Accelerated genetic investigation

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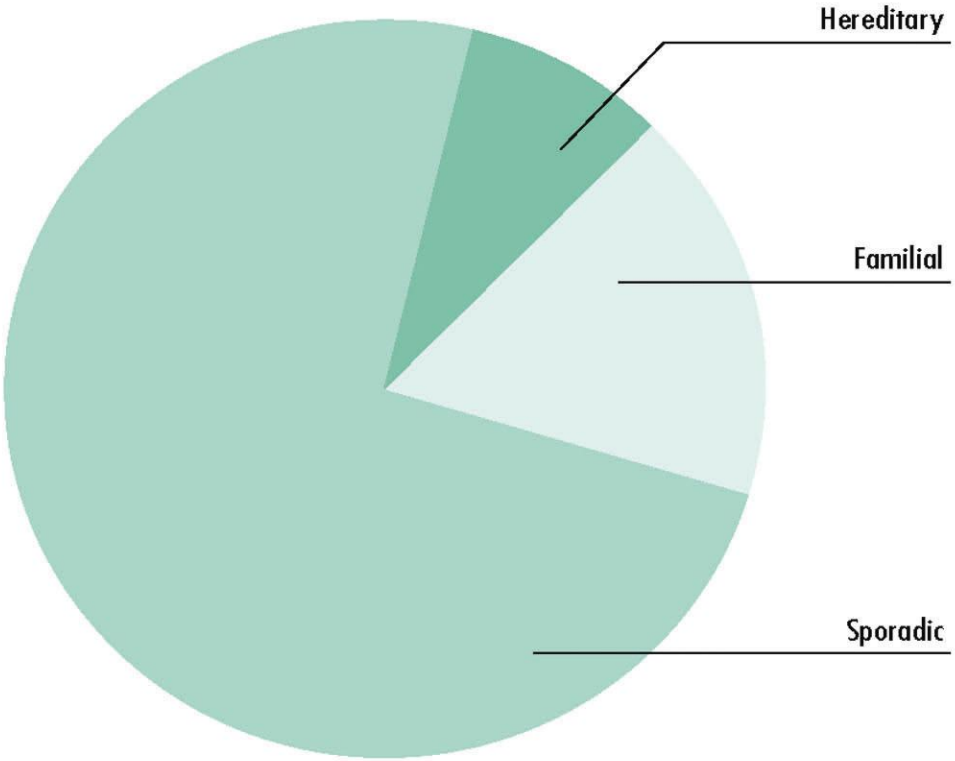
Distribution of Cancer



Hereditary

- Gene mutation is inherited in family
- Significantly increased cancer risk

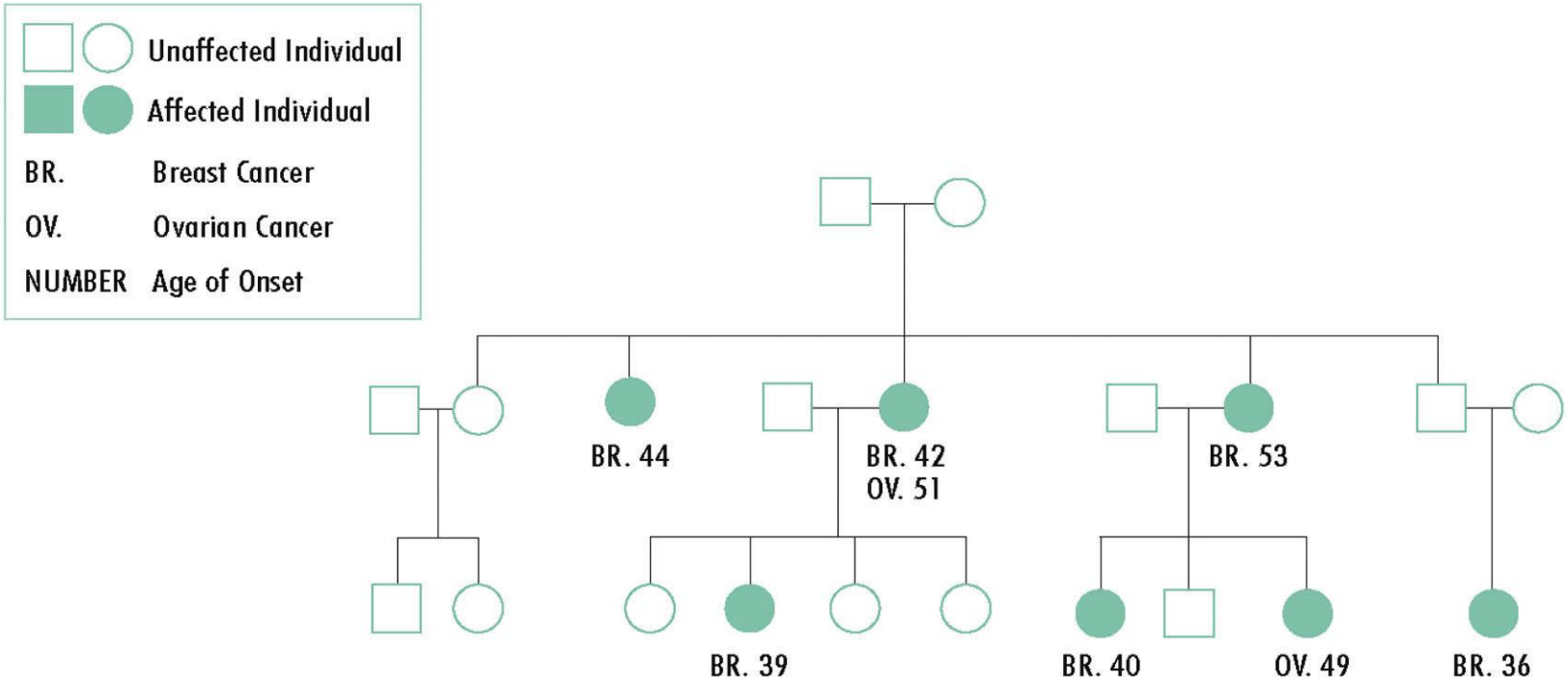
Familial

- Multiple genes & environmental factors may be involved
- Some increase in cancer risk

Sporadic

- Cancer occurs by chance or related to environmental factors
- General population cancer risk

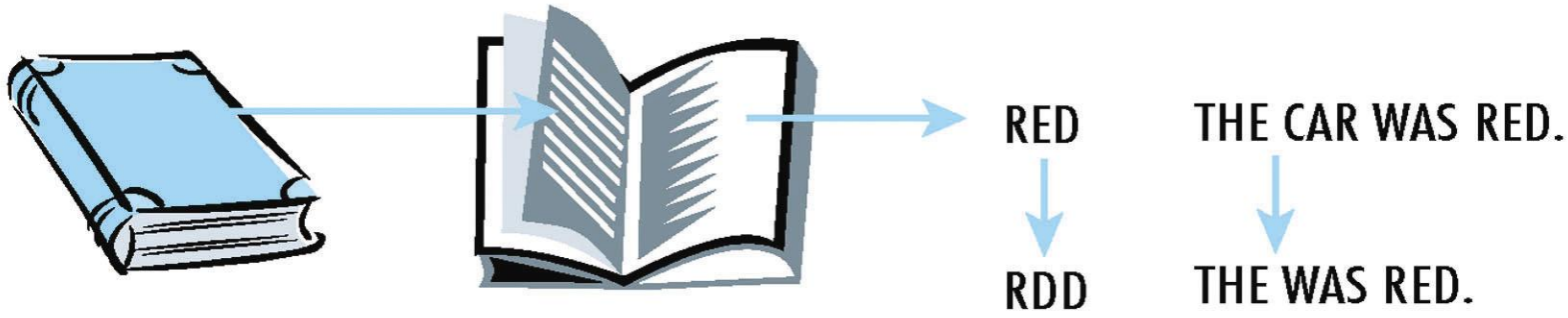
Characteristics of Hereditary Cancer



Characteristics of Hereditary Cancer

- Multiple family members with cancer
- Several relatives with same cancer or cancers that tend to cluster together (i.e. breast & ovarian; colon & uterine)
- Family members with more than one primary cancer (bilateral breast cancer, colon & uterine)
- Cancer diagnosed at early ages (<50 years of age)
- Presence of rare tumor types or unusual cancer presentations (male breast cancer)

Types of Gene Mutations



Chromosomes are like chapters in a book; one is from the mother, one is from the father.

Genes are like sentences in a chapter.

Mutations are like misspelled words or the disruption of a sentence.

Missense Mutations
change one word or letter

THE CAR WAS RED. → THE CAR WAS HAT.
→ THE CAR WAS RDD.

Insertion Mutations
add one word or letter

THE CAR WAS RED. → THE CAR WAS RED RED.
→ THE CAR WAS ERED.

Nonsense Mutations
end the instructions too soon

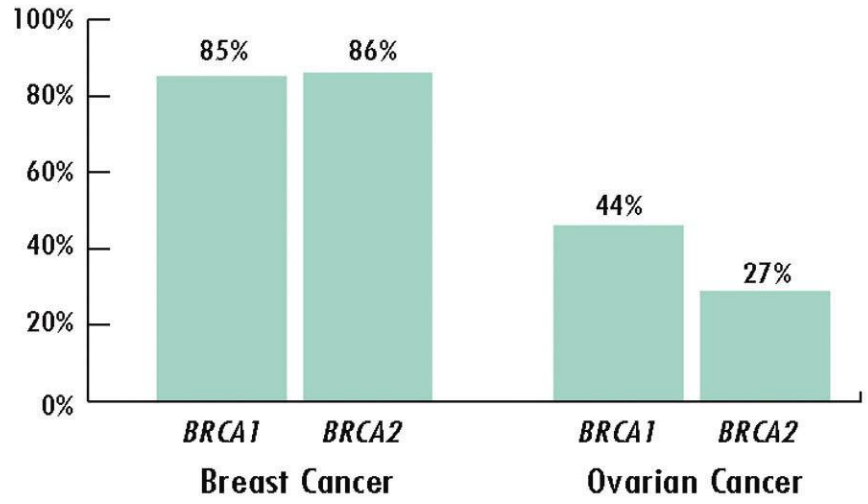
THE CAR WAS RED. → THE CAR. _____

Deletion Mutations
change the meaning by subtracting words or letters

THE CAR WAS RED. → THE ___WAS RED.
→ THE _AR WAS RED.

Hereditary Breast and Ovarian Cancer

Likelihood of Developing Cancer By Age 70 Years in Individuals with *BRCA1* or *BRCA2* Mutations



Other Genes

- Individuals may have a mutation in a gene that has not yet been associated with an increased risk of cancer.
- There may be another cancer syndrome that could explain the increased risk of cancer in the family.

BRCA1 Gene

- Gene mutations are associated with an increased risk of breast and ovarian cancer.
- *BRCA1* gene mutations are often associated with an early onset of breast cancer.
- Males also have a slightly increased risk of prostate cancer.

BRCA2 Gene

- Gene mutations are associated with an increased risk of breast and ovarian cancer.
- *BRCA2* gene mutations may be associated with a later onset of breast cancer than in families with *BRCA1* mutations.
- Male breast cancer is seen more often than in families with a *BRCA1* mutation.
- Other cancers seen in these families include:
  - Pancreas
  - Melanoma
  - Esophagus
  - Gallbladder
  - Prostate
  - Stomach
  - Larynx

Risk of second primary breast cancer

Risk of Ipsilateral and Contralateral Cancer in BRCA Mutation Carriers with Breast Cancer

-The cumulative risk of CBC, for women <50 y at diagnosis

- 5 y – 14,2%
- 10 y – 23,9%
- 15 y – 37,6%

Curr Breast Cancer Rep. 2011 September 1; 3(3): 151–155.

Cumulative risk of second primary contralateral breast cancer in BRCA1/BRCA2 mutation carriers with a first breast cancer

- Risk of CBC for BRCA1 and BRCA2 mutation carriers

- 5 y - 15% and 9%
- 10 y - 27% and 19%
- Non-BRCA carriers 3%

Breast. 2014 Dec;23(6):721-42.

Differences in Natural History between Breast Cancers in BRCA1 and BRCA2 Mutation Carriers and Effects of MRI Screening-MRISC, MARIBS, and Canadian Studies Combined, Heijnsdijk et.al, Cancer epid biomarkers prev 2012

Tumor characteristics of breast cancers in mutation carriers

Erasmus MC

	BRCA1		BRCA2	
	N	(%)	N	(%)
No. of breast cancers	31		16	
DCIS	2	(6)	3	(19)
Invasive breast cancers				
≤ 1 cm	6	(21)	8	(61)
1-2 cm	12	(43)	4	(31)
> 2 cm	10	(36)	1	(8)
N+	10	(36)	4	(33)
N-	18	(64)	8	(67)
Interval cancers	10	(32)	1	(6)

Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis.

BMJ. 2014 Feb 11;348:g226.

CONCLUSIONS:

- This study suggests that women who are positive for BRCA mutations and who are treated for stage I or II breast cancer with bilateral mastectomy are less likely to die from breast cancer than women who are treated with unilateral mastectomy.

Effectiveness of prophylactic surgeries in BRCA1 or BRCA2 mutation carriers: a meta-analysis and systematic review.

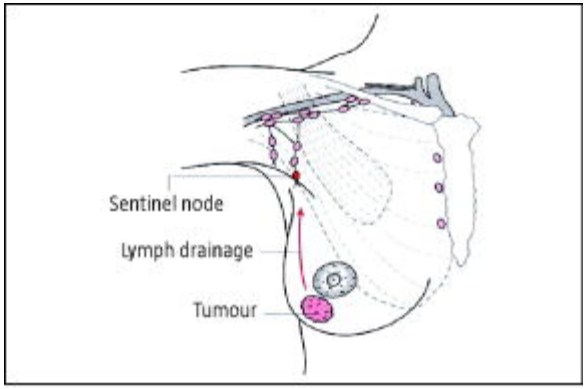
Clin Cancer Res. 2016 Mar 15.

- **PURPOSE:**
- To systematically investigate the effectiveness of prophylactic surgeries (PS) implemented in women carrying BRCA1/2 mutations.
- **RESULTS:**

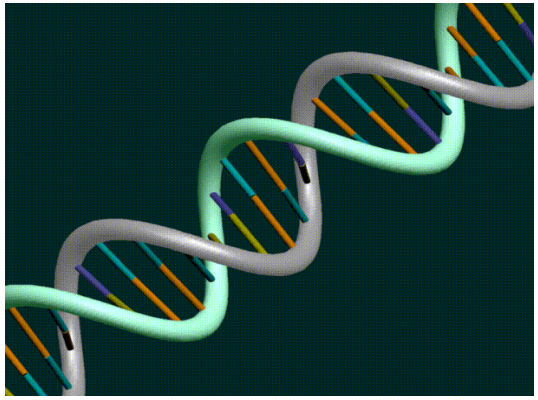
  Contralateral prophylactic mastectomy (CPM) significantly decreased contralateral BC incidence in BRCA1/2 mutation carriers.
- **CONCLUSIONS:**

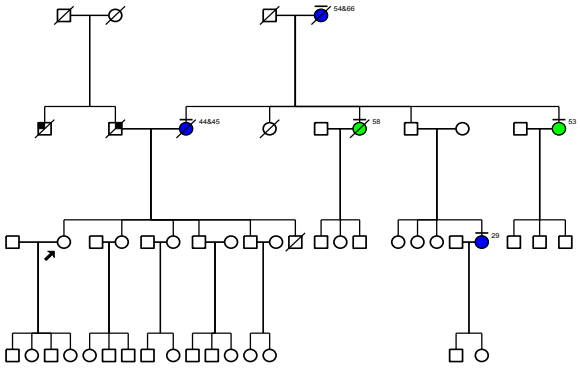
  BRCA1/2 mutation carriers who have been treated with PS have a substantially reduced BC incidence and mortality.

Integrating Cancer Genetics into Routine Clinical Practice

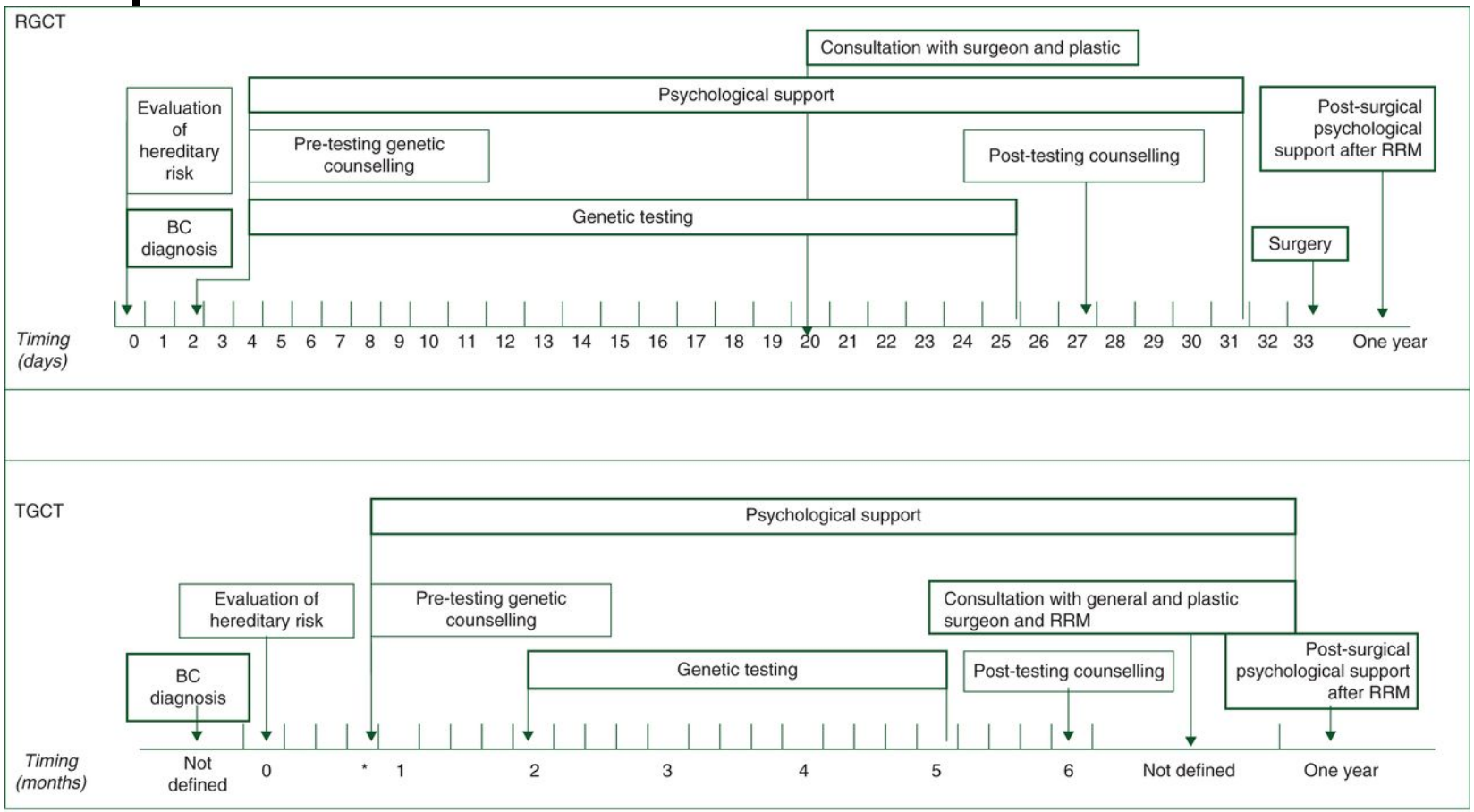


The sentinel lymph node biopsy procedure. The model illustrates the principle of the sentinel node being the first lymph node to receive lymph from the tumour area.





Multidisciplinary RGCT and TGCT pathways.



* *Three weeks*
Legend: BC = Breast Cancer; RRM = Risk Reducing Mastectomy

Cortesi L et al. Ann Oncol 2014;25:57-63

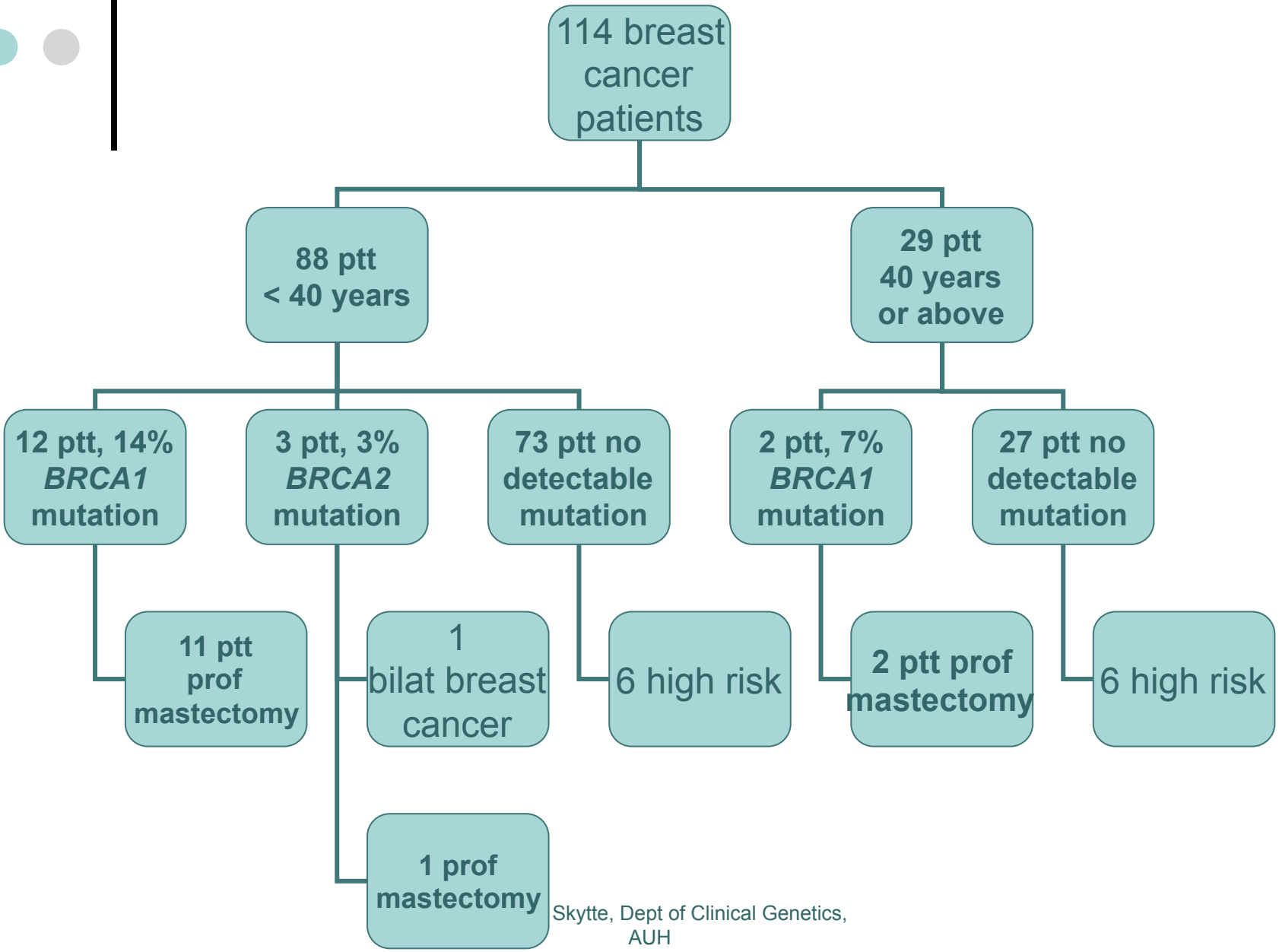
Annals of Oncology

BRCA1 and *BRCA2* Mutation Testing in Young Women With Breast Cancer

***JAMA Oncol*. Published online February 11, 2016**

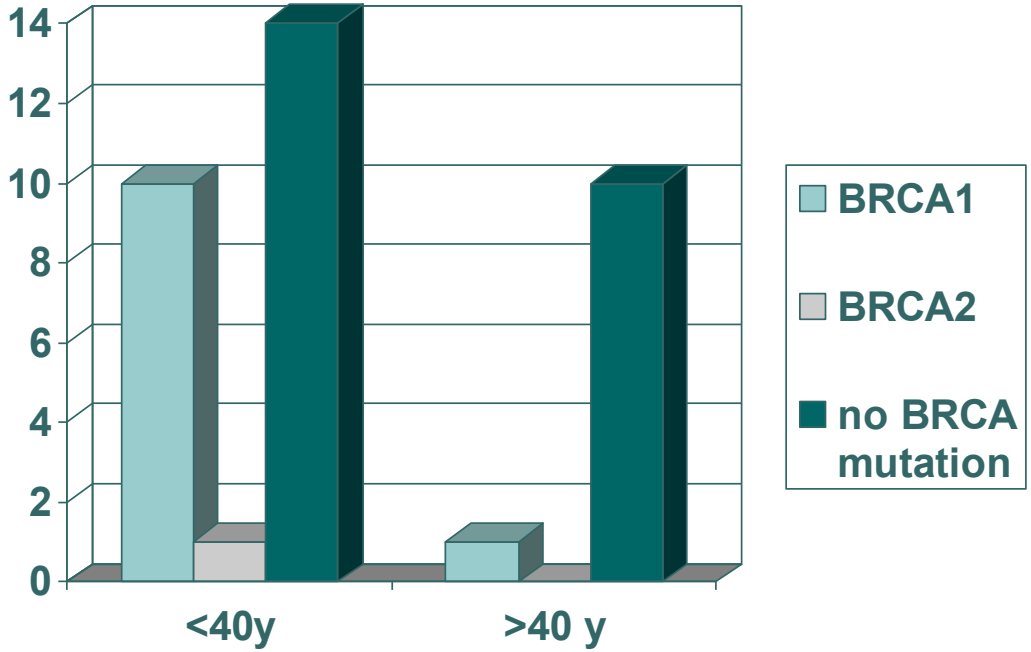
- ***BRCA* testing is recommended for young women diagnosed as having breast cancer, but little is known about decisions surrounding testing and how results may influence treatment decisions in young patients.**
- **A total of 248 (29.8%) of 831 women said that knowledge or concern about genetic risk influenced treatment decisions; among these women, 76 (86.4%) of 88 mutation carriers and 82 (51.2%) of 160 noncarriers chose bilateral mastectomy ($P < .001$).**

1. April 2013 – 1. marts 2016



Receptor status

- 36 breast cancers
  ER negative and
  Her2 negative



Risk-reducing surgery

- 17 % of patients diagnosed with breast cancer before the age of 40 y had a BRCA1 or BRCA2 mutation
- 8 % of the rest were considered high risk patiets from the pedigree
- 7% of patients 40 y or older had a BRCA1 or 2 mutation
- 22 % of the rest were considered high risk patients from the pedigree
- A total of 25 % of the cohort were high risk families
- A total of 35% underwent prophylactic surgery
  - 24 high risk ptt, 88% of BRCA mutation carriers and 83% of non-carriers
  - 16 moderat risk ptt, 30 % of moderat risk ptt

A rapid genetic counselling **and testing in newly diagnosed breast cancer is associated with high rate of risk-reducing mastectomy in BRCA1/2-positive Italian women.**

Ann Oncol. 2014 Jan;25(1):57-63.

BACKGROUND:

Risk-reducing mastectomy (RRM) decreases breast cancer (BC) risk in BRCA1/2 mutation carriers by up to 95%.

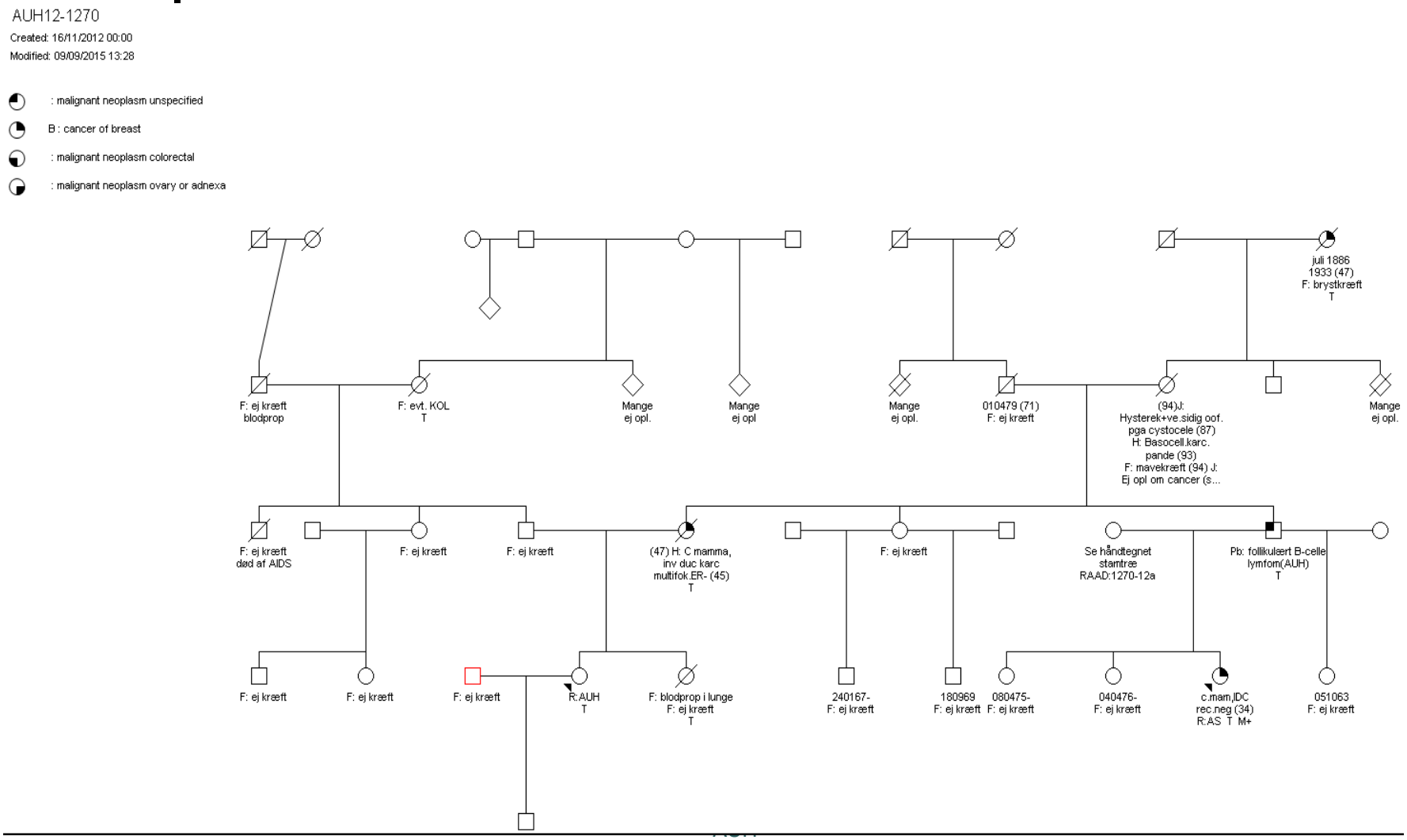
RESULTS:

In TGCT, among 1058 patients, 209 (19.7%) mutation carriers were identified, with the rate of RRM being 4.7% (10 of 209). Conversely in RGCT, among 110 patients, 36 resulted positive, of which, 15 (41.7%) underwent bilateral mastectomy at the BC surgery time,

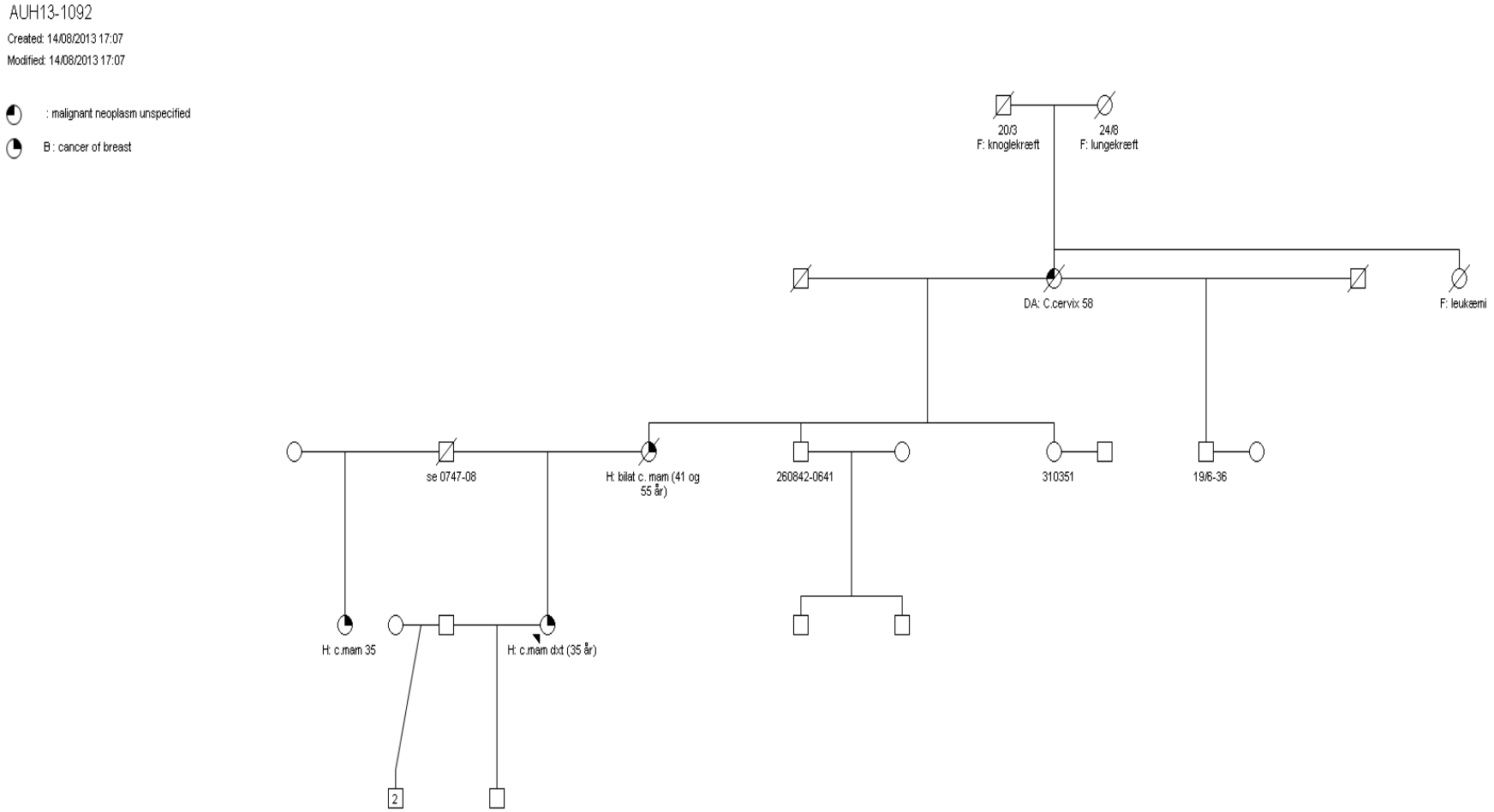
CONCLUSIONS:

Our study shows that RGCT in patients with a hereditary profile is associated with a high rate of RRM at the BC surgery time, this being the pathway offered within a multidisciplinary organization.

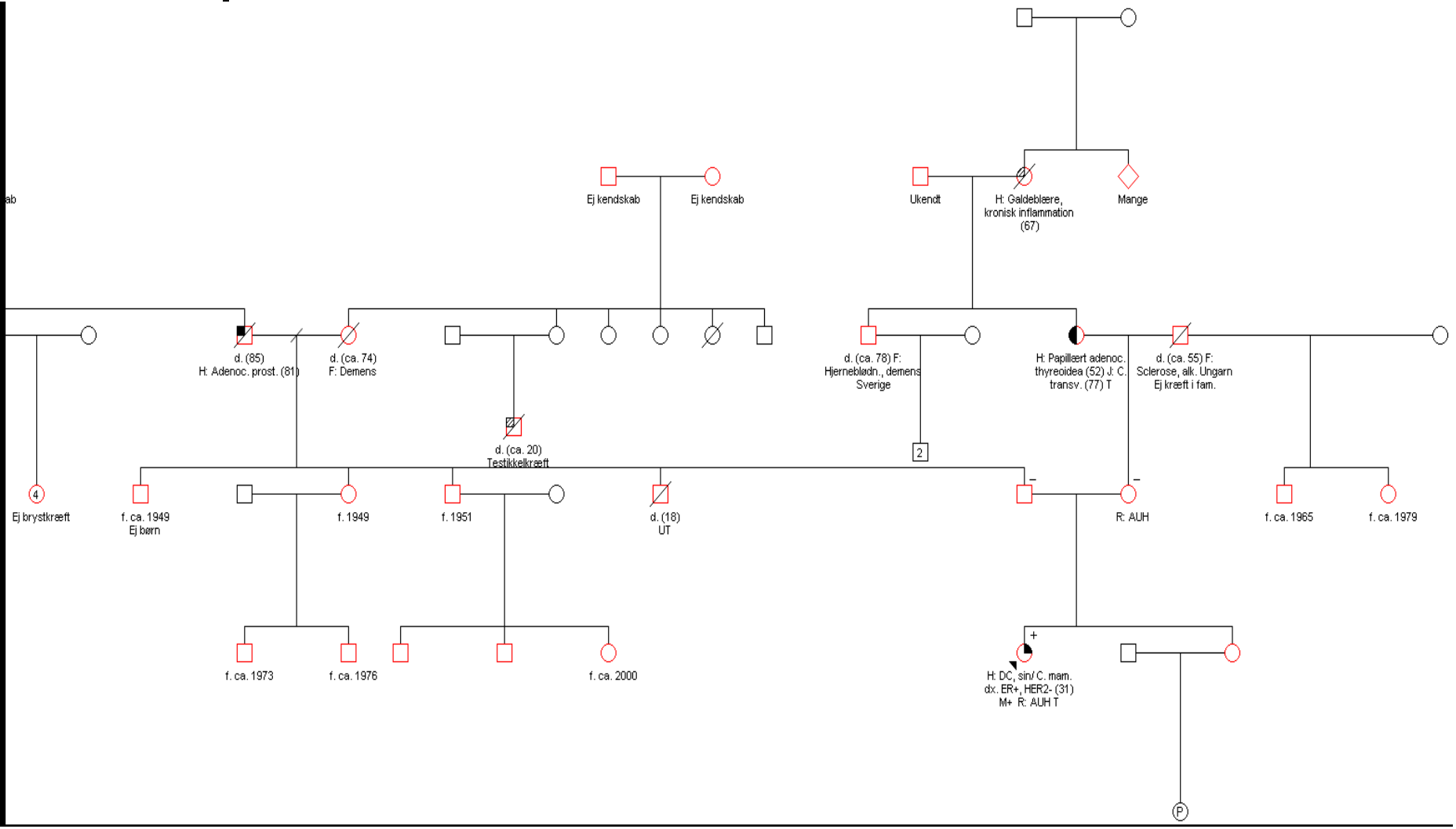
High risk, BRCA1 mutation



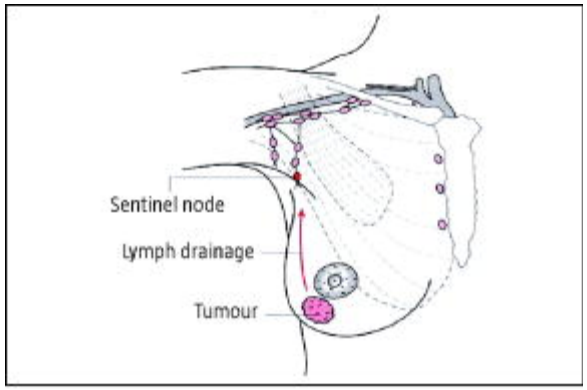
High risk, no mutation



De Novo mutation



Integrating Cancer Genetics into Routine Clinical Practice



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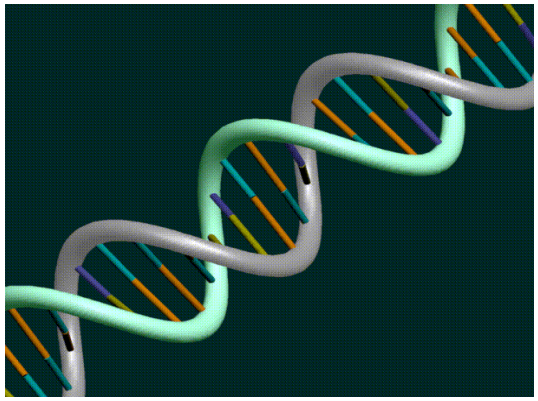

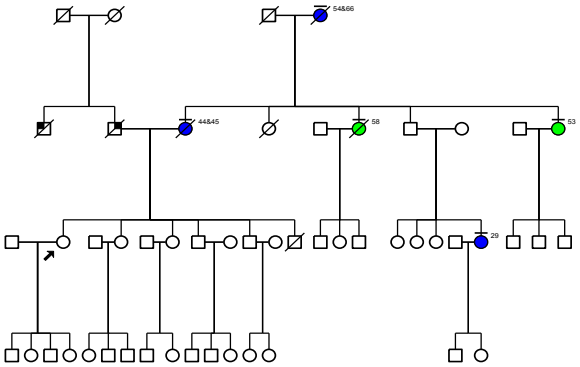

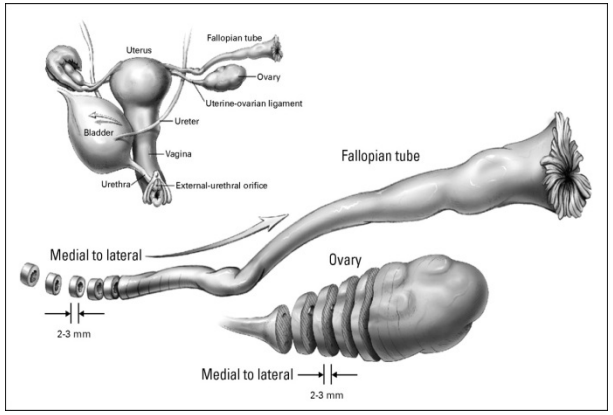

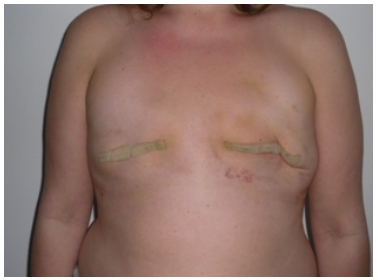

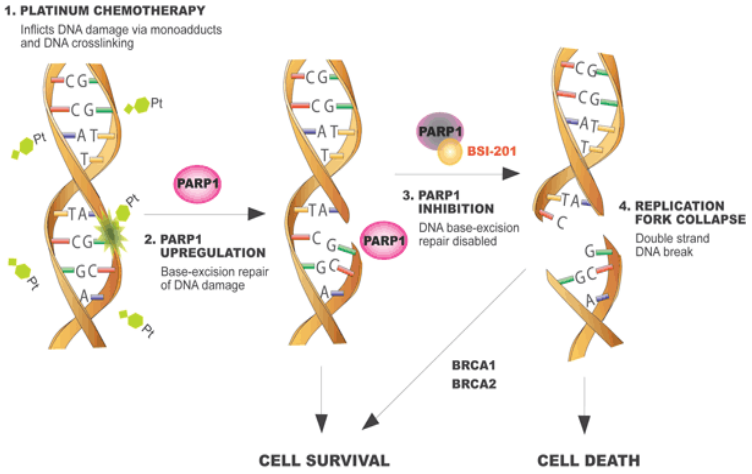

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