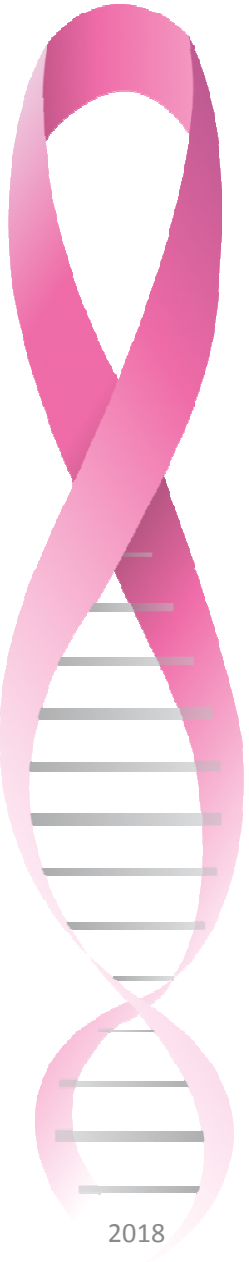

# Predisposição Hereditária ao Câncer de Mama

## *Aspectos Práticos*

Fernanda Teresa de Lima

Clube da Mama – Goiânia

2018

# ESMO / ASCO Recommendations for a Global Curriculum in Medical Oncology Edition 2016

**4.2 Basic Principles in the Management and Treatment of Malignant Diseases**

4.2.1 Pathology
4.2.2 Molecular pathology
4.2.3 Laboratory medicine
4.2.4 Translational research
4.2.5 Principles of personalised cancer medicine
4.2.6 Staging procedures (clinical staging)
4.2.7 Imaging
4.2.8 Molecular imaging
4.2.9 RECIST

**5. PSYCHOSOCIAL ASPECTS OF CANCER**

**6. COMMUNICATION**

**7. GENETIC COUNSELLING**

**8. PATIENT EDUCATION**

Dittrich C, *et al. ESMO Open* 2016;**1**:e000097. doi:10.1136/esmoopen-2016-000097

Society Position Statements/White Papers

Multi-disciplinary summit on genetics services for women with gynecologic cancers: A Society of Gynecologic Oncology White Paper

Leslie M. Randall [a,*], Bhavana Pothuri [b], Elizabeth M. Swisher [c], John P. Diaz [d], Adam Buchanan [e], Catherine T. Witkop [f], C. Bethan Powell [g], Ellen Blair Smith [h], Mark E. Robson [i], Jeff Boyd [d,j], Robert L. Coleman [k], Karen Lu [k]

# 2. Consensus Statement

- All women with epithelial ovarian, tubal, or peritoneal cancer should be offered and strongly encouraged to have genetic testing for hereditary ovarian cancer risk.
- Women diagnosed with an inherited genetic mutation associated with HBOC syndrome should be referred for management of other associated cancer risks including breast cancer surveillance and their blood relatives should be offered cascade testing.
- Multigene panel testing is acceptable for detection of hereditary ovarian or endometrial cancer risk. Genetics expertise, including that exercised by an adequately-trained oncologist, and patient preferences should help determine the most appropriate test.

Gynecologic Oncology 146 (2017) 217–224

# 2. Consensus Statement

p pp p

- Pre- and post-test counseling by a trained cancer genetics professional is optimal but not available in all practice settings. Increasing access to

- Gynecologic oncology providers who choose to order testing themselves should be able to interpret test results (positive, negative and VUS),apply results to care, be prepared to initiate cascade testing, recognize situations in which they require input from genetics professionals, and identify genetics with which professionals they can consult when indicated.





Gynecologic Oncology 146 (2017) 217–224

# Predisposição Hereditária ao Câncer

- Suspeita
- Testes
- Riscos
- Condutas

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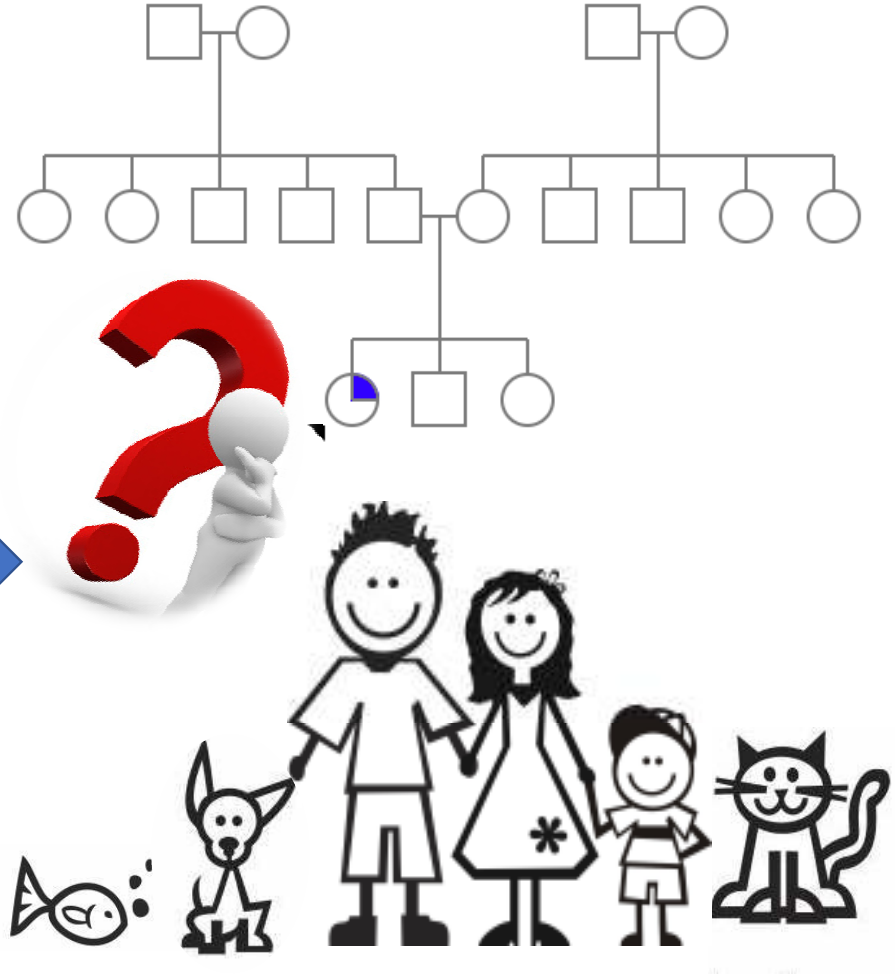
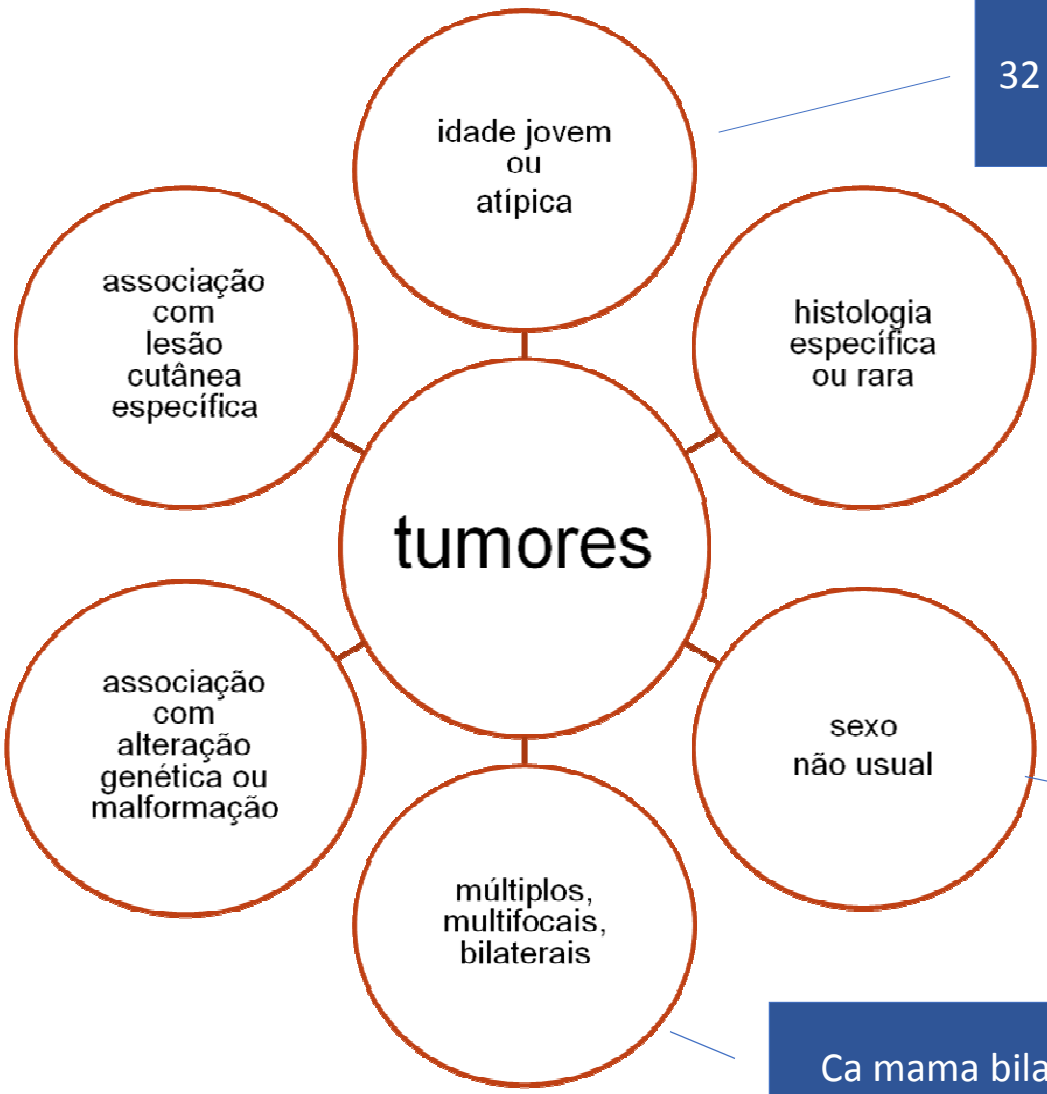
# Suspeita



# Suspeita




Fonte: NCI

32 anos, sem história familiar

Ca mama triplo negativo

Ca mama masculino

Ca mama bilateral

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# Suspeita

## Câncer de ovário

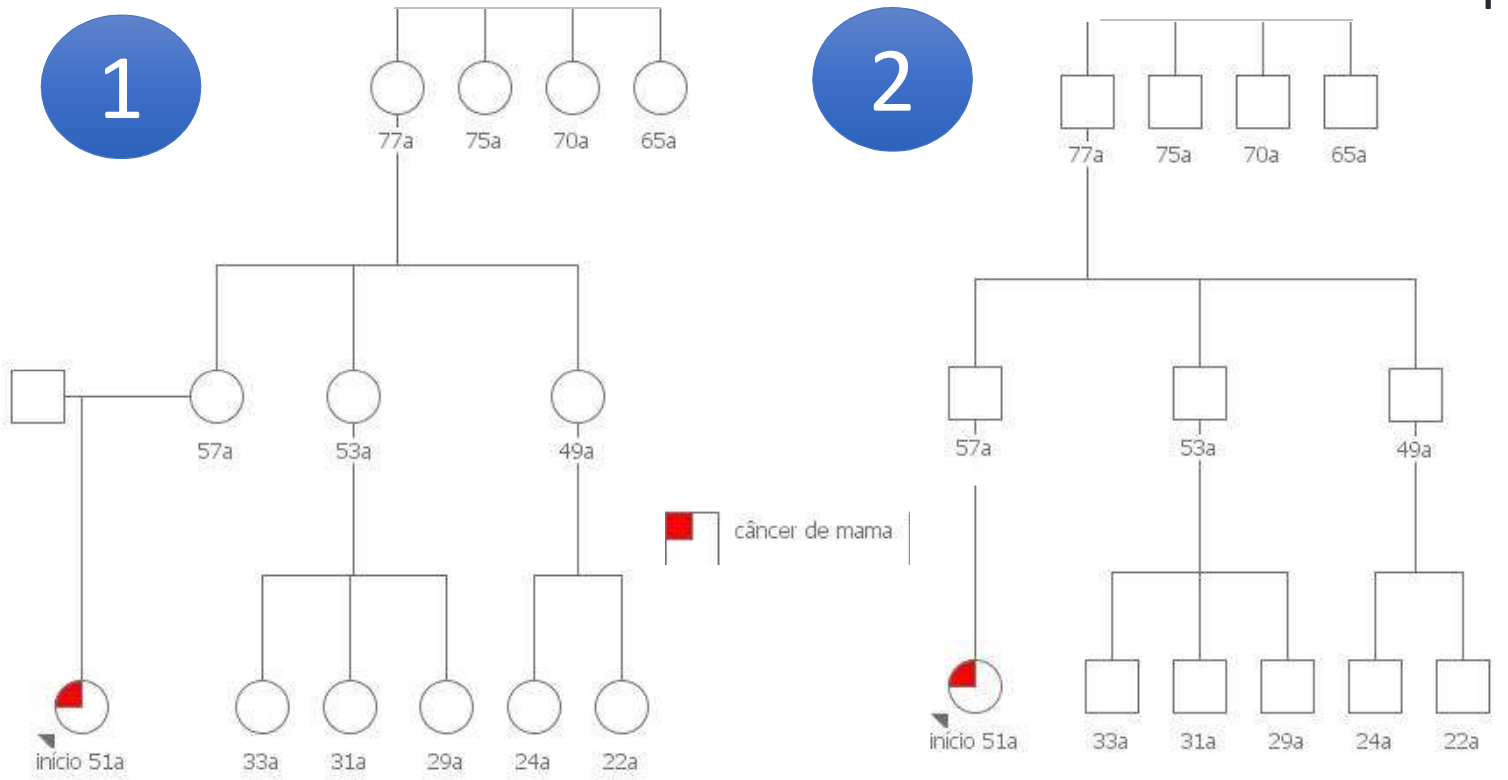
## Câncer de endométrio

- precoce (≤ 50 anos)
- Associação com CCR/tumores SL ou HF CCR

## Câncer de mama

- precoce (≤ 50 anos)
- masculino
- triplo negativo
- Associações
  - ovário, tireóide, suprarrenal, endométrio, pâncreas, SNC, sarcoma, leucemia, próstata (Gleason ≥7), endométrio, gástrico difuso
  - alterações dermatológicas, macrocefalia, pólipos GI hamartomatosos
  - no mesmo lado da família
- 2 familiares com câncer mama, um com ≤ 50 anos
- 3 familiares com câncer de mama

# Suspeita




- Poucos indivíduos

Ausência ≥ 2 mulheres ≥ 45 anos em 1 linhagem, relacionadas em 1º. ou 2º. graus ao indivíduo afetado

Fonte: Weitzel et al, 2007

**estrutura familiar limitada**

# Predisposição Hereditária ao Câncer

- Suspeita
- Testes
- Riscos
- Condutas

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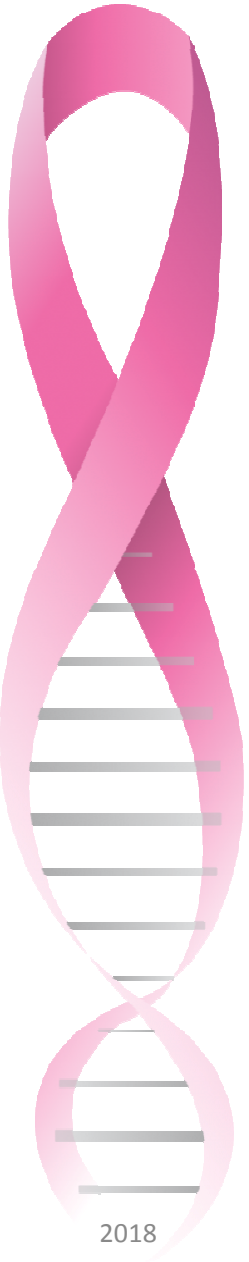
# Aconselhamento pré-teste

- Consentimento informado
  - Processo de obter a permissão do paciente para um procedimento após discussão de riscos, benefícios, alternativas do procedimento e que tudo é compreendido pelo paciente



# Testes moleculares

Nenhum teste genético deve ser solicitado sem o consentimento do paciente.

O paciente tem que entender as complexidades e implicações do resultado para fazer uma escolha informada

# Testes moleculares

## Definir o familiar a ser estudado

Identificar o familiar com tumor mais típico de predisposição hereditária ao câncer

## Definir o momento de realização do teste

Antes do primeiro tratamento

QT neoadjuvante - Cirurgia

Após o tratamento

Familiares assintomáticos

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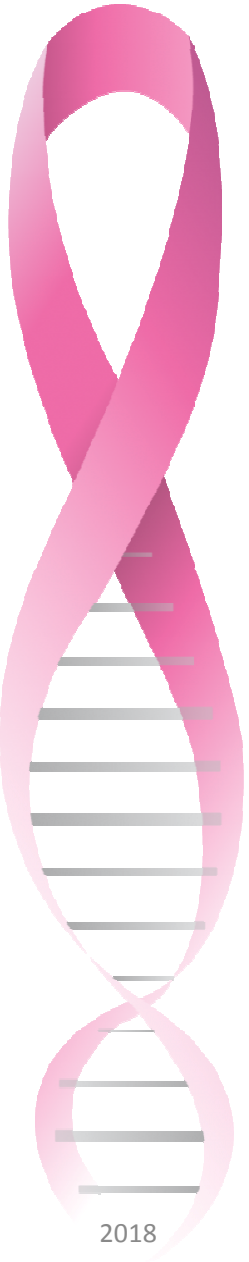

# Testes moleculares Pré-Teste

## Benefícios

- ✓Fator causal
- ✓Manejo e vigilância
- ✓Definir riscos associados
  - ✓Teste negativo em não afetado com variante fliar conhecida
- ✓Investigação de familiares

## Riscos

- Decisões difíceis sobre manejo clínico
- VUS: stress e insegurança
- Discriminação
- Culpa
  - Teste negativo em não afetado com variante fliar conhecida: culpa

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# Testes moleculares
# Pré-Teste

## Limitações

- Riscos de câncer
- Imprevisibilidade de eficácia de conduta
- Negativo em não afetado sem variante fliar conhecida
  - Técnica utilizada, qualidade do teste, fenocópia
  - Limitação de tecnologia (resultado não-informativo)
- Negativo em não afetado com variante fliar conhecida
  - Risco residual

# Painéis

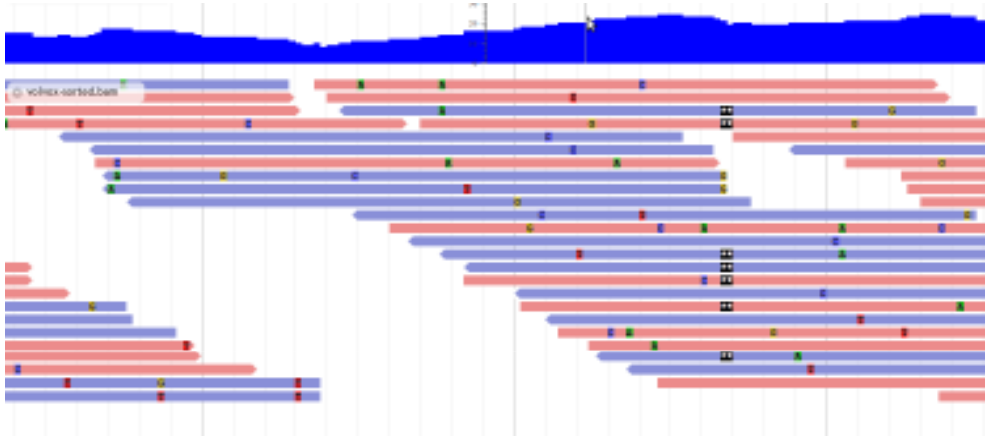
- Resultados de painel com 42 genes
  - 198 mulheres (174 com ca mama)
    - 141 sem mutações em *BRCA*s
  - concordantes com resultados prévios de *BRCA*s
  - detectam 11,4% de mutações potencialmente patogências em outros genes
  - 10,6% levam a mudança no rastreamento

| | |
|---|---|
| New recommendations | (n = 11) |
| Prophylactic surgery: bilateral salpingo-oophorectomy | (n = 1: *MLH1*, family history of ovarian cancer) |
| Consider more intensive breast surveillance | (n = 6: *ATM, SLX4, BLM, NBN, CDH1*) |
| Consider more intensive GI surveillance | (n = 6: *MLH1, MUTYH, CDH1*) |
| New procedure results to date | (n = 1) |
| Tubular adenoma excised during colonoscopy, performed for *MLH1* mutation | (n = 1) |
| Normal findings on bilateral salpingo-oophorectomy, performed for *MLH1* mutation | (n = 1) |

Kurian *et al*, 2014

# Testes moleculares

- Metodologia e equipamento
- Qualidade
  - Cobertura do gene – 100%
  - Profundidade – pelo menos 20X
- Transcritos referência para análise



**Variações**

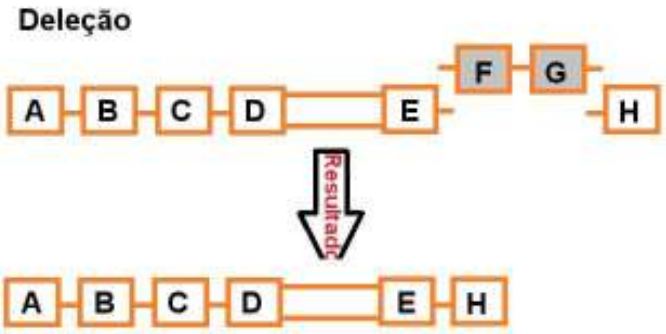
frequência populacional/bases referência

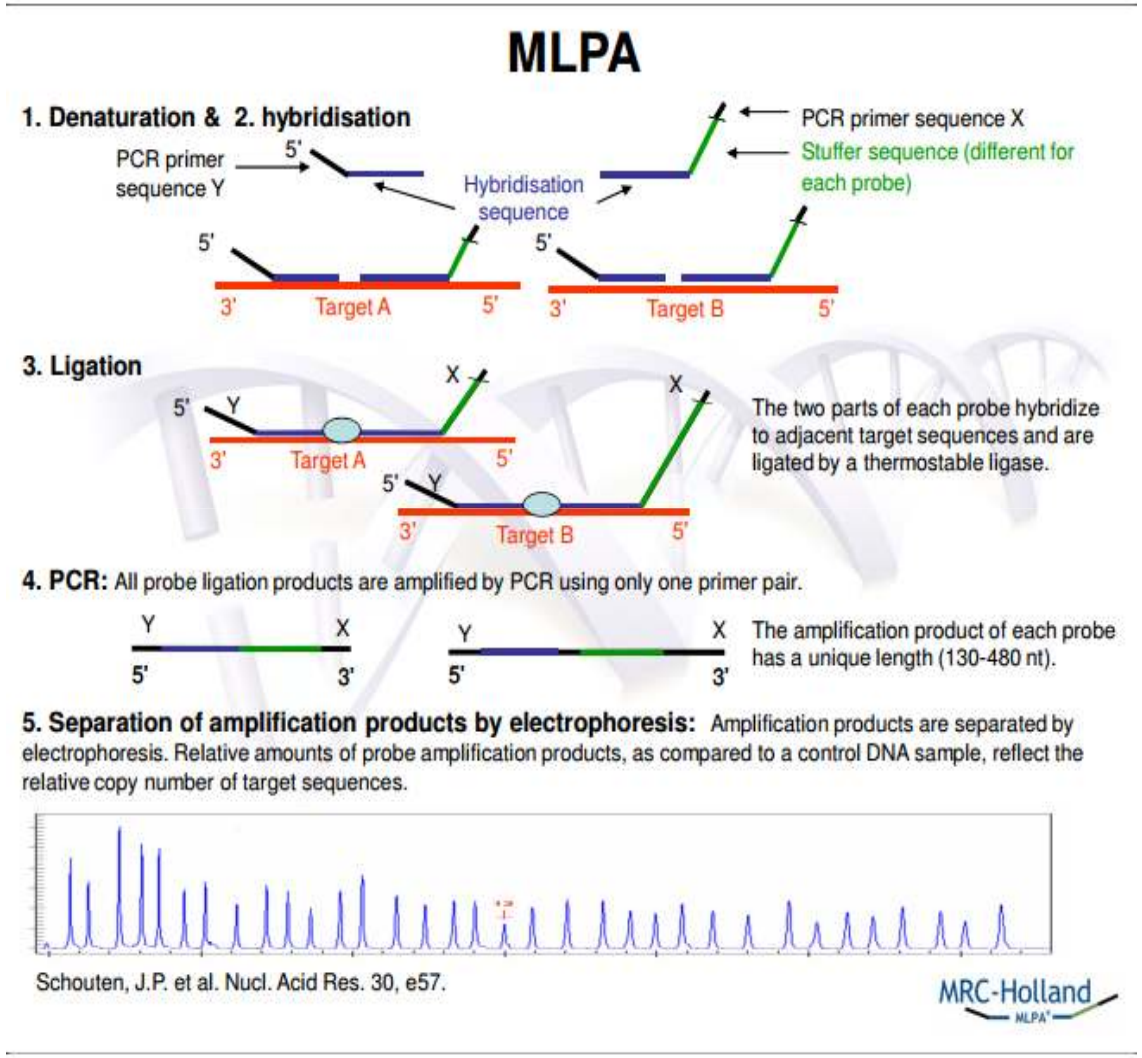
classificação/bases utilizadas para classificar

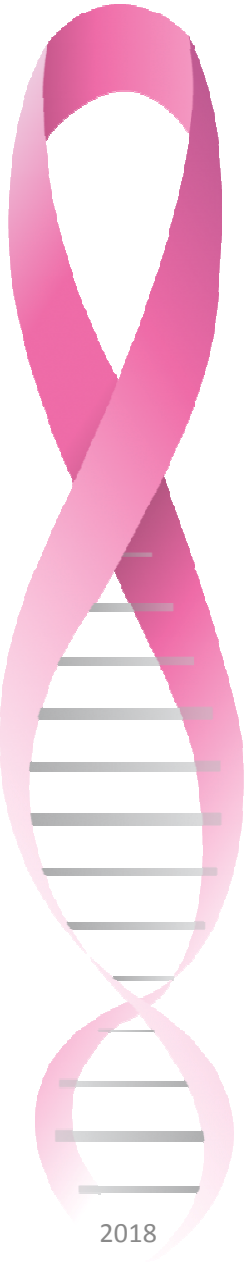
modelos computacionais para avaliar impacto na proteína

# Rearranjos

Caso o painel não contemple

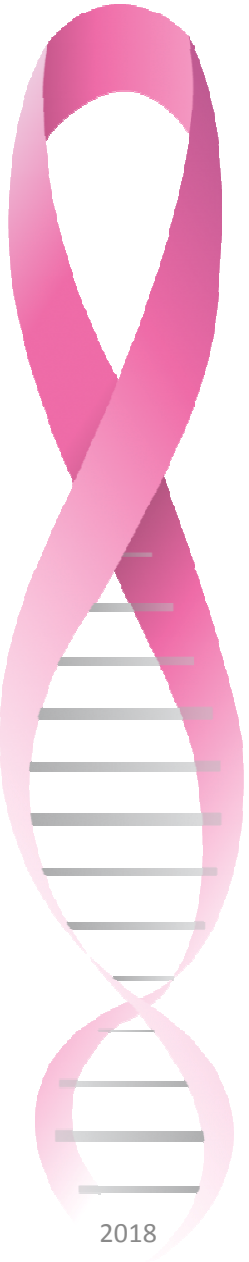




# Testes moleculares
# Pós-Teste

- Resultado do teste discutido pessoalmente
- Implicações do resultado
- Opções de manejo para cada tipo de câncer associado ao diagnóstico
- Identificar familiares de risco que se beneficiariam do teste genético
- Impacto e apoio psicológico



# Testes moleculares
# Pós-Teste

- Reações semelhantes as do pré-teste de acordo com o tipo de resultado
- Variante patogênica
  - enfatizar a importância da vigilância de risco
- Ausência de variante
  - relutância em cessar a vigilância de risco
  - risco residual

# Predisposição Hereditária ao Câncer

- Suspeita
- Testes
- Riscos
- Condutas

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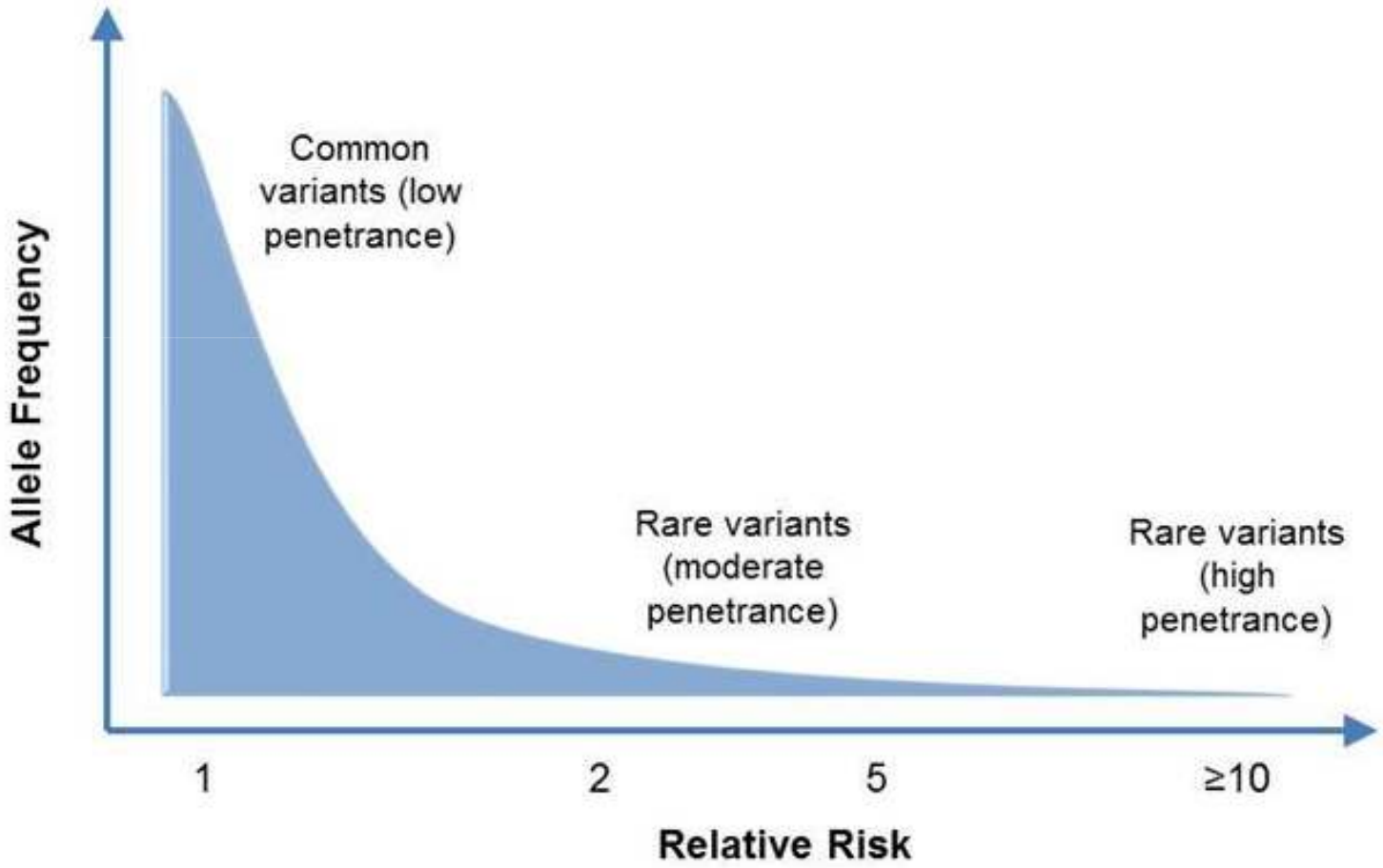
# Genetic Architecture of Cancer Risk



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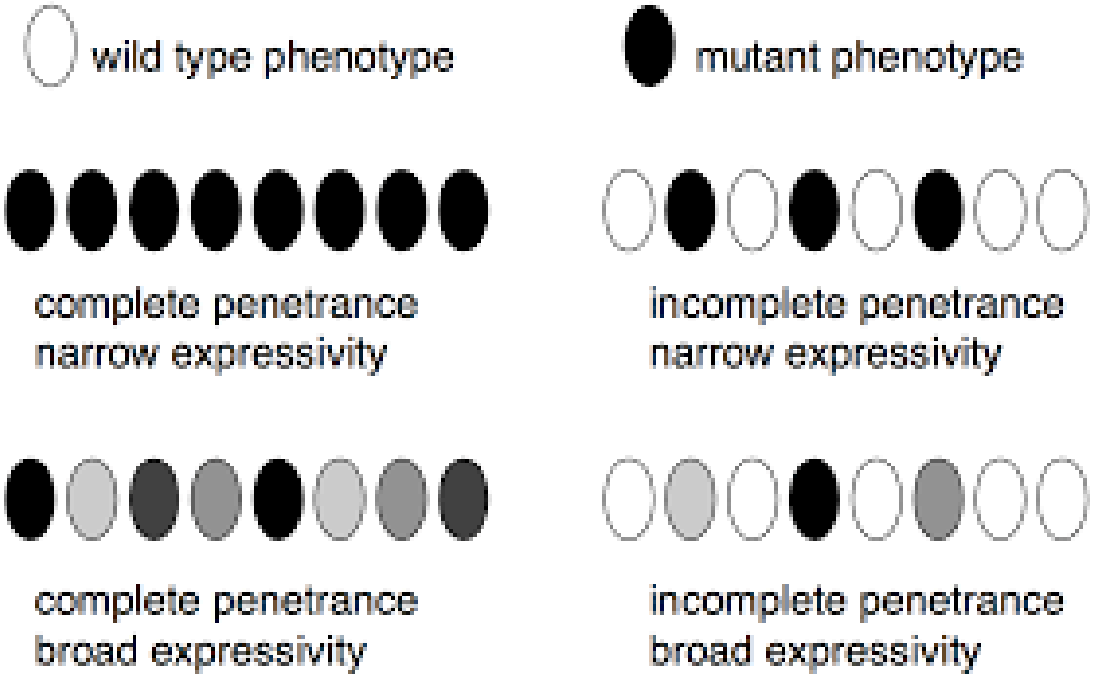
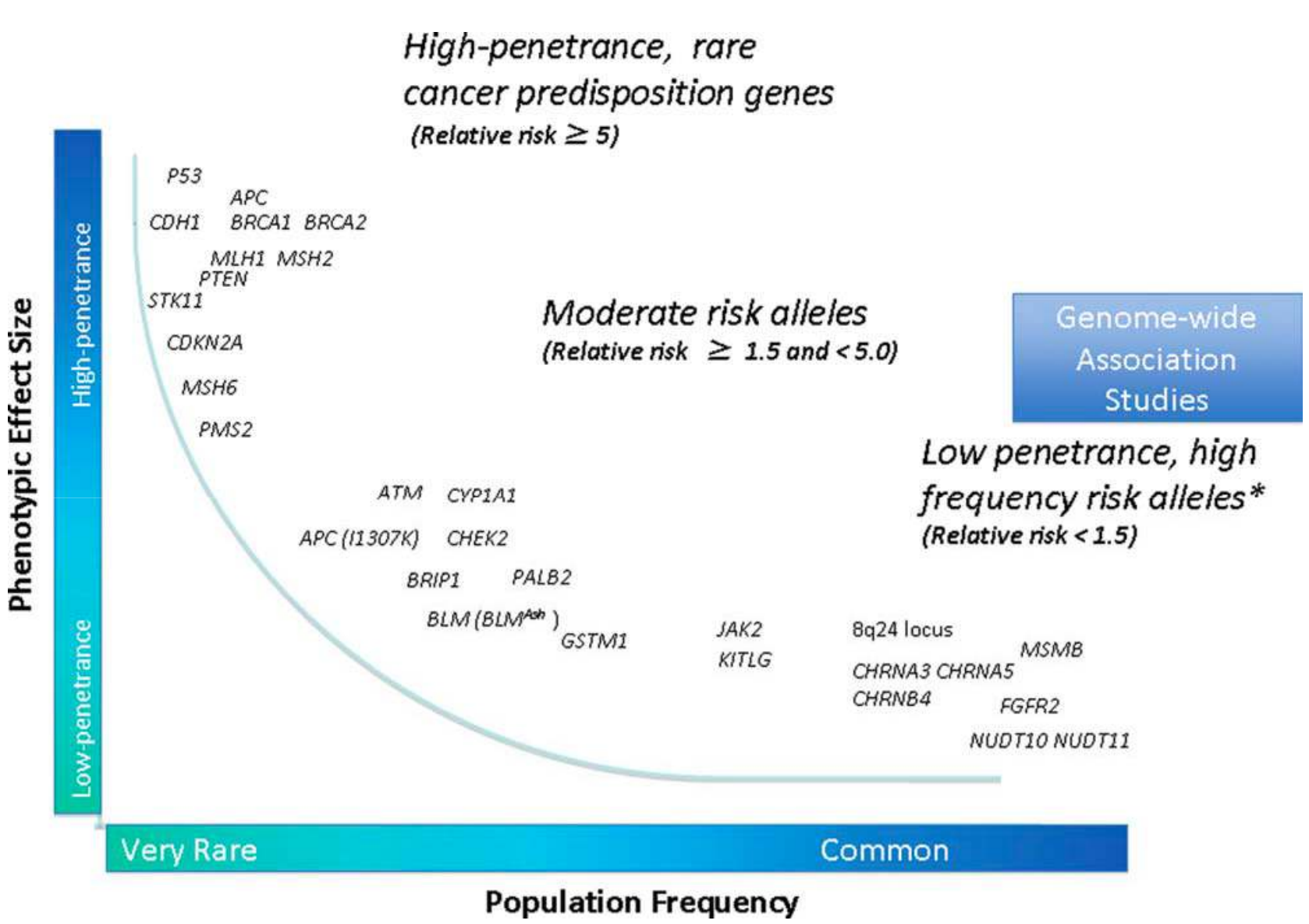
https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#section/_2730

# Penetrância

Proporção de indivíduos com uma variante genética em particular que também expressa um fenótipo associado



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# Riscos

- Diferenças no impacto geral de um determinado fator de risco entre efeitos relativos e absolutos

| Inherited risk factors | 10-year risk (%) | | |
|---|---|---|---|
| No. affected first-degree relatives | BMI = 27 kg/m$^2$ | BMI = 21 kg/m$^2$ | Risk difference |
| 0 | 1.8 | 1.5 | 0.3 |
| 1 | 3.8 | 3.0 | 0.8 |
| 2 | 5.0 | 4.0 | 1.0 |
| 3 | 9.7 | 7.8 | 1.9 |
| 3 + BRCA1 mutation carrier | 24.6 | 20.1 | 4.5 |

**Table 1** Effect of including BMI in IBIS model according to inherited risk factors



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Breast Cancer Res Treat
DOI 10.1007/s10549-015-3411-6

# Riscos x sítios

**TABLE 1 | Breast, colorectal, and ovarian cancer risk estimates by monoallelic germline mutation.**

| Cancer site | High risk (odds$^{\theta}$ ≥5.0) | Moderate risk (≥2.0 odds$^{\theta}$ <5.0) | Low risk (≤2.0 odds$^{\theta}$ ≥1.0 or growing evidence of association) |
|---|---|---|---|
| Breast (female) | *BRCA1* (20), *BRCA2* (20), *CDH1* (21), *PTEN* (22), *STK11* (23, 24), *TP53* (25) | *ATM* (26, 27), *BRIP1* (28), *CHEK2* (29, 30), *PALB2* (31, 32) | *BAP1* (33), *BARD1* (34, 35), *RAD50* (36, 37), *RAD51C* (38), *RAD51D* (39, 40), *MRE11A* (36), *MUTYH* (41), *NBN* (42, 43), *XRCC2* (44, 45) |
| Colorectal | *APC* (46), *BMPR1A* (47), $^{\Psi}$*EPCAM* (48), *MLH1* (49), *MSH2* (49), *MSH6* (49, 50), *MUTYH* (51), *PMS2* (52), *SMAD4* (47), *STK11* (53) | *CHEK2* (54, 55), *PTEN* (56), *TP53* (25) | *CDH1* (57, 58), *EXO1* (59), *GALNT12* (60, 61), *MUTYH* (62, 63), *POLD1* (64), *POLE* (64) |
| Ovary | *BRCA1* (65), *BRCA2* (65), *MLH1* (66), *MSH2* (66), *STK11* (24) | *MSH6* (66), *PALB2* (32, 65), *RAD51C* (65, 67), *RAD51D* (39) | *BARD1* (65, 68), *BRIP1* (65), *CHEK2* (65), *MRE11A* (65), *MUTYH* (69), *NBN* (65), *RAD50* (65), *TP53* (65) |

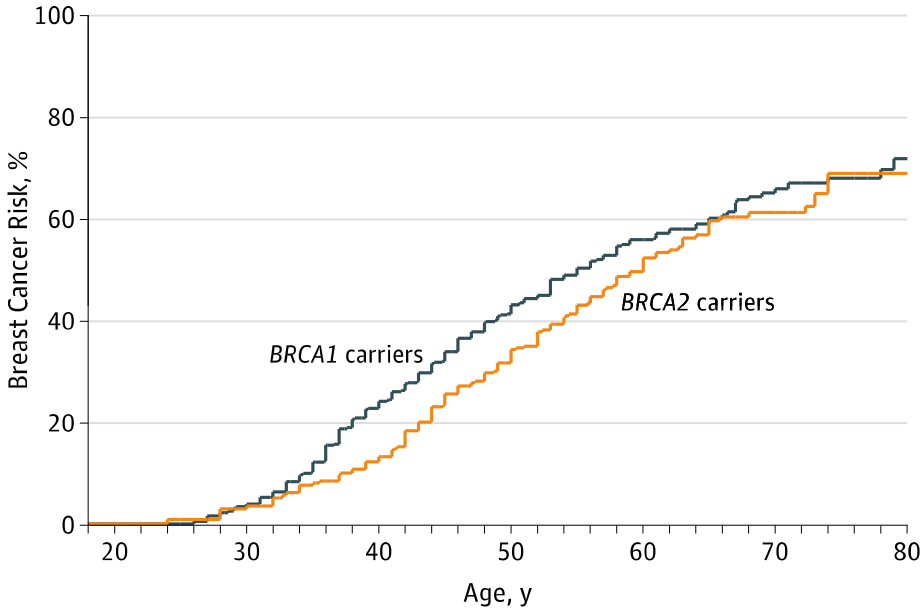




*Front. Oncol. 5:208.*
*doi: 10.3389/fonc.2015.00208*

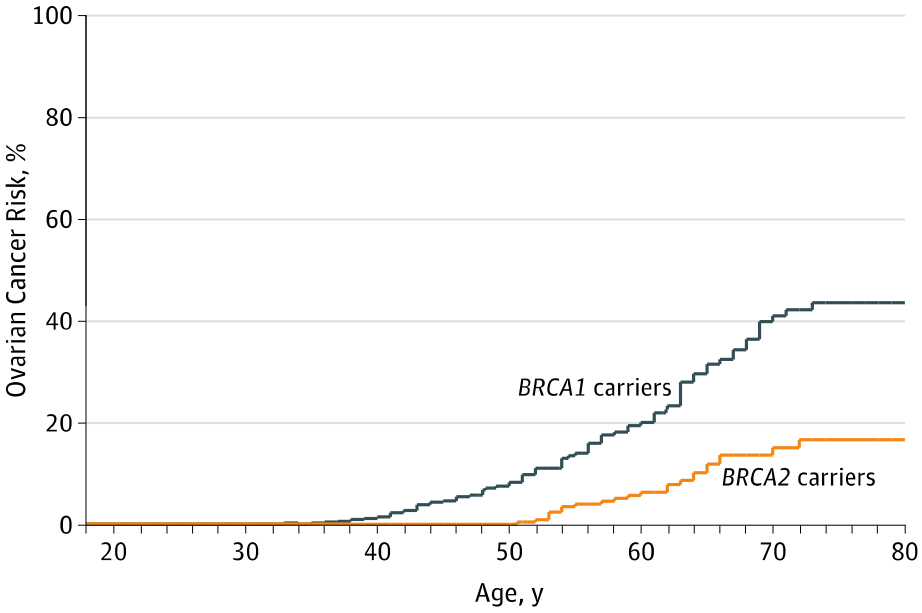
# Riscos em *BRCAs*

**A** Cumulative risk of first breast cancer among *BRCA1* and *BRCA2* mutation carriers




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| *BRCA1* | 53 | 340 | 404 | 273 | 138 | 41 | 13 |
| *BRCA2* | 30 | 160 | 267 | 204 | 110 | 35 | 21 |

**B** Cumulative risk of ovarian cancer among *BRCA1* and BRCA2 mutation carriers




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 53 | 420 | 544 | 243 | 131 | 54 | 23 |
| | 30 | 190 | 371 | 230 | 157 | 59 | 28 |

*JAMA*. 2017;317(23):2402-2416. doi:10.1001/jama.2017.7112

Table 3. Contralateral Breast Cancer Incidence Rates Per 1000 Person-Years and Kaplan-Meier Estimates of the Cumulative Risks of Contralateral Breast Cancer by Time Since First Breast Cancer, Overall and Stratified by Age at First Breast Cancer

| Years Since First Breast Cancer Diagnosis | No. of Women Contributing in Category | No. of Person-Years | No. of Events | Incidence Rate per 1000 Person-Years (95% CI) | Cumulative Risk, % (95% CI) | |
|---|---|---|---|---|---|---|
| *BRCA1* | | | | | | |
| ≤5 | | | | | | |
| >5-10 | | | | | | |
| >10-15 | | | | | | |
| >15-20 | | | | | | |
| >20-45 | | | | | | |
| First breast cancer diagnosis at age | | | | | | |
| ≤5 | | | | | | |
| >5-10 | | | | | | |
| >10-15 | | | | | | |
| [illegible] | | | | ( ) | ( ) | ( ) |
| >20-45 | 70 | 343 | 6 | 17.5 (7.9-38.9) | 60 (46-74) | 68 (29-98) |
| First breast cancer diagnosis at age ≥40-50 y | | | | | | |
| ≤5 | 283 | 725 | 15 | 20.7 (12.5-34.3) | 10 (6-16) | 6 (3-14) |
| >5-10 | 225 | 718 | 19 | 26.5 (16.9-41.5) | 21 (15-28) | 14 (8-22) |
| >10-15 | 152 | 480 | 11 | 22.9 (12.7-41.4) | 30 (23-38) | 20 (13-29) |
| >15-20 | 74 | 222 | 6 | 27.0 (12.1-60.2) | 39 (30-49) | 23 (15-35) |
| >20-39 | 52 | 280 | 4 | 14.3 (5.4-38.1 | 49 (37-62) | 28 (17-44) |
| First breast cancer diagnosis at age ≥50 y | | | | | | |
| ≤5 | 174 | 462 | 14 | 30.3 (17.9-51.2) | 14 (8-22) | 9 (5-17) |
| >5-10 | 115 | 408 | 6 | 14.7 (6.6-32.7) | 20 (14-30) | 17 (11-27) |
| >10-15 | 66 | 219 | 2 | 9.1 (2.3-36.5) | 24 (16-35) | 20 (13-30) |
| >15-20 | 33 | 75 | 3 | 40.0 (12.9-124.0) | 38 (24-57) | 20 (1330) |
| >20-27 | 10 | 38 | 0 | 0.0 | 38 (24-57) | 20 (1330) |

BRCA2



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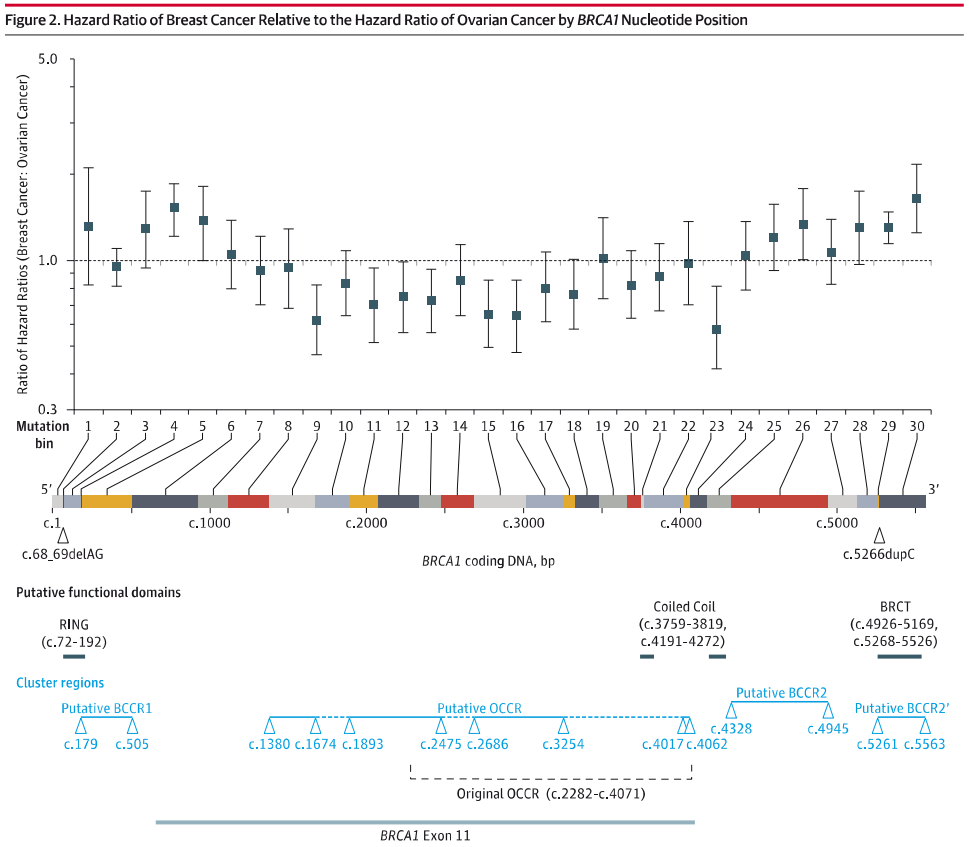
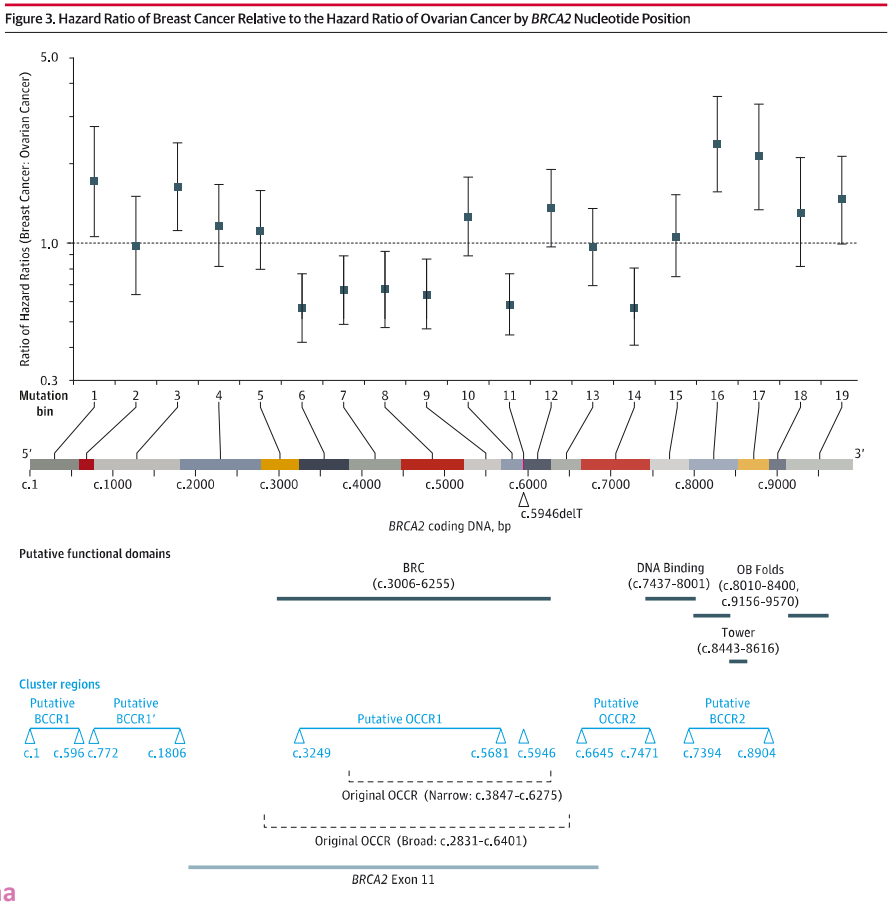
JAMA. 2017;317(23):2402-2416. doi:10.1001/jama.2017.7112

# Association of Type and Location of *BRCA1* and *BRCA2* Mutations With Risk of Breast and Ovarian Cancer




*JAMA*. 2015;313(13):1347-1361. doi:10.1001/jama.2014.5985

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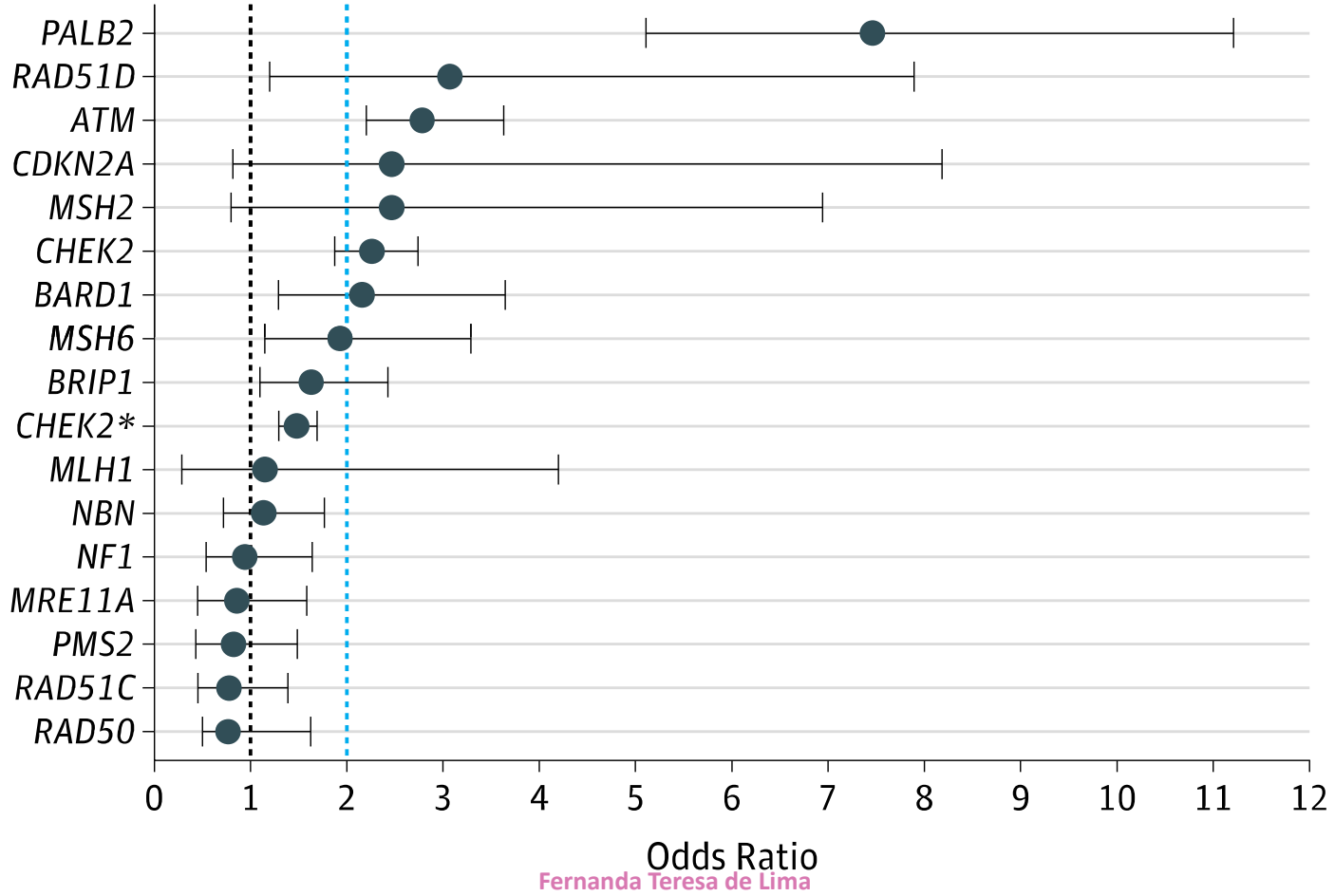
2018

# Figure. Odds Ratio Between Combined Pathogenic Variants in Each Gene and Breast Cancer Among White Women With Breast Cancer and Reference Controls

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*JAMA Oncol*. doi:10.1001/jamaoncol.2017.0424

Table 2 | **Estimated average 5-year and lifetime breast-cancer risks for women with moderate-penetrance mutations in selected genes**

| | Population | | *ATM/NBN* (RR 2.7–2.8)* | | *CHEK2* (1100delC) (RR 3.0)‡ | | *CHEK2* (I157T) (RR 1.58) | | *PALB2*[41] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age (years) | 5-year (%) | Cumulative (%) | 5-year (%) | Cumulative (%) | 5-year (%) | Cumulative (%) | 5-year (%) | Cumulative (%) | 5 year (%) | Cumulative (%) |
| 35–39 | 0.30 | 0.5 | 0.84 | 1.4 | 0.90 | 1.5 | 0.48 | 0.8 | 2.5‖ | 4 |
| 40–44 | 0.61 | 1.1 | 1.70§ | 3.0 | 1.83§ | 3.2 | 0.96§ | 1.7 | 4.25‖ | 8 |
| 45–49 | 0.94§ | 2.0 | 2.64‖ | 5.6 | 2.83‖ | 5.9 | 1.49§ | 3.2 | 6.35‖ | 14 |
| 50–54 | 1.12§ | 3.1 | 3.14‖ | 8.5 | 3.36‖ | 9.1 | 1.77§ | 4.9 | 8.00‖ | 20 |
| 55–59 | 1.33§ | 4.4 | 3.71‖ | 11.8 | 3.98‖ | 12.6 | 2.09§ | 6.8 | 7.25‖ | 26 |
| 60–64 | 1.72§ | 6.0 | 4.81‖ | 16.0 | 5.15‖ | 17.0 | 2.71‖ | 9.3 | 7.35‖ | 31 |
| 65–69 | 2.11§ | 8.0 | 5.92‖ | 20.8 | 6.34‖ | 22.1 | 3.34‖ | 12.3 | 5.95‖ | 35 |
| 70–75 | 2.20‖ | 10.0 | 6.17‖ | 25.5 | 6.61‖ | 27.1 | 3.48‖ | 15.3 | 6.70‖ | 40 |
| CLTR (80) | NA | 12.0 | NA | 30.0 | NA | 31.8 | NA | 18.3 | NA | 44 |

# Risco em homens com mutação BRCA2

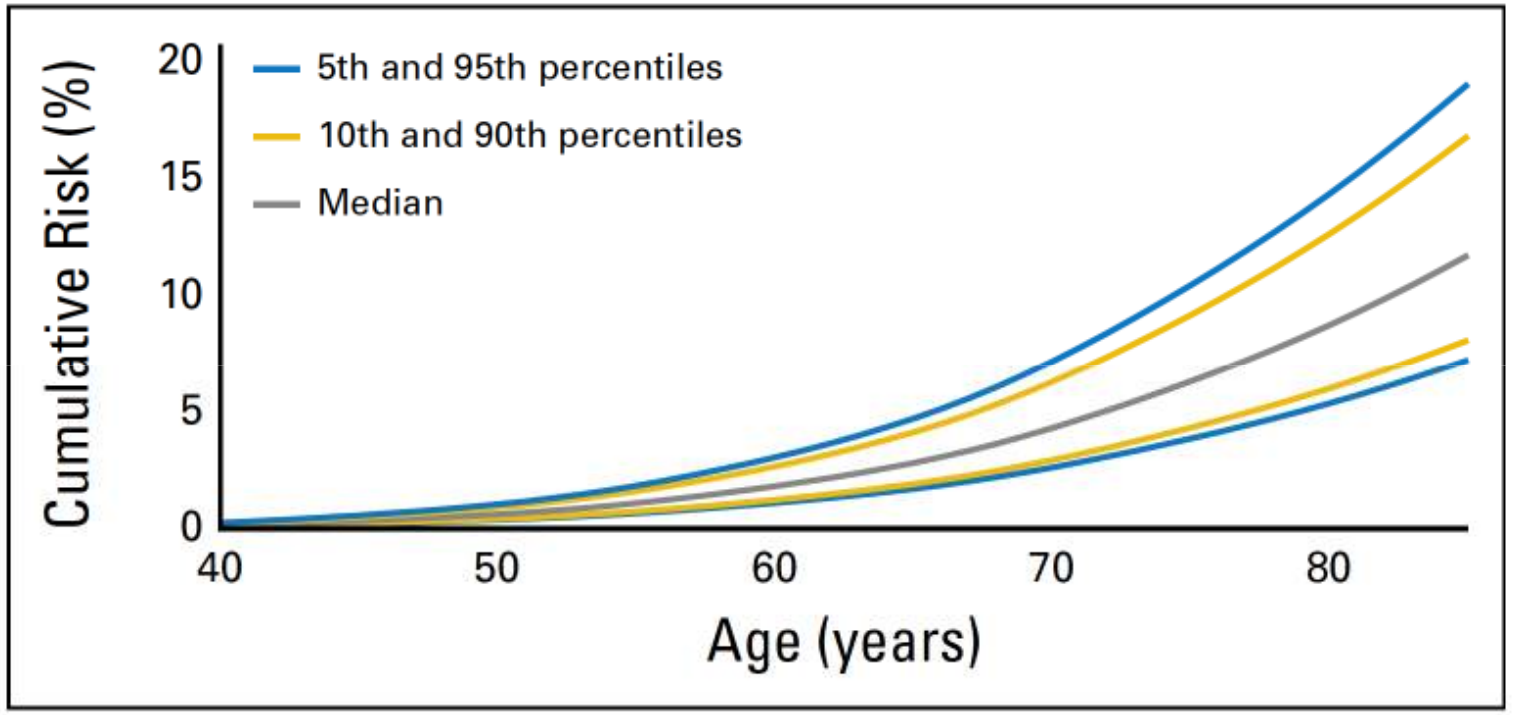



**Fig 1.** Predicted breast cancer cumulative risk for male carriers of *BRCA2* mutations by percentile of overall polygenic risk score that was constructed by using results from population-based studies.

J Clin Oncol. 2017 Jul 10;35(20):2240-2250.

# Ca mama masculino

**Table 5** Breast cancer risks associated with pathogenic variants pooled by gene among Caucasian male breast cancer cases

| Gene | Ambry cases | | ExAC controls | | Cancer risk | | | |
|---|---|---|---|---|---|---|---|---|
| | Mutated alleles | Cases | Mutated alleles | Cases | OR | 95% CI lower | 95% CI upper | *p* value |
| *ATM* | 2 | 421 | 90 | 26,644 | 1.4 | 0.3 | 5.1 | 0.66 |
| *BRCA1* | 2 | 394 | 74 | 26,911 | 1.8 | 0.3 | 6.8 | 0.30 |
| *BRCA2* | 21 | 394 | 105 | 26,791 | 13.9 | 8.5 | 22.5 | $1.92 \times 10^{-16}$ |
| *CHEK2* All | 17 | 421 | 424 | 25,215 | 2.4 | 1.4 | 3.9 | $1.82 \times 10^{-3}$ |
| *CHEK2*_c.1100delC | 8 | 421 | 127 | 25,215 | 3.8 | 1.7 | 7.8 | $1.82 \times 10^{-3}$ |
| *CHEK2* W/O I157T/S428F | 10 | 421 | 163 | 25,215 | 3.7 | 1.9 | 7.0 | $6.24 \times 10^{-4}$ |
| *CHEK2* W/O I157T | 12 | 421 | 191 | 25,215 | 3.8 | 2.1 | 6.8 | $1.51 \times 10^{-4}$ |
| *CHEK2* I157T | 5 | 421 | 233 | 25,215 | 1.3 | 0.5 | 3.0 | 0.60 |
| *PALB2* | 3 | 421 | 29 | 26,869 | 6.6 | 1.7 | 21.1 | 0.013 |





Breast Cancer Res Treat (2017) 161:575–586

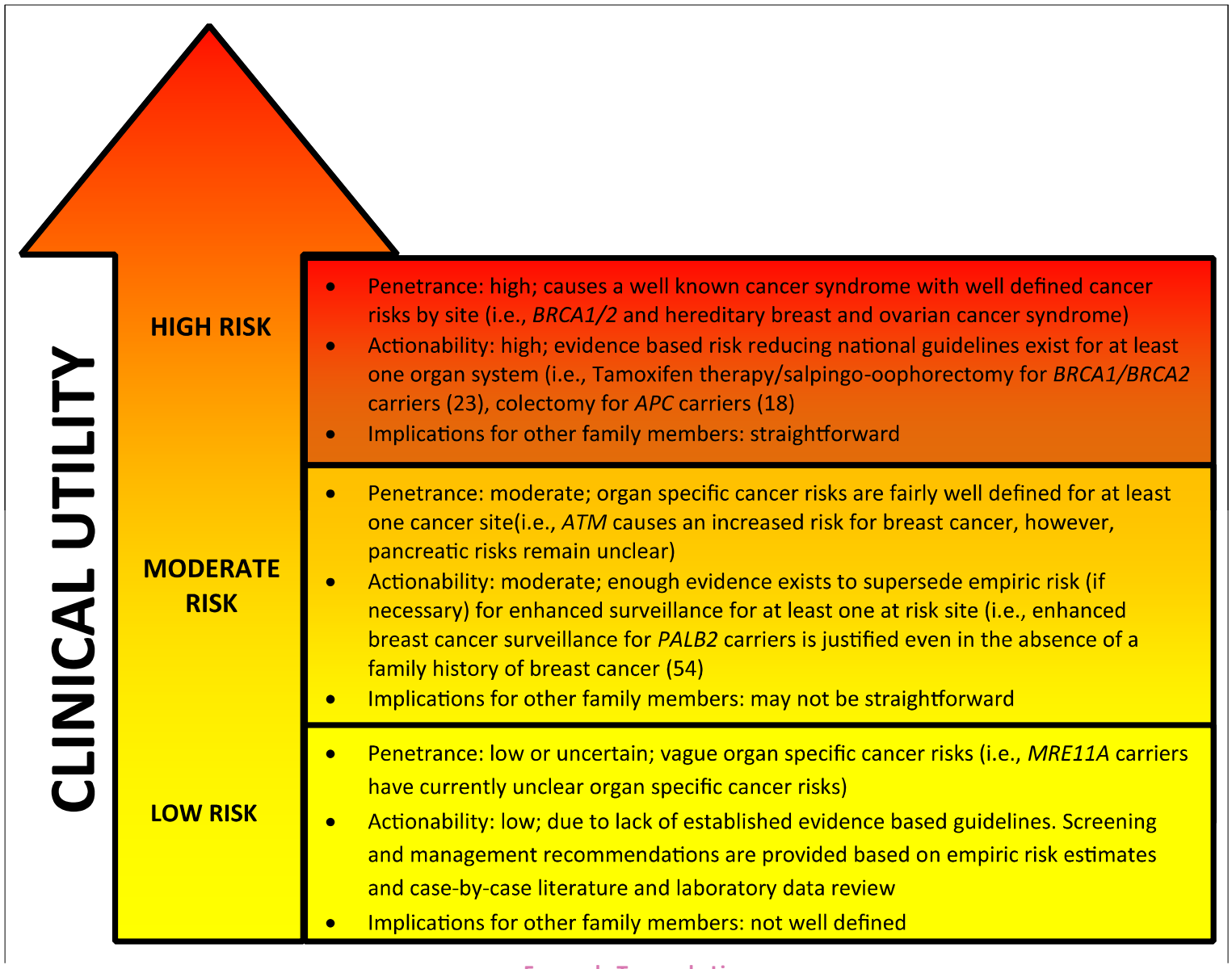
# Ca mama triplo negativo

**Table 2.** Gene-Based Age at Diagnosis and Family History of Cancer

| Gene | No. of Mutations | Age at Diagnosis (years)* | | | Family History of Cancer† | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Breast | | | | Ovarian | | | |
| | | Mean | Range | *P* | Yes | No | Percent Positive | *P* | Yes | No | Percent Positive | *P* |
| *BRCA1* | 155 | 44 | 25-80 | < .001 | 66 | 66 | 50 | < .001 | 24 | 108 | 18 | < .001 |
| *BRCA2* | 49 | 47 | 27-79 | < .001 | 16 | 24 | 40 | .31 | 5 | 35 | 13 | < .001 |
| *BRIP1* | 8 | 46 | 36-68 | .12 | 3 | 5 | 38 | .72 | 0 | 8 | 0 | 1 |
| *CDH1* | 0 | — | — | — | — | — | — | — | — | — | — | — |
| *CHEK2* | 0 | — | — | — | — | — | — | — | — | — | — | — |
| *MRE11A* | 2 | 39 | 36-41 | .11 | 1 | 1 | 50 | .54 | 0 | 2 | 0 | 1 |
| *NBN* | 1 | 59 | 59-59 | — | 1 | 0 | 100 | .32 | 0 | 1 | 0 | 1 |
| *PALB2* | 21 | 49 | 28-79 | .22 | 5 | 10 | 33 | 1 | 0 | 15 | 0 | 1 |
| *PTEN* | 1 | 45 | 45-45 | — | 1 | 0 | 100 | .32 | 0 | 1 | 0 | 1 |
| *RAD50* | 6 | 54 | 42-63 | .51 | 2 | 3 | 40 | .66 | 0 | 5 | 0 | 1 |
| *RAD51C* | 6 | 52 | 37-71 | .92 | 1 | 4 | 20 | 1 | 0 | 5 | 0 | 1 |
| *RAD51D* | 7 | 43 | 31-66 | .14 | 3 | 3 | 50 | .39 | 1 | 5 | 17 | .14 |
| *STK11* | 0 | — | — | — | — | — | — | — | — | — | — | — |
| *TP53* | 1 | 38 | 38-38 | — | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 |
| *XRCC2* | 3 | 34 | 28-40 | .04 | 1 | 2 | 33 | 1 | 0 | 3 | 0 | 1 |
| WT | 1,557 | 51 | 22-93 | Ref | 413 | 873 | 32 | Ref | 32 | 1,254 | 3 | Ref |

NOTE. — indicates no data because of absence of mutation.
Abbreviations: Ref, referent; WT, wild type.
*Associations with age at diagnosis were evaluated by *t* test.
†Associations with family history of breast or ovarian cancer were evaluated by Fisher's exact test.

Couch et al. JCO. 2015;33:304-11.

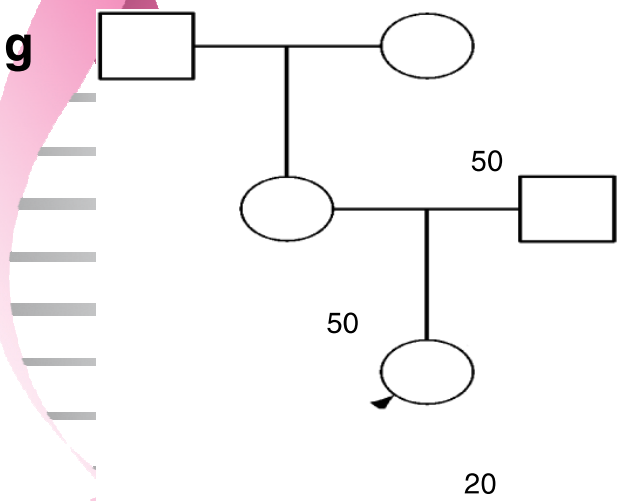


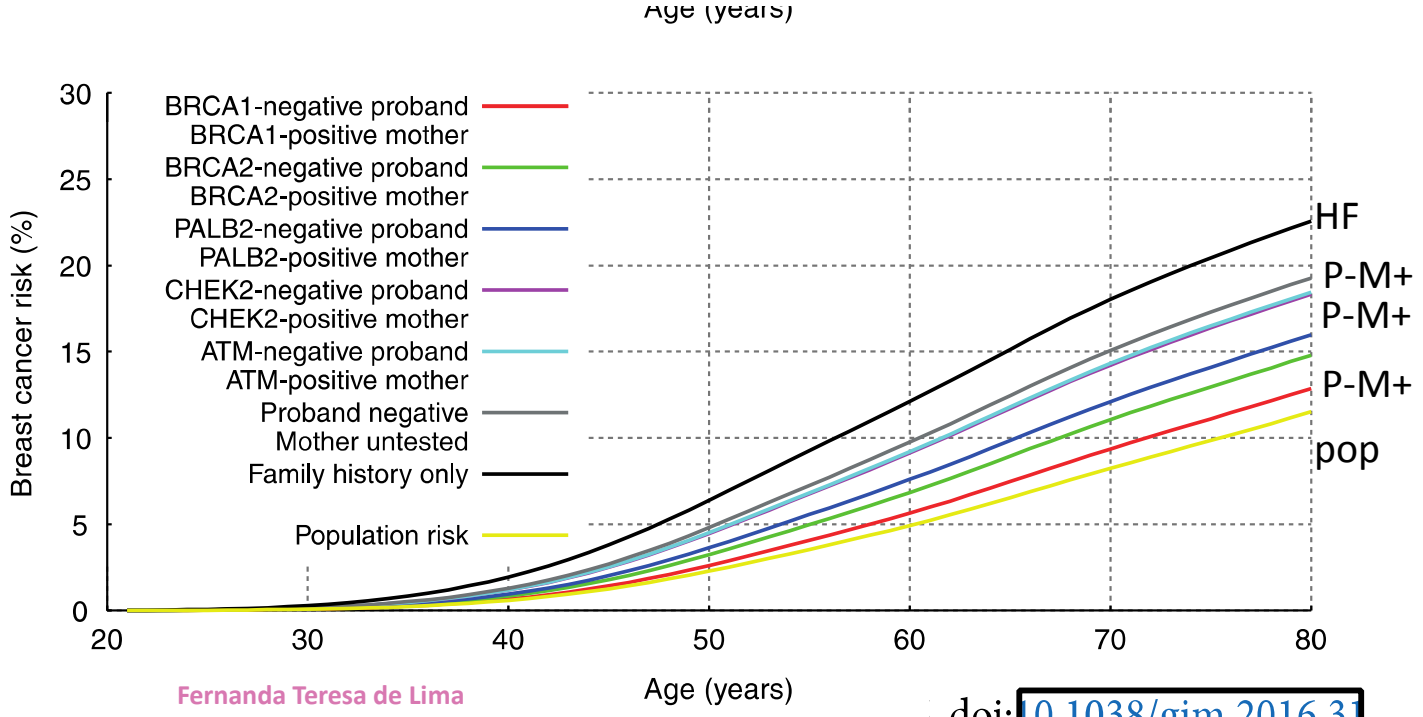

Fernanda Teresa de Lima

*Front. Oncol. 5:208.*
*doi: 10.3389/fonc.2015.00208*

# Risco Residual

- Assintomático com variante familiar positiva
- Impacto no risco depende da penetrância do gene




Fernanda Teresa de Lima

. doi:10.1038/gim.2016.31

# Predisposição Hereditária ao Câncer

- Suspeita
- Testes
- Riscos
- Condutas

Fernanda Teresa de Lima

# Prevenção e vigilância oncológicas

Prevenção

Vigilância

**Oncológicos**
Recorrência e novos primários
Escolha terapêutica

**Não-oncológicos**
Tumores benignos
malformações

**Familiar**
Transmissibilidade
Susceptibilidade

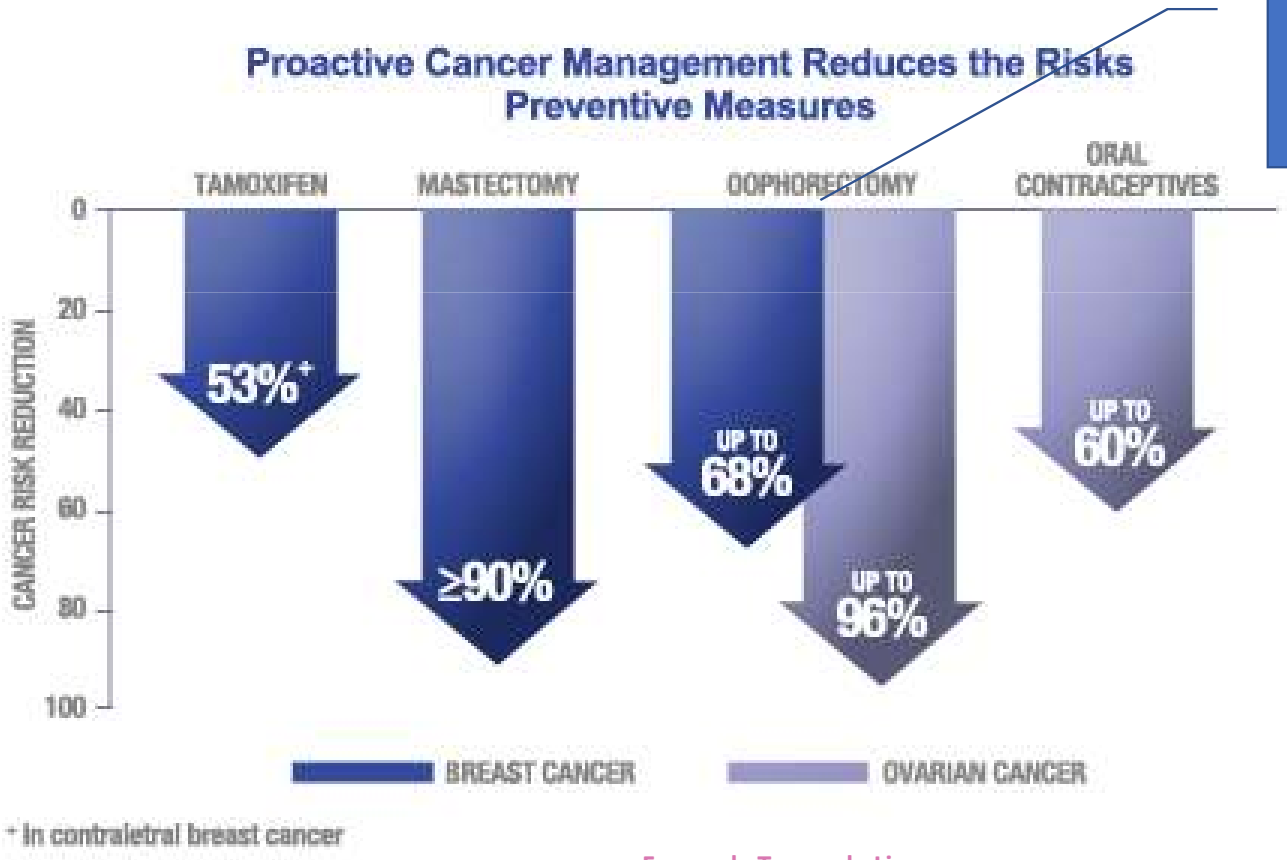
# Prevenção e vigilância oncológicas

| Tumor | Recomendação | Intervalo |
|---|---|---|
| Mama | Auto-consciência | > 18a |
| | exame clínico mamas | > 25a, a cada 6-12m |
| | MRI/mamografia | 25-29 MRI, anual<br>30-75y MRI/MMG anual<br>>75y individualizado |
| Ovário | US Pélvico + CA125<br>***Sem evidências*** | a cada 6m > 30a |
| Ambos | Cirurgias e medicamentos redutores de risco | |

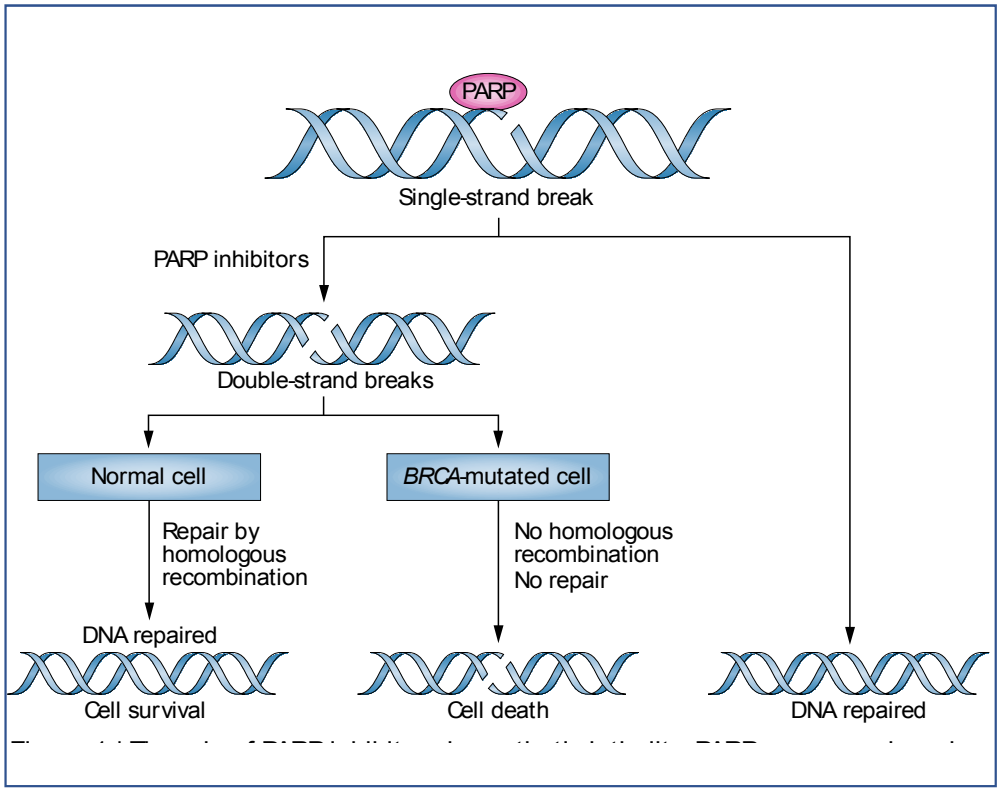
NCCN V 2.2019

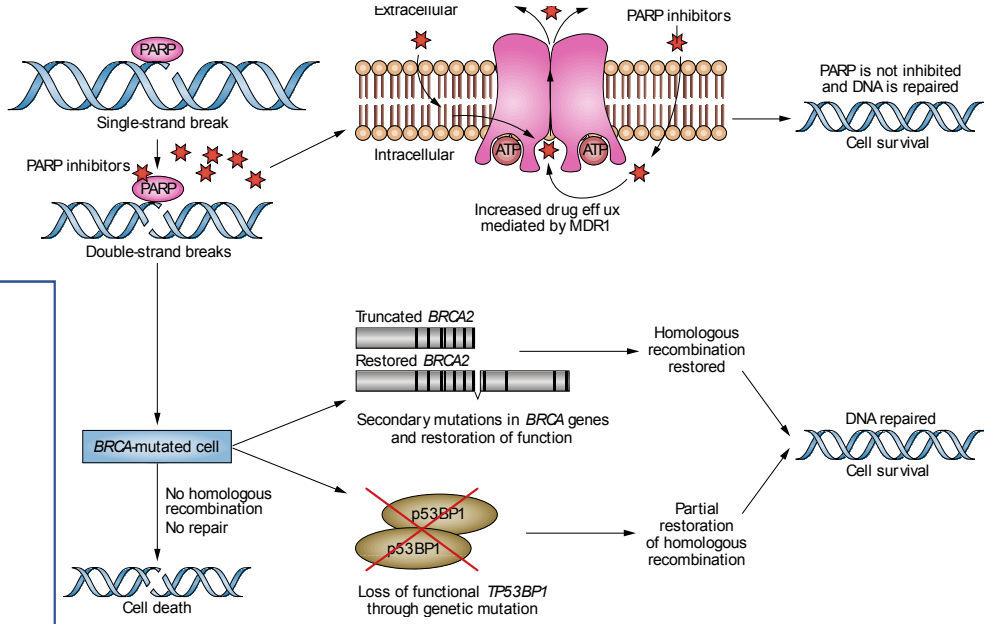
# O que o oncologista precisa saber: prevenção e vigilância oncológicas

Todas as causas de mortalidade
↓65% em pctes sem ca BRCAs+
↓57% em pctes com ca mama
*Li et al., 2016*



# Manejo




Inibidores de PARP1

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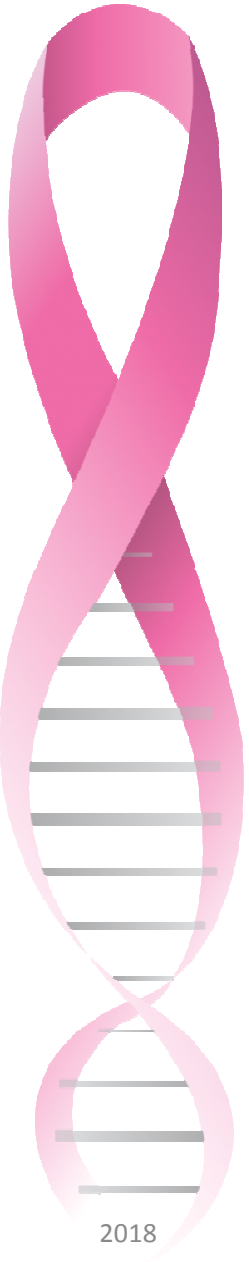

# Alertas

- Investigação de histórico familiar complexo
- Variantes patogênicas e de significado desconhecido
- Achados incidentais
- Aconselhamento genético e suporte psicológico

# Predisposição Hereditária ao Câncer

- Suspeita
- Testes
- Riscos
- Condutas

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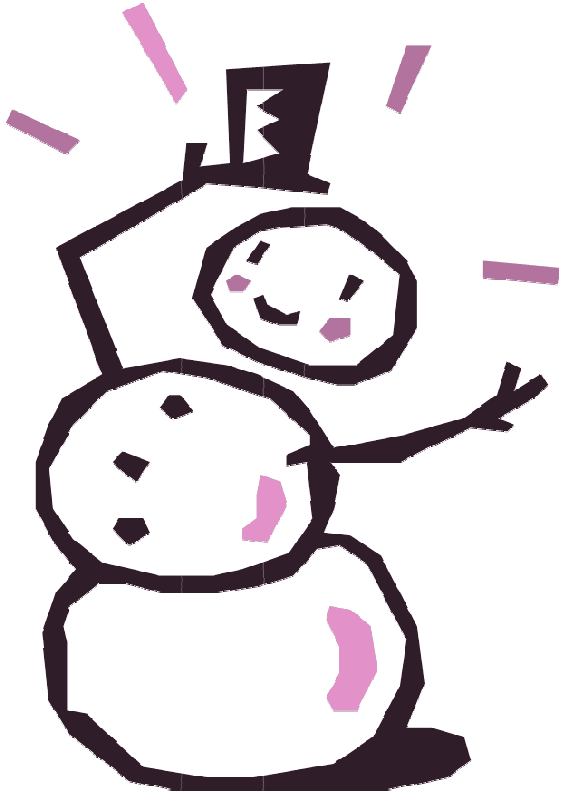

fernanda.alima@einstein.br

ALBERT EINSTEIN

GRAACC
COMBATENDO E VENCENDO
O CÂNCER INFANTIL

UNIFESP
PAULISTA
ESCOLA MEDICINA

Fernanda Teresa de Lima