Mutated breast cancer beyond BRCA: management in 2021

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- Amgen
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- mundipharma
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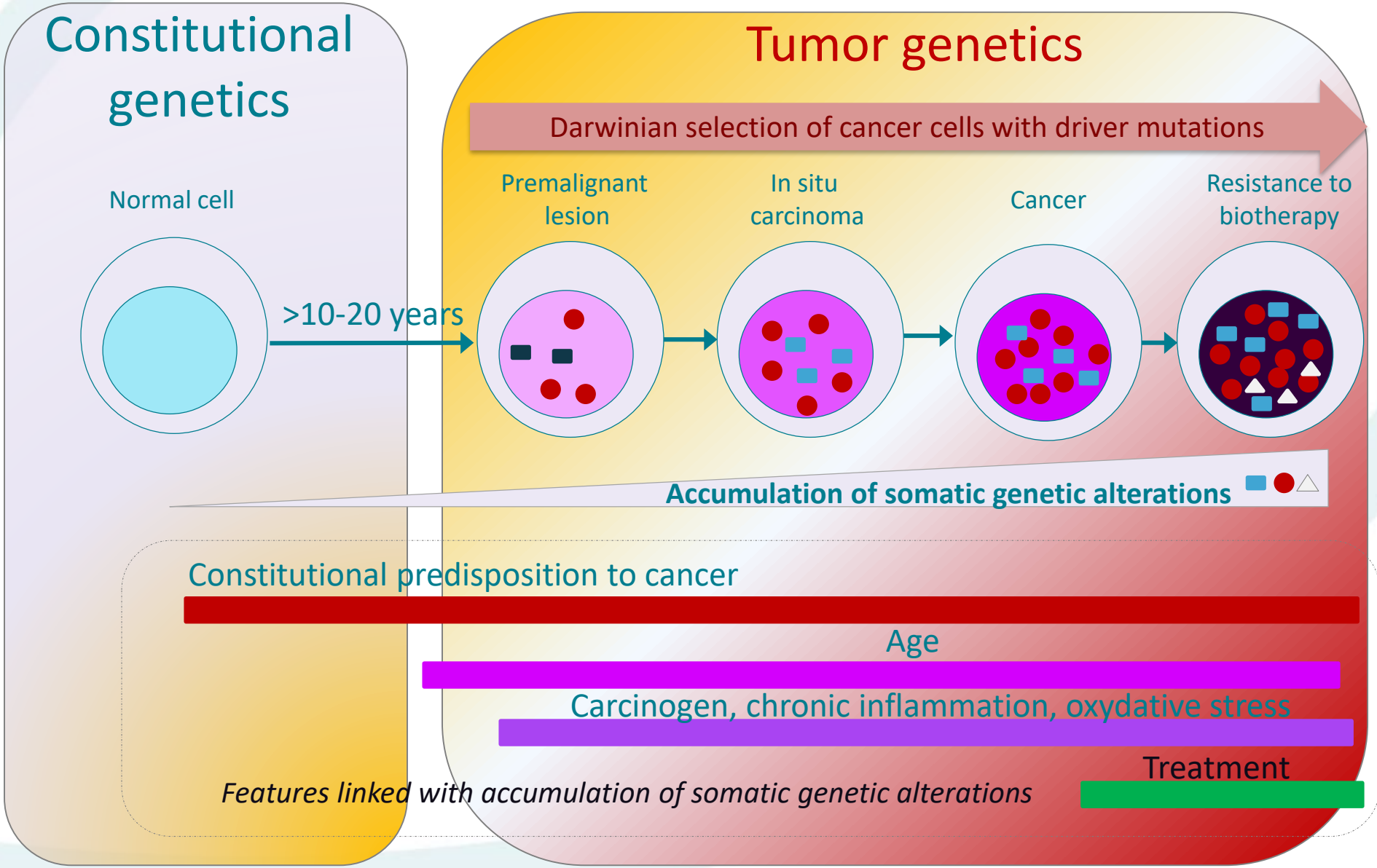
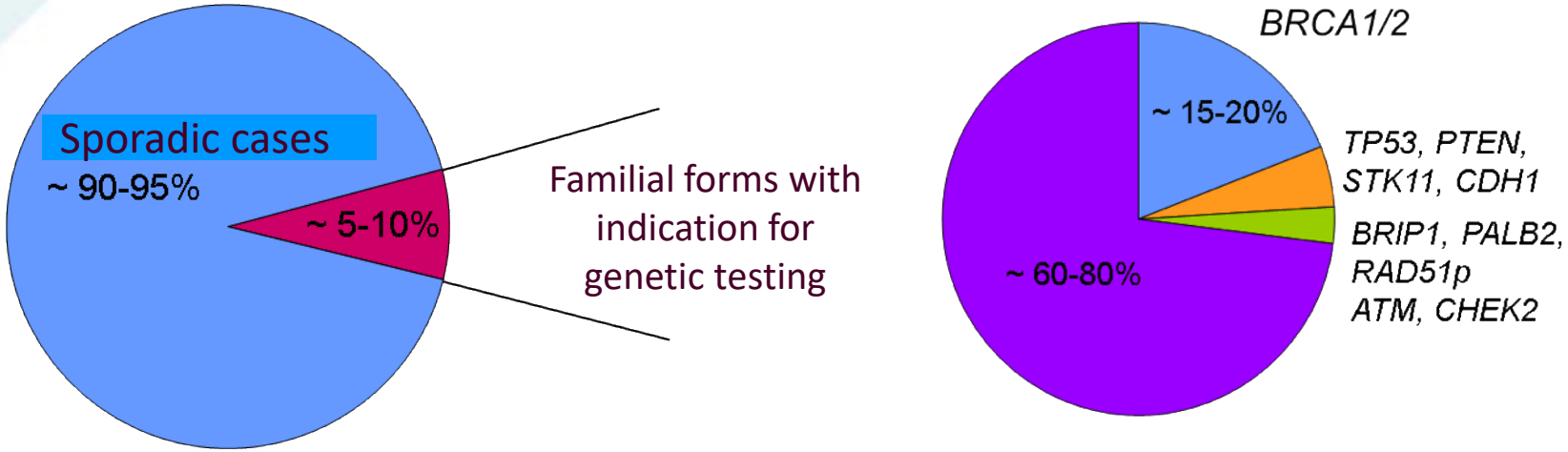
- Pfizer
- Roche
- Teva

Accumulation of genetic alterations during carcinogenesis



Stratton MR, et al. Nature 2009

Introduction



- 15% of healthy women have at least one 1st degree relative with breast cancer

  → risk x 2

- Breast cancer risk increases with the number of 1st degree relatives with breast cancer

  1: x 1.8

  2: x 2.9

  3: x 3.9

- *BRCA1* and *BRCA2* germline mutations are responsible for 15-20% of familial breast cancer cases, but < 5% of all breast cancers
- > 50% of the genetic predisposition to familial breast cancer remains unexplained

Melchor et al, Hum Genet 2013

Definitions

- Penetrance = the likelihood a given gene will result in disease

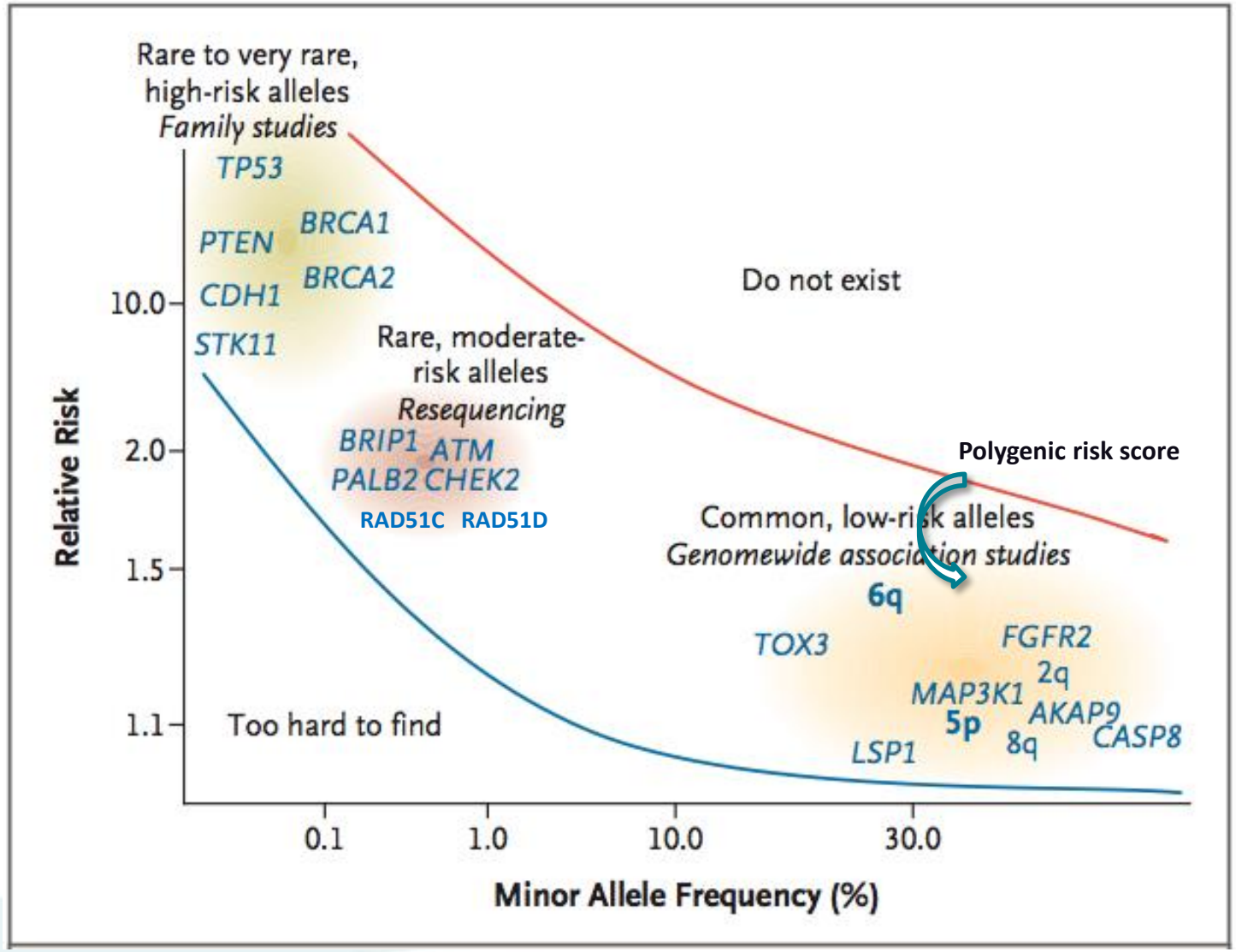
- High penetrance genes :
  - rare mutations
  - very high risk of disease
  - independently of other risk factors

- Low penetrance genes
  - frequent genetic variants
  - interact with exogenous factors to cause the diseases

« Hereditary » cancer syndromes

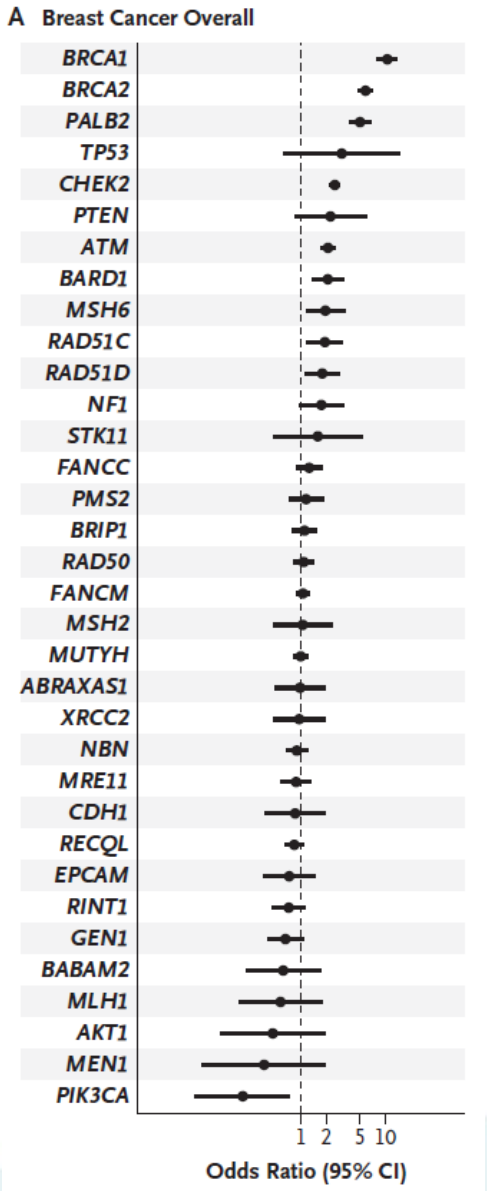
Environment

Genetics



Foulkes WD, NEJM 2008

Risk of breast cancer with protein-truncating variants in 34 genes



Breast Cancer Association Consortium, NEJM 2021

Guidelines for hereditary breast and/or ovarian cancer syndrome diagnostic testing criteria

COLLEGE GENETICS

Woman with breast cancer + one or more of the following

- diagnosed ≤ 40 yrs
- diagnosed < 50 yrs and one relative with bilateral, or ovarian, or breast < 50, or male breast cancer
- bilateral breast cancer and both diagnosed < 50 yrs
- ovarian cancer, any age
- triple negative breast cancer < 60 yrs
- three individuals with breast cancer, one is a first degree relative (FDR) of the other two (excluding male transmitters) and one diagnosed < 50 years
- individual of ethnicity associated with higher frequency of specific mutations (eg, Ashkenazi Jewish): eligible for founder mutation testing
- other family situations (eg multiple pancreatic cancer) with a priori chance of mutation >10% according to BRCAPRO or Evans criteria or Manchester score
- test more than one affected relative if criteria remain positive after excluding the negative case as a phenocopy

Women with high grade epithelial ovarian cancer at any age (excluding mucinous ovarian cancer)

Male with breast cancer

Individual with pancreatic cancer at any age with ≥ 2 FDR excluding male transmitters with breast where one diagnosed <50 or bilateral, or ovarian, or 2 more pancreatic cancer at any age

Family history

Indication for analysis for all metastatic patients

- first degree unaffected relative of any of the above on a case by case basis
- testing of unaffected family members should only be considered when no affected family member is available and then the unaffected family member with the highest probability of mutation should be tested

https://www.college-genetics.be/

BRCA1 and *BRCA2*

- Global prevalence of *BRCA1* or *BRCA2* mutations is estimated at 1/139 (Genome Medicine volume 12, Article number: 2 (2020))
- Responsible for the majority of « hereditary » breast cancer cases
- 30 - 50% of breast cancer patients carrying a mutation have no known or significant family history (Eur J Cancer, 43 (11) (2007 Jul), pp. 1713–1717)
- Specific *BRCA1* and *BRCA2* mutations are frequent in the Jewish Ashkenazi population (1/40 - 1/50)

Roles of *BRCA1* and *BRCA2* in hereditary breast and ovarian cancer syndrome (HBOC)

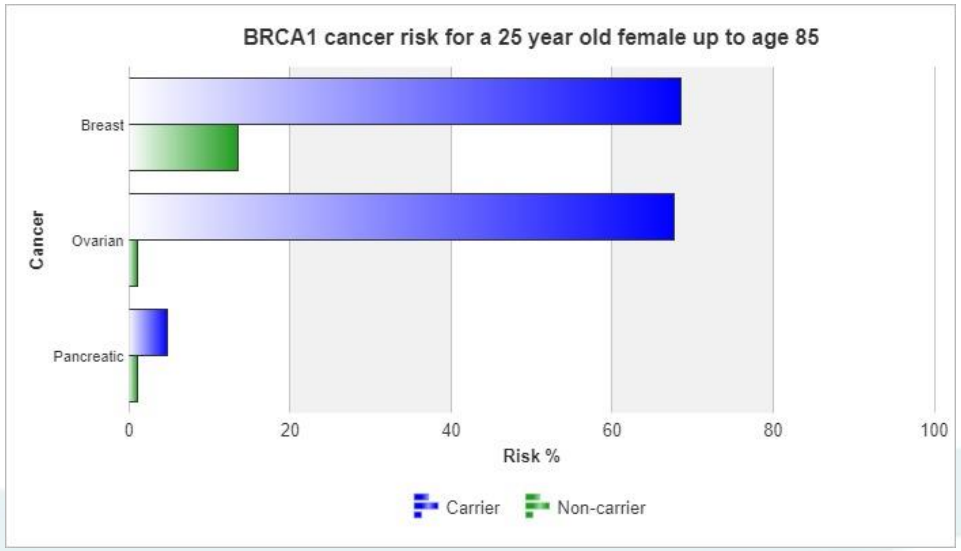
- High penetrance but variable expression :
  - Cumulative risk of breast cancer : up to 70 % (at 80 y.o.)
  - Ovarian cancer : 40% (*BRCA1*) / 20% (*BRCA2*)

ASK2ME™ | All Syndromes Known to Man Evaluator

Enter the gene that has a pathogenic mutation, the age, and gender of the patient to calculate the risk of future cancers.

Gene: BRCA1

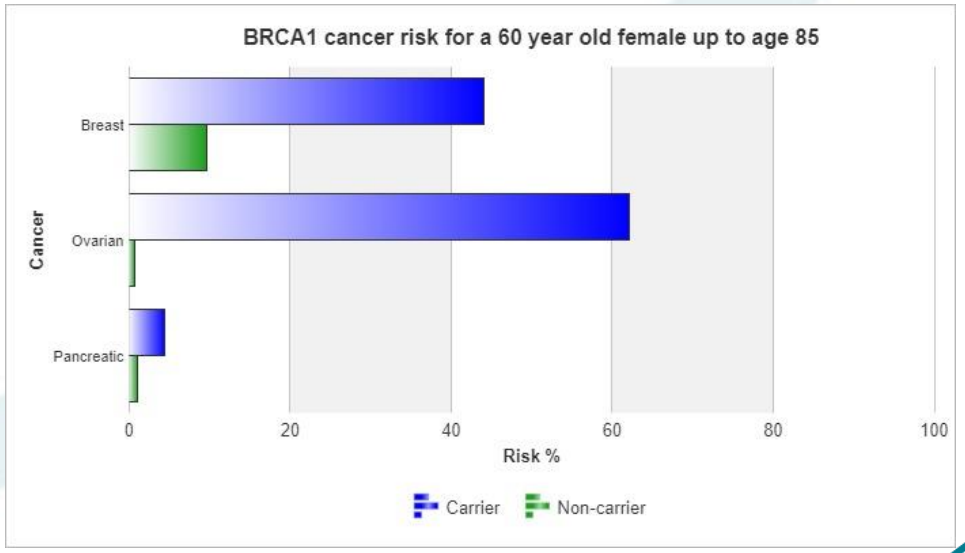
Gender: Female Age: 25



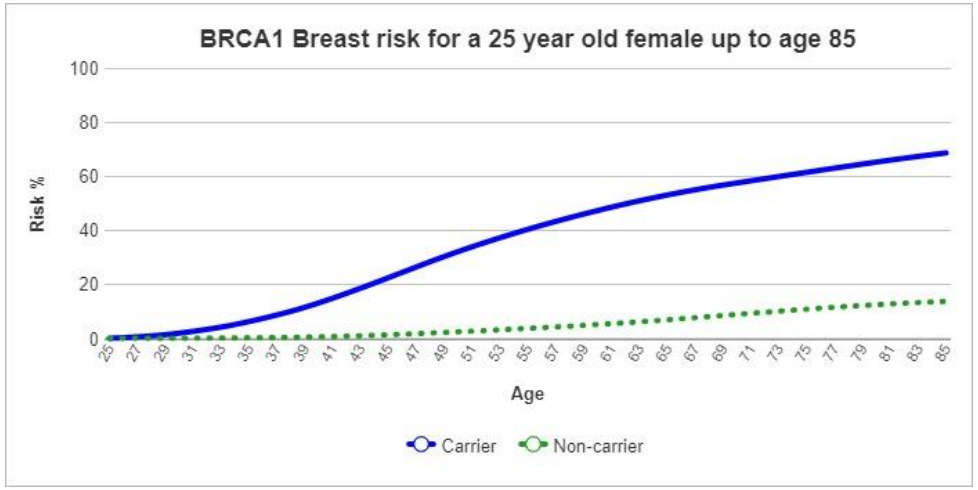
Enter the gene that has a pathogenic mutation, the age, and gender of the patient to calculate the risk of future cancers.

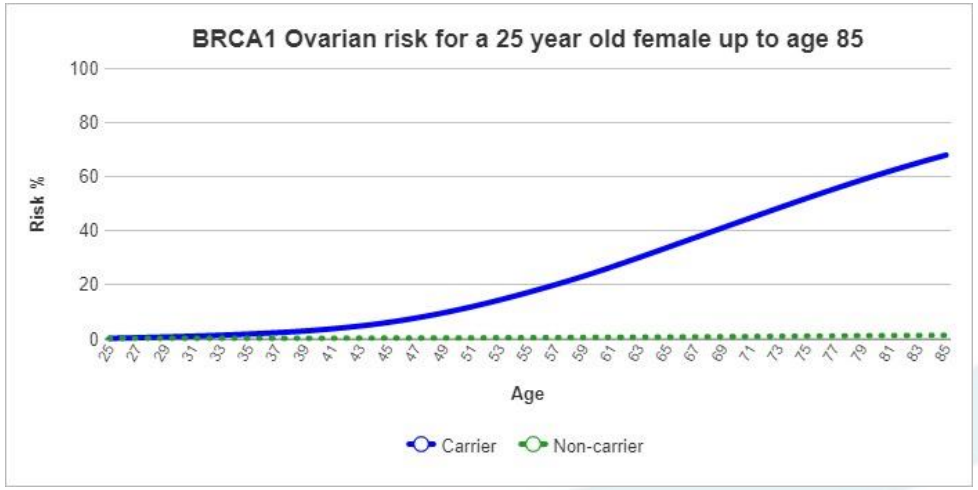
Gene: BRCA1

Gender: Female Age: 60



HBOC : the cumulative cancer risk varies with age → higher in younger women





BRCA1 and *BRCA2*

- *BRCA1* :
  - breast (women) : young age, 70% cumulative risk
    - Triple negative
    - Risk of contralateral breast cancer: 40% after 20 years
  - ovary : 40-50% cumulative risk
  - colon
  - prostate

- *BRCA2* :
  - breast (women) : cumulative risk 50-70%
    - ER and PgR positive
    - Risk of contralateral breast cancer: 25% after 20 years
  - ovary : lower cumulative risk than *BRCA1* (20%)
  - breast (men) : increased risk (10% of breast cancers in males have a *BRCA2* mutation)
  - Pancreas : 2-6%
  - colon
  - prostate
  - larynx

Kuchenbaecker et al. JAMA. 2017 Jun 20;317(23):2402-2416.

Guidelines for the managements of patients with *BRCA1* or *BRCA2* mutations

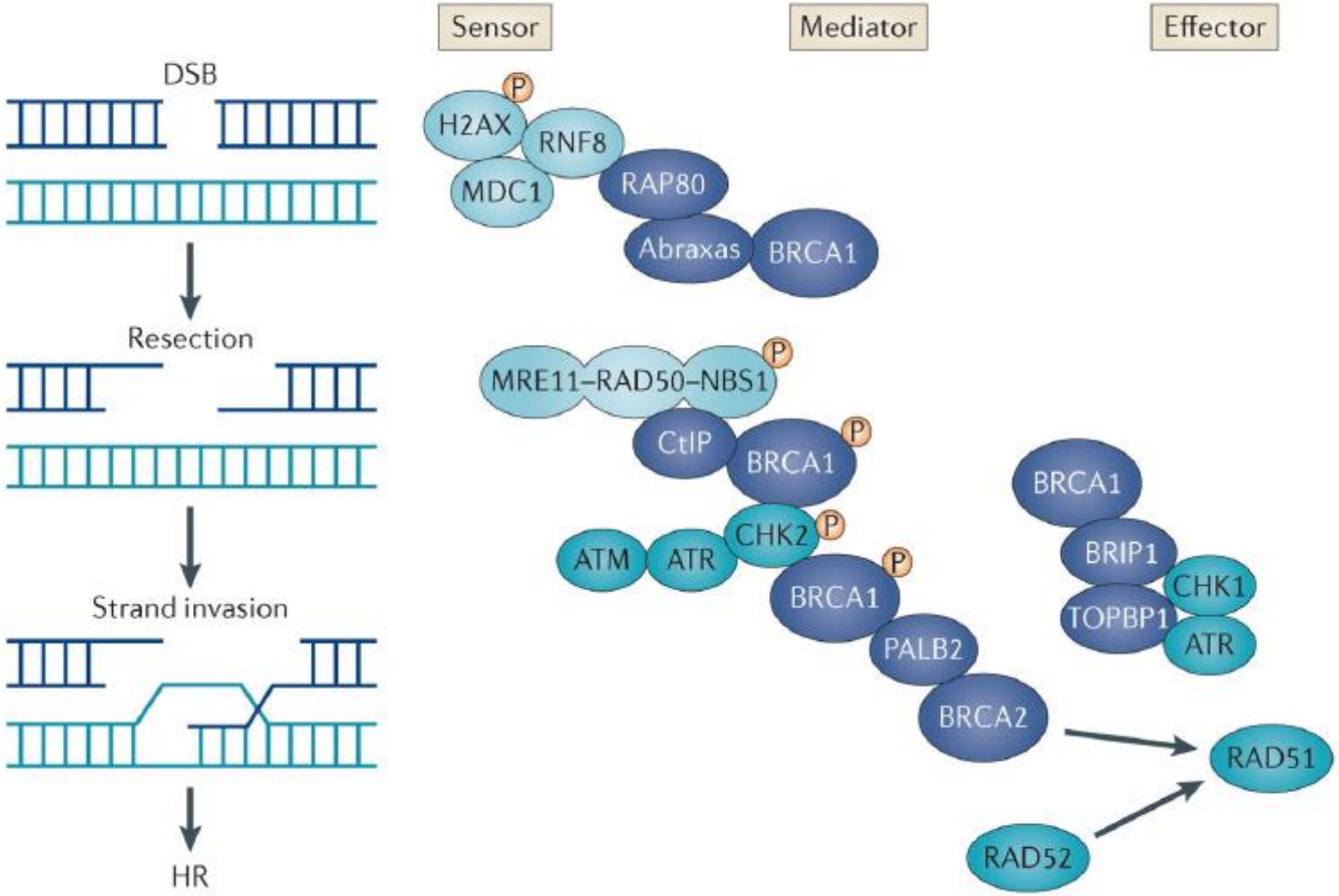
Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25* y AND • 25* – 35 y: Annual breast MRI • One mammogram at age of 30: if microcalcifications are present also do yearly mammogram (+/- US when indicted by radiologist) from age 30, else from age of 35 • 35 – 65 y: annual breast MRI and annual mammogram (+/- US when indicted by radiologist) alternating every 6 months • 65 – 75 y: Annual mammography (if quality is sufficient) • >75y: Consider mammogram every 2 y *Or 5 y younger than youngest diagnosis in the family if diagnosis <30y
	Risk reducing surgery	Bilateral mastectomy (comments: no standard follow-up with imaging after risk reducing mastectomy, nipple preservations is considered safe)
Ovarian cancer	Screening (not in folder)	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 40 y)
BRCA1	Risk reducing surgery	Strongly consider BSO < 40 y
BRCA2	Risk reducing surgery	Strongly consider BSO < 50 y

Belgian guidelines for Managing Hereditary Breast and Ovarian Cancer: 09/2020 Update

https://www.college-genetics.be/

Other genes implicated in an increased risk of breast cancer

Molecular mechanisms of double-strand break DNA repair



Nat Rev Cancer.;12(1):68-78

PALB2

- Breast (women) : cumulative risk 30-60%
  - importance of family history
  - increased risk of contralateral breast cancer
  - anticipation
- Ovary : cumulative risk 5-15%
- Breast (men) : 1%
- Pancreas: weak but increased

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25* y AND • 25* – 35 y: Annual breast MRI • One mammogram at age of 30: if microcalcifications are present also do yearly mammogram (+/- US when indicted by radiologist) from age 30, else from age of 35 • 35 – 65 y: annual breast MRI and annual mammogram (+/- US when indicted by radiologist) alternating every 6 months • 65 – 75 y: Annual mammography (if quality is sufficient) • >75y: Consider mammogram every 2 y *Or 5 y younger than youngest diagnosis in the family if diagnosis <30y
	Risk reducing surgery	Bilateral mastectomy (comments: no standard follow-up with imaging after risk reducing mastectomy, nipple preservations is considered safe)
Ovarian cancer	Screening (not in folder)	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 50 y)
	Risk reducing surgery	Strongly consider BSO at age of menopause (or earlier depending on family history

ATM

- Breast (women) : cumulative risk 30%
  - importance of family history
  - contralateral breast cancer?
- Breast (men) : 0,5-1%
- Prostate
- Pancreas

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND 35 – 40y: Annual breast MRI starting (or start 5 y before youngest diagnosis in family if diagnosis <40y) 40 -65y: Breast MRI every 2y and mammogram (+- echo) every 2y, alternating annually 65 – 75y: Annual mammogram (+- echo) >75y: Consider mammogram every 2 y (if patient is in good health)
	Risk reducing surgery	Bilateral mastectomy can be considered based on patient preference

Female non-carriers in *ATM* breast cancer families

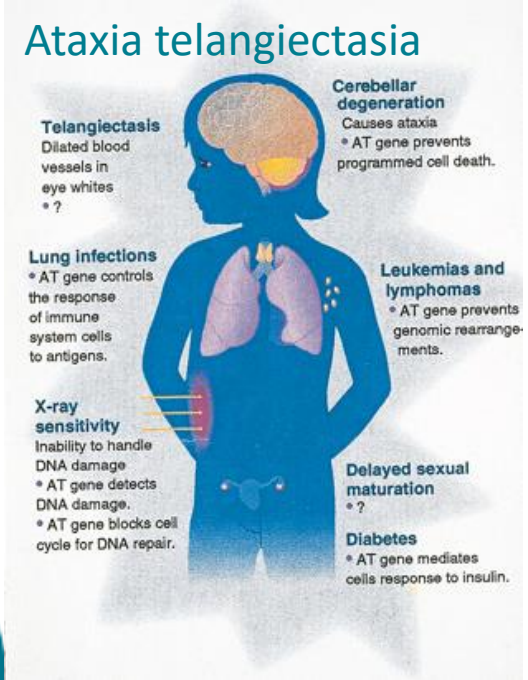
Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: Screening within population screening program

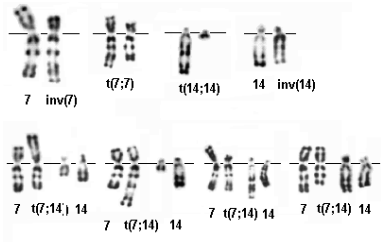
ATM

- Risk of radiosensitivity in heterozygotes?
  - Not demonstrated : mammogram recommended by NCCN 2021, but caution advised by Belgian guidelines
- No evidence of deleterious effect of radiotherapy, but debated

Int J Radiation Oncol Biol Phys, Vol. 105, No. 4, pp. 698e712, 2019
https://doi.org/10.1200/PO.20.00334 (2021)

- Beware of the risk of biallelic mutation in offspring:
  - test the partner if child wish (risk 1/100)





- Congenital dysmorphic syndrome : small size, microcephaly, abnormal thums or forearms, face, neurological or retinian signs
- Predisposition to cancer (leukemia, lymphoma, carcinoma…)
- +/- medullary insufficiency
- +/- immune abnormalities

CHEK2

- Breast (women) : cumulative risk 20-45%
  - importance of family history
  - risk of contralateral cancer : 25% after 20 years
- Breast (men) : 0,5-1%
- Prostate
- Colon: 8-10% -> colonoscopy starting at 40 years (every 5 years)

Table 8: Recommendations for CHEK2 carriers

Tumor	Intervention	Recommendation
Breast cancer	Screening	Clinical examination every 6 months from 25 y AND 35 – 65 y: Breast MRI every 2y and mammography (+/- echo) every 2y, alternating annually (or start 5 y before youngest diagnosis in family if diagnosis <40y) 65 – 75 y: Annual mammography (+/- ultrasound when indicted by radiologist) >75y: Consider mammogram every 2 y (if patient is in good health)
	Risk reducing surgery	If strong family history or if diagnosed with breast cancer: consider risk reducing bilateral mastectomy

Female non-carriers in *CHEK2* breast cancer families

Table 9: Recommendations for non-carries in CHEK2 positive breast cancer families

Tumor	Intervention	Recommendation
Breast cancer	Screening	40 – 50 y: Annual mammogram 50 – 75 y: screening within population screening program

Comment: when a coincidental *CHEK2* mutation is found in absence of a family history of breast cancer (and an informative pedigree) it is reasonable to downgrade screening to annual mammogram starting at 40y, as breast cancer risk is estimated to be 20% for *CHEK2* women without family history (first and second degree)

Homozygous CHEK2 carriers: Breast cancer screening as for BRCA carriers or bilateral mastectomy

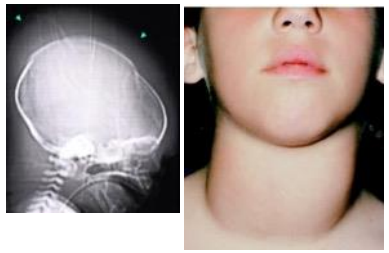
RAD51C and *RAD51D*

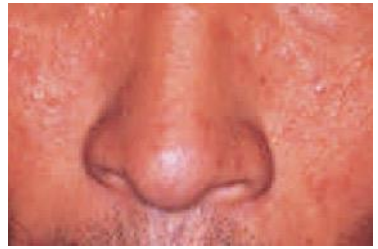
- Breast (women) : cumulative risk 20-45%
  - importance of family history
  - remaining risk in non-carriers
- Ovary: 5-10%

Table 13: Recommendations for BRIP1, RAD51C and RAD51D carriers

Tumor	Intervention	Recommendation
Breast cancer (only for RAD51C and RAD51D, **NOT for BRIP1**)	Screening	Clinical examination every 6 months from 25 y AND • **If <u>positive</u> family history (1st or 2nd degree) of breast cancer**: 35 – 65 y: Breast MRI and mammography alternating annually (or start 5 y before youngest diagnosis in family if diagnosis <40y) 65 – 75 y: Annual mammography (+/- ultrasound when indicted by radiologist) >75y: Consider mammogram every 2 y (if patient is in good health)
	Risk reducing surgery	If strong family history or if diagnosed: consider risk reducing bilateral mastectomy
Ovarian cancer	Screening **(not in folder)**	Not recommended (comment: tailored program could be offered if patient refused risk reducing BSO ≥ 50 y)
	Risk reducing surgery	Consider BSO < 50 y

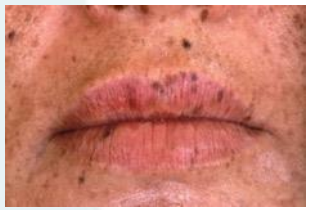
Rare syndromes

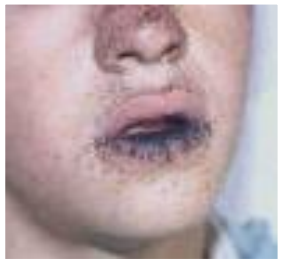


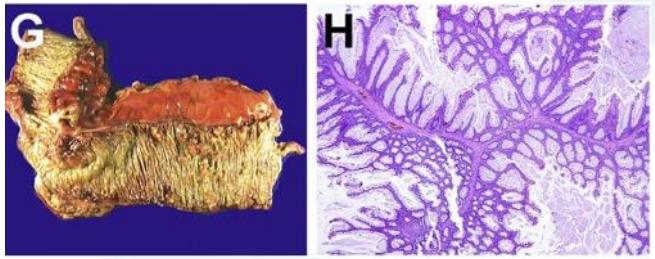


- *PTEN* – Cowden syndrome
  - Macrocephaly & autism
  - Hamartoma + trichilemmoma
  - Increased risk of breast cancer (60% at 70 y.o.) + thyroid carcinoma + endometrium + colon

- *STK11* – Peutz-Jeghers syndrome
  - Hamartoma
  - Abnormal pigmentation of skin and mucosa
  - Increased risk of breast cancer (40-60% at 70 y.o.) + cervix and endometrium + digestive tract + pancreas + lung + sex cord tumors

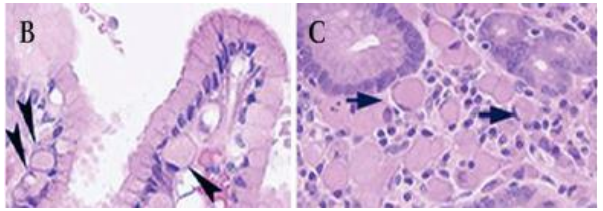


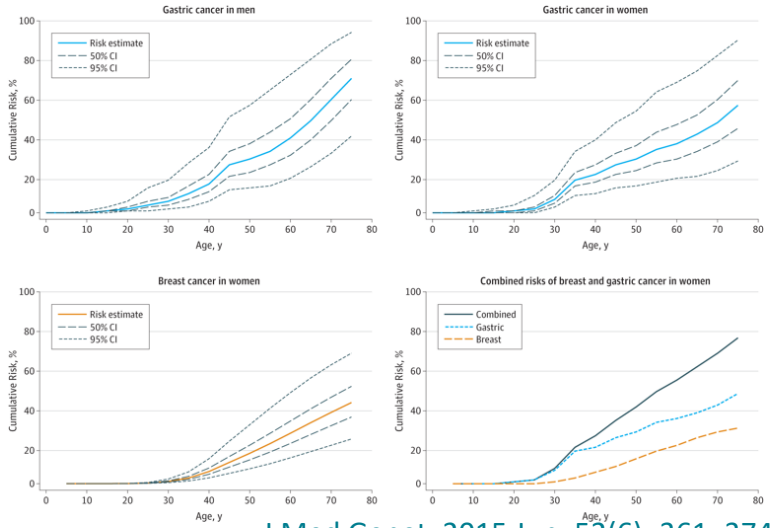




Rare syndromes

- *CDH1*
  - Lobular breast cancer (60% at 80 y.o., bilateral)
  - Diffuse gastric cancer
  - Cleft lip and palate



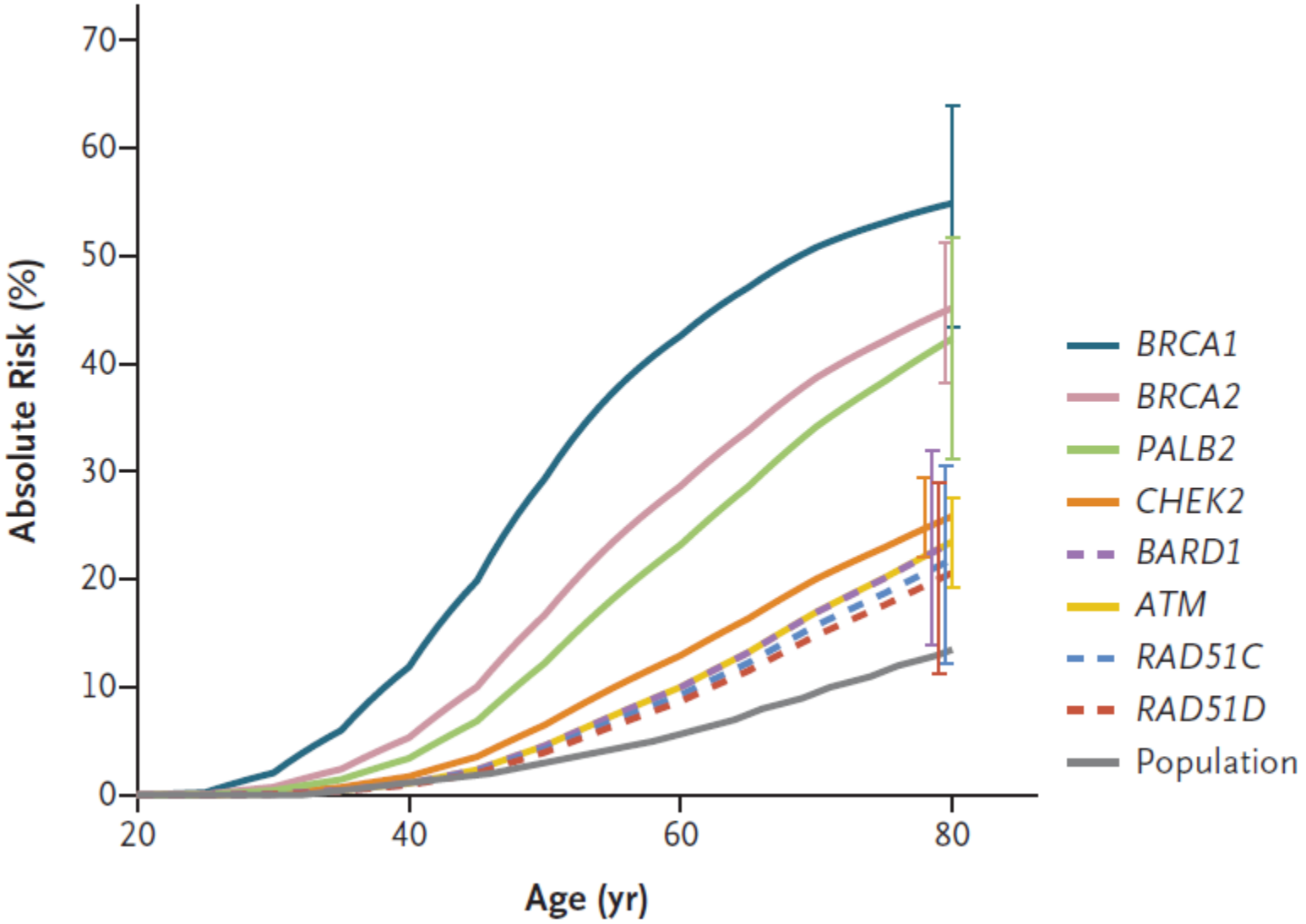


J Med Genet. 2015 Jun; 52(6): 361–374

- *TP53* – Li-Fraumeni syndrome
  - De novo mutations (7-20%), mosaicism → family history not always present
  - Breast cancer (HER2+) - 6% of women with breast cancer < 30 y.o; risk >60%
  - Sarcoma
  - Adrenocortical carcinoma
  - Leukemia
  - Brain tumor
  - Other cancers (lung, colon, pancreas, genito-urinary, skin, prostate, …)

AVOID RADIATION

Estimated absolute risk of breast cancer associated with protein-truncating variants



Breast Cancer Association Consortium, NEJM 2021

Conclusion

- Oncogenetics consultations are now standard of care for young women with breast cancer
- Secondary cancers are frequent
- Ovarian cancer risk → planning of fertility
- Implications for the other family members

Thank you for your attention

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