TUMORI DELLA MAMMELLA E DELL'OVAIO:

GENETICA E PREVENZIONE

Dott. Bernardo Bonanni

Divisione di Prevenzione e Genetica Oncologica
Istituto Europeo di Oncologia

IL TUMORE E' SEMPRE UNA MALATTIA MULTIFATTORIALE

Il rischio genetico non è l'unico e può a sua volta essere modificato da altri fattori di rischio (ormonali, metabolici, ambientali, precedenti terapie, ecc.)

MANAGEMENT OF FAMILIAL AND HEREDITARY CANCERS

New specific area of clinical oncology

Main objectives:
Personalized Prevention and Personalized Therapy

RISCHIO FAMILIARE/EREDITARIO: I TRE *PILASTRI* FONDAMENTALI

VALUTAZIONE DEL PROFILO DI RISCHIO

SORVEGLIANZA CLINICO-STRUMENTALE

STRATEGIE DI PREVENZIONE ATTIVA

"Hereditary breast cancer: ever more pieces to the polygenic puzzle"

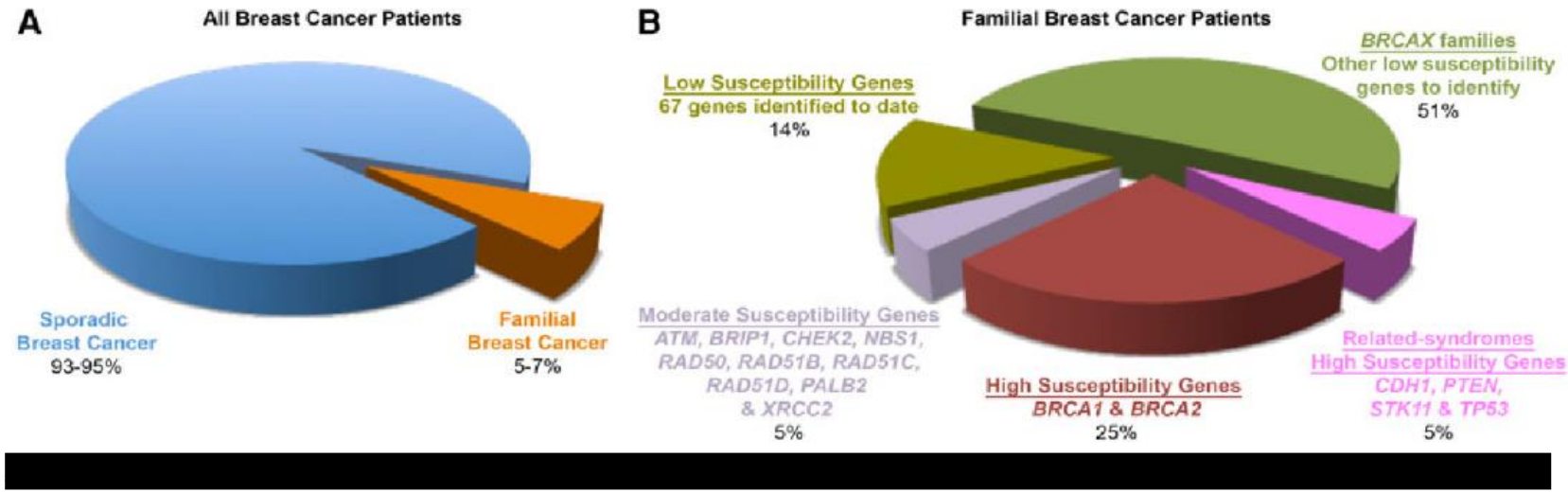


Fig. 1 Distribution of breast cancer patients. a Familial breast cancer represents a minor percentage of all breast cancer patients. b Proportion of familial breast cancer patients due to germ line mutations in high, moderate, and low penetrance cancer genes. BRCA1 and BRCA2 explain the vast majority of familial breast cancer attributed to

Modificato da: Melchor e Benitez, Human Genetics 2013

Rename the Hereditary Breast and Ovarian Cancer syndrome (HBOC) to **King syndrome**

(Nature, July 2019)

HBOC SYNDROME: beyond Breast and Ovarian Cancer

Ovarian Ca: ~**15%** (with *gBRCA1/BRCA2*), **50%** (without *gBRCA1/BRCA2*)

Bell et al. Nature 2011

TNBC: **15-20%** (with *gBRCA1/BRCA2*), **40%** (without *gBRCA1/BRCA2*)

Akashi-Tanaka et al. Clin Breast Cancer 2015

Loibl et al. Ann Oncol 2018

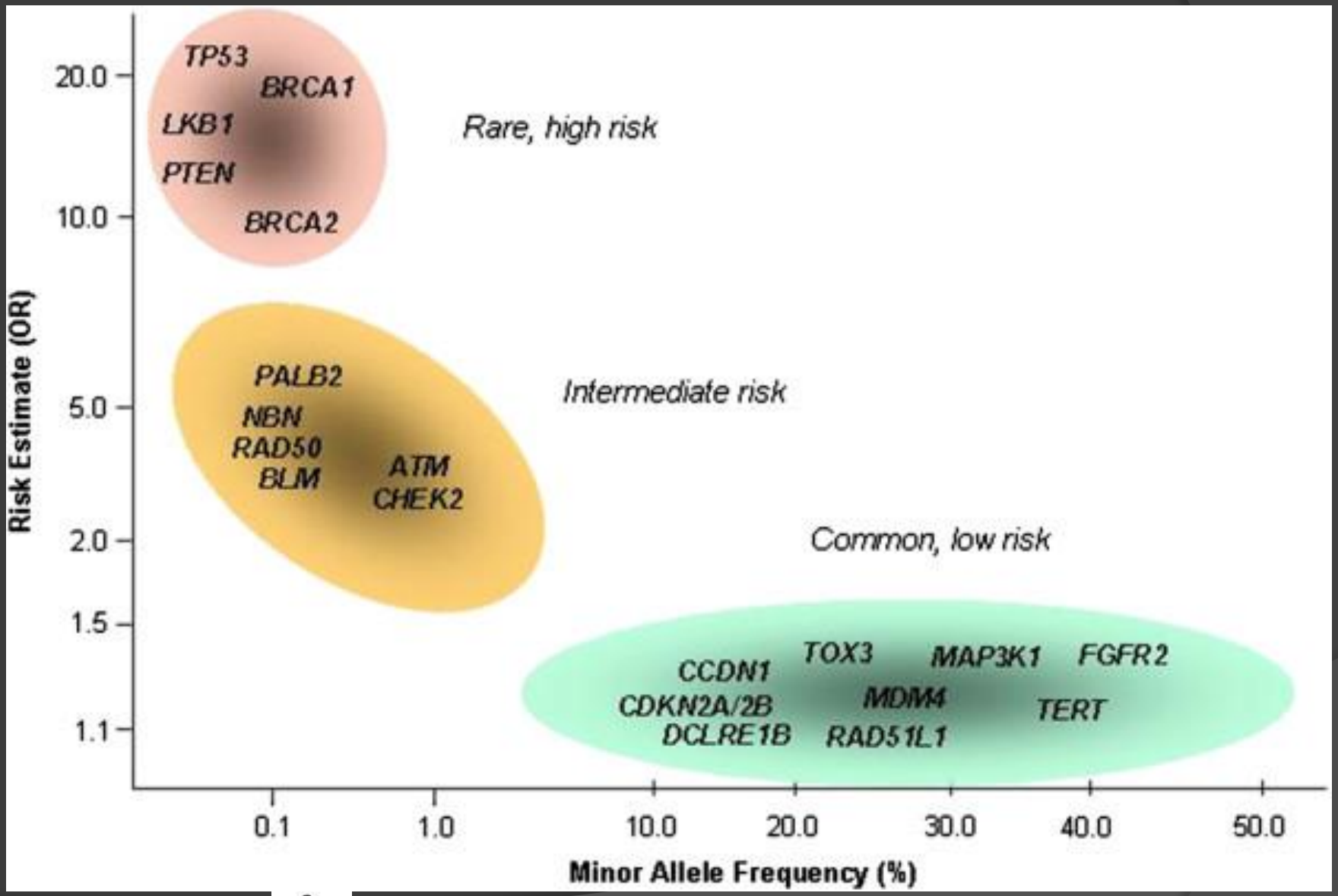
Advanced Prostate Ca: **10-12%** (with *gBRCA1/BRCA2* e/o *sBRCA1/BRCA2*), **25%** (without *gBRCA1/BRCA2*)

Robinson et al. Cell 2015

Pancreatic Ca: **~ 9%** (with g- or s-*BRCA1/BRCA2*)

Shroff et al. JCO Precis Oncol 2018

"Hereditary breast cancer: ever more pieces to the polygenic puzzle"



*Bogdanova N et al. Hered **Cancer** Clin Pract. 2013*

Not only BRCA…

HIGH PENETRANCE GENES FOR BREAST CANCER

- TP53 (Li-Fraumeni syndrome)
- CDH1 (Hereditary Diffuse Gastric Cancer (HDGC) syndrome)
- PTEN (Cowden syndrome)
- SK11 (Peutz-Jeghers syndrome)
- MMR (Lynch syndrome) (still unconfirmed)

MODERATE PENETRANCE GENES FOR BREAST CANCER

- PALB2
- CHEK2
- ATM
- NBN

MODERATE PENETRANCE GENES FOR OVARIAN CANCER

- BRIP1
- RAD51C and RAD51D

LOW PENETRANCE GENES and/or ALLELES

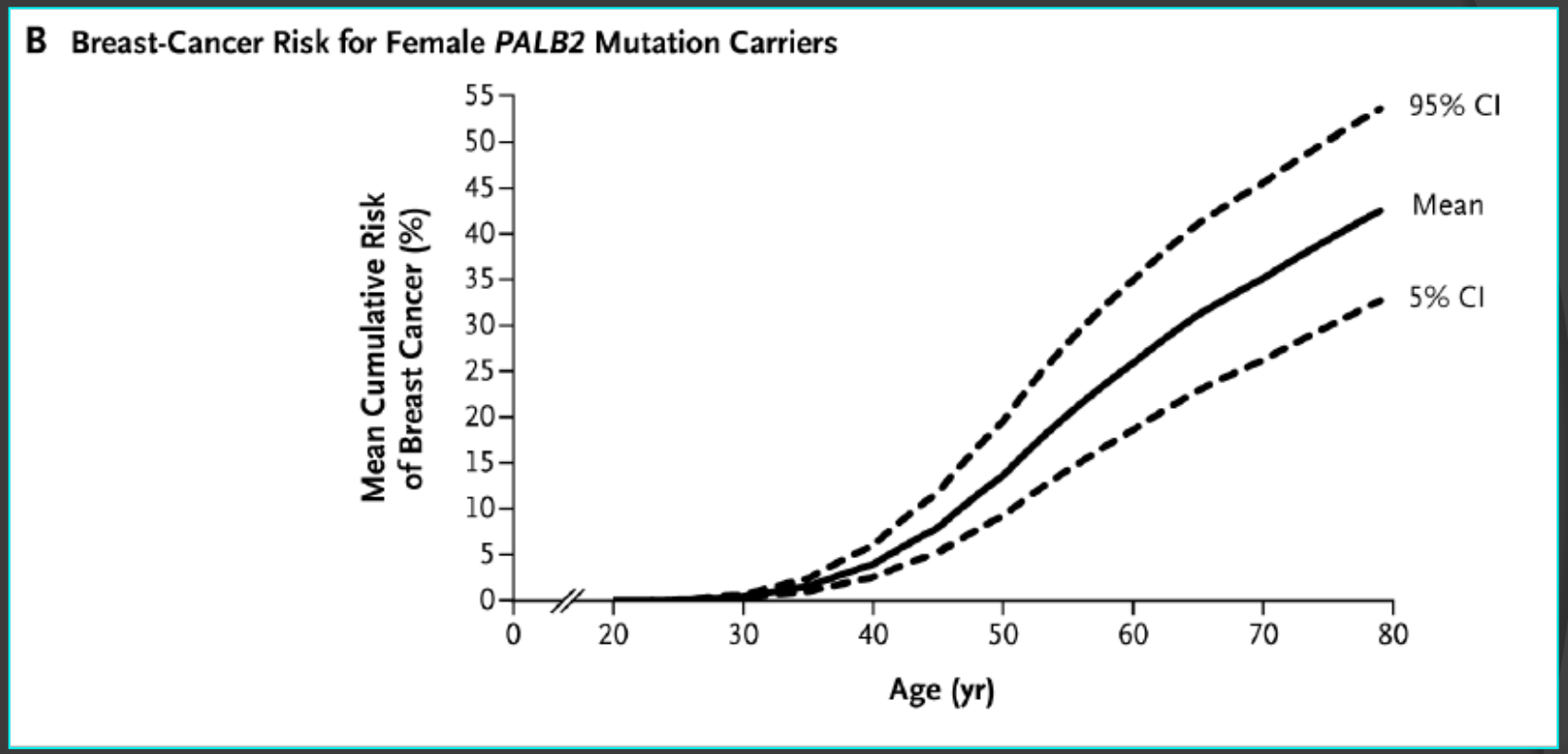
- POLIGE RISK SCORE

Moderate Penetrance Genes and BC Risk

Cancer type	Gene	Average relative risk
Breast cancer	*ATM*[6]	2.8 (90% CI 2.2–3.7)
	BARD1	Insufficient data
	BRIP1 (REFS 3, 20)	No evidence of association
	CHEK2 (truncating)[3]	3.0 (90% CI 2.6–3.5)
	CHEK2 (missense)[47]	1.58 (95% CI 1.42–1.75) for I157T
	MRE11A	Insufficient data
	NBN[68]	2.7 (90% CI 1.9–3.7) for c.657del5
	PALB2[8]	5.3 (90% CI 3.0–9.4)
	RAD50	Insufficient data
	RAD51C/RAD51D[3]	No evidence of association
	XRCC2	Insufficient data
	SLX4	Insufficient data

Modificato da Tung et al. Nat Rev Clin Oncol 2016

Moderate Penetrance Genes and BC risk



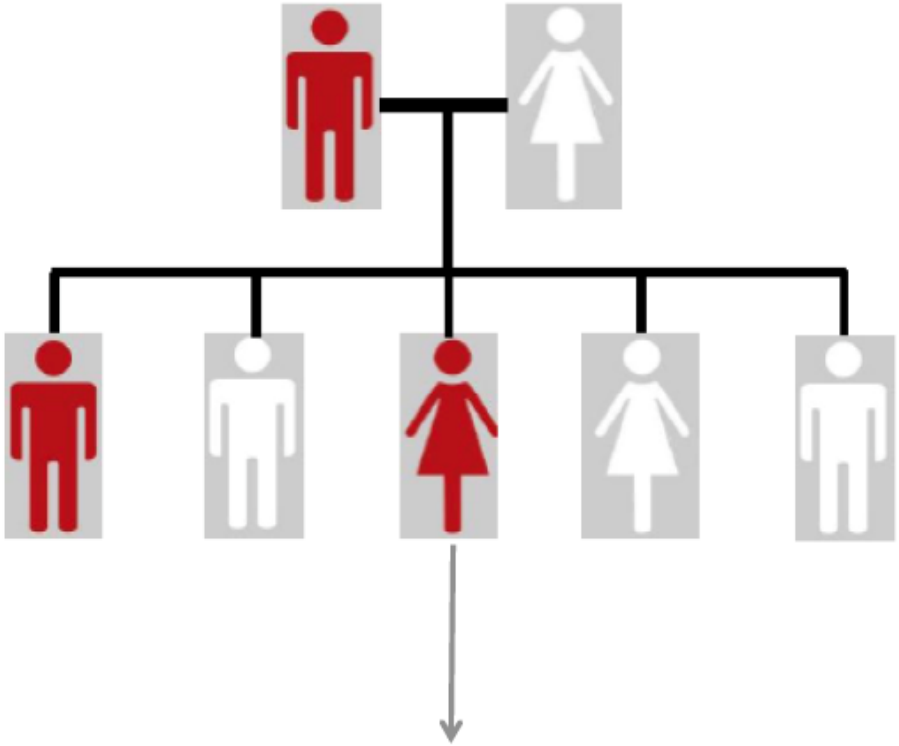
modificato da Antoniou et al. New Engl J Med 2014

PALB2

Risk at 70 yrs age: 33%

With positive FH: 58%

Lobular Breast Cancer and HDGC



LBC is a CDH1-associated cancer disease affecting women and forming part of the HDGC syndrome.

Cumulative risk for breast cancer by 80 years is 42% for women with CDH1 mutations.

Hansford et al. *Jama Oncol* 2015

DIECI PUNTI CHIAVE PER RICHIEDERE UNA CONSULENZA GENETICA (ED EVENTUALMENTE IL TEST GENETICO)

FAI ATTENZIONE SE:

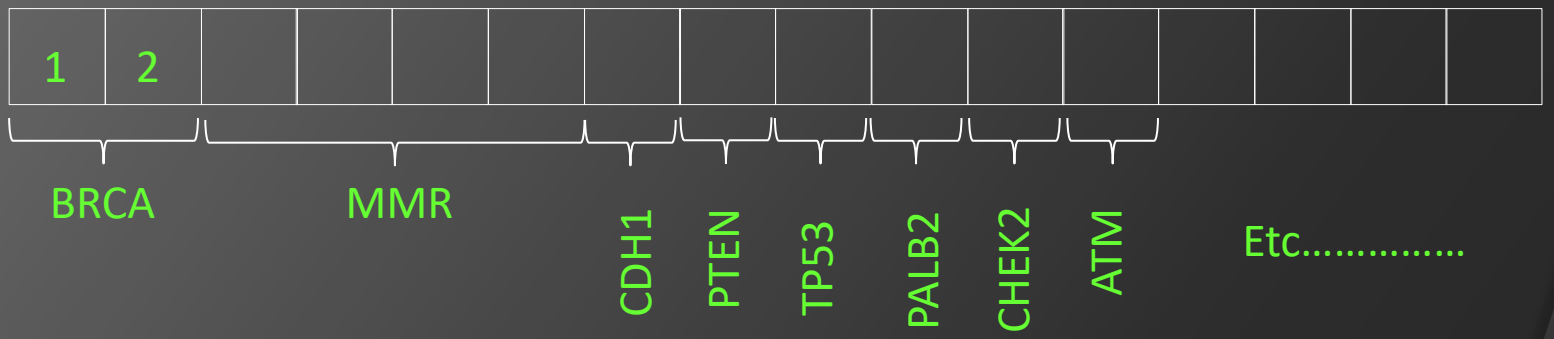
1. Hai avuto un tumore del seno in età giovanile (cioè prima dei 36 anni) oppure un tumore triplo negativo (prima dei 60 anni).
2. Hai avuto un tumore dell'ovaio.
3. Hai avuto un famigliare con tumore del seno giovanile oppure triplo negativo.
4. Hai avuto (o se in famiglia c'è stato) un tumore mammario maschile.
5. Hai famigliarità di I° o II° grado per casi di tumore del seno e/o dell'ovaio.
6. In famiglia ci sono stati uno o più casi di tumore della prostata prima dei 50 anni.
7. In famiglia ci sono stati uno o più casi di tumore del pancreas prima dei 50 anni.
8. In famiglia ci sono stati uno o più casi di tumore del seno di tipo lobulare e/o tumori dello stomaco prima dei 50 anni.
9. Nella famiglia ci sono stati più tumori, specie se in età giovanile.
10. Tu stessa o qualcuno in famiglia ha già fatto un test genetico (per avere una "*second opinion*" o per fare "test di accertamento", rispettivamente).

In questi casi, ti raccomandiamo di rivolgerti preferibilmente a Centri di Eccellenza Oncologica, con al proprio interno una High Risk Clinic

Genetic Germline Testing: Clinical Approaches

TARGET TESTING

MULTIGENE PANEL TESTING



KEY POINT: «ACTIONABILITY»!

NEXT GENERATION SEQUENCING (NGS)

Finding of variants of unknown clinical significance (VUS)
+
Incidental Findings

Which genes and which variants are clinically ACTIONABLE?

Risk of misclassification:
Unappropriate medical decisions
Patient's psychological stress

Careful selection before referral to multigene panel testing

Genetic counseling:
essential!

MULTIGENE PANEL TESTING

FENOTIPO SPECIFICI

MINOR NUMERO DI GENI

GENI SPECIFICI A PENETRANZA ALTA E MODERATA (ES. HBOC O COLON)

POSSIBILE PRESENZA DI GENI NON SPECIFICI AD ALTA PENETRANZA (ES. STK11)

NON FENOTIPO SPECIFICI

MAGGIOR NUMERO DI GENI

ELEVATA PRESENZA DI GENI A BASSA E MODERATA PENETRANZA

MAGGIOR TASSO DI VUS

MAGGIOR RISCHIO DI INCIDENTAL FINDINGS

FAST TRACK

Why? To help treatment decisions

Indications:

BREAST

- **SURG:** → conservative vs mastectomy (mono or bilat.)
- **RT:** → yes or no (TP53 no!! BRCA1/BRCA2 yes)
- **ONC:** → Trials with PARP-i/LH-RH an. versus salpingoophorectomy

OVARY — Target Therapy (PARP-i; others?)

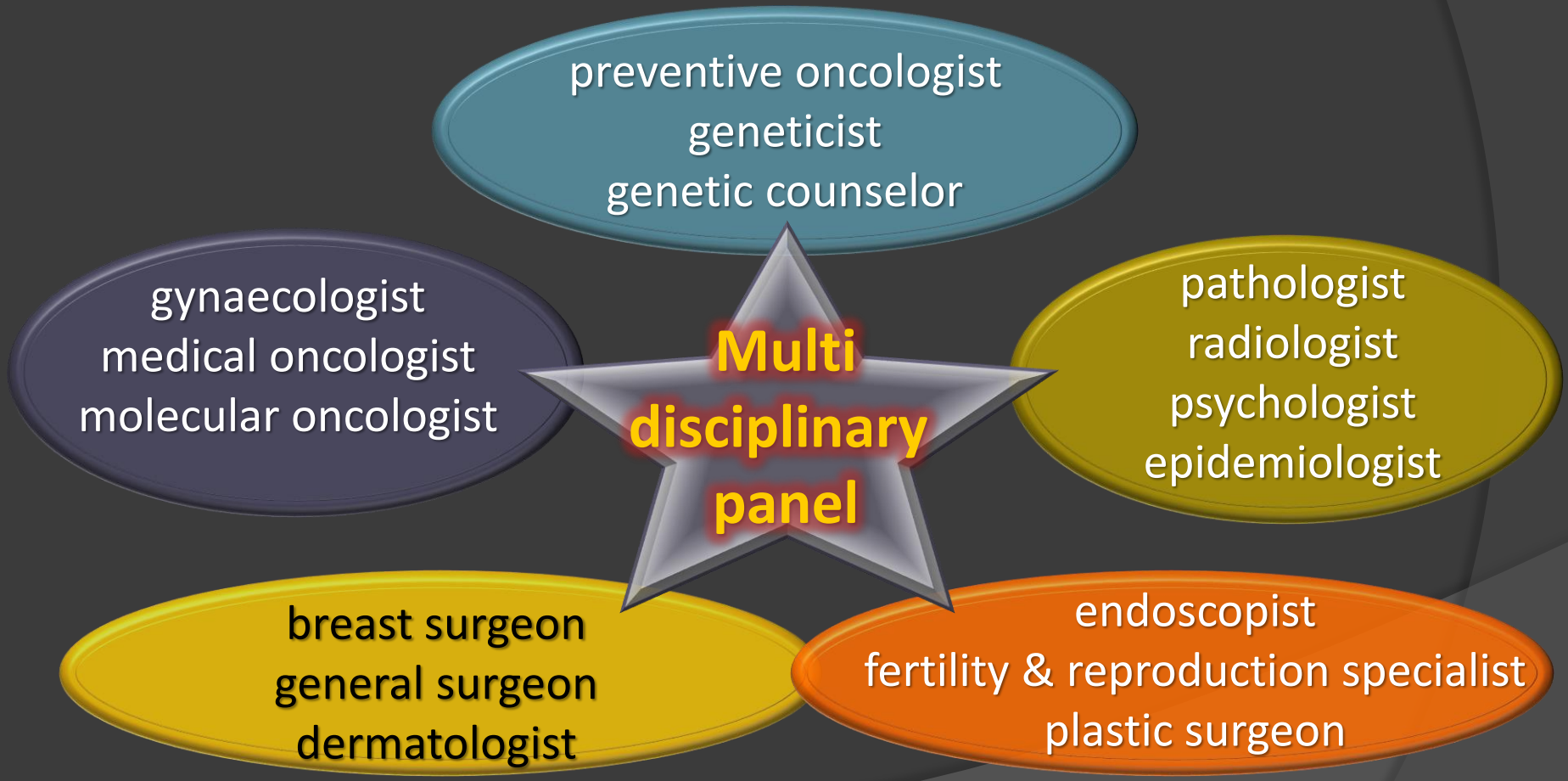
CANCER PREVENTION IN HIGH RISK SUBJECTS

NB: these options are complementary and sequential !

PERSONALIZZAZIONE!

Recommended management of high risk subjects:

IEO HIGH RISK CENTER



High Risk Center
Prevenzione e Genetica
Oncologica

SURVEILLANCE OF HIGH RISK (BRCA carriers)

Importance of the combination:

Mammography + TS

+

Breast US and Transvaginal US (+ Ca125)

+

Breast MRI (W.B.MRI in TP53)

+

Clinical visit

LIFESTYLE MODIFICATIONS

- **Mediterranean diet**
- **Season vegetables**
- **Legumes - Fish**
- **No refined food**
- **Reduce red meat consumption**
- **Cooking methods**

Physical Exercise

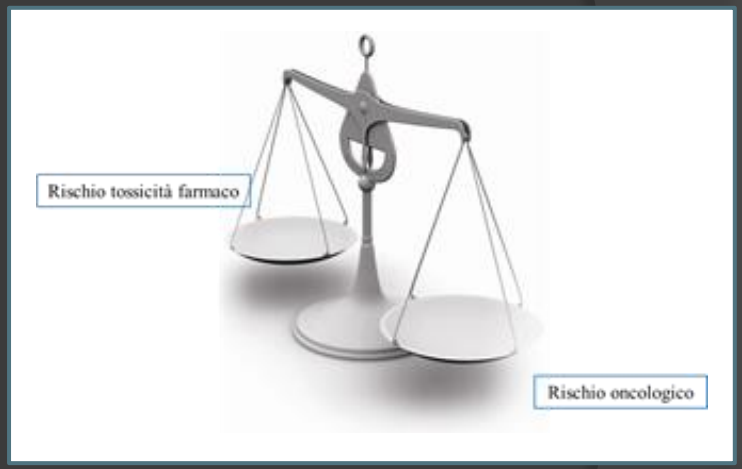
Holmes et Al. Physical activity and survival after breast cancer diagnosis

JAMA. 2005 May 25;293(20):2479-86.

MEDICAL PREVENTION

BREAST CANCER MEDICAL PREVENTION

- Tamoxifen at low dose («Baby Tam»)
- Aromatase Inhibitors (Exemestane at low dose)
- Metformin, Vit. D, NSAIDs
- PARP-inhibitors



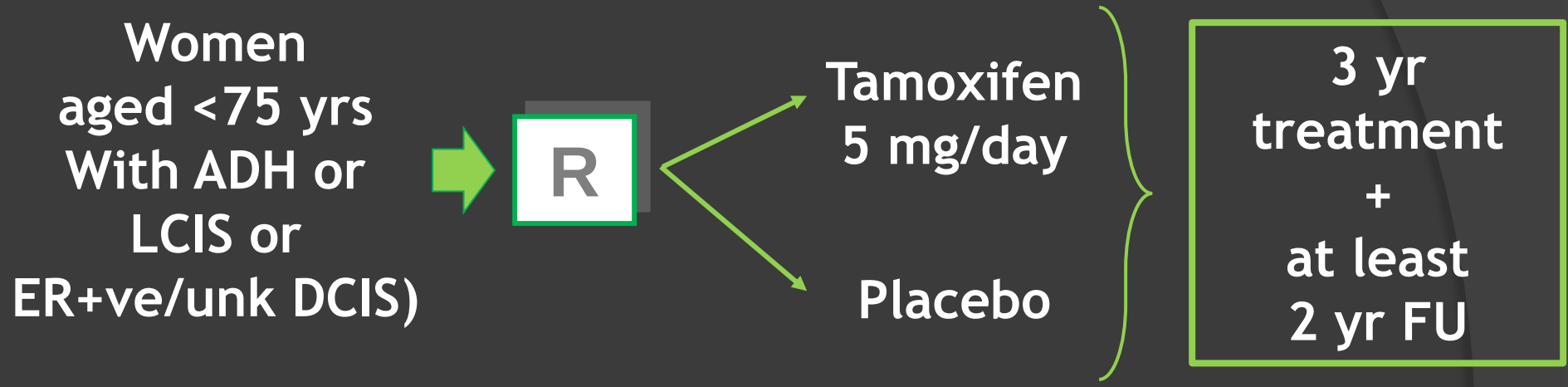
BRCA1 and BRCA2 mutations induce mostly different breast cancer phenotypes

BRCA1 → ~ 90% non-endocrine responsive BC (frequently triple negative and early onset)

BRCA2 → ~ 80% endocrine responsive and later onset

Targetable by SERMs (esp. tamoxifen) and AIs

Randomized placebo controlled trial of low dose tamoxifen ("Baby-tam") - Study Tam01



Primary endpoint: Incidence of invasive breast cancer or DCIS

500 participants enrolled from 14 centers in Italy

Median follow up = 5.1 years (IQR 3.9-6.3)

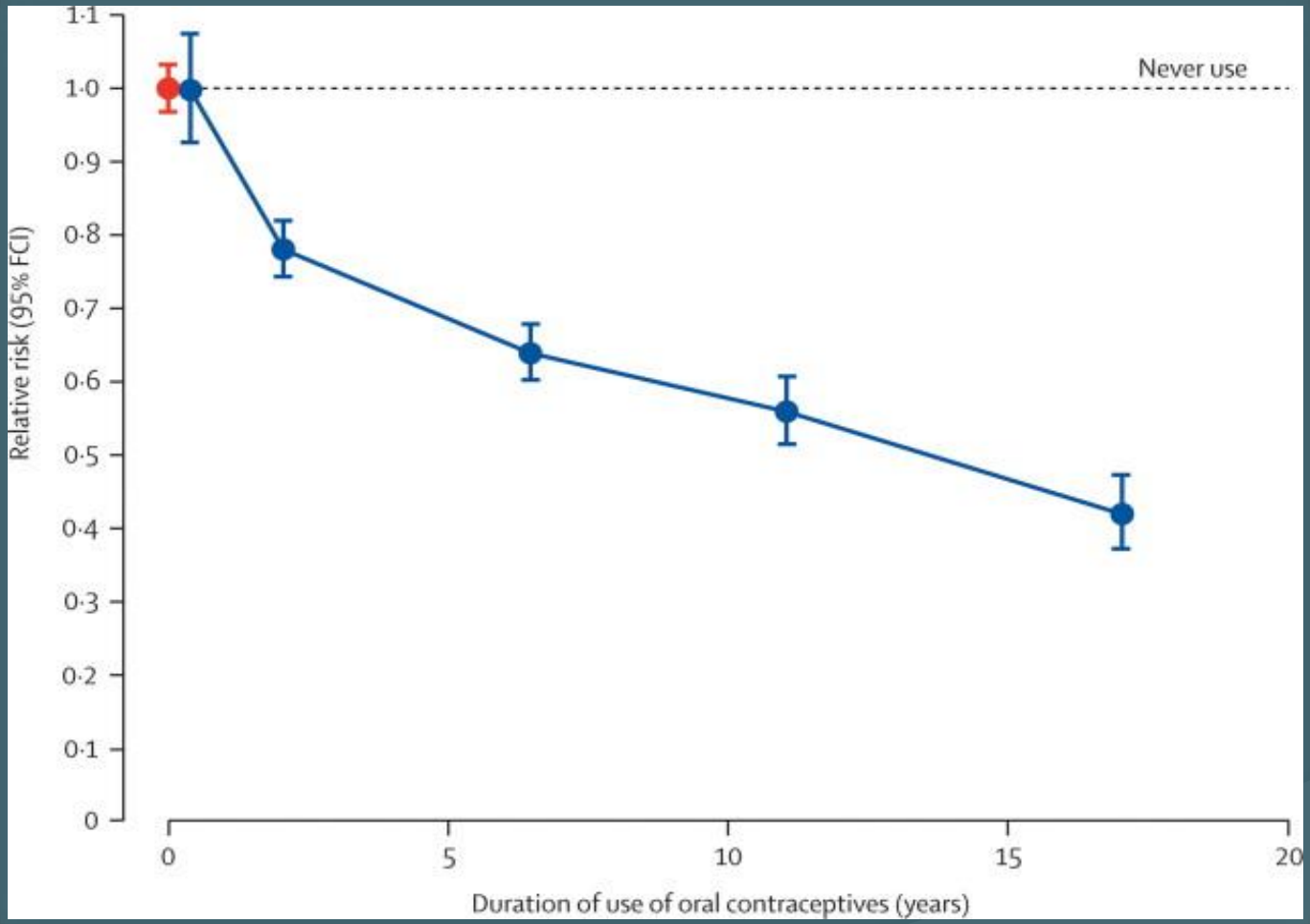
Primary events: 42

LOW-DOSE TAMOXIFEN (5 mg/day) («Baby-TAM»)

- Now it is practice–changing in ER+ DCIS, LCIS and AH
- Next step: a phase III study of «*Baby-TAM*» in healthy women at high risk (BRCA2 mutation carriers, Tyrer-Cuzick High-Risk, High Mammographic density) to be designed

Oral contraceptives on ovarian cancer risk and breast cancer risk in BRCA mutation carriers

Ovarian cancer and oral contraceptives analysis of 45 epidemiological studies for a total of 23.257 women with ovarian cancer and 87.303 controls



Relative risk of ovarian cancer based on duration of use of oral contraceptives stratified for study, age, parity and hysterectomy.

Effect of oral contraceptives on ovarian and breast cancer risk in women with a known BRCA1/2 pathogenic or likely pathogenic variant:

Risk reduction:

- oral contraceptives **reduce the risk for ovarian cancer by 45% to 50% in *BRCA1 mutation carriers and by 60% in BRCA2 mutation carriers***
- risks appeared to decrease with longer duration of oral contraceptive use

McLaughlin JR et al. Lancet Oncol 2007.
Narod SA et al. N Engl J Med 1998.
Iodice S et al. Eur J Cancer 2010.
Moorman PG et al. J Clin Oncol 2013..

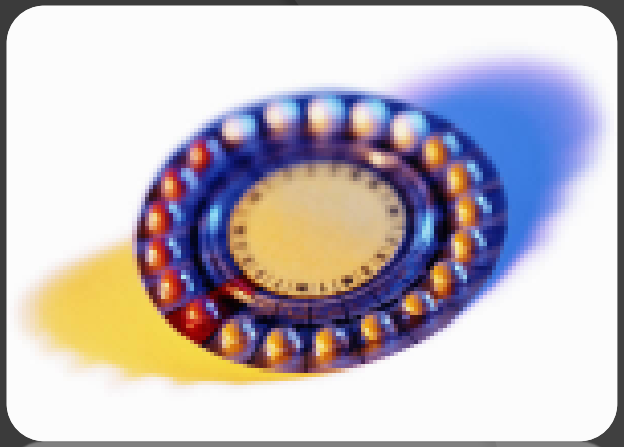
Effect of oral contraceptive use on breast cancer risk among BRCA1/2 mutation carriers:

Conflicting data:

- modest but statistically significant increase: *Narod SA et al. J Natl Cancer Inst 2002; Haile RW et al. Cancer Epidemiol Biomarkers Prev 2006.*

- not significantly associated with breast cancer risk: *Lee E et al. Cancer Epidemiol Biomarkers Prev 2008; Milne RL et al. Cancer Epidemiol Biomarkers Prev 2005.*

Prevenzione farmacologica del carcinoma ovarico con i contraccetivi orali



- La pillola contraccettiva riduce il rischio ovarico fino al 50%
- La protezione permane per almeno 15 anni
- L'uso della pillola moderna non appare aumentare significativamente il rischio del seno, specie iniziandola in giovane età (>20-25 anni)

PROFILASSI CHIRURGICA

MASTECTOMY

- ✓PROPHYLACTIC (in healthy carriers)
- ✓CONTRALATERAL / RR (in patients)

Genetic Counseling

POSITIVE
Genetic Test

ALWAYS
AFTER

Multidisciplinary discussion

Decision-making counseling with psichologist

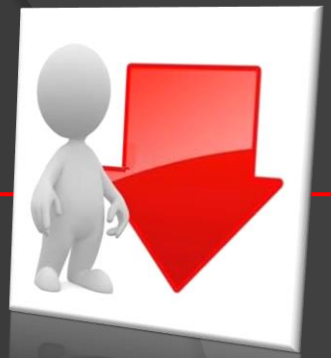
TIME TO DECIDE !

ALWAYS PERSONAL DECISION !

MASTECTOMIA PROFILATTICA

PRO

- Riduzione del rischio
- Riduzione dell'ansia
- Soddisfazione estetica



CONTRO

- Più chirurgia
- Irreversibilità
- Riduzione del rischio non completa (rischio residuo: differenti punti di vista in letteratura)
- Complicazioni (post chirurgiche o nel tempo)
- Riduzione della sensibilità, modificazione corporea
- Insoddisfazione estetica

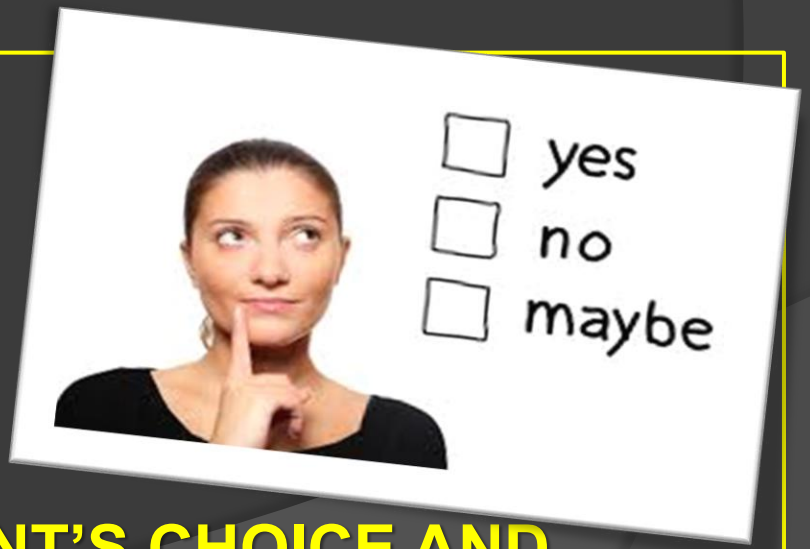
PROPHYLACTIC SURGERY IN BRCA MUT. CARRIERS

PRIORITA': RISCHIO GINECOLOGICO!

SALPINGO-OPHORECTOMY → BC risk reduction but early menopause

SALPINGECTOMY? → Preserves fertility but still under studies

RIGHT TIMING



PATIENT'S CHOICE AND PERSONALIZED PROGRAM

HIGH RISK SUBJECTS MANAGEMENT: WHAT IS NEEDED?

ESSENTIALS:

- High Risk Clinic
- New physician-patient relationship
- Share certainties and uncertainties
- Non-directive medicine
- Time to decide (on genetic testing and RR measures)
- Psichological/decision support
- To any person one personalized pathway:

NO ONE SIZE FITS ALL !

HEREDITARY CANCER

Thank you!