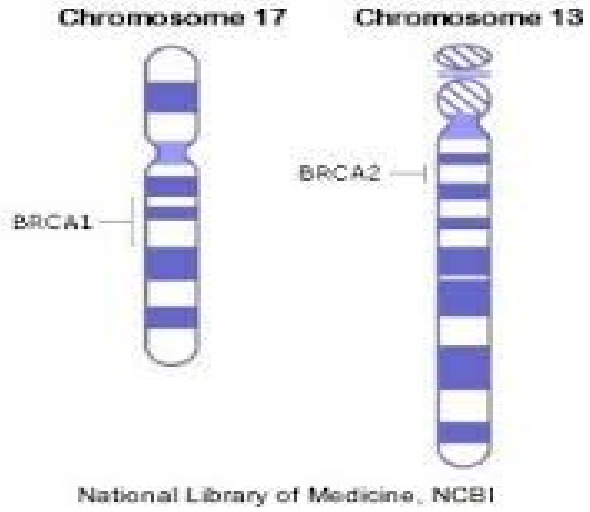
Screening recommendations: High-risk population only? General population?

Ilan Bruchim, MD

Hillel Yaffe, Hadera, Israel



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Disclosure

- **Nothing to disclose**

Effectiveness of genetic counseling/testing

- Reduces distress, improves risk perception
- Interventions – reduce/prevent cancer
- Test relatives
- Therapeutic implications

	Breast Cancer	Ovarian Cancer	All cause
Mastectomy	85-100%		
BSO	37-100%	69-100%	55%

Ann Intern Med. 2013;158:604-614.

Who should we test?

- High risk- Family history
- Affected patients- BRCA related cancers
- General population

Annals of Internal Medicine | CLINICAL GUIDELINE

Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Screen women whose <u>family history</u> may be associated with an increased risk for potentially harmful BRCA

- **Breast cancer: <50y, Bilateral, Multiple**
- **BrCa & Ovarian ca/FTC/PPC**
- **Male breast cancer**
- **Relatives with 2 primary types of BRCA-related cancer**
- **Ashkenazi Jewish ethnicity**

Family History Screening and Risk Assessment

Table 1. **Ontario Family History Assessment Tool***

Risk Factor	Points
Breast and ovarian cancer	
Mother	10
Sibling	7
Second-/third-degree relative	5
Breast cancer relative	
Parent	4
Sibling	3
Second-/third-degree relative	2
Male relative (add to above)	2
Breast cancer characteristics	
Onset at age 20–29 y	6
Onset at age 30–39 y	4
Onset at age 40–49 y	2
Premenopausal/perimenopausal	2
Bilateral/multifocal	3
Ovarian cancer relative	
Mother	7
Sibling	4
Second-/third-degree relative	3
Age at ovarian cancer onset	
<40 y	6
40–60 y	4
>60 y	2
Age at prostate cancer onset	
<50 y	1
Age at colon cancer onset	
<50 y	1
Family total	
Referral†	≥10

* From reference 19.
† Referral with a score of ≥10 corresponds to doubling of lifetime risk for breas cancer (22%).

Table 2. **Manchester Scoring System***

Risk Factor	*BRCA1* Score	*BRCA2* Score
Age at onset of female breast cancer†		
<30 y	6	5
30–39 y	4	4
40–49 y	3	3
50–59 y	2	2
≥60 y	1	1
Age at onset of male breast cancer†		
<60 y	5‡	8§
≥60 y	5‡	5§
Age at onset of ovarian cancer†		
<60 y	8	5
≥60 y	5	5
Pancreatic cancer	0	1
Age at onset of prostate cancer†		
<60 y	0	2
≥60 y	0	1

* From reference 13. D
combined score of 15 for
identifying a *BRCA1* or *
† For relatives in direct l
‡ If *BRCA2* tested.
§ If *BRCA1* tested.

Table 3. **Referral Screening Tool***

Risk Factor	Breast Cancer at Age ≤50 y	Ovarian Cancer at Any Age
Yourself		
Mother		
Sister		
Daughter		
Mother's side		
Grandmother		
Aunt		
Father's side		
Grandmother		
Aunt		
≥2 cases of breast cancer after age 50 y on the same side of the family		
Male breast cancer at any age in any relative		
Jewish ancestry		

* From reference 16. A patient completes the checklist if she has a family history of breast or ovarian cancer and receives a referral if she checks ≥2 items.

Table 4. **Pedigree Assessment Tool***

Risk Factor	Score†
Breast cancer at age ≥50 y	3
Breast cancer at age <50 y	4
Ovarian cancer at any age	5
Male breast cancer at any age	8
Ashkenazi Jewish heritage	4

* From reference 17. A score of ≥8 is the optimum referral threshold.
† For every family member with a diagnosis of breast or ovarian cancer, including second- or third-degree relatives.

Affected patients- BRCA related cancers?

NCCN Guidelines 2015

- **Individual from a family with known deleterious BRCA1/2 mutation**
- **BrCa ≤ 45y, ≤50y + affected relatives**
- **BrCa in -ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish)**
- **Personal history of invasive OvCa/ FTC/PPC**

Breast cancer -BRCA prevalence

	Prevalence BRCA1/2 %
General BrCa	5
< 35yo	7.8
Ashkenazi Jewish	10.5
Bilateral BrCa	15.5
FH- OvCa	23.2
FH- BrCa & OvCa	39

Malone, Cancer research 2006
King, Science 2003
Nelson et al, Ann Intern Med 2014

Original Investigation

Effect of Oophorectomy on Survival After Breast Cancer in *BRCA1* and *BRCA2* Mutation Carriers

Kelly Metcalfe, PhD; Henry T. Lynch, MD; William D. Foulkes, MBBS, PhD; Nadine Tung, MD; Charmaine Kim-Sing, MD; Olufunmilayo I. Olopade, MBBS; Andrea Eisen, MD; Barry Rosen, MD; Carrie Snyder, MSN; Shelley Gershman, RN; Ping Sun, PhD; Steven A. Narod, MD

JAMA Oncol. 2015;1(3):306-313.

Table 5. Hazard Ratios (HRs) Associated With Oophorectomy by Gene (*BRCA1* vs *BRCA2*), by Various Subgroups

Subgroup	No.	Univariate HR (95% CI)	Univariate *P* Value	Multivariate[a] HR (95% CI)	Multivariate[a] *P* Value
***BRCA1* Carriers**					
All *BRCA1* carriers	411	0.36 (0.19-0.68)	.002	0.38 (0.19-0.77)	.007
Age at diagnosis, y					
<50	358	0.40 (0.20-0.77)	.006	0.46 (0.22-0.97)	.04
≥50	53	0.22 (0.03-1.74)	.15	0.07 (0.01-0.86)	.04
Chemotherapy					
Yes	292	0.29 (0.13-0.66)	.003	0.27 (0.11-0.68)	.005
No	112	0.58 (0.20-1.72)	.32	0.52 (0.15-1.86)	.32
Stage					
I	179	0.22 (0.07-0.76)	.02	0.17 (0.04-0.64)	.02
II	232	0.47 (0.23-0.99)	.05	0.47 (0.21-1.07)	.07
Estrogen receptor status					
Negative	221	0.06 (0.01-0.43)	.005	0.07 (0.01-0.54)	.01
Positive	74	0.50 (0.16-1.53)	.22	0.62 (0.14-2.66)	.52
Missing	116	0.92 (0.36-2.37)	.86	0.79 (0.27-2.30)	.66
***BRCA2* Carriers**					
All *BRCA2* carriers	254	0.70 (0.32-1.52)	.36	0.57 (0.23-1.43)	.23
Age at diagnosis, y					
<50	191	0.63 (0.25-1.56)	.32	0.49 (0.17-1.45)	.20
≥50	63	0.99 (0.21-4.73)	.99	1.16 (0.15-9.19)	.89
Chemotherapy					
Yes	147	0.59 (0.22-1.62)	.31	0.37 (0.11-1.26)	.11
No	102	0.82 (0.23-2.95)	.86	0.47 (0.09-2.39)	.36
Stage					
I	112	1.04 (0.32-3.35)	.85	0.53 (0.13-2.17)	.37
II	142	0.50 (0.17-1.48)	.21	0.45 (0.13-1.62)	.22
Estrogen receptor status					
Negative	41	0 (0.00-unlimited)	.99	0 (0.00-unlimited)	.99
Positive	150	0.84 (0.34-2.07)	.70	0.86 (0.29-2.56)	.79
Missing	63	0.53 (0.07-4.24)	.55	0.42 (0.05-3.81)	.44

Ovarian cancer- BRCA prevalence

	Population n=		Ovarian cancer	BRCA1/2 frequency
Hirsh-Yechezkel, 2003 Israel	896 Ashkenazi Jewish	3 founder mutation	779 invasive 117 BOT	Invasive- 29.4% BOT- 4%
Malander, 2004 Sweden	161 unselected	PTT and DHPLC	All invasive	Overall- 11% Serous- 18%
Risch, 2006, Canada	977 unselected	PTT and DHPLC	All invasive	Overall- 13.2%
Soegaard, 2008 Denmark	445 unselected	Sequencing and MLPA	All invasive	Overall -6%
Alosp, 2012 Australia	1001 unselected	Sequencing and MLPA	All invasive nonmucinous	Overall- 14% Serous- 17%

Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing

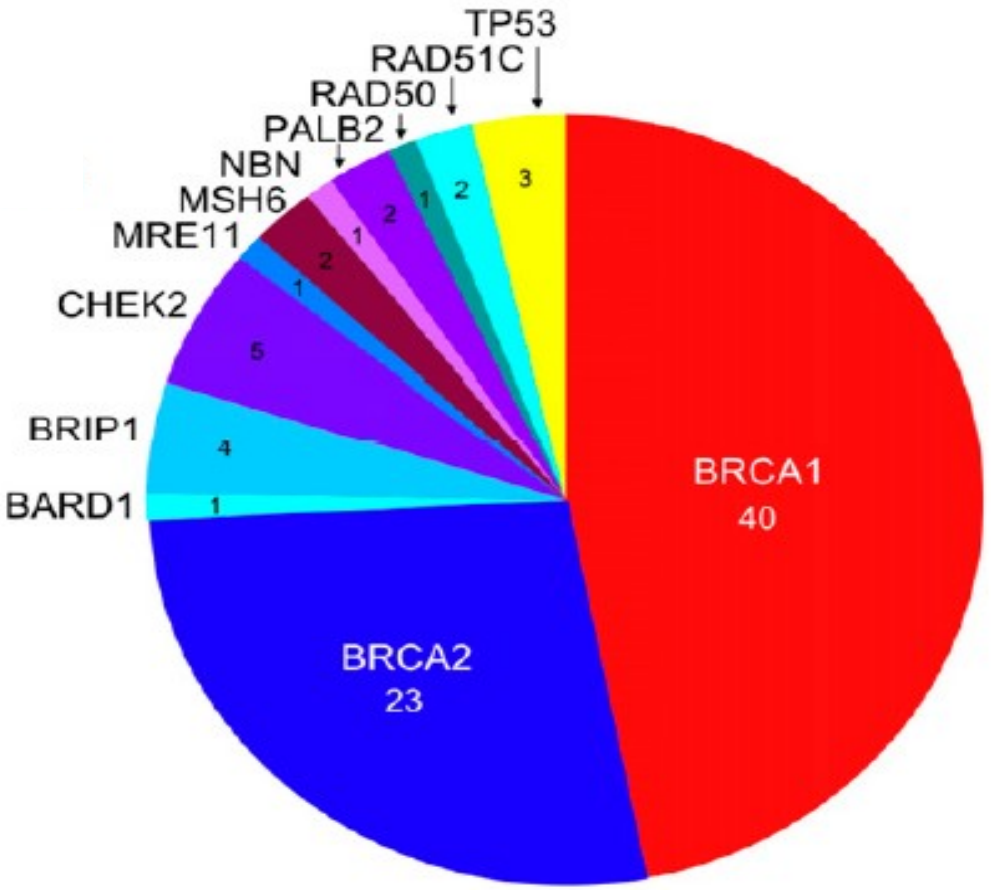
Tom Walsh[a], Silvia Casadei[a], Ming K. Lee[a], Christopher C. Pennil[b], Alex S. Nord[a], Anne M. Thornton[a], Wendy Roeb[a], Kathy J. Agnew[b], Sunday M. Stray[a], Anneka Wickramanayake[b], Barbara Norquist[b], Kathryn P. Pennington[b], Rochelle L. Garcia[c], Mary-Claire King[a,1], and Elizabeth M. Swisher[a,b,1]

PNAS | November 1, 2011 |

24% (85/360) of OvCa pts carried germ line loss-of function mutation

BRCA1/2- 18%

Other - 6%



General population testing?

Annals of Internal Medicine

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

RISK ASSESSMENT, GENETIC COUNSELING, AND GENETIC TESTING FOR BRCA-RELATED CANCER IN WOMEN
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Women who have not been diagnosed with BRCA-related cancer and who have no signs or symptoms of the disease	
Recommendation	Screen women whose family history may be associated with an increased risk for potentially harmful BRCA mutations. Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. Grade: B	Do not routinely recommend genetic counseling or BRCA testing to women whose family history is not associated with an increased risk for potentially harmful BRCA mutations. Grade: D

Does family history predict BRCA1/2 mutation?

	Population Invasive ovarian cancer N=	BRCA1/2 + With Family history (%)	BRCA1/2 + Without Family history (%)
Soegaard, 2008 Denmark	445	27	54
Risch, 2006 Canada	1171	34	37
Walsh , 2011 USA	360	18% (6%- Non BRCA)	30
Alsop, 2012 Australia	1001	39	44
Song et al, 2014 UK, USA	1862 Invasive OvCa	19	39

30-50% *of BRCA1/2* mutation carriers do not have family history

Population-based screening for breast and ovarian cancer risk due to *BRCA1* and *BRCA2*

Efrat Gabai-Kapara[a,b,1], Amnon Lahad[b,c,1], Bella Kaufman[d], Eitan Friedman[e,f], Shlomo Segev[g], Paul Renbaum[a], Rachel Beeri[a], Moran Gal[a], Julia Grinshpun-Cohen[a], Karen Djemal[h], Jessica B. Mandell[i], Ming K. Lee[i], Uziel Beller[j], Raphael Catane[d], Mary-Claire King[i,2], and Ephrat Levy-Lahad[a,b,2]

PNAS, 2014

8195 AJ healthy men

Tested- 3 common mutation in BRCA1/2

- **50% of families with BRCA1/2 mutation, had no significant family history**

Population Testing for Cancer Predisposing BRCA1/BRCA2 Mutations in the Ashkenazi-Jewish Community: A Randomized Controlled Trial

JNCI J Natl Cancer Inst (2015) 107(1)

Ranjit Manchanda, Kelly Loggenberg, Saskia Sanderson, Matthew Burnell, Jane Wardle, Sue Gessler, Lucy Side, Nyala Balogun, Rakshit Desai, Ajith Kumar, Huw Dorkins, Yvonne Wallis, Cyril Chapman, Rohan Taylor, Chris Jacobs, Ian Tomlinson, Alistair McGuire, Uziel Beller, Usha Menon, Ian Jacobs

1034 AJ pts- Randomized – Family History, Population Screening

- **No Diff. -anxiety, depression, distress, QL**
- **56% of carriers no sig. FH**

Absence of population-wide screening – these BRCA mutation carriers would not been identified

Cancer risk in BRCA1/2 mutation carriers that were identified via PS?

Table 1. Cumulative incidence of breast or ovarian cancer among women with mutations in *BRCA1* or *BRCA2*, ascertained via unaffected males

	To age, y	*BRCA1* (SE)	*BRCA2* (SE)
Risk of breast cancer			
	30	0.02 (0.02)	0
	40	0.17 (0.04)	0.04 (0.03)
	50	0.35 (0.06)	0.09 (0.05)
	60	0.41 (0.06)	0.26 (0.08)
	70	0.52 (0.08)	0.32 (0.09)
	80	0.60 (0.10)	0.40 (0.11)
Risk of ovarian cancer			
	40	0	0
	50	0.05 (0.03)	0.03 (0.03)
	60	0.27 (0.07)	0.07 (0.05)
	70	0.47 (0.10)	0.13 (0.07)
	80	0.53 (0.11)	0.62 (0.18)
Risk of either breast or ovarian cancer			
	30	0.03 (0.02)	0
	40	0.23 (0.05)	0.04 (0.03)
	50	0.41 (0.06)	0.16 (0.06)
	60	0.60 (0.07)	0.33 (0.09)
	70	0.77 (0.07)	0.47 (0.11)
	80	0.83 (0.07)	0.76 (0.13)

Gabai-Kapara et al PNAS, 2014

Population-based screening-
Pros

- **20% of physicians - assed family history for BRCA**
- **35% of high risk families - genetic counseling**
- **The cost of BRCA1/2 testing is dropping**

Mary-Claire King, JAMA 2014

Mary-Claire King, Science 2014

Population-based screening- *Cons*

- **Screen- ~500w - 1 single BRCA1/2 mutation**

  ~800w- 1 OvCa

- **Financial costs**
- **Unclear test results (VUS)**

Potential harms:

- **Unneeded Imaging- mammography**
- **Unneeded biopsies and surgeries**
- **Complications, SE -RR mastectomy/BSO**

Beverly Levine and Karen Steinberg, JAMA 2014

Cost-effectiveness of Population Screening for BRCA Mutations in Ashkenazi Jewish Women Compared With Family History–Based Testing

Ranjit Manchanda, Rosa Legood, Matthew Burnell, Alistair McGuire, Maria Raikou, Kelly Loggenberg, Jane Wardle, Saskia Sanderson, Sue Gessler, Lucy Side, Nyala Balogun, Rakshit Desai, Ajith Kumar, Huw Dorkins, Yvonne Wallis, Cyril Chapman, Rohan Taylor, Chris Jacobs, Ian Tomlinson, Uziel Beller, Usha Menon, Ian Jacobs

JNCI J Natl Cancer Inst (2015) 107(1):

- **Lowered OvCa (0.34%) and BrCa (0.62%)**
- **PS- cost saving -ICER of £2079/QALY**
- **PS is cost-effective compared with current FH policy**

Conclusions

- Cancer prevention will be successful if carriers detected early (30y, RRSO<40y)
- Population screening enables better identification of carriers

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BRCA Testing
Determine Your Risk

Conclusions

- High risk (Unaffected)- **Yes**
- Affected patients- BrCa/OvCa- **Yes**
- General population - **further research**
- **Consider-** general testing in high prevalence populations like AJ

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BRCA Testing
Determine Your Risk