step ?

The old auntis BRCA negative



Some pedigrees to discuss
The challenging pedigree…

Indeed, the 4 daughters are safe ?



One nephew has a BRCA1 mutation