El cáncer familiar en el contexto de los Programas de Cribado.

Criterios de identificación de riesgo familiar para los síndromes relacionados con el cáncer de mama y colorrectal.
Criterios de seguimiento.

Isabel Chirivella González
Unidad de Consejo Genético en Cáncer
Hospital Clínico Universitario de Valencia
Valencia, 21 de Junio de 2012

Clasificación del cáncer

- **Cáncer de mama**
  - Esporádico
  - Familiar
  - Hereditario
- **Cáncer de colon hereditario no asociado a poliposis**
  - Esporádico
  - Familiar
  - Hereditario: S. de Lynch y el síndrome de cáncer de colon tipo X

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Hereditary Cancer Predisposition Syndromes

Judy E. Garber and Kenneth Offit

From the Division of Population Sciences, Dana Farber Cancer Institute, Boston, MA; and Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY.

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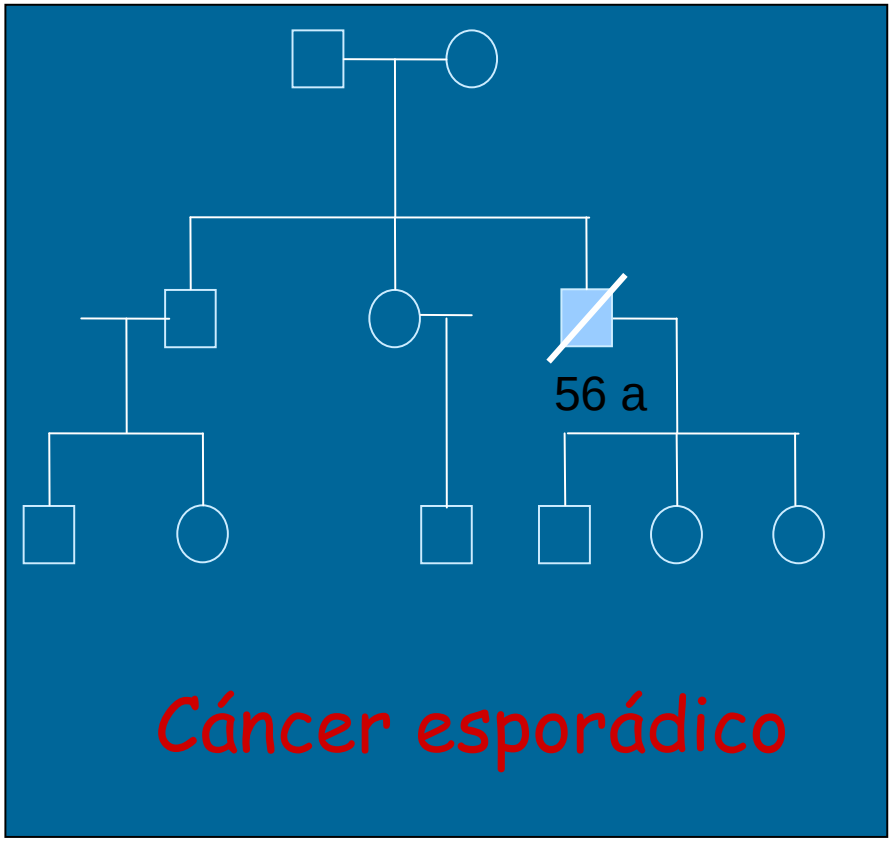
Authors' disclosures of potential conflicts of interest are found at the end of this article.

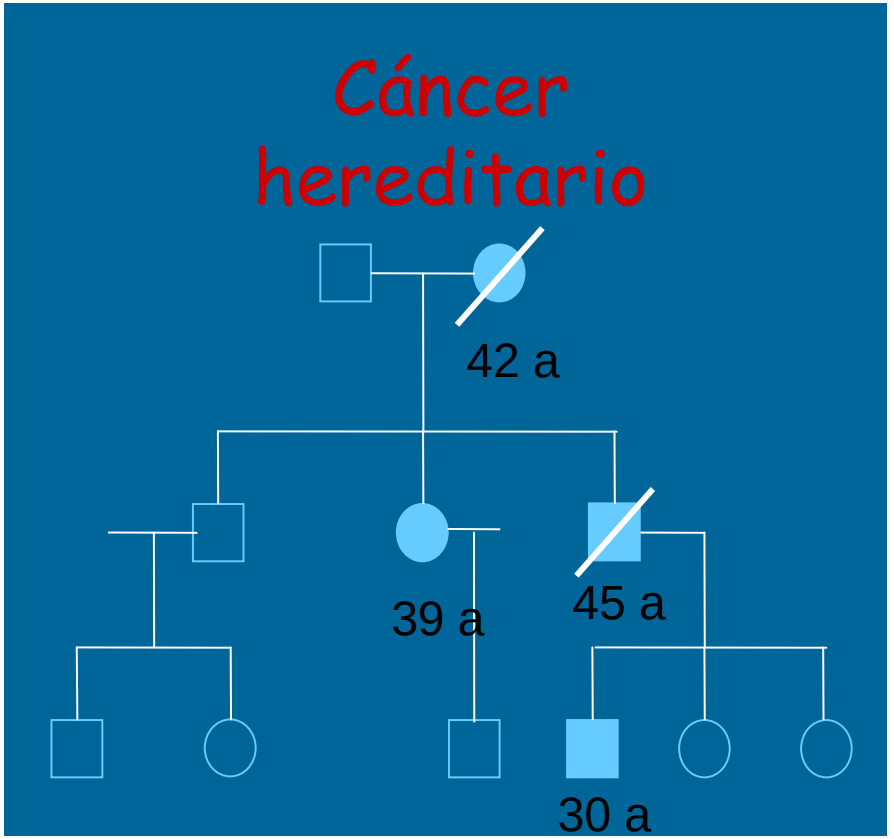
Address reprint requests to Judy E. Garber, MD, MPH, Dana-Farber Cancer Institute, 44 Binney St—SM 209, Boston, MA 02115; e-mail: judy_garber@dfci.harvard.edu; and Kenneth Offit, MD,

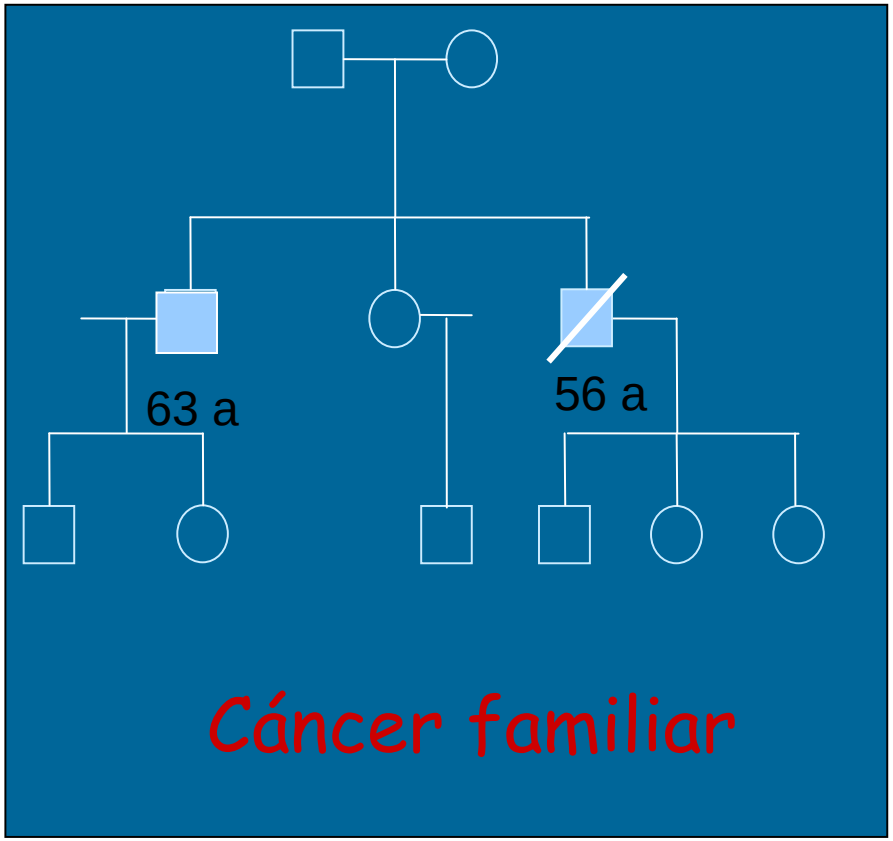
ABSTRACT

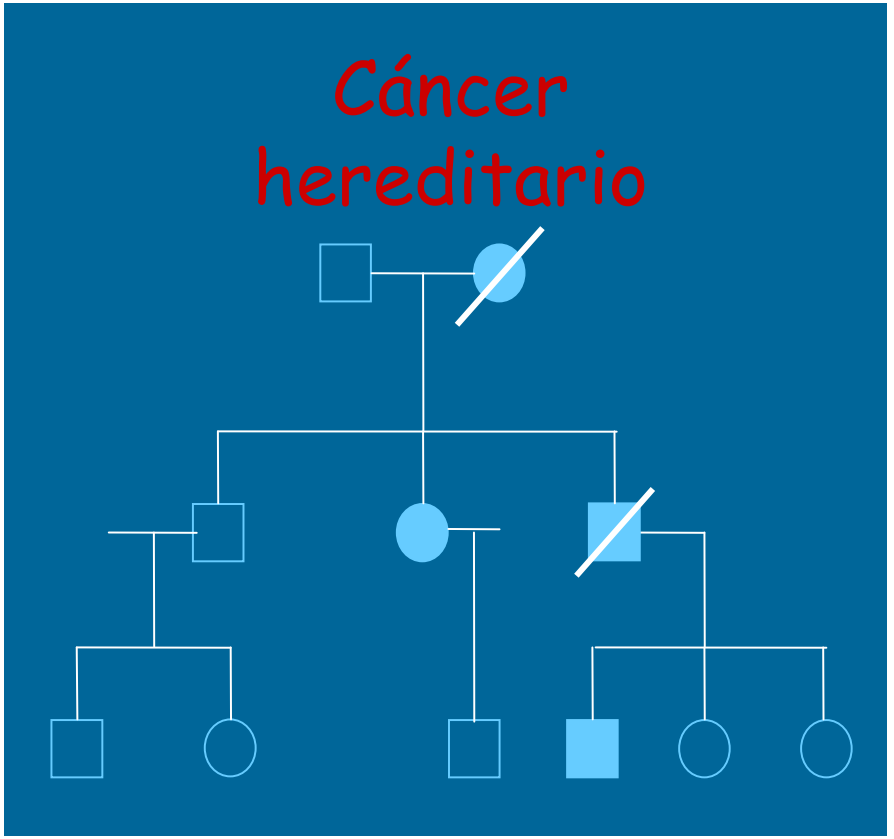
Cancer genetics is increasingly becoming integrated into the practice of modern medical oncology. The ability to distinguish a growing proportion of the 5% to 10% of all cancers that develop in individuals who have inherited a genetic mutation conferring heightened susceptibility to specific cancers may permit targeted efforts in cancer surveillance and prevention. While these individuals comprise a small proportion of the overall burden of cancer, strategies successful in reducing their remarkable cancer risks may be generalizable to the broader population. In this review, we highlight the most common hereditary cancer syndromes, most attributable to genes inherited in an autosomal dominant manner with incomplete penetrance, and a number of rare syndromes in which particular progress has been made. The prevalence, penetrance, tumor spectrum, and underlying genetic defects are discussed and summarized in a large table in which a more comprehensive enumeration of syndromes is provided.

J Clin Oncol 23:276-292.


56 a
Cáncer esporádico


Cáncer hereditario
42 a
39 a
45 a
30 a


63 a
56 a
Cáncer familiar

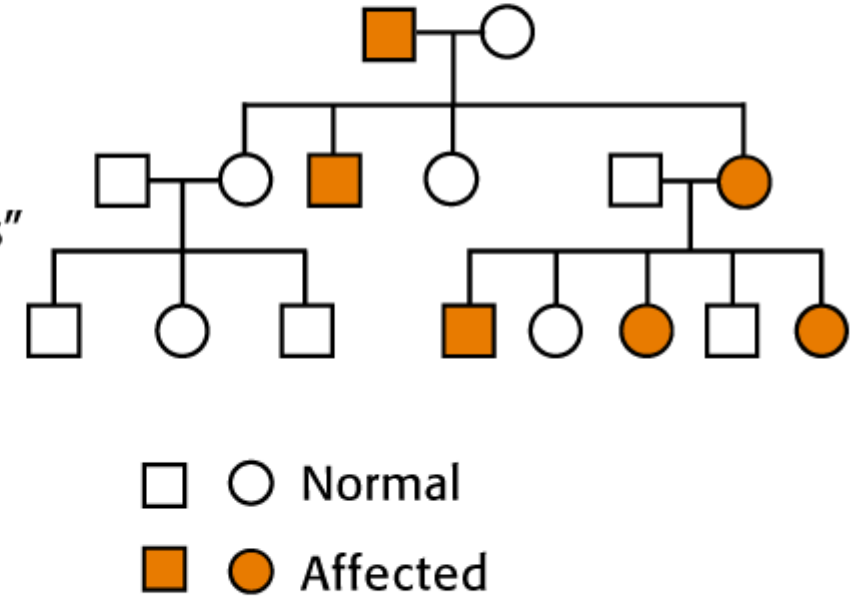

Cáncer hereditario

Riesgos de cáncer esporádico vs hereditario

TIPO DE CANCER	INCIDENCIA (casos/año)	MORTALIDAD (casos/año)	RIESGO BAS (%)	C. H. (%)
Colon/recto	19.166	10.952	5	70-80%
Pulmón	18.373	17.668	5	
Melanoma cutáneo	2.157	676	2	
Mama	14.934	6.381	8	40-85%
Útero	4.041	1.075	2	
Ovario	2.635	1.638	1	
Leucemias	3.718	2.807	1	
TOTAL (menos piel)	143.435	92.763	33	

Cáncer hereditarios: Herencia autosómica dominante

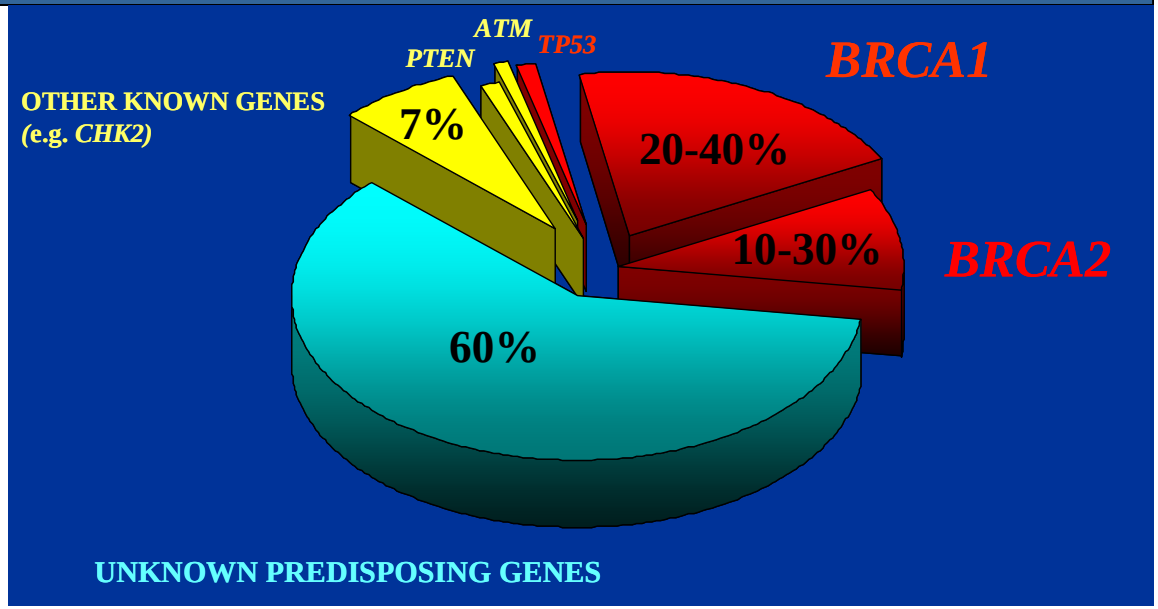
- Each child has a 50% chance of inheriting the mutation
- No "skipped generations"
- Equally transmitted by men and women

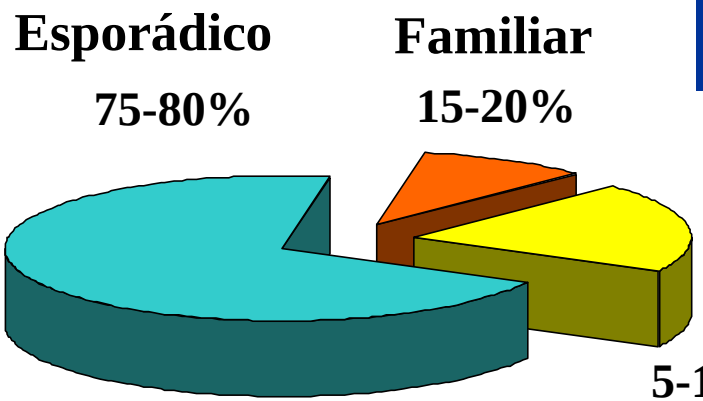


Síndrome de Mama y Ovario Hereditario

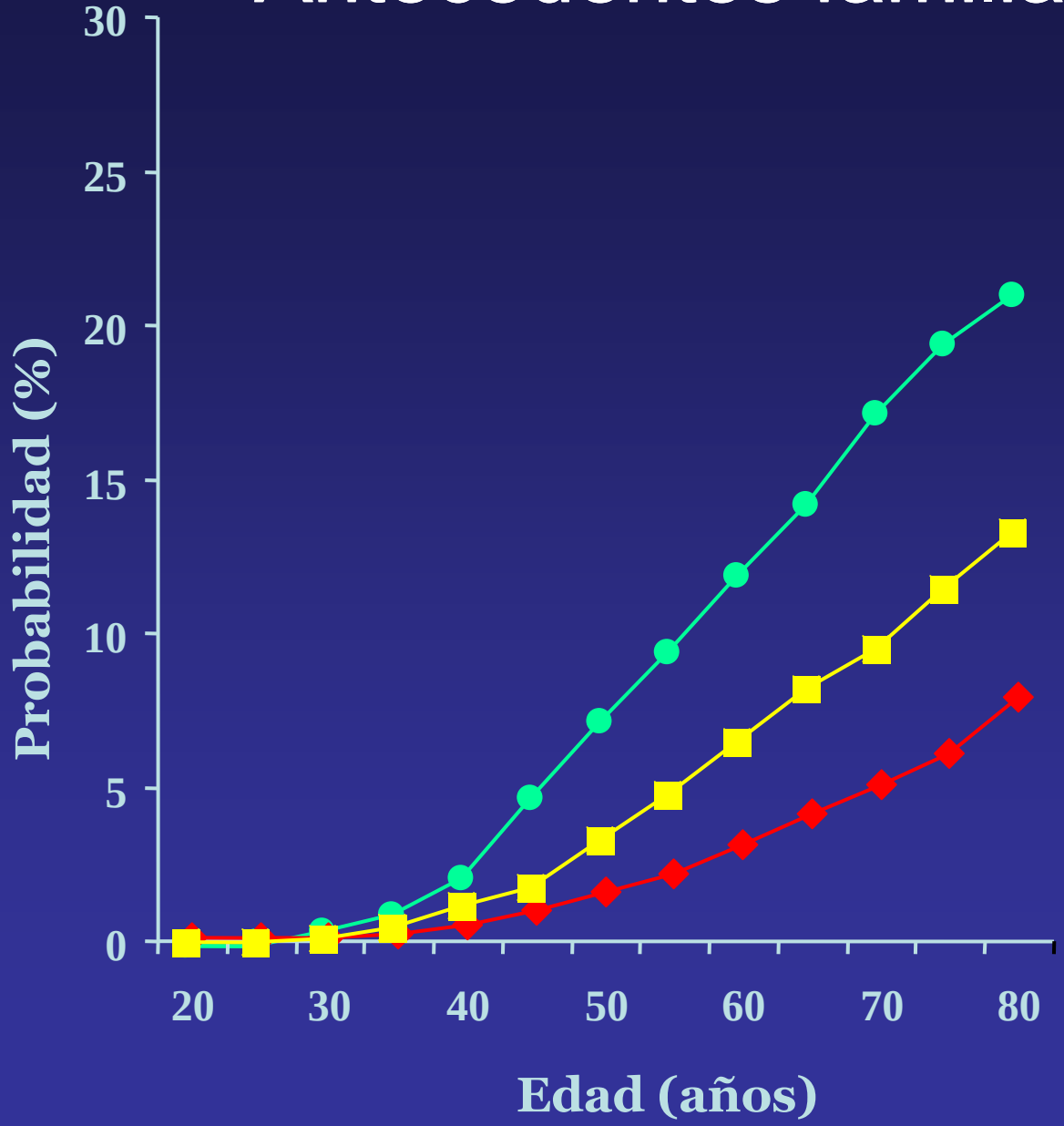
Genes: **BRCA1, BRCA2**

Causas de susceptibilidad hereditaria al cáncer de mama





Antecedentes familiares c. mama



2 familiares → 21,1 %
(1:5)

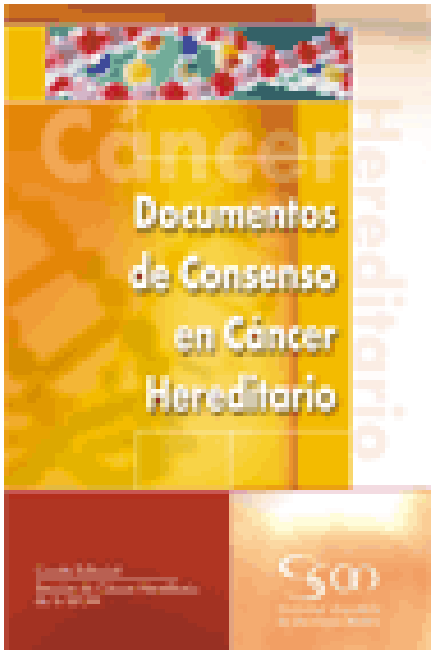
1 familiar → 13,3 %
(1:8)

No familiares → 7,8 %
(1:13)

Lancet 2001; 358:1389-99

Criterios de identificación de riesgo hereditario (SEOM)

Guía de la SEOM 2004



CRITERIOS DE ALTO RIESGO

- Un caso de cáncer menor o igual a 40 años.
- Diagnóstico de cáncer de mama y ovario mismo individuo.
- Dos o más casos de cáncer de mama, uno de los cuales es menor de 50 años o bilateral.
- Un caso de cáncer de mama menor o igual a 50 años o bilateral y un caso de cáncer de ovario en familiar 1º o 2º grado.
- Tres casos de cáncer de mama y ovario (al menos un caso de ovario) en familiares de 1º o 2º grado.
- Dos casos de cáncer de ovario en familiares de 1º y 2º grado.
- Un caso de cáncer de mama en el varón y familiar de 1º o 2º grado con cáncer de mama u ovario.

Nota: estos criterios también podrían ser aplicables a la hora de indicar la realización de tests genéticos.

Criterios de identificación de riesgo hereditario (Oncoguía catalana)

Oncoguía Catalana (2006)

Familias de alto riesgo de cáncer de mama y ovario hereditarios

- Tres o más familiares de primer grado* afectos de cáncer de mama y/u ovario
- Dos casos entre familiares de primer/segundo grado*:
  - Dos casos de cáncer de ovario
  - Un caso de cáncer de mama y otro de cáncer de ovario
  - Un caso de cáncer de mama en varón y otro de cáncer de mama/ovario
  - Dos casos de cáncer de mama en menores de 50 años
  - Un caso de cáncer de mama bilateral y otro de cáncer de mama (uno menor de 50 años)
- Cáncer de mama diagnosticado antes de los 30 años
- Cáncer de mama y ovario en una misma paciente
- Cáncer de mama bilateral diagnosticado antes de los 40 años

Criterios de identificación de riesgo hereditario (guía C.Valenciana)

- Guía de la Comunidad Valenciana (2008)

Familias con un único caso de cáncer de mama

- ·Cáncer de mama diagnosticado antes de los 30 años, o
- ·Cáncer de mama primario bilateral antes de los 40 años (al menos uno de los tumores) o
- ·Un cáncer de mama y un cáncer de ovario en la misma paciente

Familias con dos casos en familiares de primer grado *

- ·Dos casos de cáncer de mama o cáncer de mama bilateral, al menos uno diagnosticado antes de los 50 años, o
- ·Dos o más casos de cáncer de ovario (independientemente de la edad), o
- ·Un cáncer de mama y un cáncer de ovario en dos familiares (independientemente de la edad), o
- ·Un casos de cáncer de mama en varón y otro de mama/ovario mujer (independientemente de la edad)

Familias con tres o más casos afectados por cáncer de mama, al menos dos en familiares de primer grado

No considerar a los varones al contabilizar el grado de parentesco.

*Familiares de primer grado son madres, hijas o hermanas

Criterios de identificación de riesgo hereditario (SEOM)

Clin Transl Oncol (2011) 13:580-586
DOI 10.1007/s12094-011-0701-2

CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guidelines for hereditary cancer

Table 1 Criteria for genetic testing in hereditary breast and ovarian cancer syndrome

- Families with 3 or more breast and/or ovarian cancer cases in the same paternal o maternal lineage
- Families with 2 affected members with breast and/or ovarian cancer and at least one of the following characteristics:
  - Male with breast cancer or
  - History of ovarian cancer/fallopian tube/primary peritoneal or
  - Both breast cancer diagnosed prior to age 50 or
  - One of them is bilateral and the other <50 years
- Families with 1 affected member with breast and/or ovarian cancer if:
  - Women with a personal history of breast and ovarian cancer
  - Women with breast cancer diagnosed at age 30 or younger
  - Women with bilateral breast cancer diagnosed < 40 years
- Known deletereous mutation identified in the family

Criterios de identificación de riesgo hereditario (ESMO)

clinical practice guidelines

Annals of Oncology 22 (Supplement 6): vi31–vi34, 2011
doi:10.1093/annonc/mdr373

BRCA in breast cancer: ESMO Clinical Practice

referral for BRCA testing

Genetic testing criteria may differ between countries based on mutation prevalence. Widely accepted clinical criteria for referral include: three or more breast and/or ovarian cancer cases, at least one <50 years; two breast cancer cases <40 years; male breast cancer and ovarian cancer or early onset female breast cancer; Ashkenazi Jew with breast cancer of <60 years; young onset bilateral breast cancer; and breast and ovarian cancer in the same patient [IV, C]. In some countries, the criterion for testing is based on an *a priori* 10–20% probability of finding a mutation based on predictive models such as BRCAPRO, BOADICEA or Manchester Score, while less specific criteria include a potential benefit in the medical or surgical management of the individual or his/her relatives. The addition of pathological features of breast cancer such as medullary carcinoma and triple negative phenotype (estrogen receptor, progesterone receptor and no overexpression of HER2neu) in women younger than 50 has been evaluated as a cost-effectiveness strategy for mutation detection.

Criterios de identificación de riesgo hereditario (NCCN)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2012
Hereditary Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
Genetics Table of Contents
Discussion

HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA[a,b,c]

- Individual from a family with a known deleterious BRCA1/BRCA2 mutation
- Personal history of breast cancer[d] + one or more of the following:
  - Diagnosed age ≤ 45 y
  - Diagnosed age ≤ 50 y with ≥ 1 close blood relative[e] with breast cancer ≤ 50 y and/or ≥ 1 close blood relative[e] with epithelial ovarian[f] cancer at any age
  - Two breast primaries[g] when first breast cancer diagnosis occurred ≤ age 50 y
  - Diagnosed age ≤ 60 y with a triple negative breast cancer
  - Diagnosed age ≤ 50 y with a limited family history[c]
  - Diagnosed at any age, with ≥ 2 close blood relatives[e] with breast and/or epithelial ovarian[f] cancer at any age
  - Diagnosed at any age with ≥ 2 close blood relatives[e] with pancreatic cancer at any age
  - Close male blood relative[e] with breast cancer
  - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[h]
- Personal history of epithelial ovarian[f] cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer at any age with ≥ 2 close blood relatives[e] with breast and/or ovarian[f] and/or pancreatic cancer at any age
- Family history only
  (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. Significant limitations of interpreting test results should be discussed.)
  - First- or second-degree blood relative meeting any of the above criteria
  - Third-degree blood relative with breast cancer[d] and/or ovarian[f] cancer with ≥ 2 close blood relatives[e] with breast cancer (at least one with breast cancer ≤ 50 y) and/or ovarian[f] cancer

HBOC criteria met → See Follow-up (HBOC-2)

HBOC criteria not met → See NCCN Breast Cancer Screening and Diagnosis Guidelines

[a] One or more of these criteria is suggestive of hereditary breast/ovarian cancer syndrome that warrants further personalized risk assessment, genetic counseling and management. The maternal and paternal sides should be considered independently. Other malignancies reported in some HBOC

[d] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

[e] Close blood relatives include first-, second-, and third-degree relatives. (See BR/OV-3)

[f] For the purposes of these guidelines, fallopian tube and primary peritoneal cancers

Evaluación del riesgo de Cáncer de Mama

Riesgos de cáncer de mama empíricos

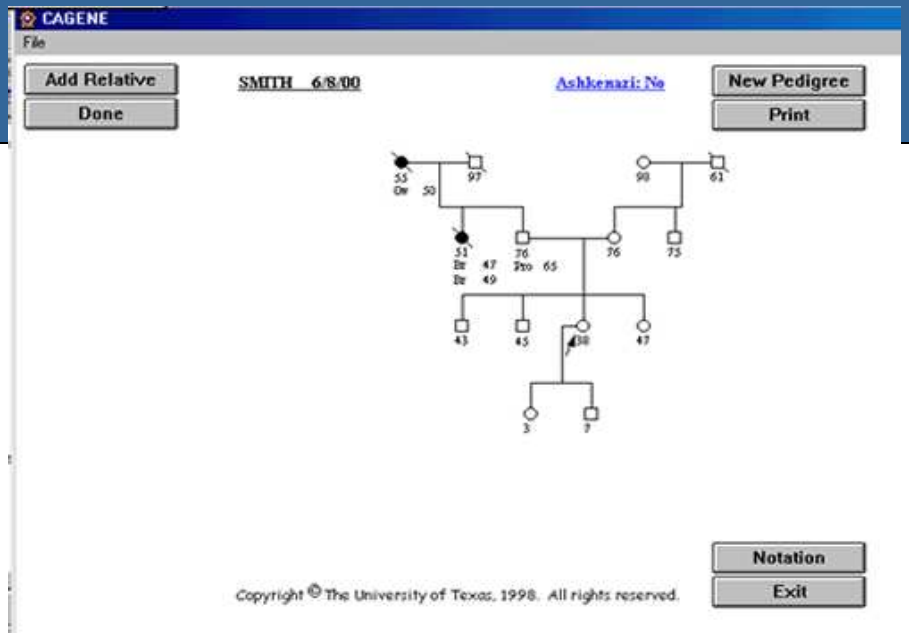
Riesgos de cáncer de mama basados en modelos:

1. Modelo de Gail
2. Tablas de Claus

Riesgo de cáncer de mama derivados de probabilidades de ser portador de mutaciones en BRCA1 y BRCA2

1. Modelos Bayesianos (BRCAPRO, BOADICEA)
2. Regresión logística/modelos de laboratorio (Couch, U Penn)
3. Datos empíricos de laboratorio (Myriad II)

CaGene


CAGENE
File
Add Relative
Done
SMITH 6/8/00
Ashkenazi: No
New Pedigree
Print
Notation
Exit
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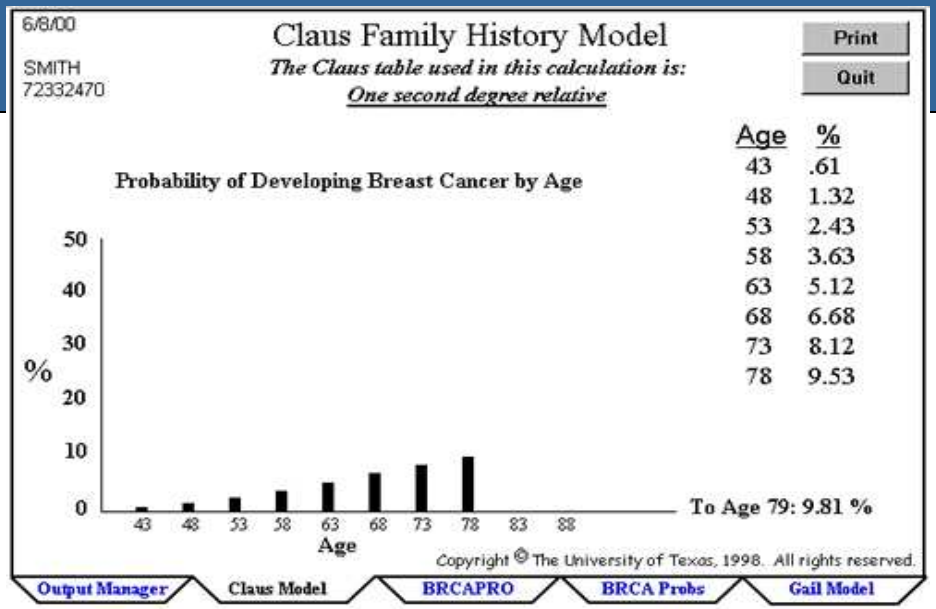
6/8/00
SMITH
72332470
Claus Family History Model
The Claus table used in this calculation is:
One second degree relative
Print
Quit
Probability of Developing Breast Cancer by Age
Age %
43 .61
48 1.32
53 2.43
58 3.63
63 5.12
68 6.68
73 8.12
78 9.53
%
Age
To Age 79: 9.81 %
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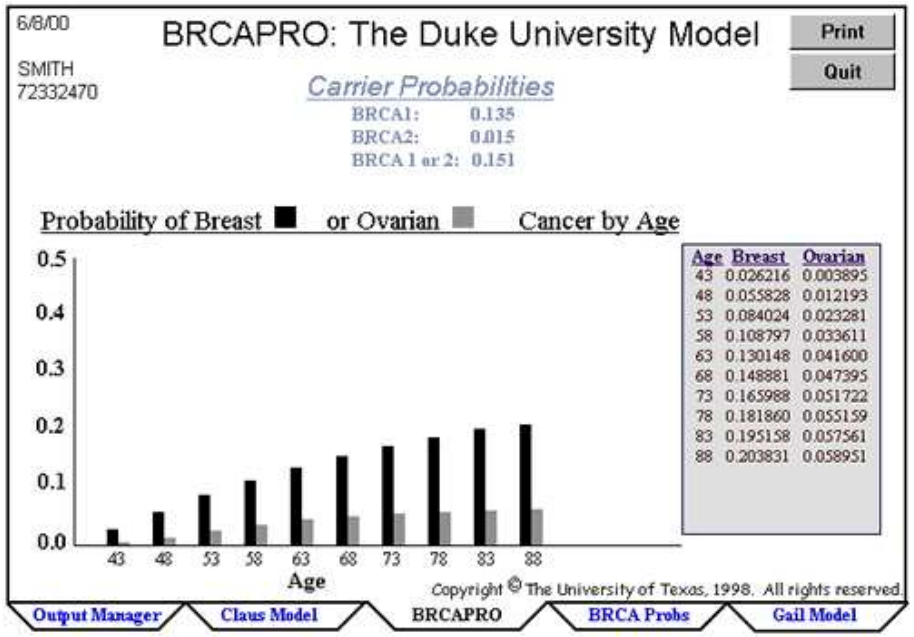
Output Manager
Claus Model
BRCAPRO
BRCA Probs
Gail Model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BRCAPRO: The Duke University Model
Print
Quit
Carrier Probabilities
BRCA1: 0.135
BRCA2: 0.015
BRCA 1 or 2: 0.151
Probability of Breast or Ovarian Cancer by Age
Age Breast Ovarian
43 0.026216 0.003895
48 0.055828 0.012193
53 0.084024 0.023281
58 0.108797 0.033611
63 0.130148 0.041600
68 0.148881 0.047395
73 0.165988 0.051722
78 0.181860 0.055159
83 0.195158 0.057561
88 0.203831 0.058951
Age
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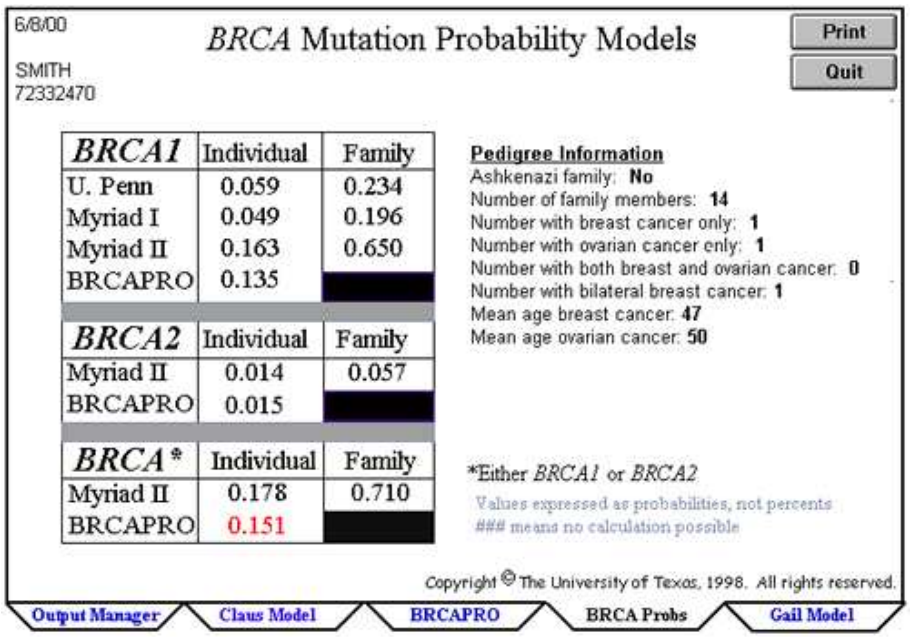
Output Manager
Claus Model
BRCAPRO
BRCA Probs
Gail Model


6/8/00
SMITH
72332470
BRCA Mutation Probability Models
Print
Quit
BRCA1 Individual Family
U. Penn 0.059 0.234
Myriad I 0.049 0.196
Myriad II 0.163 0.650
BRCAPRO 0.135
BRCA2 Individual Family
Myriad II 0.014 0.057
BRCAPRO 0.015
BRCA* Individual Family
Myriad II 0.178 0.710
BRCAPRO 0.151
Pedigree Information
Ashkenazi family: No
Number of family members: 14
Number with breast cancer only: 1
Number with ovarian cancer only: 1
Number with both breast and ovarian cancer: 0
Number with bilateral breast cancer: 1
Mean age breast cancer: 47
Mean age ovarian cancer: 50
*Either BRCA1 or BRCA2
Values expressed as probabilities, not percents
means no calculation possible
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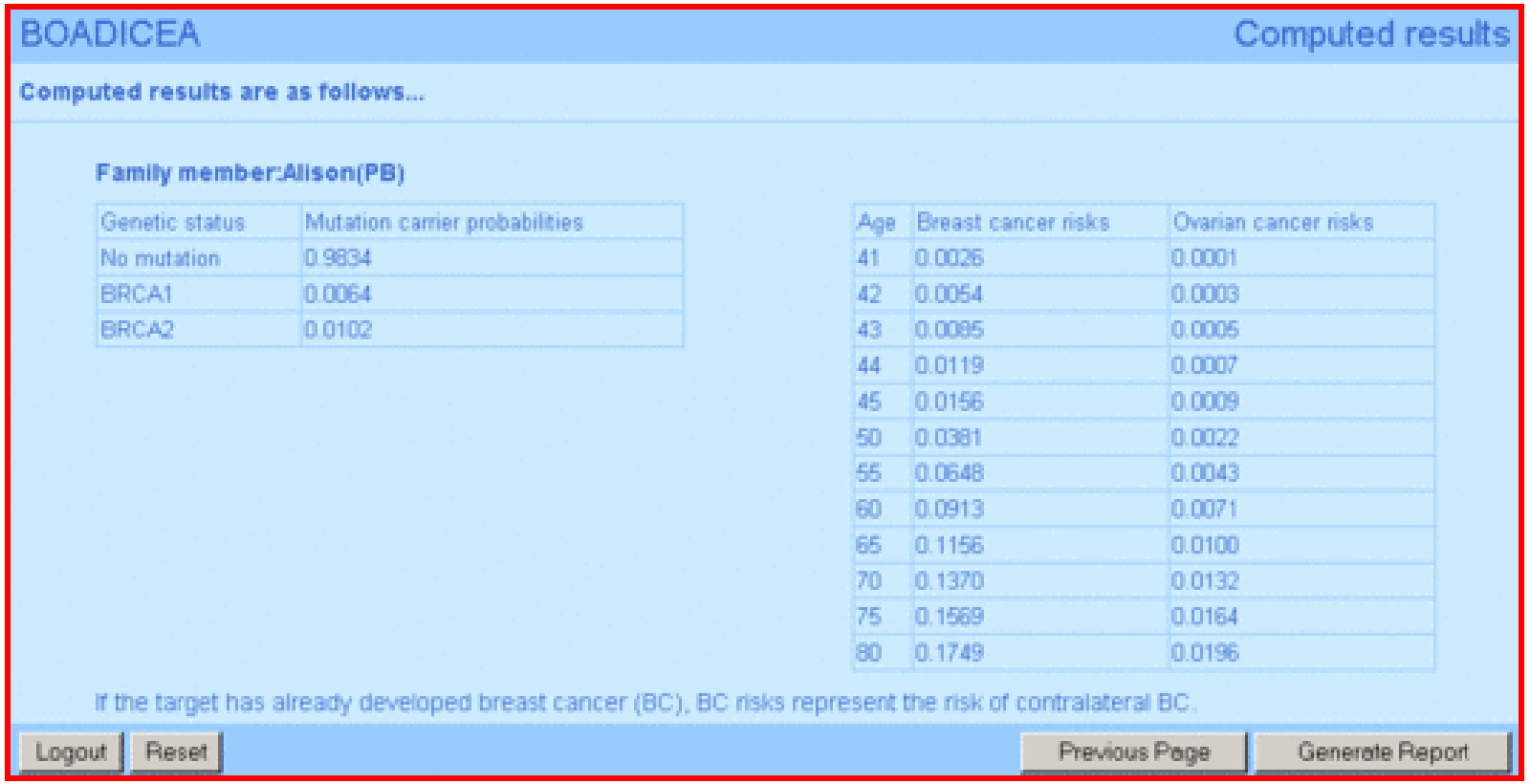
Output Manager
Claus Model
BRCAPRO
BRCA Probs
Gail Model

BOADICEA



BOADICEA Computed results

Computed results are as follows...

Family member:Alison(PB)

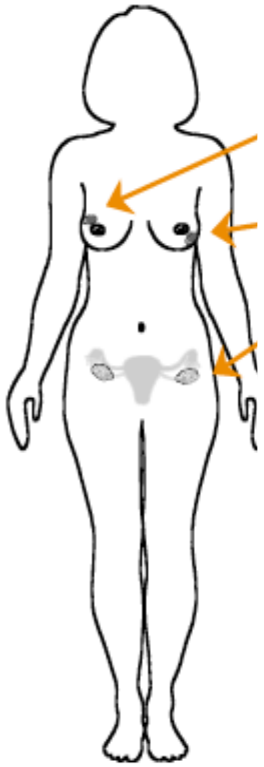
Genetic status	Mutation carrier probabilities
No mutation	0.9834
BRCA1	0.0064
BRCA2	0.0102

Age	Breast cancer risks	Ovarian cancer risks
41	0.0026	0.0001
42	0.0054	0.0003
43	0.0085	0.0005
44	0.0119	0.0007
45	0.0156	0.0009
50	0.0381	0.0022
55	0.0648	0.0043
60	0.0913	0.0071
65	0.1156	0.0100
70	0.1370	0.0132
75	0.1569	0.0164
80	0.1749	0.0196

If the target has already developed breast cancer (BC), BC risks represent the risk of contralateral BC.

Logout Reset Previous Page Generate Report

*BRCA*1 y *BRCA*2 asociación con cáncer: riesgo a lo largo de la vida



Cáncer de mama: 40-85% (a menudo a edad temprana)

Cáncer de mama contralateral: 40-60%

Cáncer de ovario: 15-40%

En hombres, aumento del riesgo de cáncer de mama, también de cáncer de próstata y páncreas

Breast Cancer Linkage Consortium. *J Natl Cancer Inst.* 1999;91:1310-1316.
Ford D et al. *Am J Hum Genet.* 1998;62:676-689.

Am. J. Hum. Genet. 72:1117–1130, 2003

Average Risks of Breast and Ovarian Cancer Associated with *BRCA1* or *BRCA2* Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies

A. Antoniou,[1,*] P. D. P. Pharoah,[2,*] S. Narod,[3] H. A. Risch,[4] J. E. Eyfjord,[5,6] J. L. Hopper,[7] N. Loman,[8] H. Olsson,[8] O. Johannsson,[8] Å. Borg,[8] B. Pasini,[9] P. Radice,[9,10] S. Manoukian,[9] D. M. Eccles,[11] N. Tang,[12] E. Olah,[13] H. Anton-Culver,[14] E. Warner,[3] J. Lubinski,[15] J. Gronwald,[15] B. Gorski,[15] H. Tulinius,[5] S. Thorlacius,[5] H. Eerola,[16,17] H. Nevanlinna,[16] K. Syrjäkoski,[18] O.-P. Kallioniemi,[18] D. Thompson,[1] C. Evans,[1] J. Peto,[19,20] F. Lalloo,[21] D. G. Evans,[21] and D. F. Easton[1]

RRs of Breast and Ovarian Cancer in Mutation Carriers

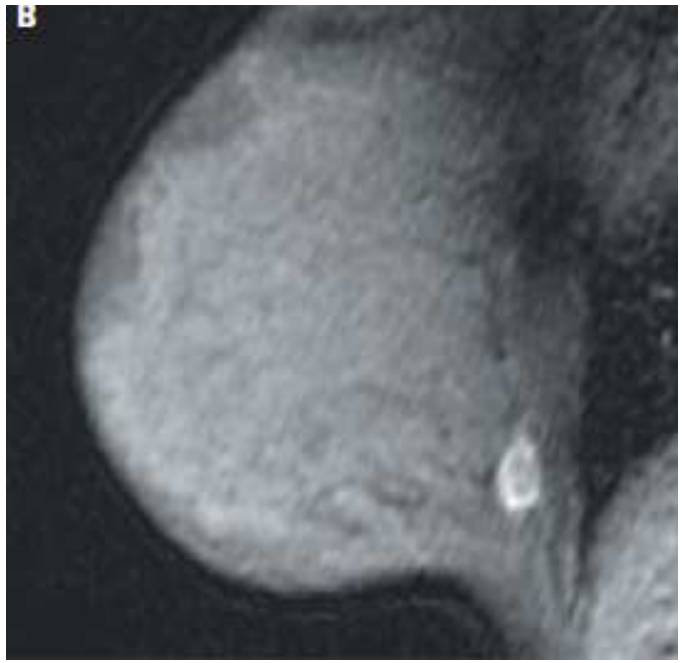
	RR[a] (95% CI) of Cancer for Carriers of Mutations in			
	BRCA1		*BRCA2*	
Age Group	Breast Cancer	Ovarian Cancer	Breast Cancer	Ovarian Cancer
20–29 years	17 (4.2–71)	1.0	19 (4.5–81)	1.0
30–39 years	33 (23–49)	49 (21–111)	16 (9.3–29)	1.0
40–49 years	32 (24–43)	68 (42–111)	9.9 (6.1–16)	6.3 (1.4–28)
50–59 years	18 (11–30)	31 (14–66)	12 (7.4–19)	19 (9.0–41)
60–69 years	14 (6.3–31)	50 (22–114)	11 (6.3–20)	8.4 (2.2–32)

[a] As compared to incidences for England and Wales in 1973–77.

Mamografia en mujeres jóvenes

mamografía

Baja sensibilidad por densidad mamográfica importante y tumores de rápido crecimiento



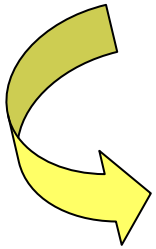
RNM

Resultados de 6 estudios prospectivos no-randomizados de screening con Mx y RNM en mujeres de alto riesgo

	Nº de pacientes		Nº de Cánceres	Cánceres detectados durante el cribado	Nº (%) de cánceres detectado con cada modalidad		
	Global	Portadoras			mamografía	Ecografía	RNM
Holanda-Kriege (2004)	1.909	358	45	41 (91%)	18 (40%)	-	32 (71%)
Canadá-Warner (2004)	236	236	22	21 (95%)	8 (36%)	7 (32%)	17 (77%)
UK-Leach (2005)	649	120	35	33 (94%)	14 (40%)	-	27 (77%)
Alemania-Kuhl (2005)	529	43	43	40 (93%)	14 (33%)	17 (39%)	39 (90%)
US-Lehman (2005)	390	?	4	4 (100%)	1 (25%)	-	4 (100%)
Italia-Sardanelli (2007)	278	156	18	18 (100%)	10 (55%)	11 (60%)	15 (83%)
TOTAL	**3.991**	**828**	**167**	**157 (94%)**	**65 (39%)**	**35 (42%)**	**134 (80%)**

Resultados de 6 estudios prospectivos no-aleatorizados de screening con Mx y RNM en mujeres de alto riesgo

- De los tumores identificados por la RNM, un 15-25% eran DCIS
- De los cánceres invasivos:
  - 75-94% eran ≤ 2 cm
  - 75-83% eran N-
- De los 157 cánceres detectados por el screening, un 12% (10 DCIS + 8 CDI) fueron detectados por la Mx pero no por la RNM



La RNM mamaria debería considerarse complementaria a la Mx, y no como un sustituto

Seguimiento en mujeres BRCA +

Clin Transl Oncol (2011) 13:580-586
DOI 10.1007/s12094-011-0701-2

CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guidelines for hereditary cancer

Table 2 Management of women at risk of hereditary breast and/or ovarian cancer syndrome

- Regular monthly breast self-exam (BSE) starting at age 18
- **Semianual clinical breast exam** starting at age 25
- **Annual mammogram and breast MRI screening** starting at age 25 or individualized based on earliest case of breast cancer in the family
- **Risk-reducing salpingo-oophorectomy** after completion of child bearing, between 35-40 years old/or individualised based on family history
- **Risk-reducing bilateral mastectomy**
- For those not interested in risk-reducing salpingo-oophorectomy consider transvaginal ultrasound + Ca 125 every 6 months starting at age 35 or 5-10 years earlier than the earliest ovarian cancer in the family
- Chemoprevention strategies for breast and ovarian cancer
- Reproductive options

Seguimiento en mujeres BRCA no informativo (BRCA X)

Clin Transl Oncol (2011) 13:580-586
DOI 10.1007/s12094-011-0701-2

SEOM clinical guidelines for hereditary cancer

Management of high-risk women without identified BRCA *mutations*

On average, more than 70% of HBOC families are negative for *BRCA1/2* germline mutations, considering these results as uninformative. The ability to quantify cancer risks in uninformative high-risk families is hampered by limited research. Women with a significant lifetime risk of breast cancer (>20–25%) who test negative for *BRCA1/2* should consider high-risk BC management. However, studies suggest that women from *BRCA1/2* mutation-negative site-specific breast cancer families are not at increased risk for ovarian cancer. Therefore, no further measure on reducing OC risk is needed [15].

Seguimiento en mujeres de alto riesgo (NCCN)

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NCCN Guidelines Version 1.2012
Hereditary Breast and/or Ovarian Cancer Syndrome

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HBOC SYNDROME MANAGEMENT (1 of 2)

WOMEN

- Breast self-exam training and education starting at age 18 y.
- Clinical breast exam, every 6-12 mo,[1] starting at age 25 y.
- Annual mammogram and breast MRI[2] screening starting at age 25 y, or individualized based on earliest age of onset in family.[3]
- Discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, reconstruction options, and risks.
- Recommend risk-reducing salpingo-oophorectomy,[4] ideally between 35 and 40 y, and upon completion of child bearing, or individualized based on earliest age of onset of ovarian cancer in the family. Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short term hormone replacement therapy (HRT) to a recommended maximum age of natural menopause, and related medical issues.
- For those patients who have not elected risk-reducing salpingo-oophorectomy, consider concurrent transvaginal ultrasound (preferably day 1-10 of menstrual cycle in premenopausal women) + CA-125 (preferably after day 5 of menstrual cycle in premenopausal women),[5] every 6 mo starting at age 30 y or 5-10 y before the earliest age of first diagnosis of ovarian cancer in the family.
- Consider chemoprevention options for breast and ovarian cancer, including discussing risks and benefits[6] (See NCCN Breast Cancer Risk Reduction Guidelines).
- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies and more frequent screening intervals) in the context of a clinical trial.

Continued on next page

[1] Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical breast exam every 6-12 mo is the concern for interval breast cancers.

[2] High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably day 7-15 of menstrual cycle for premenopausal women.

EUROPEAN JOURNAL OF CANCER 46 (2010) 1296–1316

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Position Paper

Magnetic resonance imaging of the breast: Recommendations from the EUSOMA working group

(3) Annual MRI screening should be available starting from the age of 30. Starting annual screening before age 30 may be discussed, such as mutation carrier of *BRCA1* or *BRCA2* (starting from 25 to 29) and *TP53* (starting from 20) (LoE-2b, DoR-B).

(4) Annual MRI screening should be offered to:
- *BRCA1*, *BRCA2*, and *TP53* mutation carriers;
- women at 50% risk for *BRCA1*, *BRCA2*, or *TP53* mutation that runs in their family (first-degree relatives of mutation carriers);
- women from families not tested or inconclusively tested for *BRCA* mutation with a 20–30% lifetime risk or greater (LoE-2, DoR-B) (for different thresholds, see point 1);
- women who have had previous mantle radiotherapy before age 30 (e.g. for Hodgkin disease), starting 8 years after their treatment[109] (LoE-3, DoR-B).

(8) Screening XRM should not be performed in high-risk women below 35 years as there is no evidence that the benefits outweigh the risks at this young age (EPO). In *TP53* mutation carriers of any age annual XRM can be avoided based on discussion on risks and benefits from radiation exposure (EPO).

(9) Annual XRM may be considered for high-risk women from age 35 (LoE-2–3, DoR-B).

(10) If annual MRI is performed, screening whole breast US and CBE are not necessary as there is no evidence of any additional benefit to MRI (LoE-2, DoR-B). They are recommended in women under 35 who do not tolerate or have contraindication to MRI or to gadolinium-based contrast material administration (EPO).

Recomendaciones de la ACS para el screening con RNM mamaria (2007)

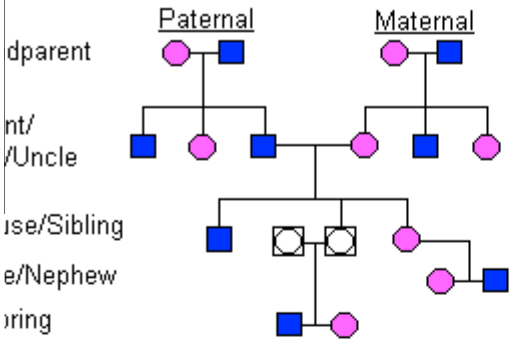
TABLE 1 Recommendations for Breast MRI Screening as an Adjunct to Mammography

Recommend Annual MRI Screening (Based on Evidence*)
BRCA mutation
First-degree relative of *BRCA* carrier, but untested
Lifetime risk ~20–25% or greater, as defined by BRCAPRO or other models that are largely dependent on family history
Recommend Annual MRI Screening (Based on Expert Consensus Opinion†)
Radiation to chest between age 10 and 30 years
Li-Fraumeni syndrome and first-degree relatives
Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives
Insufficient Evidence to Recommend for or Against MRI Screening‡
Lifetime risk 15–20%, as defined by BRCAPRO or other models that are largely dependent on family history
Lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH)
Atypical ductal hyperplasia (ADH)
Heterogeneously or extremely dense breast on mammography
Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS)
Recommend Against MRI Screening (Based on Expert Consensus Opinion)
Women at <15% lifetime risk

*Evidence from nonrandomized screening trials and observational studies.
†Based on evidence of lifetime risk for breast cancer.
‡Payment should not be a barrier. Screening decisions should be made on a case-by-case basis, as there may be particular factors to support MRI. More data on these groups is expected to be published soon.

Riesgo moderado de cáncer de mama (c. de mama familiar)

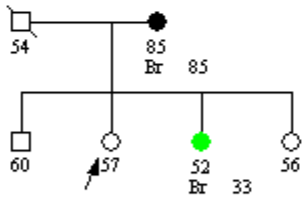
Add Relative



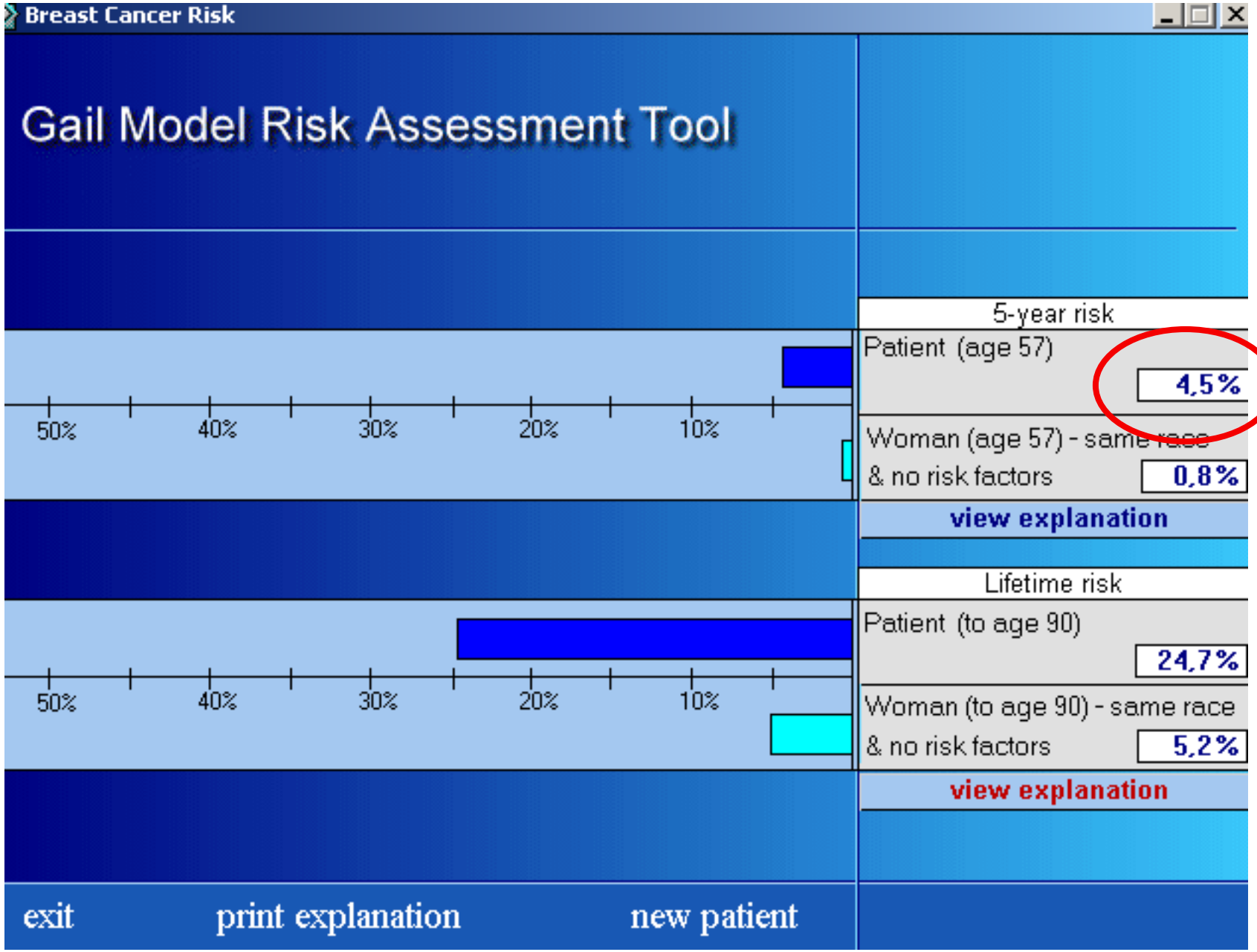
? Shortcut Keys

FERRANDOPONS
1277
Ashkenazi: No

Done | New Pedigree
Change Proband | Print
Notation | Exit



BRCA Positive
BRCA Negative
HNPCC Tested


Breast Cancer Risk
Gail Model Risk Assessment Tool
50%
40%
30%
20%
10%
5-year risk
Patient (age 57)
4,5%
Woman (age 57) - same race
& no risk factors
0,8%
view explanation
Lifetime risk
Patient (to age 90)
24,7%
Woman (to age 90) - same race
& no risk factors
5,2%
view explanation
exit
print explanation
new patient

Aumento del riesgo de c. mama (NCCN)

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Breast Cancer Screening and Diagnosis

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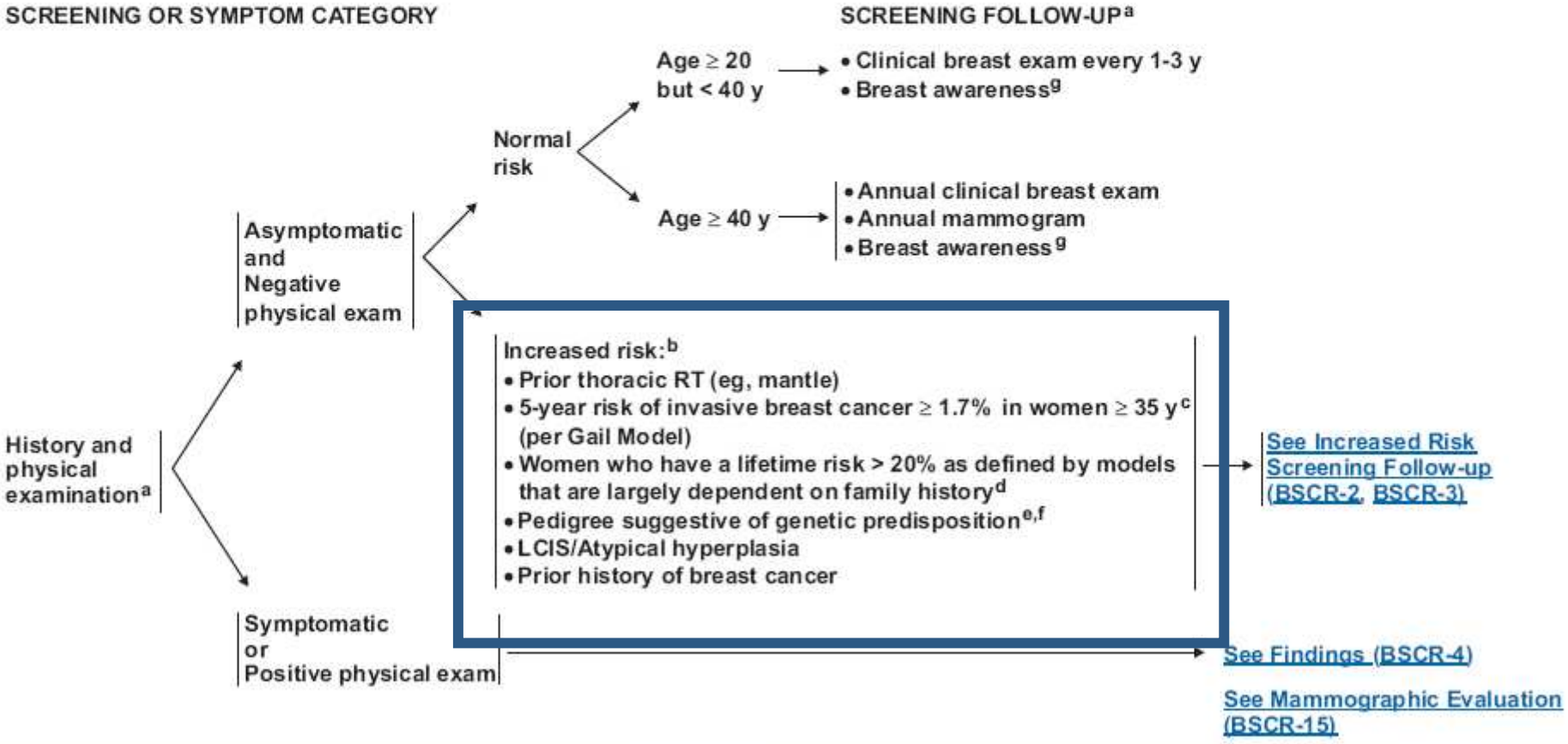
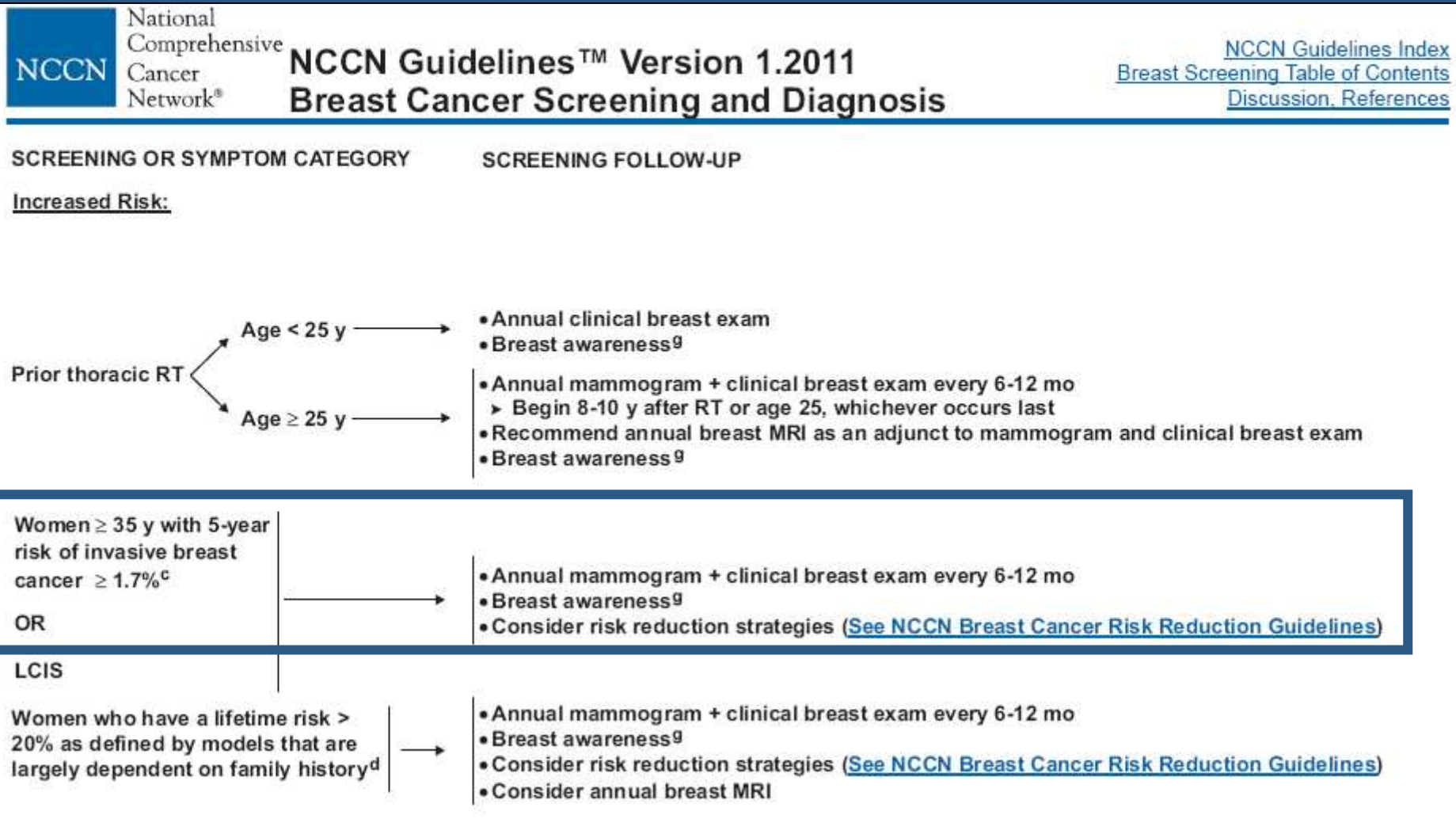


c: Gail
d: others than Gail

Riesgo moderado de c. mama (NCCN)



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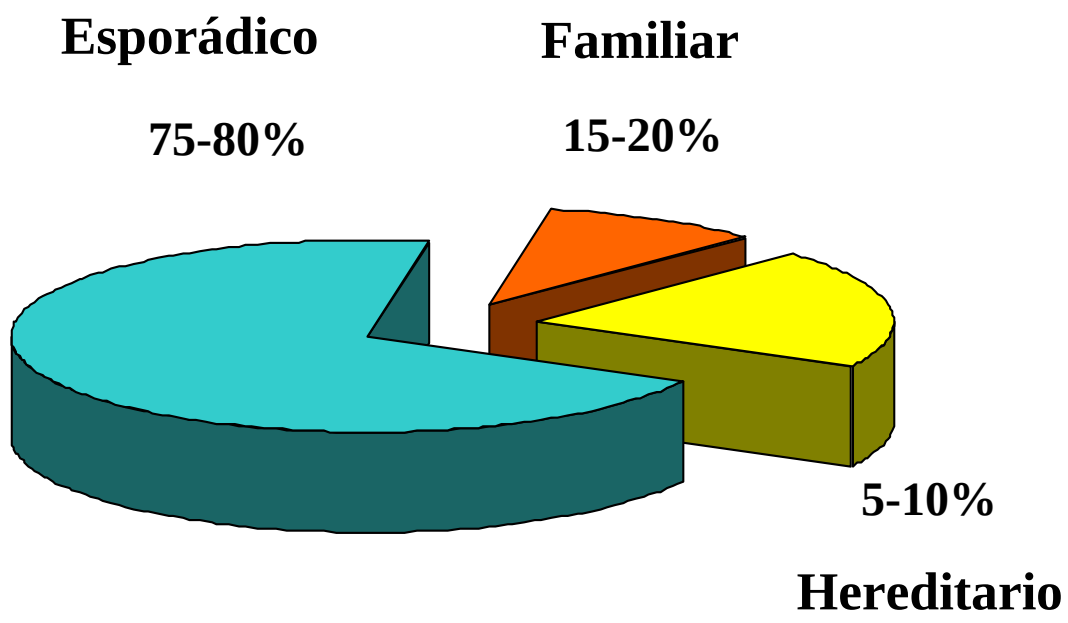
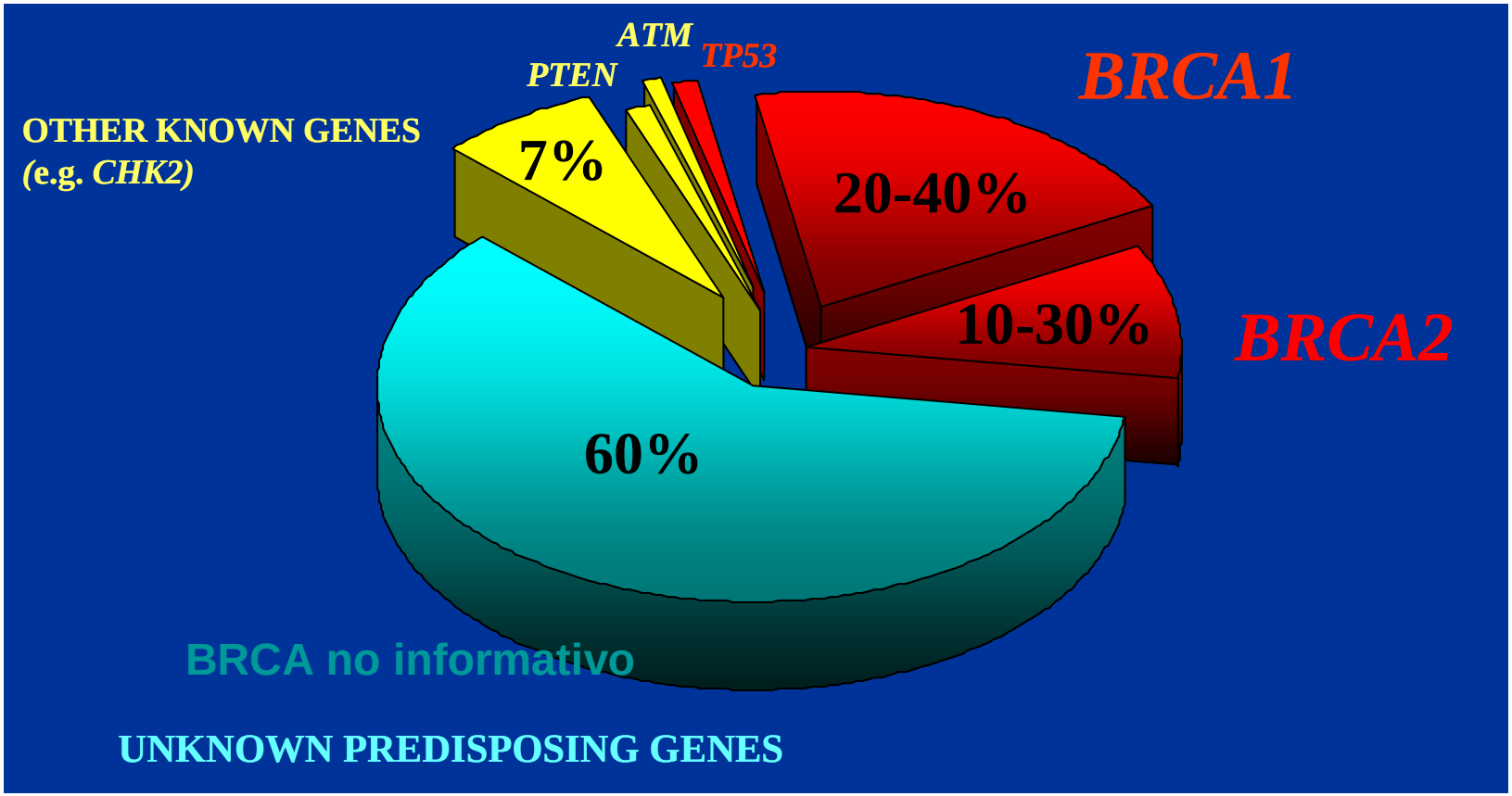
SCREENING OR SYMPTOM CATEGORY	SCREENING FOLLOW-UP
Increased Risk:	
Prior thoracic RT — Age < 25 y	• Annual clinical breast exam • Breast awareness[g]
Prior thoracic RT — Age ≥ 25 y	• Annual mammogram + clinical breast exam every 6-12 mo ▸ Begin 8-10 y after RT or age 25, whichever occurs last • Recommend annual breast MRI as an adjunct to mammogram and clinical breast exam • Breast awareness[g]
Women ≥ 35 y with 5-year risk of invasive breast cancer ≥ 1.7%[c] OR LCIS	• Annual mammogram + clinical breast exam every 6-12 mo • Breast awareness[g] • Consider risk reduction strategies (See NCCN Breast Cancer Risk Reduction Guidelines)
Women who have a lifetime risk > 20% as defined by models that are largely dependent on family history[d]	• Annual mammogram + clinical breast exam every 6-12 mo • Breast awareness[g] • Consider risk reduction strategies (See NCCN Breast Cancer Risk Reduction Guidelines) • Consider annual breast MRI

Clasificación de cáncer de mama



BRCA no informativo



Conclusiones seguimiento c. mama alto riesgo y moderado

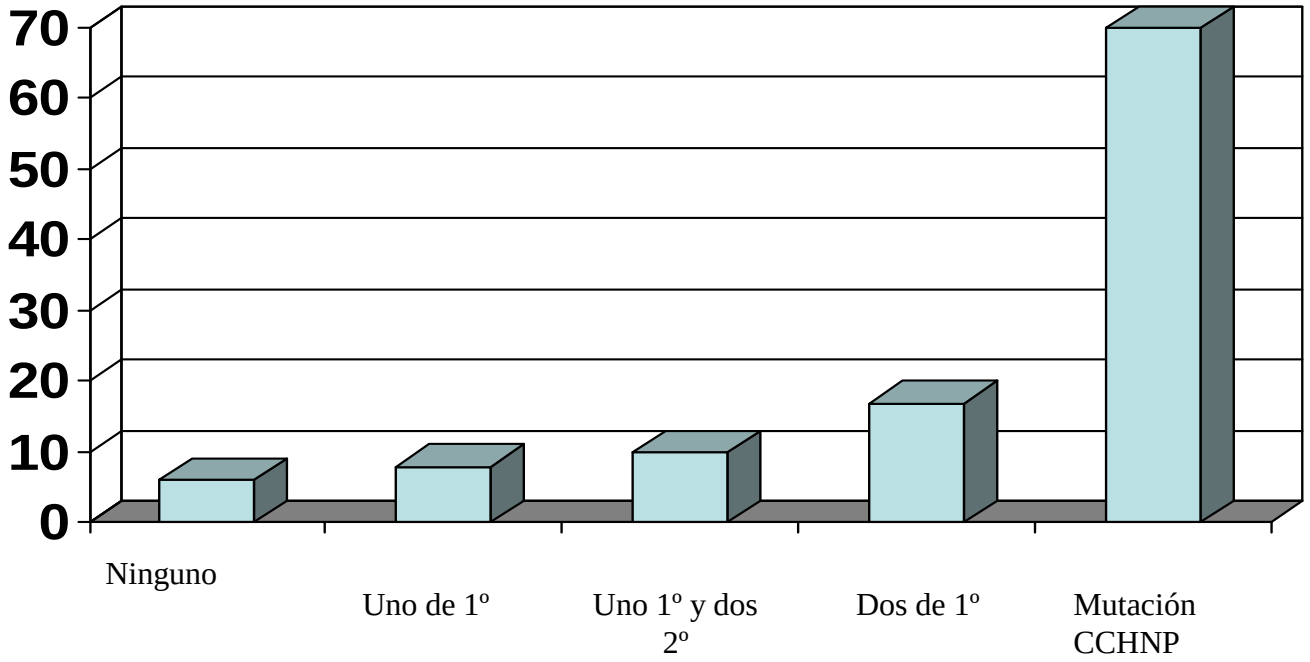
	mamografía	**RNM**
BRCA +	25-35 a	25 a
BRCA no informativo **> 20-25 % (BRCAPRO)**	25-35 a	25-30 a
BRCA no informativo **< 20-25 % (BRCAPRO)**	25-35 a	no
≥ 35 a y riesgo de c. mama a 5 a **Gail ≥ 1.7%**	35 a	no

CÁNCER DE COLON HEREDITARIO NO ASOCIADO A POLIPOSIS

- Asociado a defectos en MMR: Síndrome de Lynch.

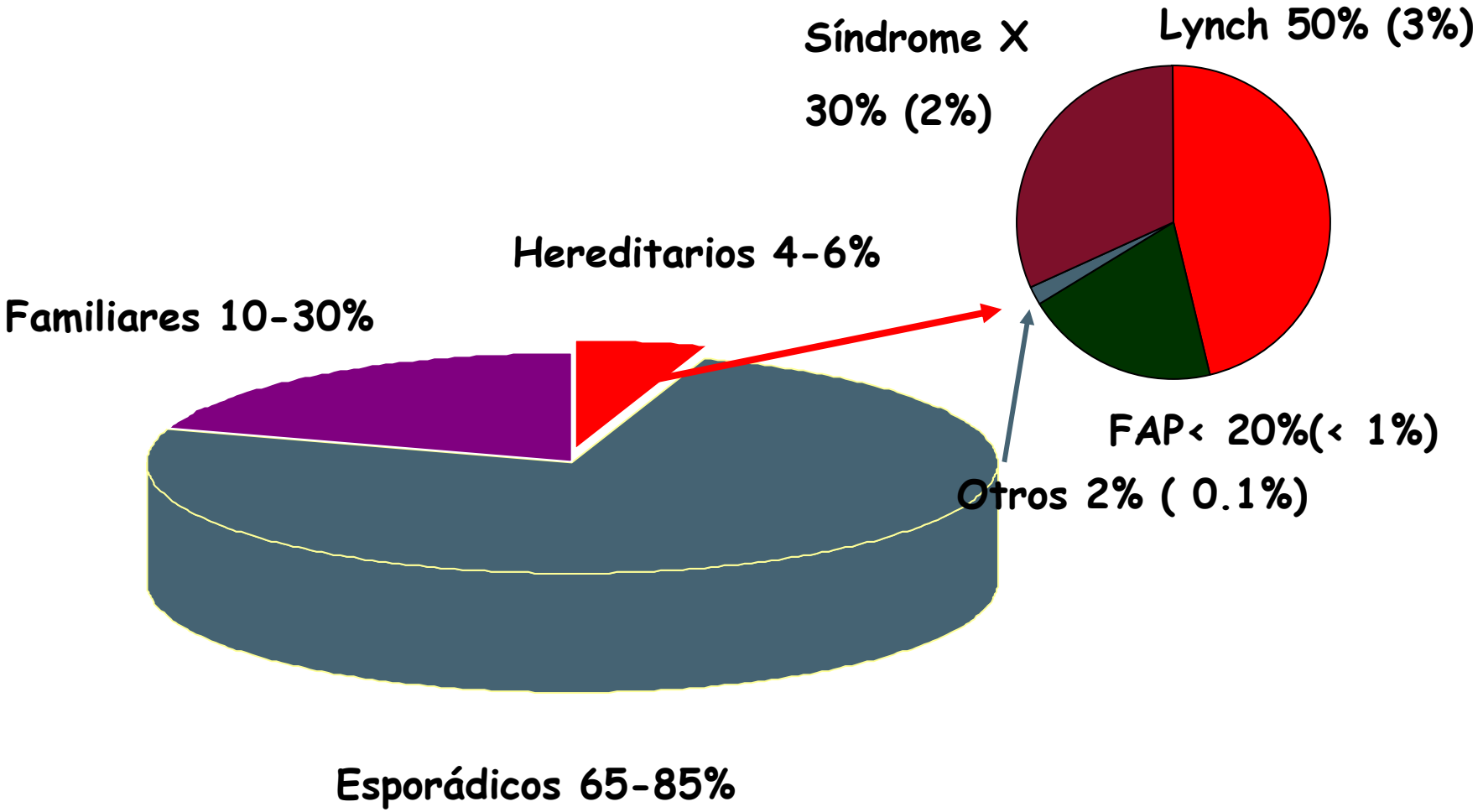
- No asociado a MMR: Cáncer colorrectal familiar tipo X.

Factores de riesgo y antecedentes familiares



Vasen. JCO 2001;19:4074-4080

Clasificación del cáncer de colon



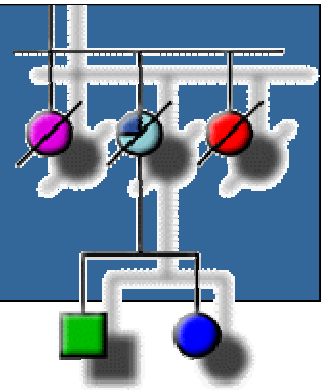
Criterios de Amsterdam

Table 3 Amsterdam criteria (AC)

– There should be at least three relatives with colorectal cancer (CRC) or other a Lynch syndrome-associated tumour[a]: (AC type I include only CRC; AC type II include all the cancers listed)
– One relative should be a first-degree relative of the other two
– At least two successive generations should be affected
– At least one tumour should be diagnosed before the age of 50 years
– Familial Adenomatous Polyposis should be excluded in CRC cases
– Tumours should be verified by histopathological examination

[a]Lynch syndrome-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract and brain tumours, carcinoma of the small bowell, sebaceous gland adenomas and keratoacanthomas

CÁNCER DE COLON HEREDITARIO NO POLIPÓSICO
Criterios de Amsterdam II



MSI

+ ~ 60%

- Mutaciones en genes reparadores
- Mayor incidencia CCR
- Colon proximal
- Mucinosos, pobremente diferenciados
- Contenido DNA diploide
- Edad aparición de tumores temprana

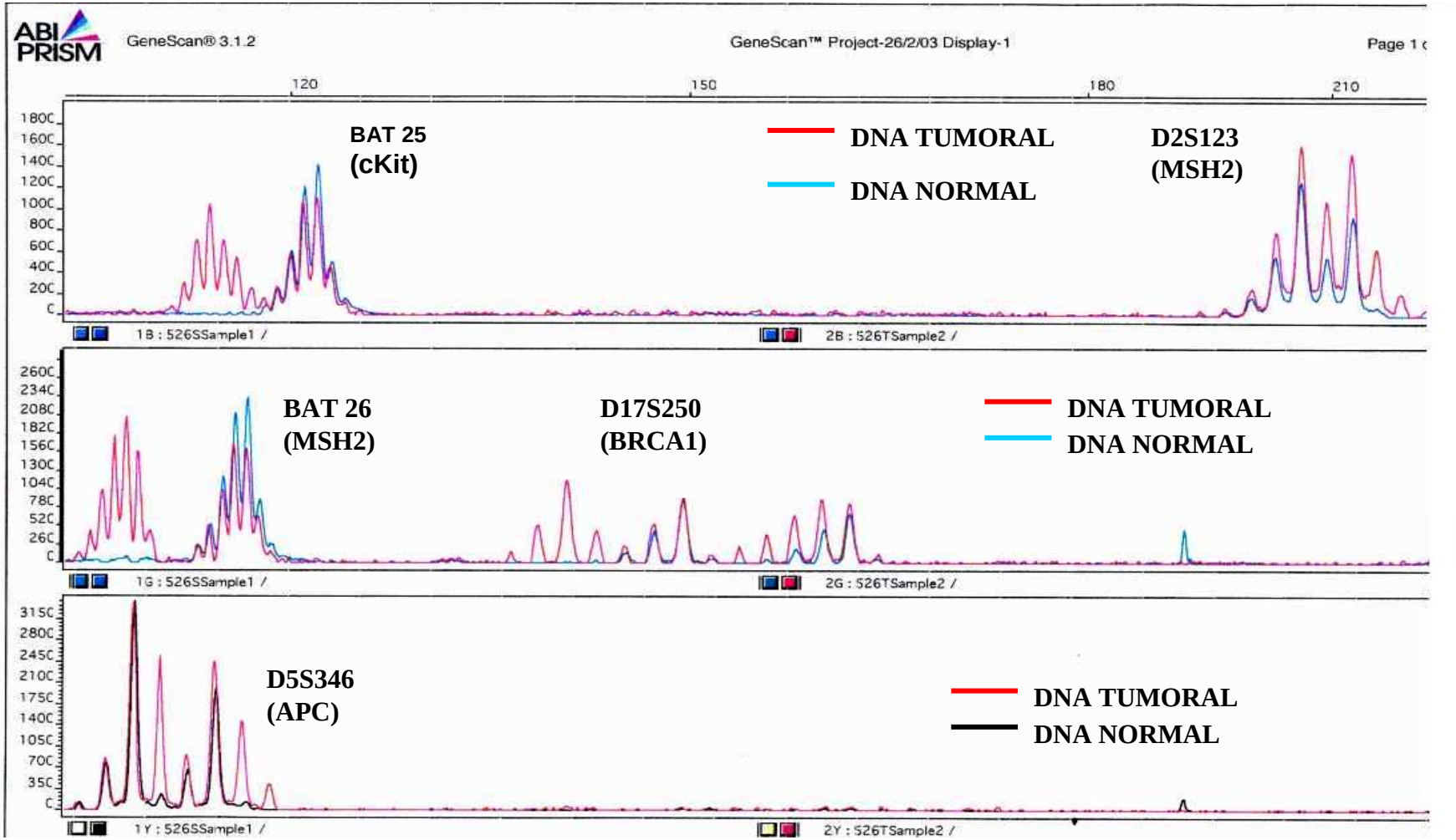
SÍNDROME DE LYNCH

– ~ 40%

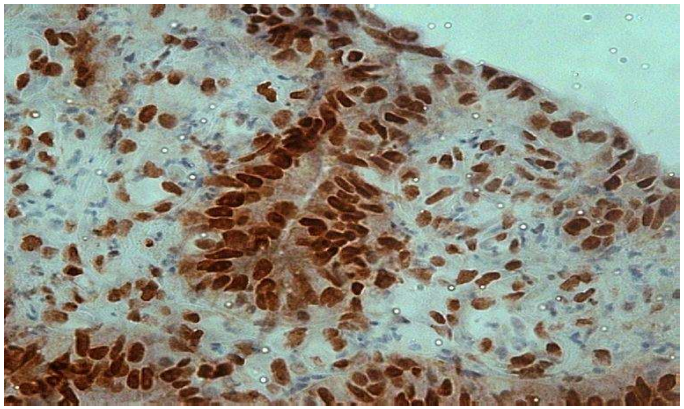
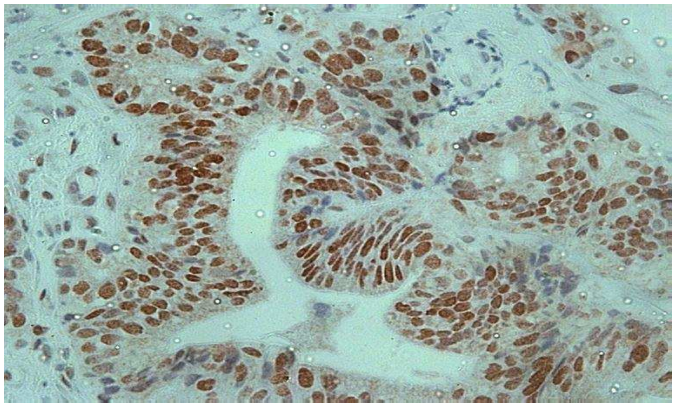
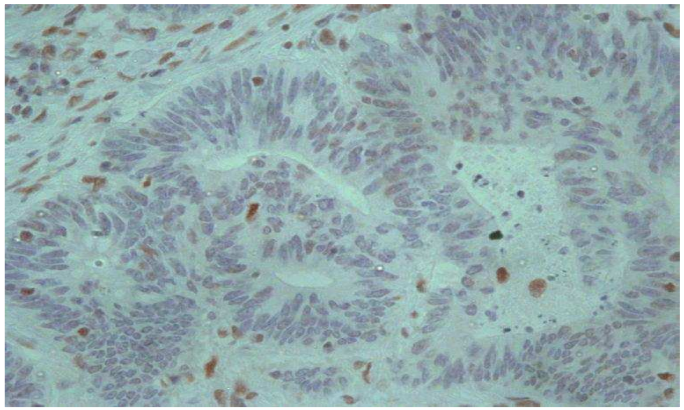
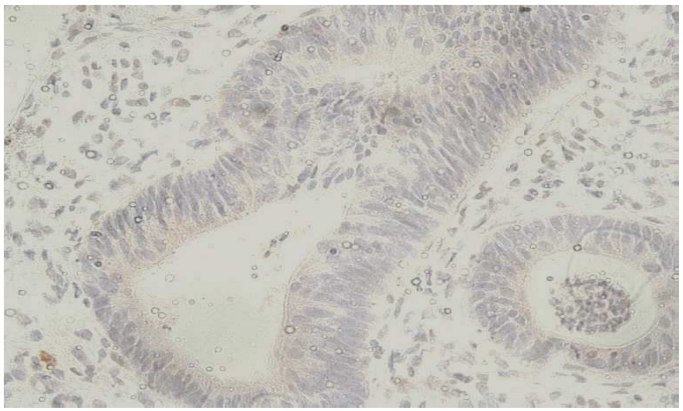
- Genes reparadores raramente mutados
- Menor incidencia CCR
- No predominio de colon proximal
- No predominio de mucinosos, pobremente diferenciados.
- No mayor riesgo de otras neoplasias
- Contenido DNA aneuploide
- Edad aparición de tumores más tardía

CÁNCER COLORRECTAL FAMILIAR TIPO X

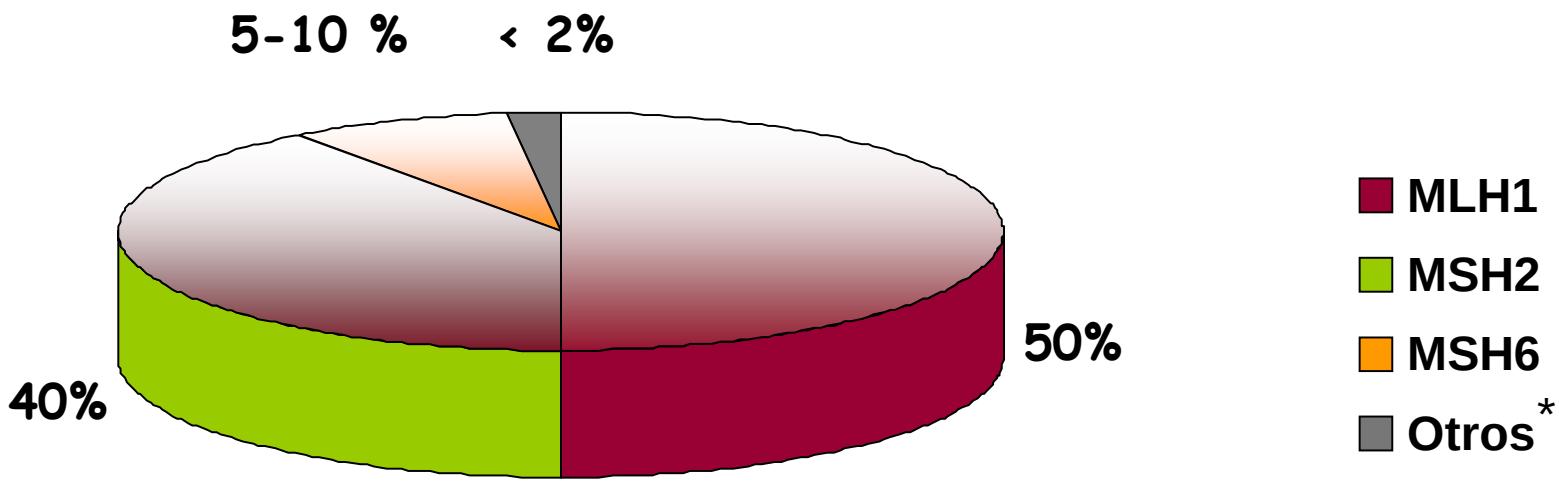
Panel de Bethesda: IMS



Inmunohistoquímica

	MLH1	MSH2
+		
–		

Mutaciones en los genes MMR



*** PMS2, EXO 1, TGFβRII, PMS1?, MLH3?**

Se distribuyen a lo largo de los genes sin puntos calientes

Criterios de Bethesda para estudio de IMS e IHQ

Table 4 Revised bethesda guidelines (BG)

1. CRC diagnosed in a patient <50 years
2. Presence of synchronous, metachronous colorectal or other Lynch syndrome-related tumours[a], regardless of age
3. CRC with high MSI phenotype diagnosed in a patient aged <60 years
4. Patient with CRC and a first-degree relative with a Lynch syndrome-related tumour[a], with one of the cancers diagnosed at age <50 years
5. Patient with CRC with two or more first-degree or second-degree relatives with a Lynch syndrome-related tumour[a], regardless of age

[a]Lynch syndrome-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract and brain tumours, carcinoma of the small bowell, sebaceous gland adenomas and keratoacanthomas

Seguimiento en HNPCC (SEOM)

Table 5 Recommended screening protocol for Lynch syndrome and familial clustering of colorectal cancer

Disorder	Lower age limit (years)	Examination	Interval (years)
Lynch syndrome	20-25	Colonoscopy	1-2
	30-35	Gynecological examination, transvaginal ultrasound, aspiration biopsy	1-2
	30-35	Gastroduodenoscopy[a]	1-2
	30-35	Abdominal ultrasound, urinalysis and cytology urine[b]	1-2
FCC-X and other familial clustering of colorectal cancer case in the family	45 or 5-10 years before the youngest case	Colonoscopy	3-5

[a]If gastric cancer is present in the family or in countries with high incidence of gastric cancer
[b]If urinary tract cancer is present in the family
FCC-X, familial colorectal cancer type X

Seguimiento en HNPCC (NCCN)

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2012
Lynch Syndrome

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SURVEILLANCE[f,g]

Colon cancer:

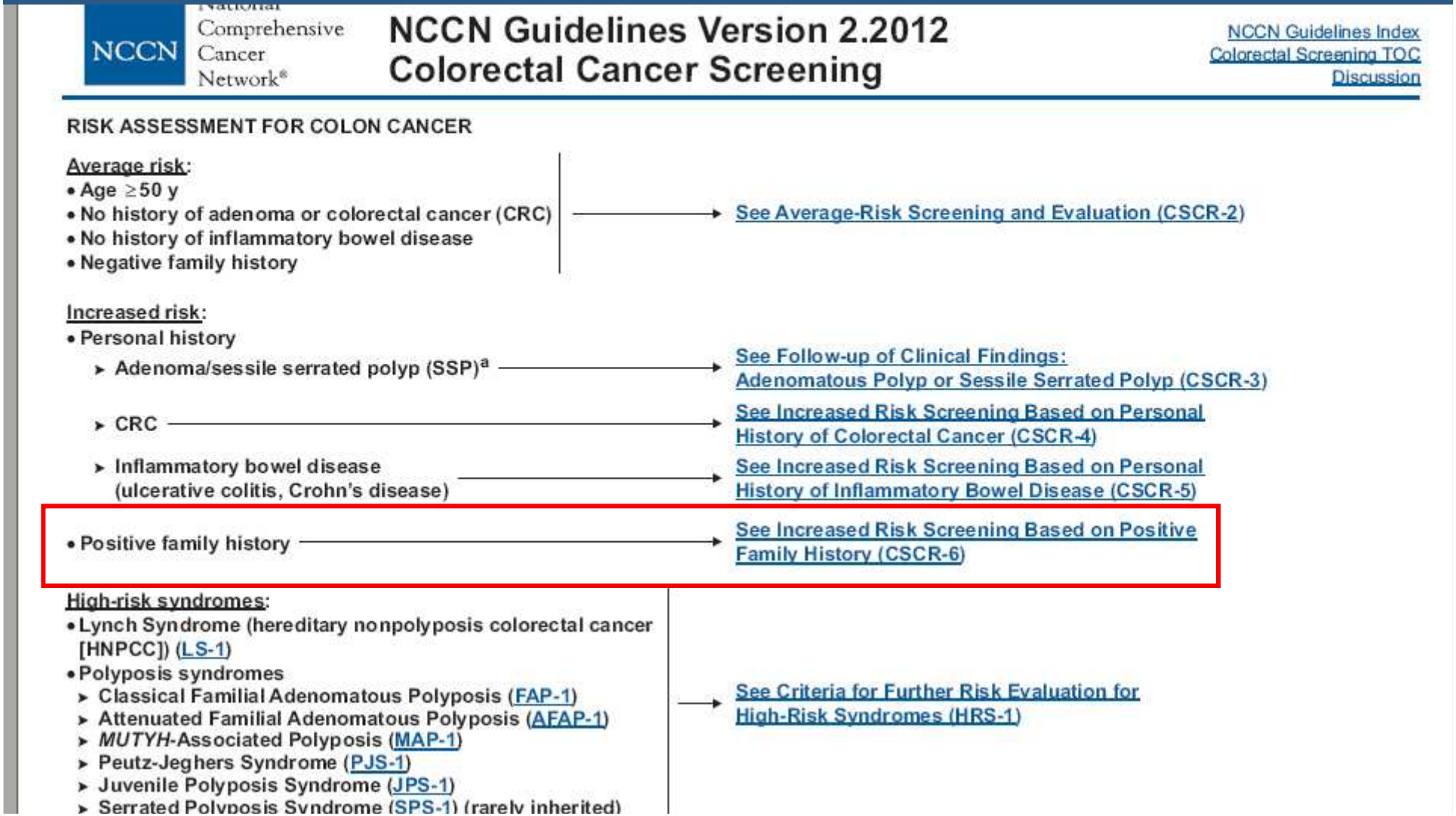
- Colonoscopy at age 20-25 y[h] or 2-5 y prior to the earliest colon cancer if it is diagnosed before age 25 y and repeat every 1-2 y.

Extra colonic:

- Endometrial and ovarian cancer:
  - Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option that should be considered by women who have completed childbearing.
  - Patients must be aware that dysfunctional uterine bleeding warrants evaluation.
  - There is no clear evidence to support screening for endometrial cancer for LS. However, annual office endometrial sampling is an option.
  - While there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening for LS. Transvaginal ultrasound for ovarian and endometrial cancer has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.
- Gastric and small bowel cancer:
  - There is no clear evidence to support screening for gastric and small bowel cancer for LS, may consider:
    - Esophagogastroduodenoscopy (EGD) with extended duodenoscopy (to distal duodenum or into the jejunum) at 2- to 3-y intervals beginning at age 30-35 y. Consider capsule endoscopy for small bowel cancer at 2- to 3-y intervals beginning at age 30-35 y.
- Urothelial cancer: Consider annual urinalysis starting at 25-30 y.
- Central nervous system cancer: Annual physical examination starting at 25-30 y; no additional screening recommendations have been made.
- Pancreatic cancer: Due to limited data, no recommendation is possible at this time.

→ See Follow-up of Surveillance Findings (LS-3)

Clasificación según el riesgo de cáncer de colon



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RISK ASSESSMENT FOR COLON CANCER

Average risk:
- Age ≥50 y
- No history of adenoma or colorectal cancer (CRC)
- No history of inflammatory bowel disease
- Negative family history

→ See Average-Risk Screening and Evaluation (CSCR-2)

Increased risk:
- Personal history
  - Adenoma/sessile serrated polyp (SSP)[a] → See Follow-up of Clinical Findings: Adenomatous Polyp or Sessile Serrated Polyp (CSCR-3)
  - CRC → See Increased Risk Screening Based on Personal History of Colorectal Cancer (CSCR-4)
  - Inflammatory bowel disease (ulcerative colitis, Crohn's disease) → See Increased Risk Screening Based on Personal History of Inflammatory Bowel Disease (CSCR-5)
- Positive family history → See Increased Risk Screening Based on Positive Family History (CSCR-6)

High-risk syndromes:
- Lynch Syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) (LS-1)
- Polyposis syndromes
  - Classical Familial Adenomatous Polyposis (FAP-1)
  - Attenuated Familial Adenomatous Polyposis (AFAP-1)
  - *MUTYH*-Associated Polyposis (MAP-1)
  - Peutz-Jeghers Syndrome (PJS-1)
  - Juvenile Polyposis Syndrome (JPS-1)
  - Serrated Polyposis Syndrome (SPS-1) (rarely inherited)

→ See Criteria for Further Risk Evaluation for High-Risk Syndromes (HRS-1)

Seguimiento en riesgo familiar

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INCREASED RISK BASED ON POSITIVE FAMILY HISTORY

FAMILY HISTORY CRITERIA[y]	SCREENING	
1 first-degree relative with CRC aged <50 y[z] or 2 first-degree relatives with CRC at any age[z]	Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of CRC	Repeat every 3-5 y depending on individual family history[bb]
First-degree relative with CRC aged ≥50 y[aa]	Colonoscopy beginning at age 50 y or 10 y before earliest diagnosis of CRC	Repeat every 5 y[bb,cc]
1 second-degree relative with CRC aged <50 y	Colonoscopy beginning at age 50 y	Repeat every 5 y[bb,cc]
≥ 2 second-degree relatives with CRC at any age	Colonoscopy beginning at age 50 y	Repeat every 7-8 y (every 5 y if grandparent with CRC)[cc]
1 second-degree relative and ≥ 2 third-degree relatives with CRC at any age	Colonoscopy beginning at age 50 y	Repeat every 7-8 y[cc]
Grandparent aged >50 y with CRC	Colonoscopy beginning at age 50 y	Repeat every 7-8 y[cc]
Aunt/uncle aged >50 y with CRC or 3 third-degree relatives with CRC at any age	Colonoscopy beginning at age 50 y	Repeat every 10 y
First-degree relative with advanced adenoma(s)	Colonoscopy beginning at age 50 y or at age of onset, whichever is first	Repeat every 7-8 y[cc] or per colonoscopy findings

Conclusiones seguimiento c. colon alto riesgo y moderado

	EXPLORACION	EDAD INICIO	INTERVALOS
Síndrome de Lynch	Colonoscopia	20-25 años	1-2 años
Síndrome X	Colonoscopia	45 años ó *	3-5 años
Colon familiar (riesgo moderado)	Colonoscopia	40-50 años o *	3-5 años

* o 10 años antes del tumor más joven de la familia