Quesito clinico 2:
Nelle pazienti con early breast cancer BRCA mutate, è opportuno considerare una mastectomia profilattica controlaterale?

SINTESI DELLE EVIDENZE E PROBLEMATICHE EMERSE (DAL GRUPPO DI LAVORO)

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Epidemiology of BC in BRCA1/2 carriers

- 7% of all breast cancers are BRCA1/2
- 3750 patients

  - Luminal 2400

  - TNBC 1350

Courtesy of Laura Cortesi

Contralateral breast cancer in BRCA

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	827	2107	60	28.5 (22.1-36.7)	13 (10-16)
>5-10	618	2071	53	25.6 (19.6-33.5)	23 (20-27)
>10-15	435	1438	33	22.9 (16.3-32.3)	32 (28-36)
>15-20	236	675	17	25.2 (15.7-40.5)	40 (35-45)
>20-45	132	661	10	15.1 (8.1-28.1)	53 (44-62)
BRCA2					
≤5	565	1468	27	18.4 (12.6-26.8)	8 (6-12)
>5-10	476	1543	26	16.9 (11.5-24.8)	16 (12-21)
>10-15	285	880	11	12.5 (6.9-22.6)	21 (17-26)
>15-20	138	355	5	14.1 (5.9-33.8)	26 (20-33)
>20-43	68	290	3	10.3 (3.3-32.1)	65 (25-98)

Kuchenbaecker KB et al. JAMA 2017

Quality of the studies

- Lack of randomized studies
- Retrospective studies
- Eterogeneity

Mastectomy or no mastectomy

- ✓ Controlateral mastectomy discussion
  - Pro/contra of controlateral mastectomy
    - Effects on controlateral BC
    - Effects on breast cancer specific mortality
    - Effects on a potential adj chemotherapy/…
- ✓ Other prevention tools
  - MNR/Intensive follow up
  - Ooforectomy/tamoxifen

Pro controlateral mastectomy

Prophylactic mastectomy for the prevention of breast cancer: Review of the literature

AVICENNA
-JOURNAL OF MEDICINE-
Sponsored by The Syrian American Medical Society

Table 6: Studies reporting the impact of contralateral mastectomy

Study (author, year)	Population	Main findings
Metcalfe, 2004[97]	BRCA1/2	Decreased occurrence of CBC after PM (HR=0.03; *P*=0.0005)
van Sprundel, 2005[96]	BRCA1/2	Decreased occurrence of CBC after PM (*P*<0.001)
Manning, 2015[44]	BRCA1/2	No newly diagnosed breast cancers
Peralta, 2000[98]	Unilateral BC	Decreased occurrence of CBC after PM (*P*=0.005)
Herrinton, 2005[99]	Unilateral BC	Decreased occurrence of CBC after CPM (HR=0.03; 95% CI=0.006-0.13)
Boughey, 2010[100]	Stage I or II BC and family history	95% decreased risk of CBC (HR=0.05; 95% CI=0.01-0.22; *P*<0.0001)
Babiera, 1997[101]	IFLC	No significant difference in DFS between mastectomy and conservation (*P*=0.98)

BRCA1: Breast cancer 1, BRCA2: Breast cancer 2, CBC: Contralateral breast cancer, PM: Prophylactic mastectomy, HR: Hazard ratio, BC: Breast cancer, CPM: Contralateral prophylactic mastectomy, CI: Confidence interval, IFLC: Infiltrating lobular carcinoma, DFS: Disease free survival

Alaofi R, 2018

Predictive factors of controlateral BC

Contralateral Breast Cancer in *BRCA1* and *BRCA2* Mutation Carriers

Kelly Metcalfe, Henry T. Lynch, Parviz Ghadirian, Nadine Tung, Ivo Olivotto, Ellen Warner, Olufunmilayo I. Olopade, Andrea Eisen, Barbara Weber, Jane McLennan, Ping Sun, William D. Foulkes, and Steven A. Narod

A B S T R A C T

Purpose

To estimate the risk of contralateral breast cancer in *BRCA1* and *BRCA2* carriers after diagnosis and to determine which factors are predictive of the risk of a second primary breast cancer.

Patients and Methods

Patients included 491 women with stage I or stage II breast cancer, for whom a *BRCA1* or *BRCA2*

Predictive factors of controlateral BC

Table 4. Risks of Contralateral Breast Cancer Associated With Selected Factors

Factor	Univariate HR	Univariate 95% CI	Univariate *P*	Multivariate HR	Multivariate 95% CI	Multivariate *P*
BRCA		0.47 to 1.15	.17		0.39 to 1.09	.10
BRCA1	1.0			1.0		
BRCA2	0.73			0.65		
Age, years		0.36 to 1.10	.11		0.45 to 1.51	.52
< 50	1.0			1.0		
> 50	0.63			0.82		
Oophorectomy		0.21 to 0.91	.03		0.18 to 0.90	.03
No	1.0			1.0		
Yes	0.44			0.41		
Chemotherapy		0.68 to 1.55	.90		0.68 to 1.70	.74
No	1.0			1.0		
Yes	1.03			1.08		
Radiotherapy		0.51 to 1.16	.21		0.56 to 1.34	.51
No	1.0			1.0		
Yes	0.77			0.86		
Tamoxifen		0.35 to 1.01	.05		0.34 to 1.14	.12
No	1.0			1.0		
Yes	0.59			0.62		

NOTE. Multivariate estimates are adjusted for age, mutation (*BRCA1* or *BRCA2*), and other treatments. Analyses restricted to 336 women with intact contralateral breast.

Abbreviation: HR, hazard ratio.

Oophorectomy and controlateral BC

Bilateral Oophorectomy and Breast Cancer Risk in *BRCA1* and *BRCA2* Mutation Carriers

Table 4. Bilateral oophorectomy and risk of breast cancer, stratified by BRCA mutation status and by age at diagnosis

Variable	Age-adjusted HR (95% CI)	P	Multivariable* HR (95% CI)	P
All women				
BRCA1† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.96 (0.73 to 1.26)	.76	0.97 (0.73 to 1.29)	.85
BRCA2† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.65 (0.37 to 1.16)	.14	0.68 (0.38 to 1.21)	.19
Breast cancer diagnosed prior to age 50 y§				
BRCA1† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.79 (0.55 to 1.13)	.51	0.84 (0.58 to 1.21)	.34
BRCA2† mutation carriers				
Oophorectomy‡				
No	1.00 (Referent)		1.00 (Referent)	
Yes	0.18 (0.05 to 0.63)	.007	0.17 (0.05 to 0.61)	.006

Oophorectomy was associated with a statistically significant 82% reduction in breast cancer diagnosed prior to age 50 years among women with a BRCA2 mutation.

Kotsopoulos J, et al. JNCI 2017

But…oophorectomy and controlateral BC

VHIO
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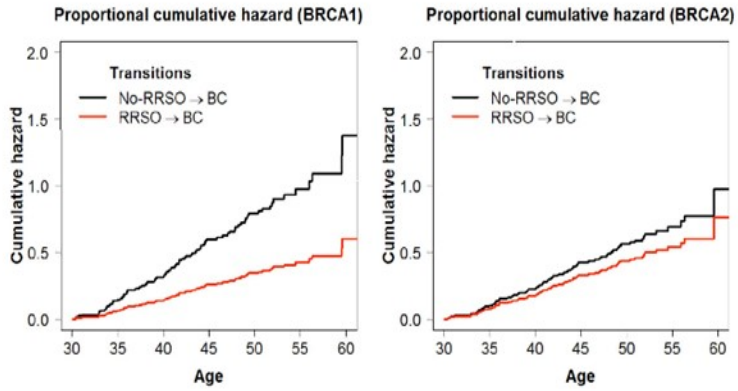
IMPACT OF PREMENOPAUSAL RRSO ON BREAST CANCER RISK IN *BRCA1/2* MUTATION CARRIERS: MAXIMIZING BIAS-REDUCTION

Neda Stjepanovic[1], Guillermo Villacam
Lupe Gomez[4], Katherine L Nathanson
Teresa Ramon y Cajal[7], Gemma Llort[8],
Montserrat Rue[9], Susan Domchek[2,3], J



PREMENOPAUSAL RRSO AND BC RISK

	N	HR (CI 95%)	P-value
Total population	853	0.57 (0.32 – 1.00)	0.05
BRCA1 carriers	444	0.45 (0.22 – 0.92)	0.03
BRCA2 carriers	409	0.77 (0.35 – 1.67)	0.51

SENSITIVITY ANALYSIS (Censoring at age 51)

PREMENOPAUSAL RRSO AND PREMENOPAUSAL BC RISK

	N	HR (CI 95%)	P-value
Total population	853	0.54 (0.29-1.00)	0.05
BRCA1 carriers	444	0.35 (0.15-0.82)	0.02
BRCA2 carriers	409	0.88 (0.39-1.96)	0.75

Conclusions

- Our bias-reducing analysis suggests that premenopausal RRSO significantly reduces the BC risk in *BRCA1* carriers.
- In our cohort *BRCA1* carriers who have not had a premenopausal RRSO showed a trend towards a higher risk of developing BC compared to *BRCA2* carriers.
- A longer follow-up may be needed to estimate the potential benefit of the premenopausal RRSO in *BRCA2* carriers.

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Mastectomy contra

Journal of Plastic, Reconstructive & Aesthetic Surgery (2017) 70, 1191–1199

ELSEVIER

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Review

A systematic review of complications associated with direct implants vs. tissue expanders following Wise pattern skin-sparing mastectomy

Jason Corban [a], Hani Shash [b,c], Tyler Safran [d], Nicolas Sheppard-Jones [d], Omar Fouda-Neel [b,e,*]

Results: A total of 16 articles met the inclusion criteria for this investigation, representing 561 direct-to-implant or two-step breast reconstruction procedures. For direct-to-implant reconstructions, the pooled complication rate was 30%, while for those using tissue expansion, it was 20.3%. Rates of skin flap necrosis (9.70%, 4.69%), delayed wound healing (2.77%, 0.78%), infection (2.54%, 3.91%), seroma (1.15%, 4.68%), and hematoma (0.92%, 0.78%) were calculated for direct-to-implant procedures and two-step tissue expansion, respectively.

Mastectomy contra

The New England Journal of Medicine

VOLUME 336 MARCH 6, 1997 NUMBER 10

COMPLICATIONS LEADING TO SURGERY AFTER BREAST IMPLANTATION

SHERINE E. GABRIEL, M.D., M.Sc., JOHN E. WOODS, M.D., W. MICHAEL O'FALLON, PH.D., C. MARY BEARD, R.N., M.P.H., LEONARD T. KURLAND, M.D., DR.P.H., AND L. JOSEPH MELTON III, M.D.

INDICATION	NO. OF PROCEDURES†	BREASTS OPERATED ON		WOMEN OPERATED ON	
		NO.‡	% OF TOTAL (1454)	NO.§	% OF TOTAL (749)
Clinical					
Capsular contracture	272	212	14.6	131	17.5
Rupture	60	56	3.9	43	5.7
Hematoma	55	51	3.5	43	5.7
Wound infection	23	21	1.4	19	2.5
Wound seroma	17	16	1.1	16	2.1
Extrusion of implant	15	14	1.0	14	1.9
Leakage, sweating of implant	14	14	1.0	9	1.2
Chronic pain	13	13	0.9	8	1.1
Necrosis of nipple, areola, or flap	12	12	0.8	11	1.5
Filler-port malfunction	5	5	0.3	5	0.7
Wound dehiscence	5	5	0.3	4	0.5
Other¶	4	4	0.3	4	0.5
Total	359	274	18.8	178	23.8

When patients shoul be tested?

- ✓ Timing of BRCA identification
- ✓ Psychosocial issues:
  - ✓ Role of comunication
  - ✓ Role of previous patient experiences
  - ✓ Patient empowerment

original articles

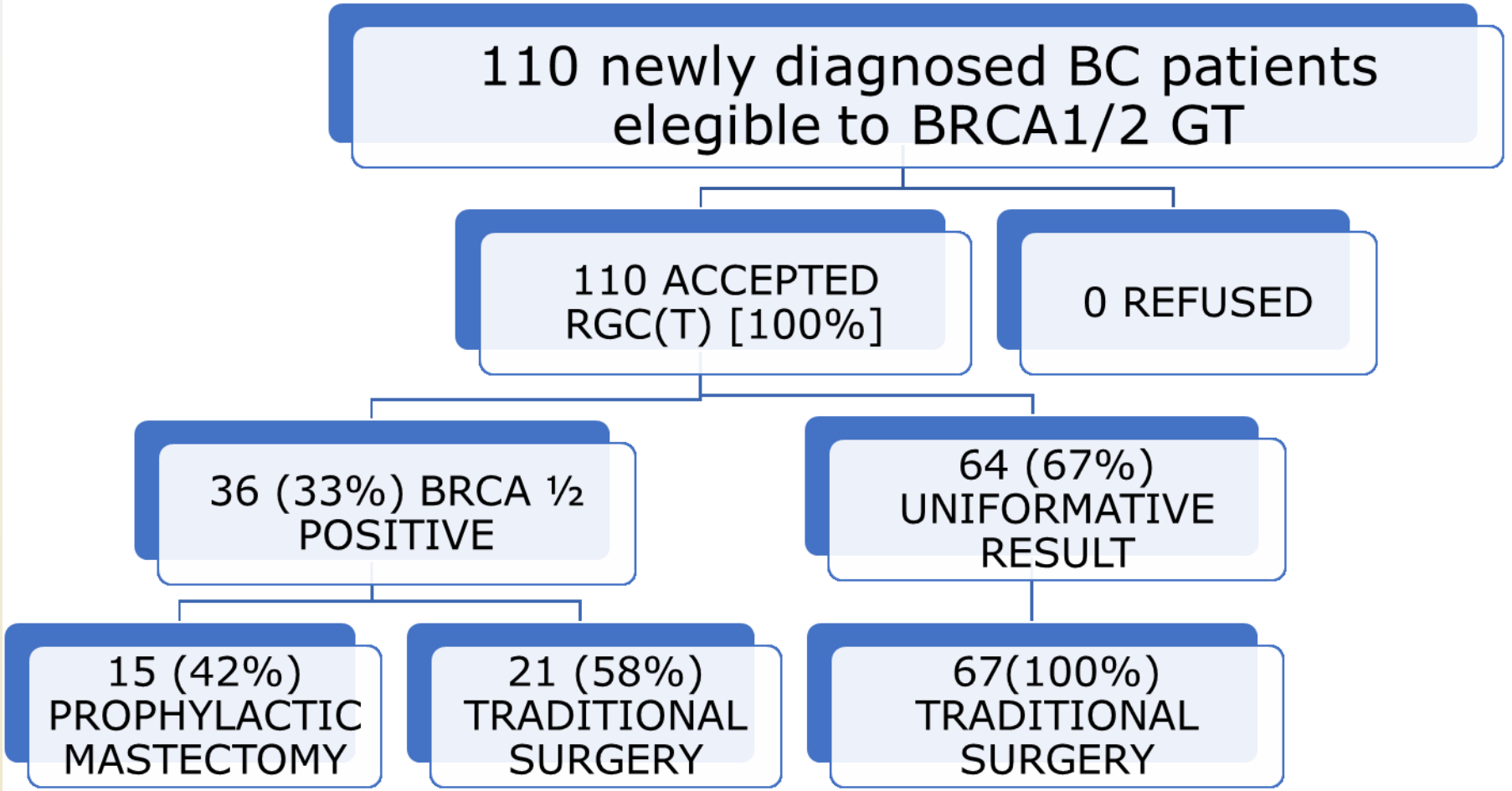
Annals of Oncology 25: 57–63,
doi:10.1093/annonc/m
Published online 24 November

A rapid genetic counselling and testing in newly diagnosed breast cancer is associated with high rate of risk-reducing mastectomy in BRCA1/2-positive Italian women†

L. Cortesi[1]*, E. Razzaboni[1], A. Toss[1], E. De Matteis[1], I. Marchi[1], V. Medici[1], G. Tazzioli[2], A. Andreotti[2], G. De Santis[2], M. Pignatti[2] & M. Federico[1]

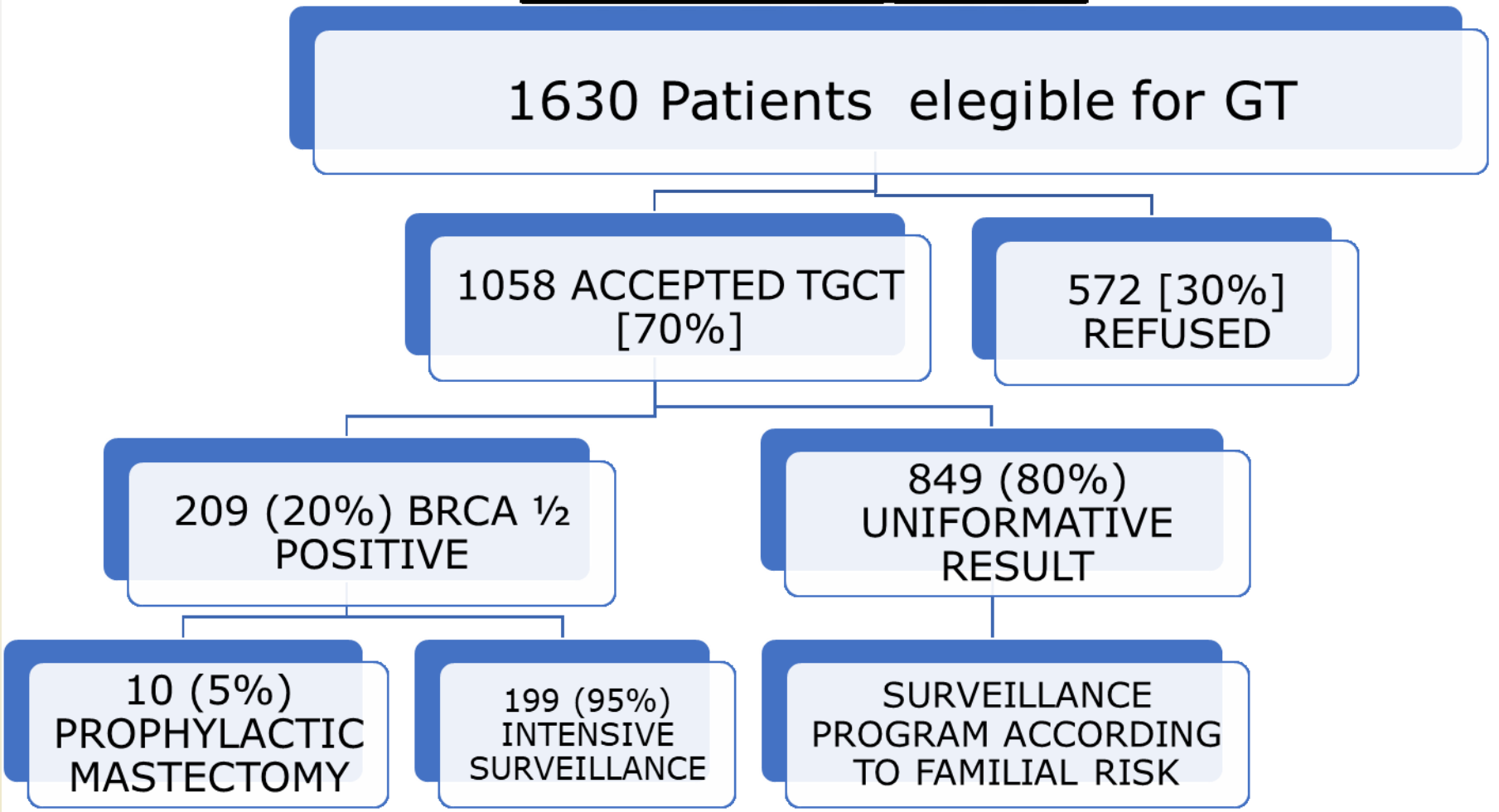
Rapid genetic counselling and testing (RGCT), at the time of BC diagnosis, versus traditional genetic counselling and testing (TGCT)

Results of RGCT



Cortesi et al. Annals of Oncology, 2014

Results of TGCT



Cortesi et al. Annals of Oncology, 2014

Synthesis

- Weak evidences in literature
- Further studies are warrented
- No role for randomized prospective study in this population
- Role for prospective trials, with early test and prespecified follow up, record of surgery, patient's preferences, indications, …