



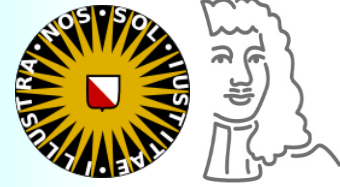
Genetic testing: When and for whom?

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Tribute to Angelina Jolie



- Increased awareness
- Putative influence on Supreme Court decision that put a ban on gene patenting
- 'Angelina Jolie effect': Increased referral for genetic testing resulting in doubling of identified BRCA germline mutation carriers

Justices, 9-0, Bar Patenting Human Genes, New York Times, June 13, 2013

Evans et al. Breast Cancer Res, 2014

The case of Angelina Jolie



- 38 years old
- 6 children with Brad Pitt, of which 3 children adopted
- Her mother died of ovarian cancer at the age of 49 years
- Her mother had had breast cancer before ovarian cancer
- In her mother's family many women had had breast and/or ovarian cancer

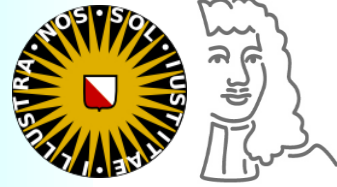
The case of Angelina Jolie



Whom of you would refer her to a medical geneticist?

Please raise your hands

That is reassuring



Next time better

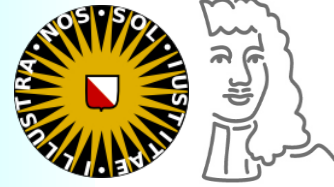


Why genetic testing?



- To take precautions in case of being affected
 - Screening
 - Chemoprevention
 - Prophylactic surgery
- Preimplantation genetic diagnosis
 - Embryo selection
- Increase treatment options, *e.g.*
poly(ADP)ribose polymerase (PARP) inhibitors

Referral is not equal to genetic testing

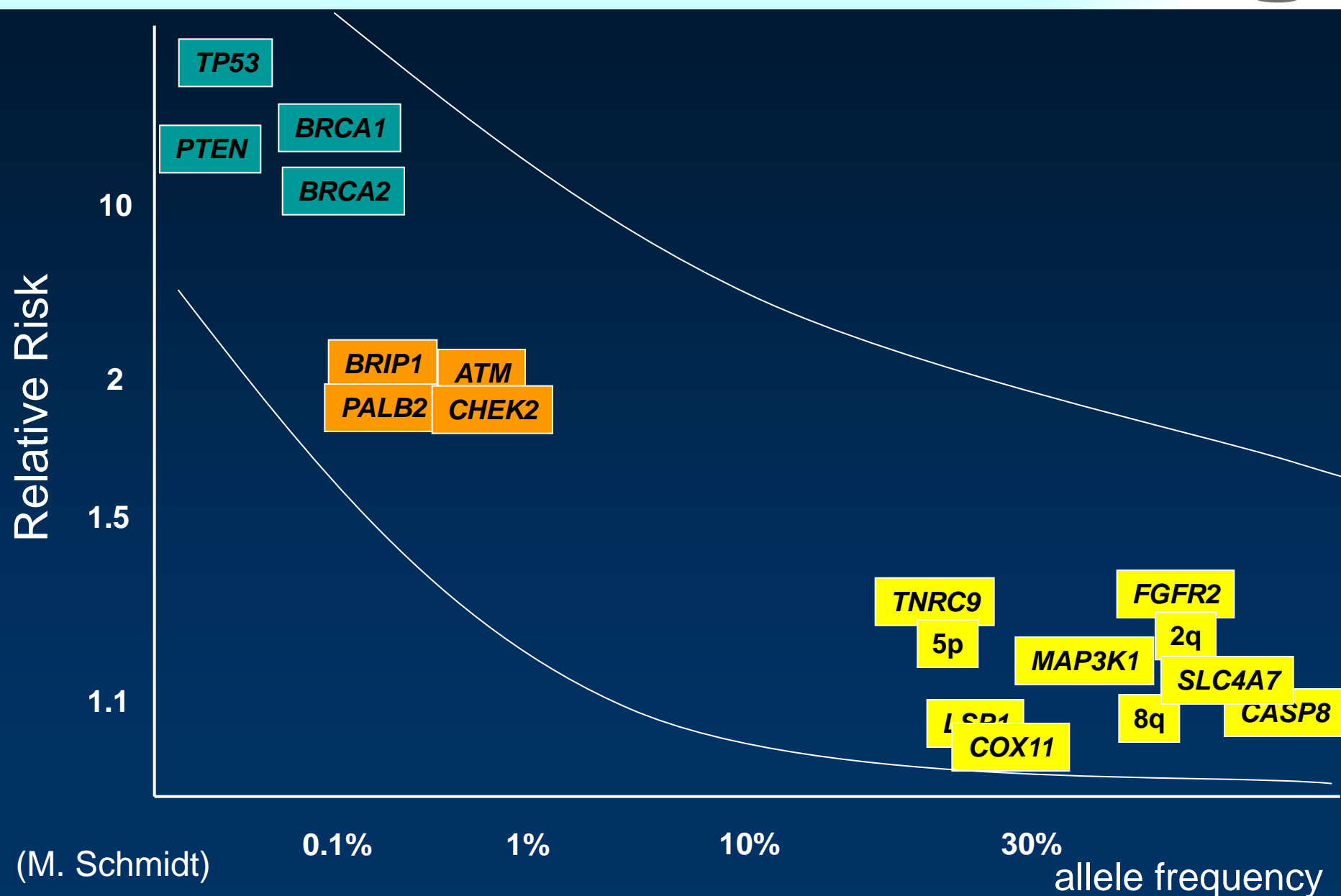


Criteria for referral are less stringent than
for genetic testing

medical geneticist and patient decide

genetic counseling requires a team

Breast cancer susceptibility genes and risk



Life time risk breast and ovarian cancer



	Breast	Ovarian
<i>BRCA1</i>	35-80%	30-65%
<i>BRCA2</i>	40-85%	10-25%
General population	9%	1%

For whom referral to a medical geneticist? (I)



Affected individual with one or more of the following:

- Age \leq 50 years (UK - NICE \leq 40 years)
- A known mutation in a breast cancer susceptibility gene within the family
- With triple negative breast cancer, or ovarian cancer, or male breast cancer
- Two breast primaries in a single individual
- Breast cancer at any age AND \geq 1 close blood relative with ovarian cancer OR being of increased risk population, OR \geq 2 close blood relatives with pancreatic cancer AND/OR breast cancer any age

For whom referral to a medical geneticist? (II)



Affected individual or unaffected individual with following:

- ≥ 1 family member on the same side with a combination of breast cancer and one of the following (especially if early onset):
- Pancreatic cancer OR diffuse gastric cancer OR hamartomatous polyps of GI tract (*BRCA1/2, CDH1, STK11*)
- Prostate cancer (Gleason ≥ 7) (*BRCA1/2*)
- Sarcoma, melanoma (*TP53, BRCA2*)
- Endometrial cancer (*BRCA1/2, TP53, PTEN*)
- Adrenocortical cancer OR thyroid cancer (*TP53, BRCA1, PTEN*)
- Brain tumors (*TP53*)
- Leukemia/lymphoma (*TP53*)
- Dermatologic manifestations and/or macrocephaly (F ≥ 58 cm; M ≥ 60 cm) (e.g. Cowden syndrome (*PTEN*), Peutz-Jeghers (*STK11*))

Think BRCA1 / 2 when



Combination of 'BOMPP'

- **B**reast cancer
- **O**varian cancer
- **M**ale breast cancer
- **P**ancreatic cancer
- **P**rostate cancer (Gleason ≥ 7)



When genetic testing?



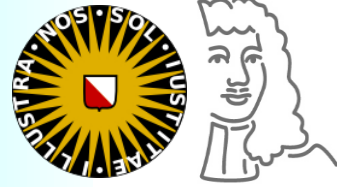
When is the genetic test result needed?

- To take preventive measures
- To guide therapy in the case of breast cancer
 - Type of surgery
 - Type of systemic therapy

Neoadjuvant: add carboplatin

Adjuvant: OlympiA trial, 1 year olaparib vs placebo

The case of Angelina Jolie

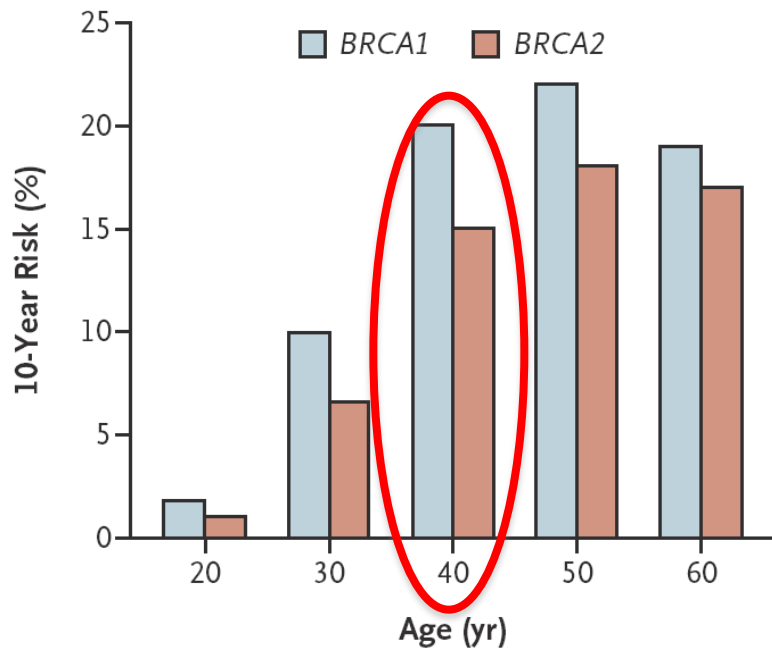


- Was 38 years the right age?
- Was a double preventive mastectomy necessary?
- When you think 'YES' please raise your hand

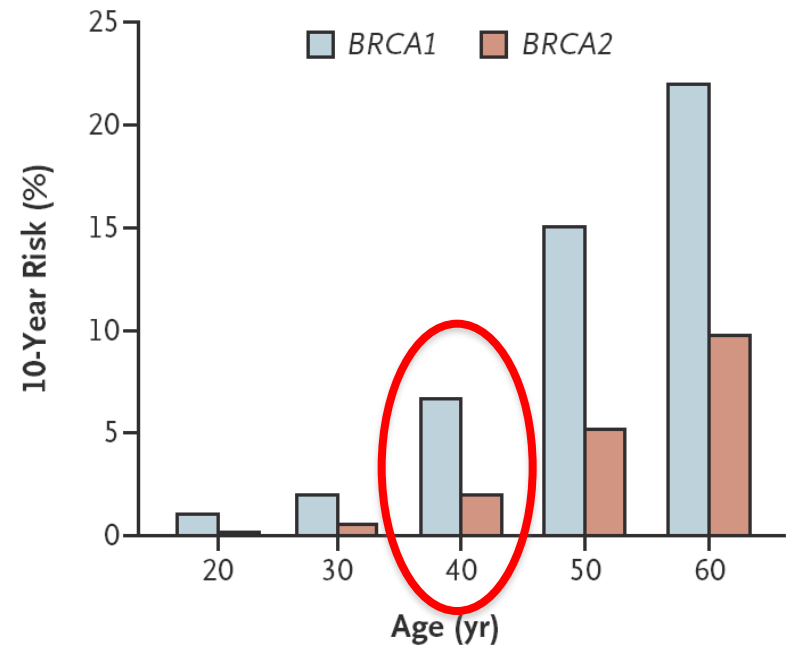
BRCA, age and incidence of cancer



A Breast Cancer



B Ovarian Cancer



Robson, NEJM 2007; Chen, JCO 2007

The case of Angelina Jolie



- Was 38 years the right age?
- YES, also because the next generation contracts breast and/or ovarian cancer at a 5-10 years younger age¹
- Was a double preventive mastectomy necessary?
- Reduces lifetime breast cancer risk to $\pm 7\%$ ^{2,3}
- Prophylactic bilateral salpingo-oophorectomy only⁴
 - 50% reduction lifetime breast cancer risk
 - risk of dying of breast cancer to $\pm 10\%$ ^{4,5}
 - lifetime ovarian cancer risk 1-3%^{4,7}

¹Litton, Cancer, 2012; ²Hartmann et al. NEJM 1999; ³Rebbeck et al. JCO 2004;

⁴Rebbeck et al. NEJM 2002; ⁵Robson, NEJM, 2007;

Miscellaneous



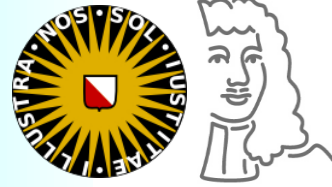
- Breast cancer at age ≤ 35 years and HER2 pos – think *TP53*
- *TP53* germline mutation carriers:
 - avoid radiation/mammograms
- Triple negative breast cancer at age ≤ 60 years:
 - recommend genetic testing
- BRCA1m carrier and breast cancer:
 - 10-year risk of contralateral breast cancer \pm 20-30%
- Prophylactic contralateral mastectomy improves survival in BRCA1/2m carriers after primary breast cancer

Conclusions



- When in doubt, refer to medical geneticist
 - Age ≤ 35 years
 - Triple negative breast cancer
 - 'BOMPP' combination in family
- Consider rapid genetic testing & counseling if
 - Neoadjuvant chemotherapy is indicated
 - Affects choice of chemotherapy
 - May affect choice of surgery
- Consider contralateral prophylactic surgery in BRCA1/2m carriers, especially when primary BC low risk, and age < 40 years

Thank you for your attention



BRCA2 genetic
code cycle path
between
Cambridge and
Great Shefford,
UK

For whom referral to a medical geneticist? (III)



Unaffected individual with one or more of the following:

- A known mutation in a breast cancer susceptibility gene within the family
- Two breast primaries in a single close blood relative
- ≥ 2 close blood relatives with breast cancer on the same side of the family
- ovarian cancer in a close blood relative
- First or second degree relative with breast cancer ≤ 45 years
- Male breast cancer in a close blood relative

For whom *genetic testing*? (I)

NCCN guidelines 2014



Breast cancer patient with one or more of the following:

- Age ≤ 45 years (UK - NICE ≤ 40 years)
- A known mutation in a breast cancer susceptibility gene within the family or Ashkenazi Jewish descent
- With triple negative breast cancer ≤ 60 years
- ≥ 1 close relative with epithelial ovarian cancer OR male breast cancer at any age
- ≥ 2 close relatives with breast cancer at any age OR pancreatic OR prostate cancer (Gleason ≥ 7) at any age
- Two breast primaries (ipsi-or contralateral) synchronously or asynchronously with 1 at age ≤ 50 years