Breast Cancer… from Biology to Surgery

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I herein disclaim any conflict of interest

Marco Bernini

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 Novembre 2009

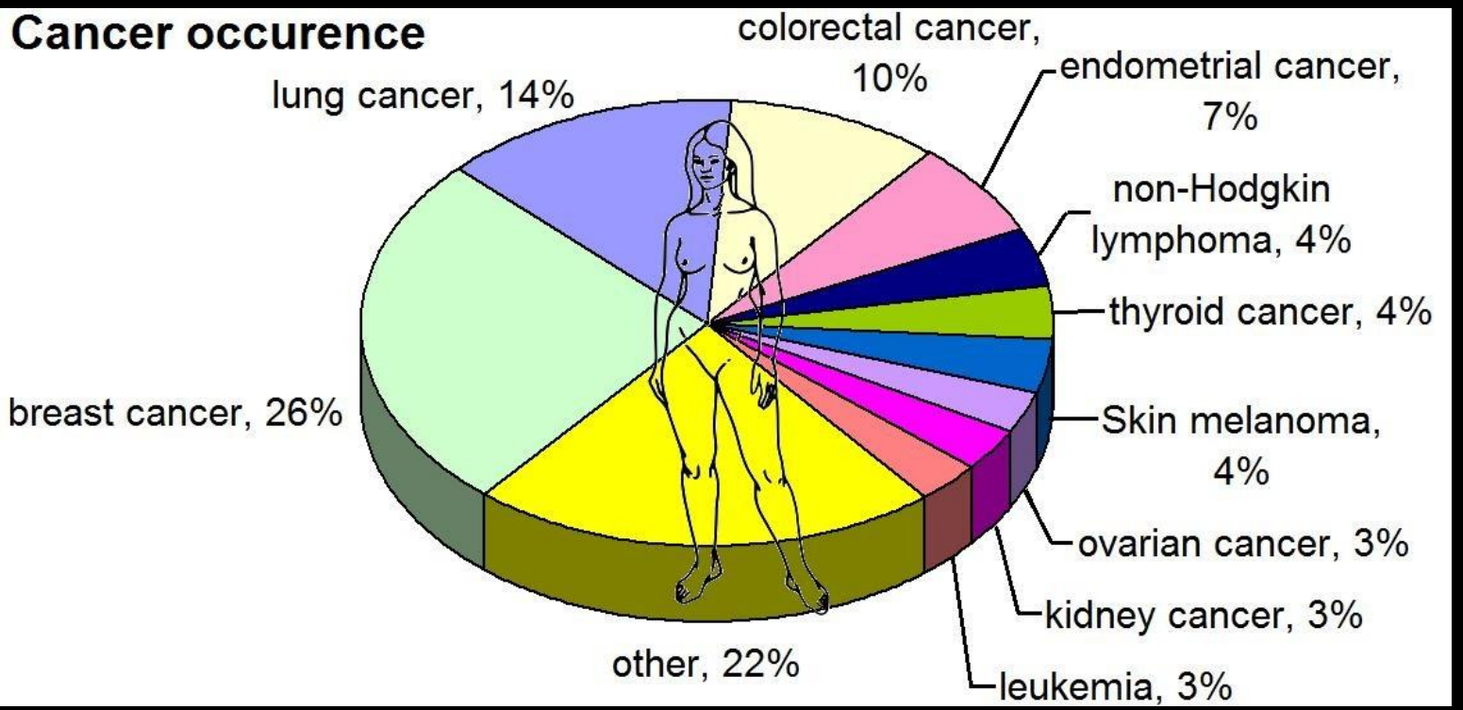
Topics

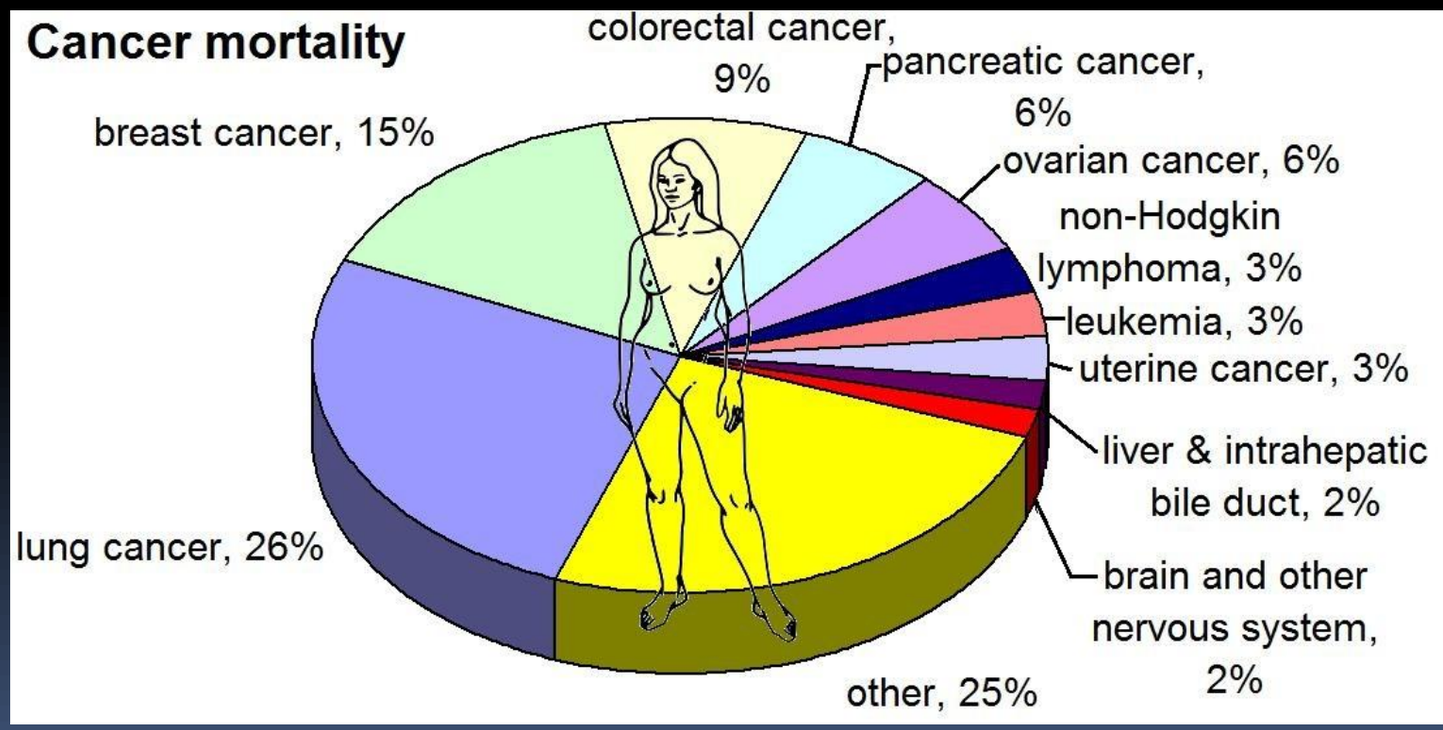
- ✓ **Biology of breast cancer:**
  - × Epidemiology and risk factors
  - × Screening importance
  - × Diagnosis
- ✓ **Cure**
  - × Hot topics:
    - ✓ New developments in breast surgery
    - ✓ BRCA mutations

Topics

- ✓**Biology of breast cancer**

Epidemiology



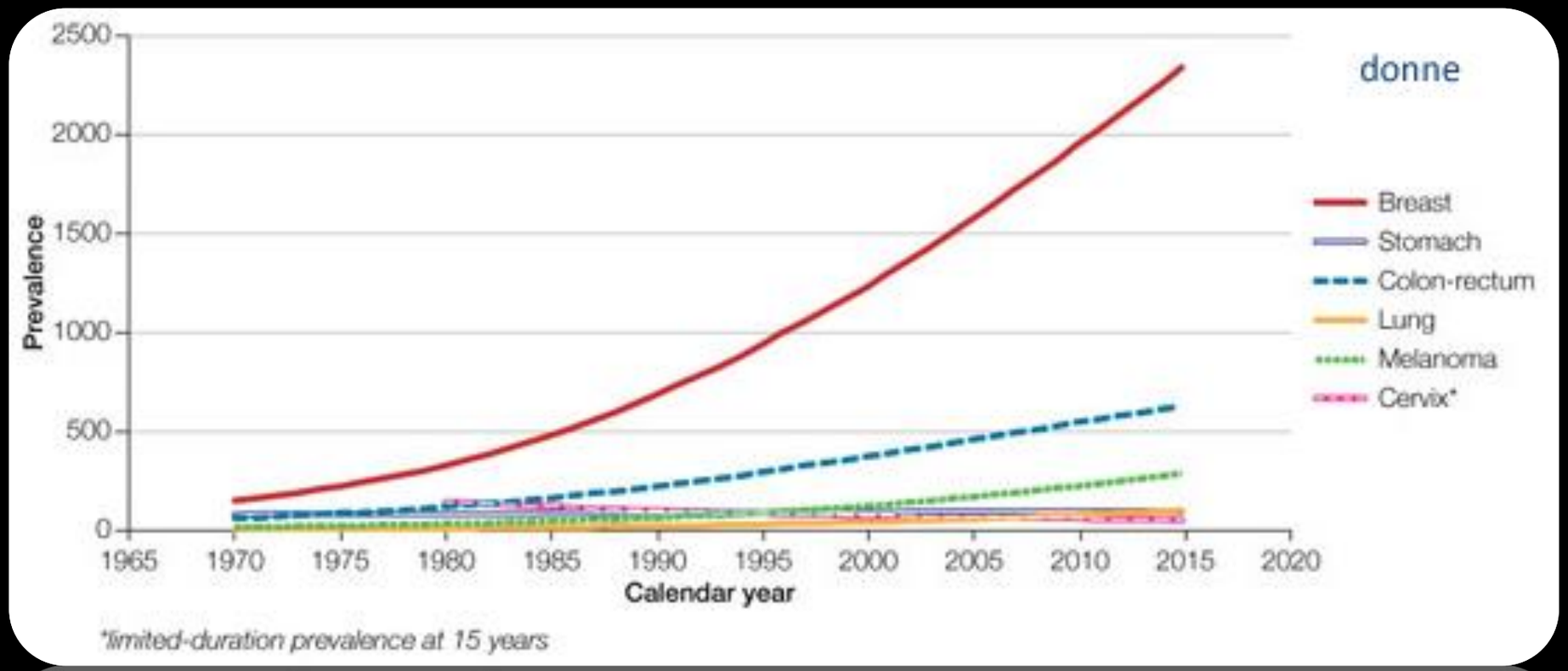


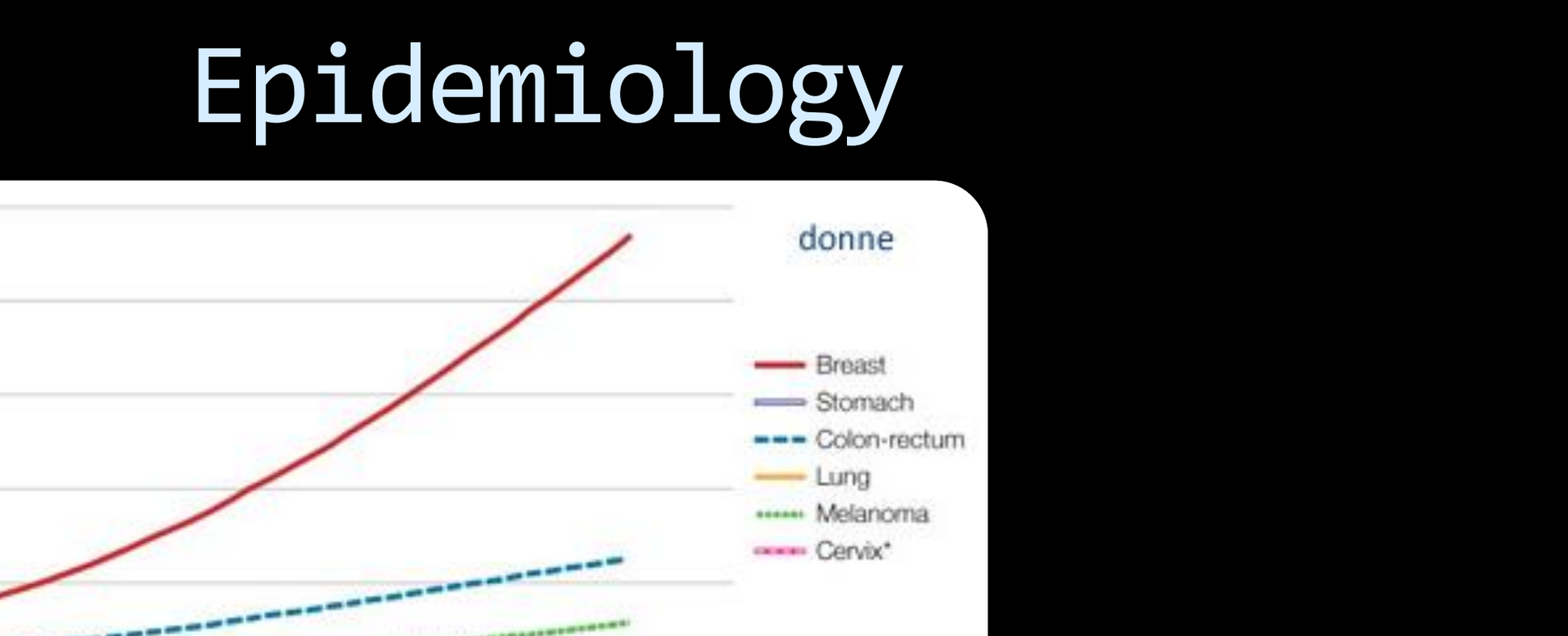
Epidemiology

Rango	♂ Maschi	♀ Femmine	Tutta la popolazione
1°	Prostata (20%)	Mammella (29%)	Mammella (14%)
2°	Polmone (15%)	Colon-retto (13%)	Colon retto (13%)
3°	Colon-retto (14%)	Polmone (6%)	Prostata (11%)
4°	Vescica* (11%)	Tiroide (5%)	Polmone (11%)
5°	Stomaco (5%)	Utero corpo (5%)	Vescica (7%)

TABELLA 4. Primi cinque tumori più frequentemente diagnosticati e proporzione sul totale dei tumori (esclusi i carcinomi della cute) per sesso. Pool Airtum 2007-2011.

Epidemiology





Estimates of cancer burden in Italy. Tumori 2013;99(3):416-424

Epidemiology

	♂ Maschi			♀ Femmine		
Rango	anni 0-49	anni 50-69	anni 70+	anni 0-49	anni 50-69	anni 70+
1°	Testicolo (12%)	Prostata (22%)	Prostata (20%)	Mammella (41%)	Mammella (35%)	Mammella (21%)
2°	Cute (melanomi) (9%)	Polmone (15%)	Polmone (17%)	Tiroide (14%)	Colon-retto (12%)	Colon-retto (17%)
3°	Linfoma non-Hodgkin (9%)	Colon-retto (14%)	Colon-retto (14%)	Cute (melanomi) (7%)	Utero corpo (7%)	Polmone (7%)
4°	Colon-retto (8%)	Vescica* (10%)	Vescica* (12%)	Colon-retto (5%)	Polmone (6%)	Stomaco (6%)
5°	Tiroide (7%)	Vie aerodigestive superiori (5%)**	Stomaco (5%)	Utero cervice (4%)	Tiroide (5%)	Pancreas (6%)

TABELLA 11. Primi cinque tumori in termini di frequenza e proporzione sul totale dei tumori incidenti (esclusi i carcinomi della cute) per sesso e fascia di età. Pool Airtum 2007-2011.

Epidemiology

	♂ Maschi			♀ Femmine		
Rango	anni 0-49	anni 50-69	anni 70+	anni 0-49	anni 50-69	anni 70+
1°	Polmone (15%)	Polmone (30%)	Polmone (27%)	Mammella (29%)	Mammella (23%)	Mammella (16%)
2°	Sist. nervoso centrale (9%)	Colon-retto (10%)	Colon-retto (10%)	Polmone (9%)	Polmone (14%)	Colon-retto (12%)
3°	Colon-retto (8%)	Fegato (8%)	Prostata (8%)	Colon-retto (7%)	Colon retto (10%)	Polmone (11%)
4°	Leucemie (7%)	Pancreas (6%)	Fegato (7%)	Ovaio (6%)	Pancreas (7%)	Pancreas (7%)
5°	Stomaco (6%)	Stomaco (6%)	Stomaco (6%)	Sist. nervoso centrale (6%)	Ovaio (7%)	Stomaco (6%)

TABELLA 7. Prime cinque cause di morte oncologica e proporzione sul totale dei decessi per tumore per sesso e fascia di età. Pool Airtum 2007-2011.

Epidemiology

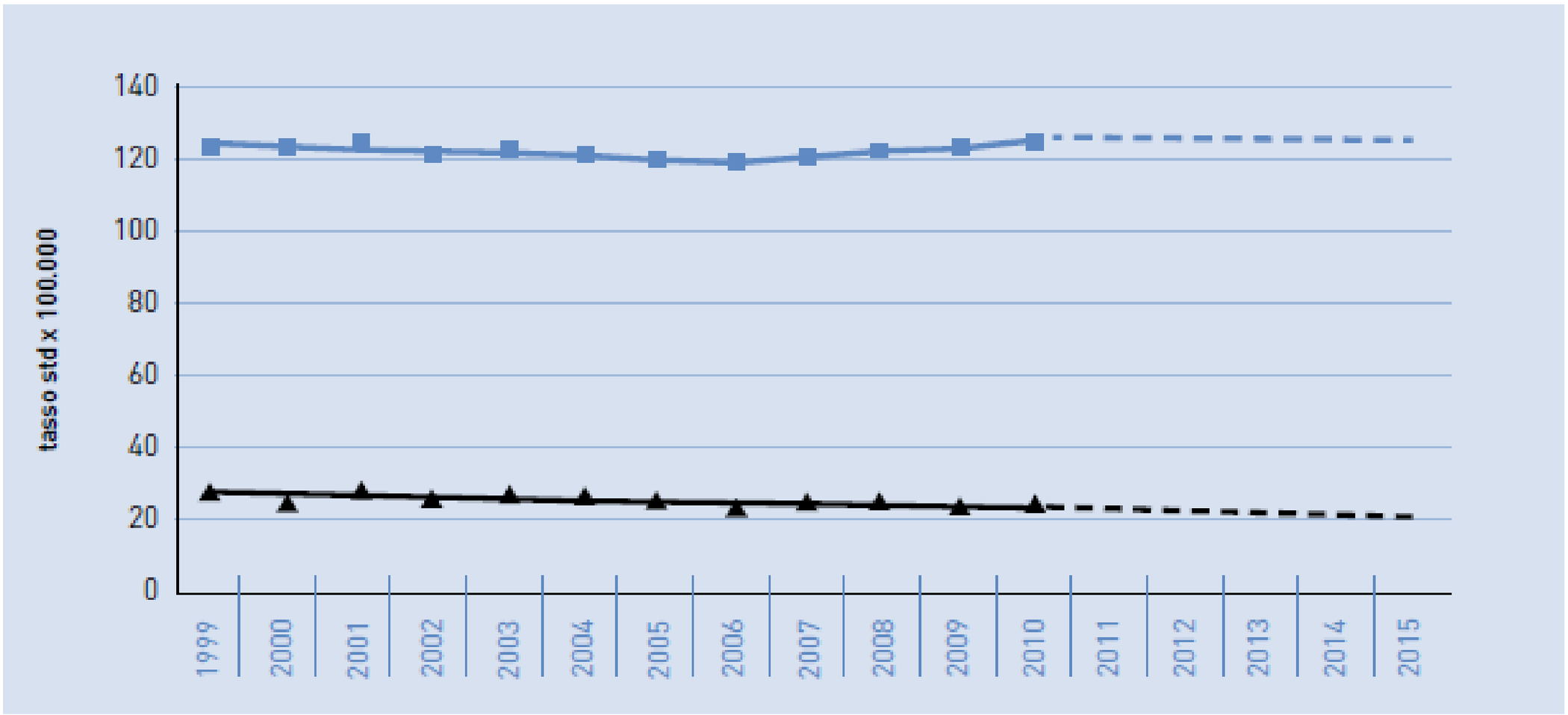


FIGURA 14. Tumore della mammella femminile.

■ I-APC: 1999-2006: –0,5^ (–0,8; –0,1); 2006-2010: 1,0^ (0,2; 1,8) ▲ M-APC: 1999-2010: –1,4^ (–2,1; –0,7)

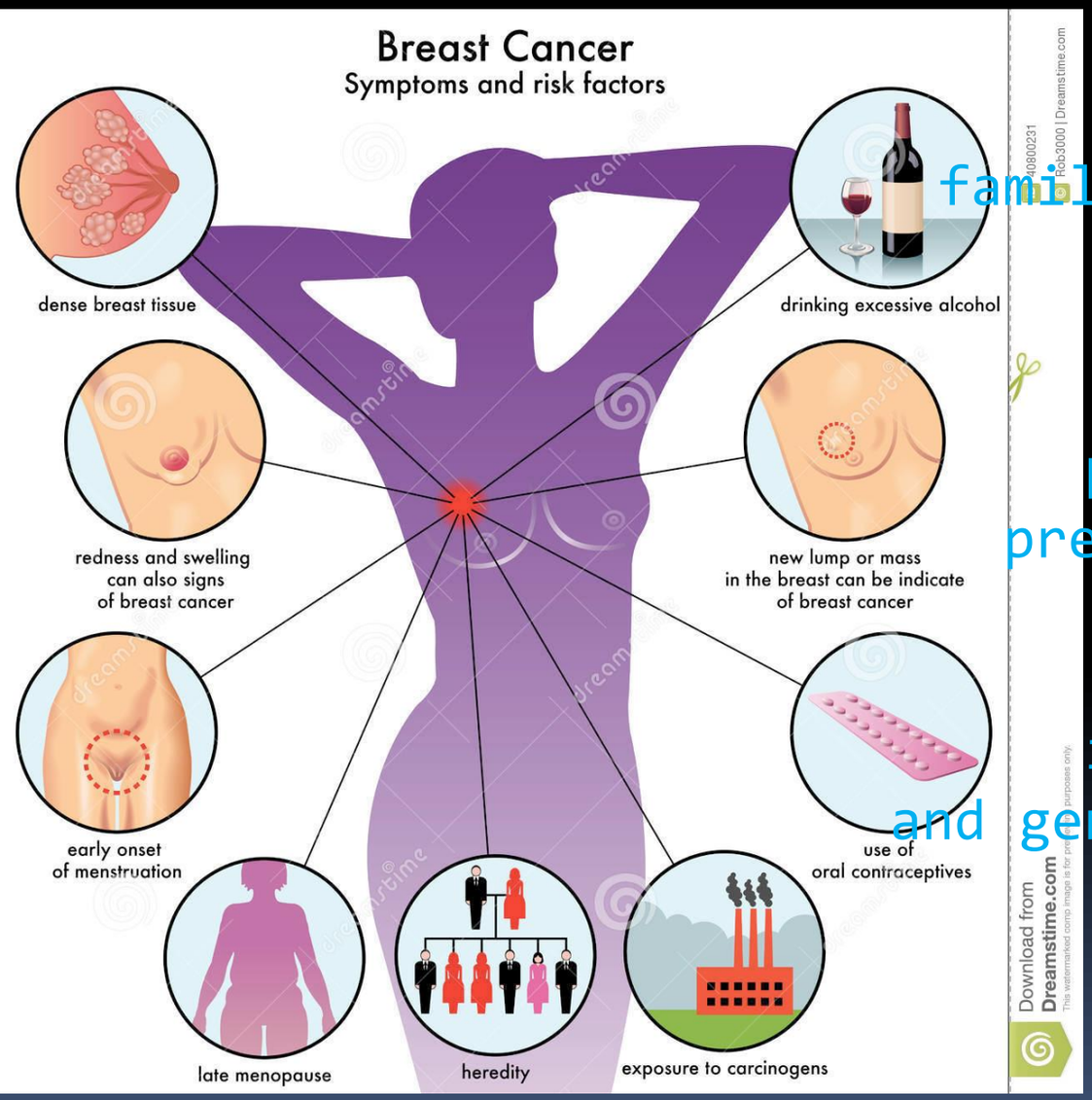
AIRTUM: stima dei trend tumorali di incidenza e mortalità 1999-2015. Tassi standardizzati pop. europea.

APC = Annual Percent Change (Variazione percentuale media annua), I = incidenza, M = mortalità.

Breast Cancer SURVIVAL RATE

- 5-year Overall Survival (OS) rate: 90%
- 5-year Ca in situ: ~100%
- 5-year Stage IV: ~20%

Risk factors



female gender;
increasing patient age;
family history of breast cancer at a young age;
early menarche;
late menopause;
older age at first live childbirth;
prolonged hormone replacement therapy;
previous exposure to therapeutic chest wall irradiation;
benign proliferative breast disease;
increased mammographic breast density;
and genetic mutations such as of the BRCA1/2 genes

Primary prevention

Risk factors

Gail model

Risk assessment tool

Gives you the risk of developing a Breast Cancer in the following 5 years

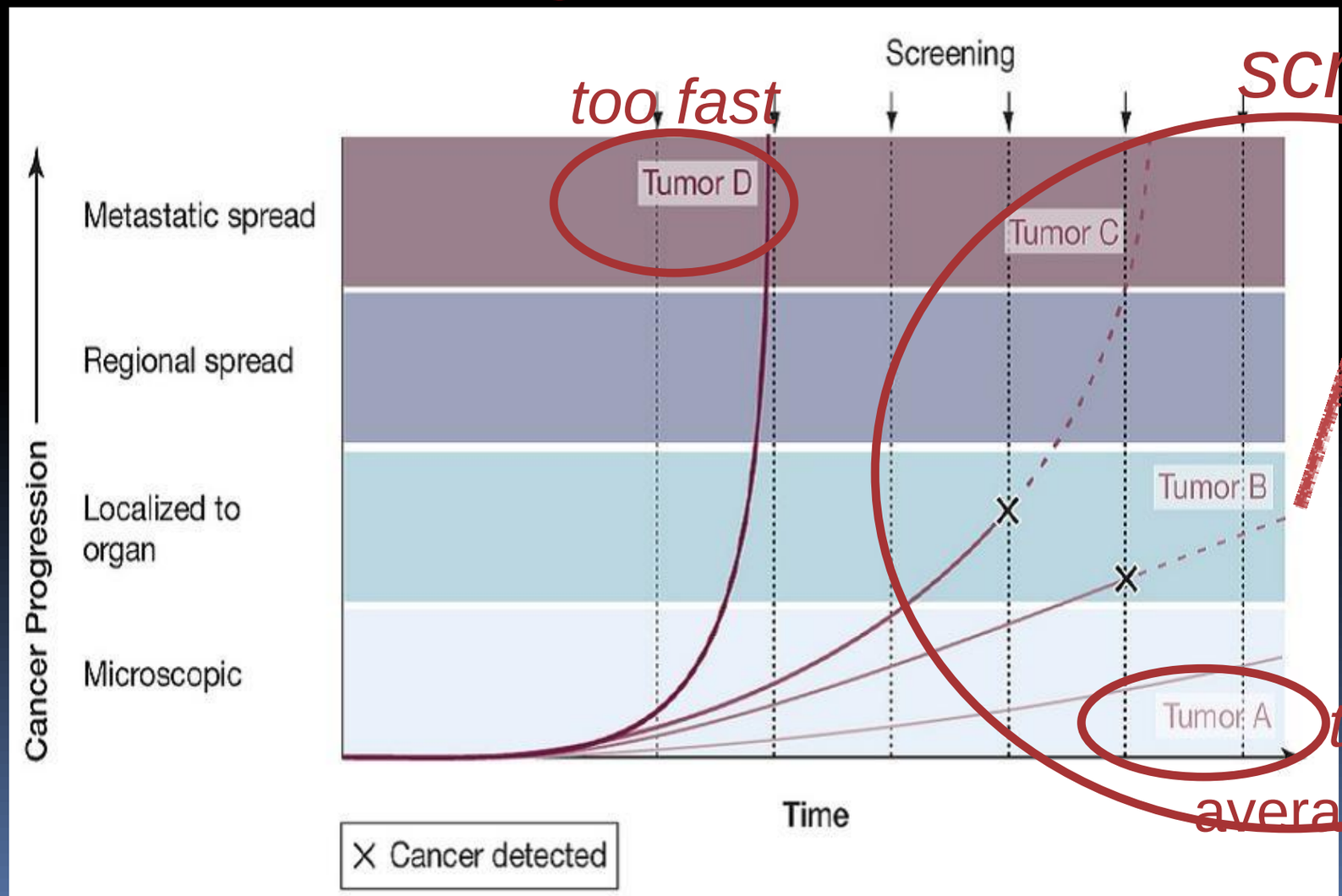
>=1.67%, risk reduction strategies

NCCN guidelines

Screening and Biology of breast cancer

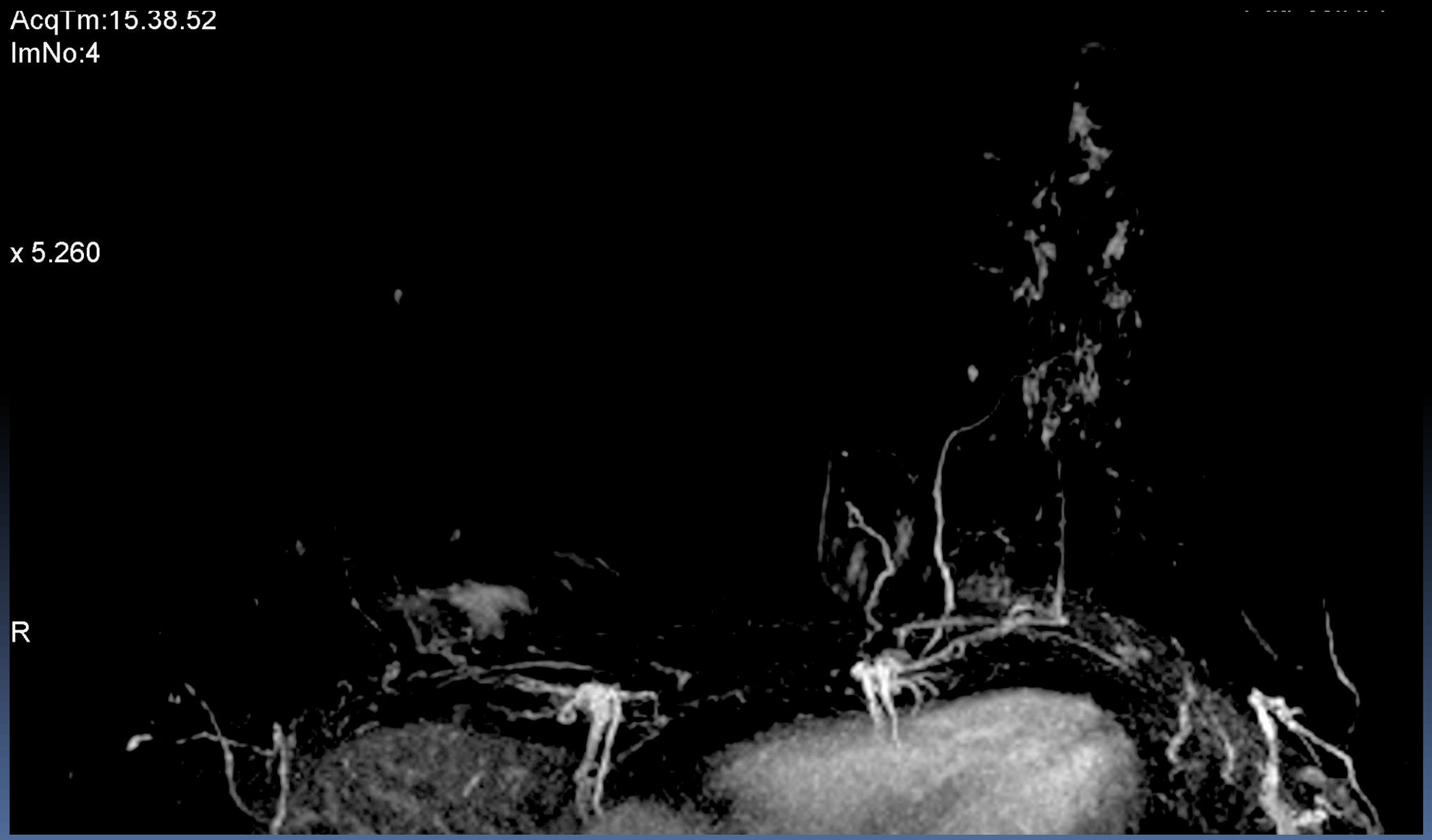
Breast cancer has approximately four patterns of natural history of tumor growth

Secondary prevention



Diagnosis

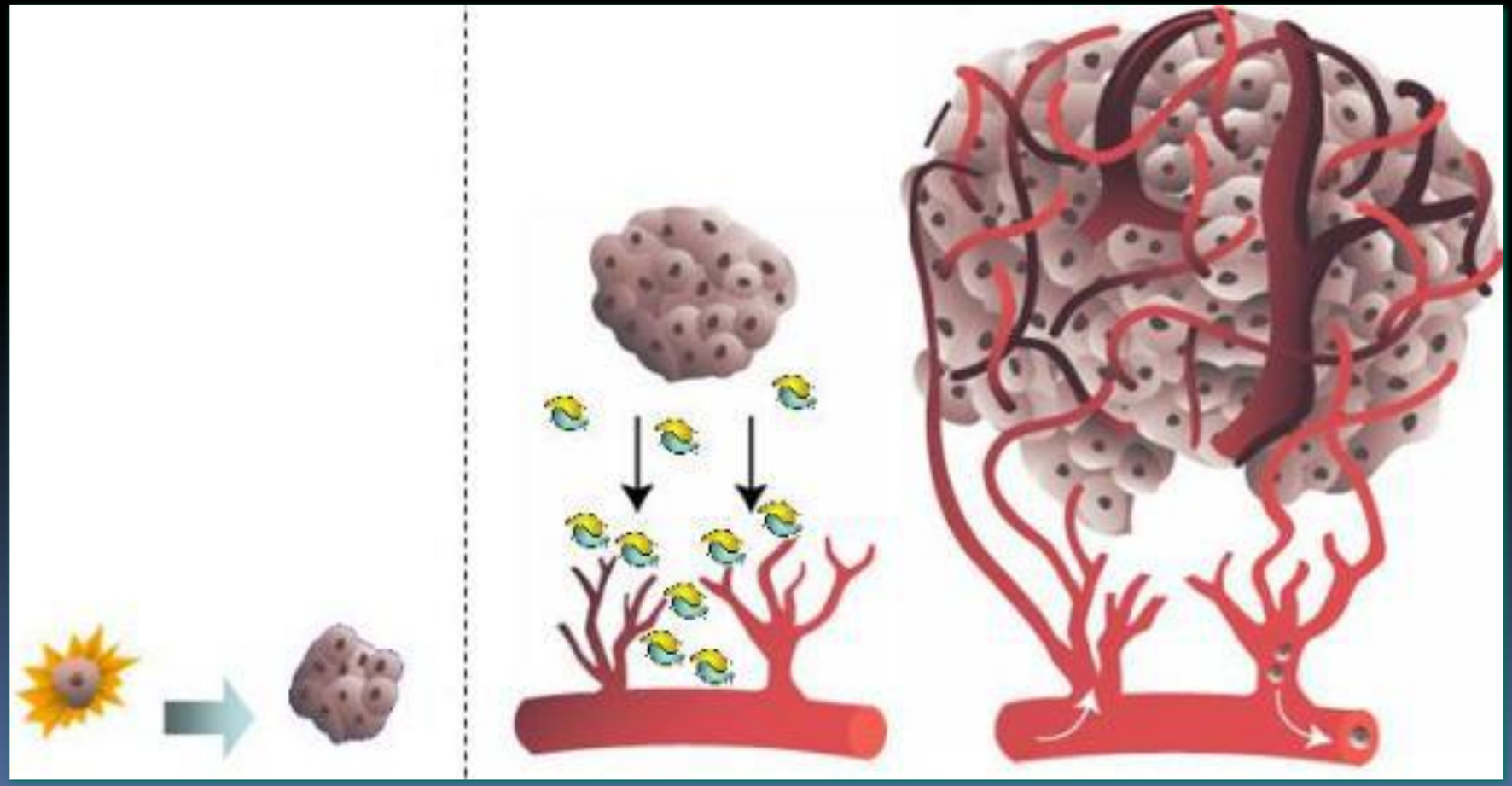
Magnetic Resonance Imaging (MRI)



Diagnosis

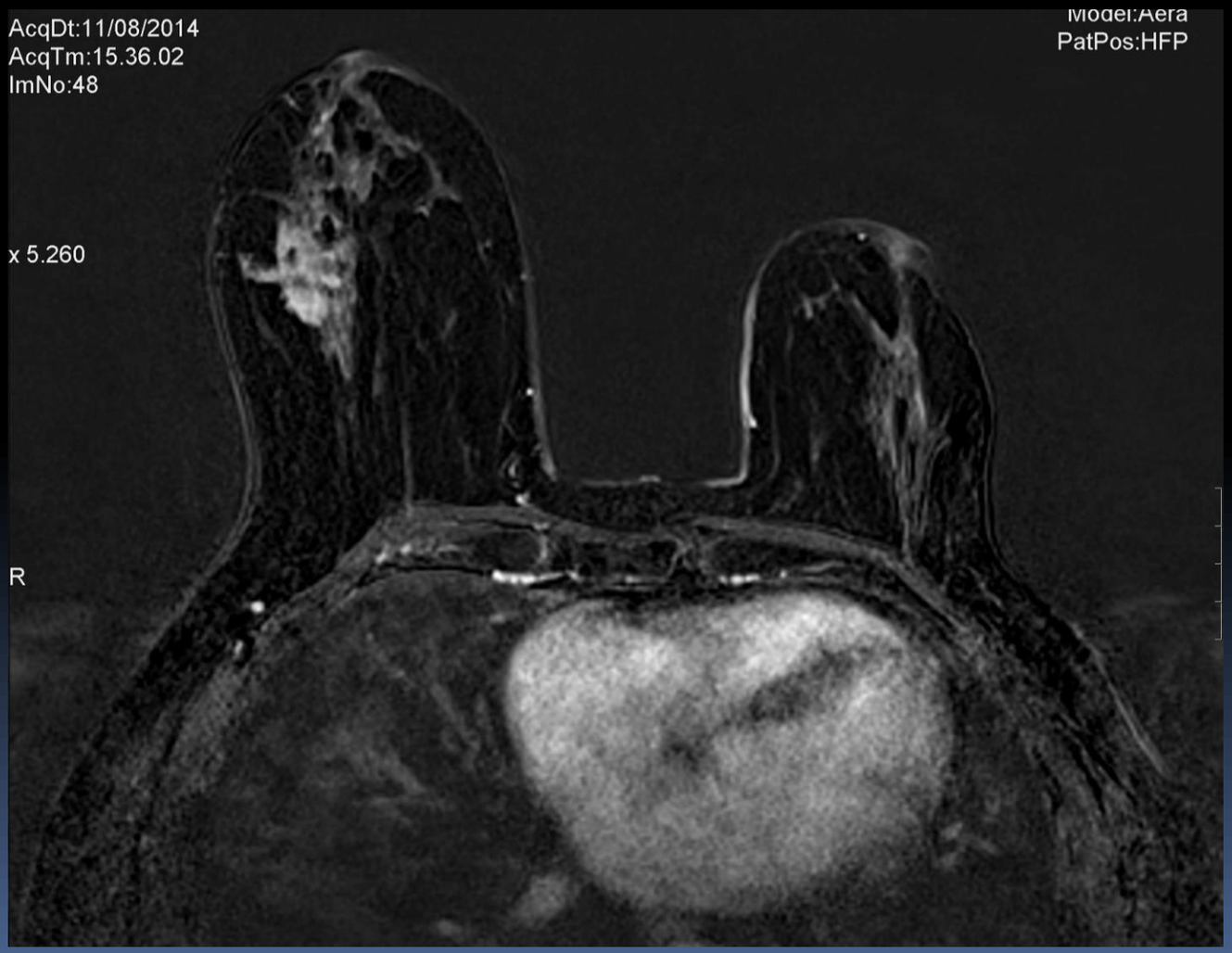
Magnetic Resonance Imaging (MRI)

NEOANGIOGENESIS



Diagnosis

Magnetic Resonance Imaging (MRI)



NEOANGIOGENESIS
is the reason of
contrast enhancement

Cure

BC treatment options

- LOCAL THERAPIES:

  ✓ **Surgery**

  ✓ Radiotherapy

- SYSTEMIC THERAPIES:

  ✓ Hormone therapy

  ✓ Chemotherapy

  ✓ Target therapy

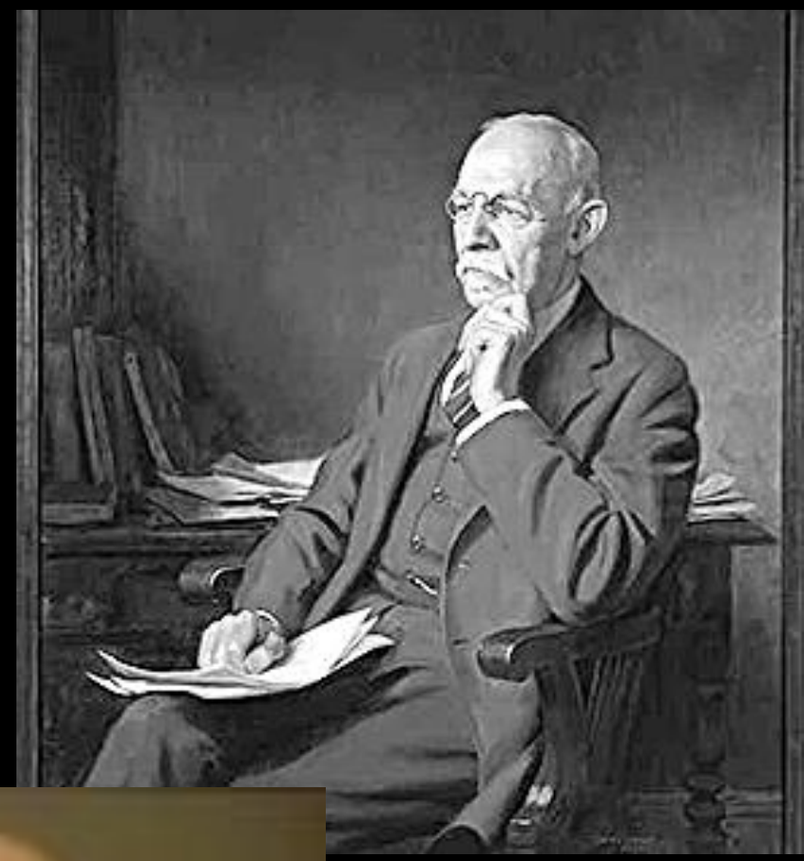
SURGERY

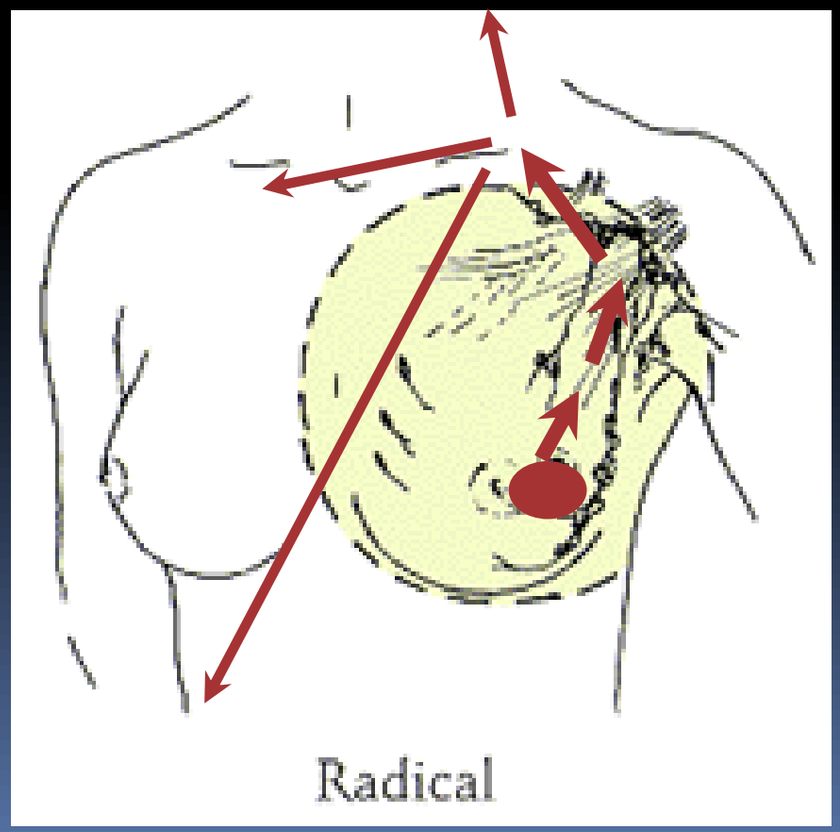
“Breast cancer surgery has become a model for evidence-based cancer therapy, and that can be attributed largely to the work of the NSABP under the leadership of Dr. Bernard Fisher, and also the work of Milan’s Dr. Umberto Veronesi, who led prospective randomized trials that answered probing questions about this disease.”

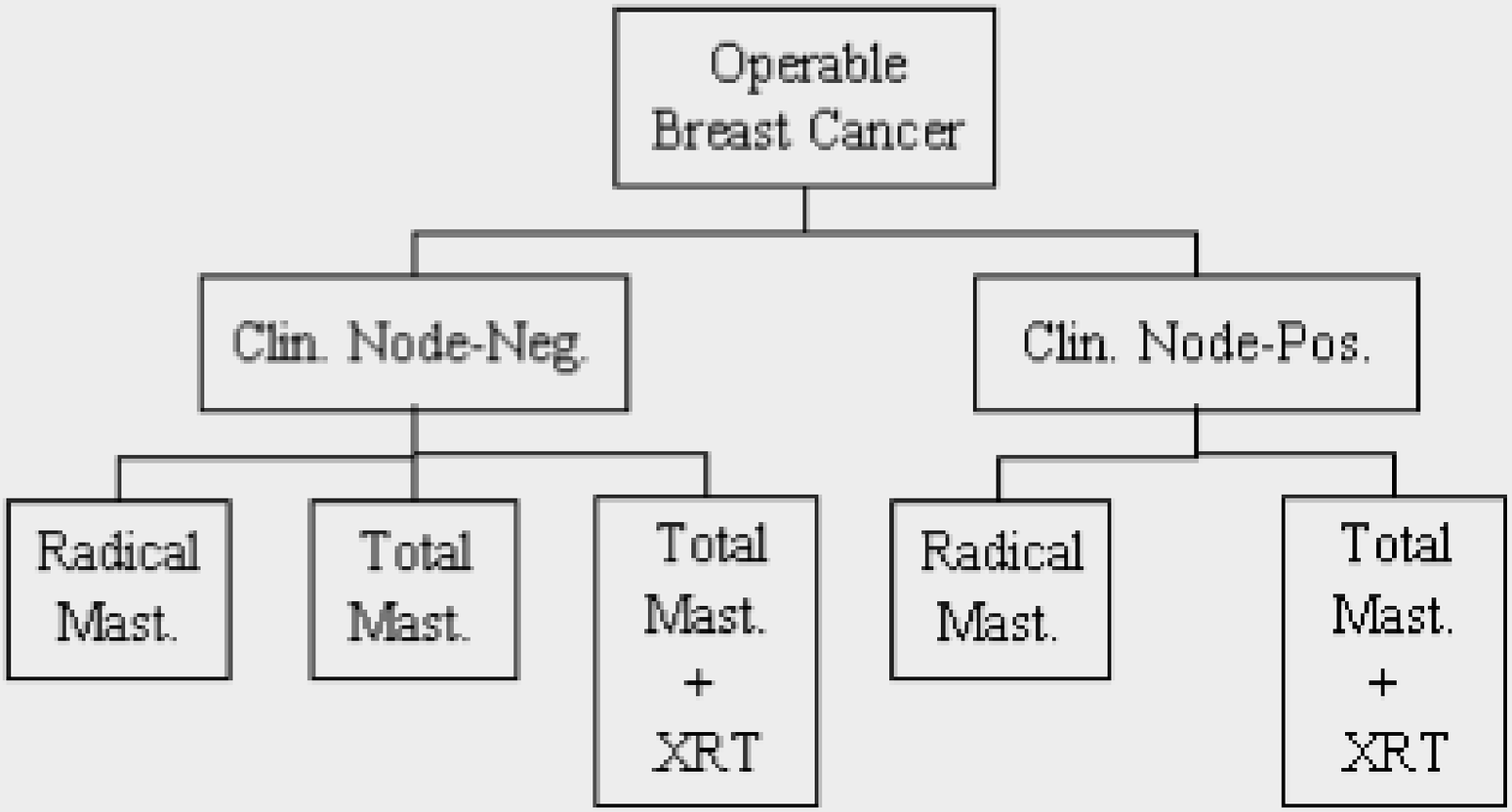
—Monica Morrow, MD, FACS

Halsted theory, radical mastectomy

William Stewart Halsted in 1882. From about 1895 to the mid-1970s about 90% of the women being treated for breast cancer in the U.S. underwent the Halsted radical mastectomy.





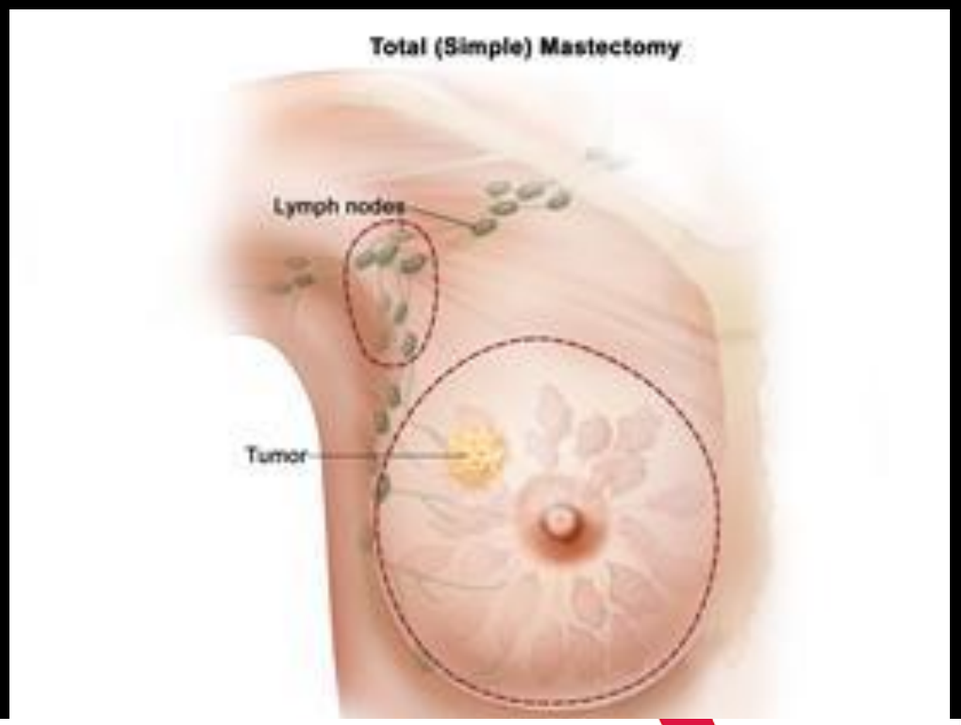


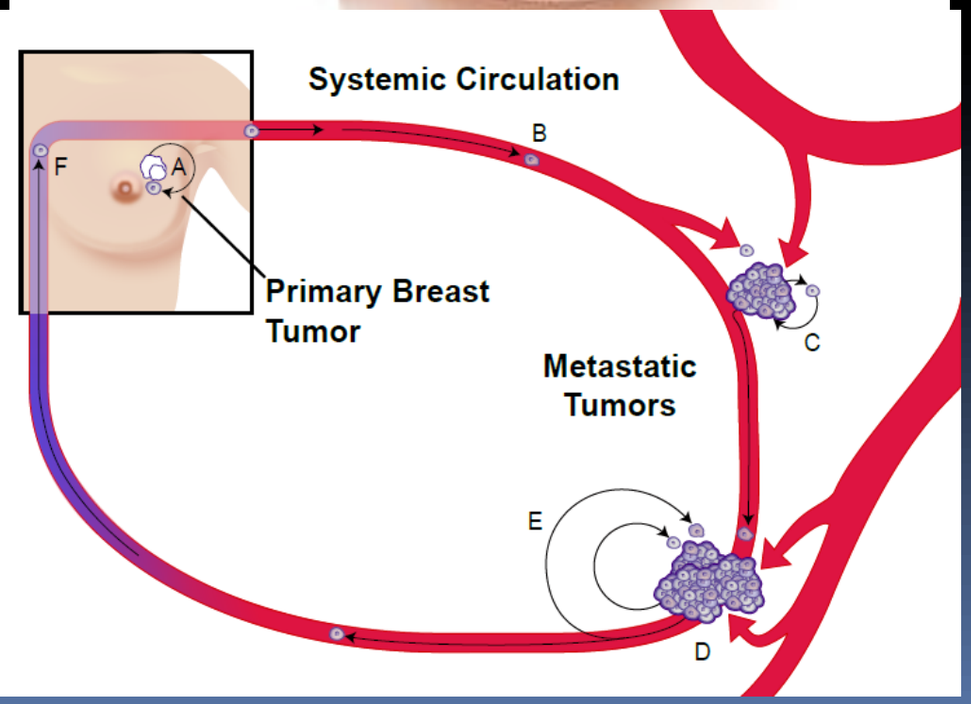
"In 1971 we received 200.000 dollars to conduct the NSABP B-04 trial. In that study, patients were randomly assigned to receive Halsted radical mastectomy, a total (simple) mastectomy or a total mastectomy followed by radiation therapy. In the 25-year follow-up of that study which was published in 2002 in the *New England Journal of Medicine,* the results of the B-04 trial continued to indicate that there was no difference in OS and DFS among the three groups of women "

–Bernard Fisher

Fisher theory, Simple mastectomy

breast cancer is a systemic disease from the very beginning





Veronesi quadrantectomy, Milan I trial

The New England
Journal of Medicine

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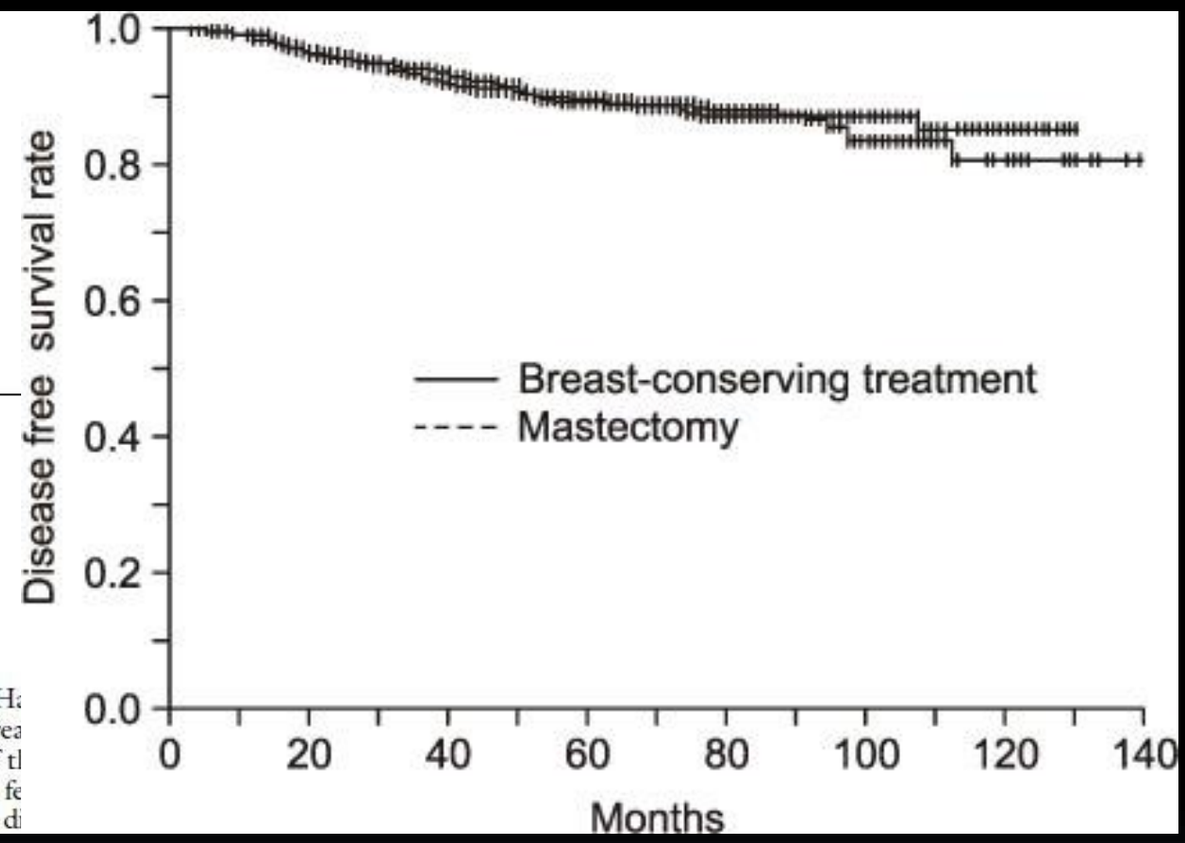
TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED STUDY COMPARING BREAST-CONSERVING SURGERY WITH RADICAL MASTECTOMY FOR EARLY BREAST CANCER

UMBERTO VERONESI, M.D., NATALE CASCINELLI, M.D., LUIGI MARIANI, M.D., MARCO GRECO, M.D., ROBERTO SACCOZZI, M.D., ALBERTO LUINI, M.D., MARISEL AGUILAR, M.D., AND ETTORE MARUBINI, PH.D.

ABSTRACT

Background We conducted 20 years of follow-up of women enrolled in a randomized trial to compare the efficacy of radical (Halsted) mastectomy with that of breast-conserving surgery.

THE radical mastectomy introduced by Ha sted[1] was the treatment of choice for brea cancer of any size or type, regardless of th patient's age, for 80 years. Apart from a fe modifications, such as enlarging the extent of the di



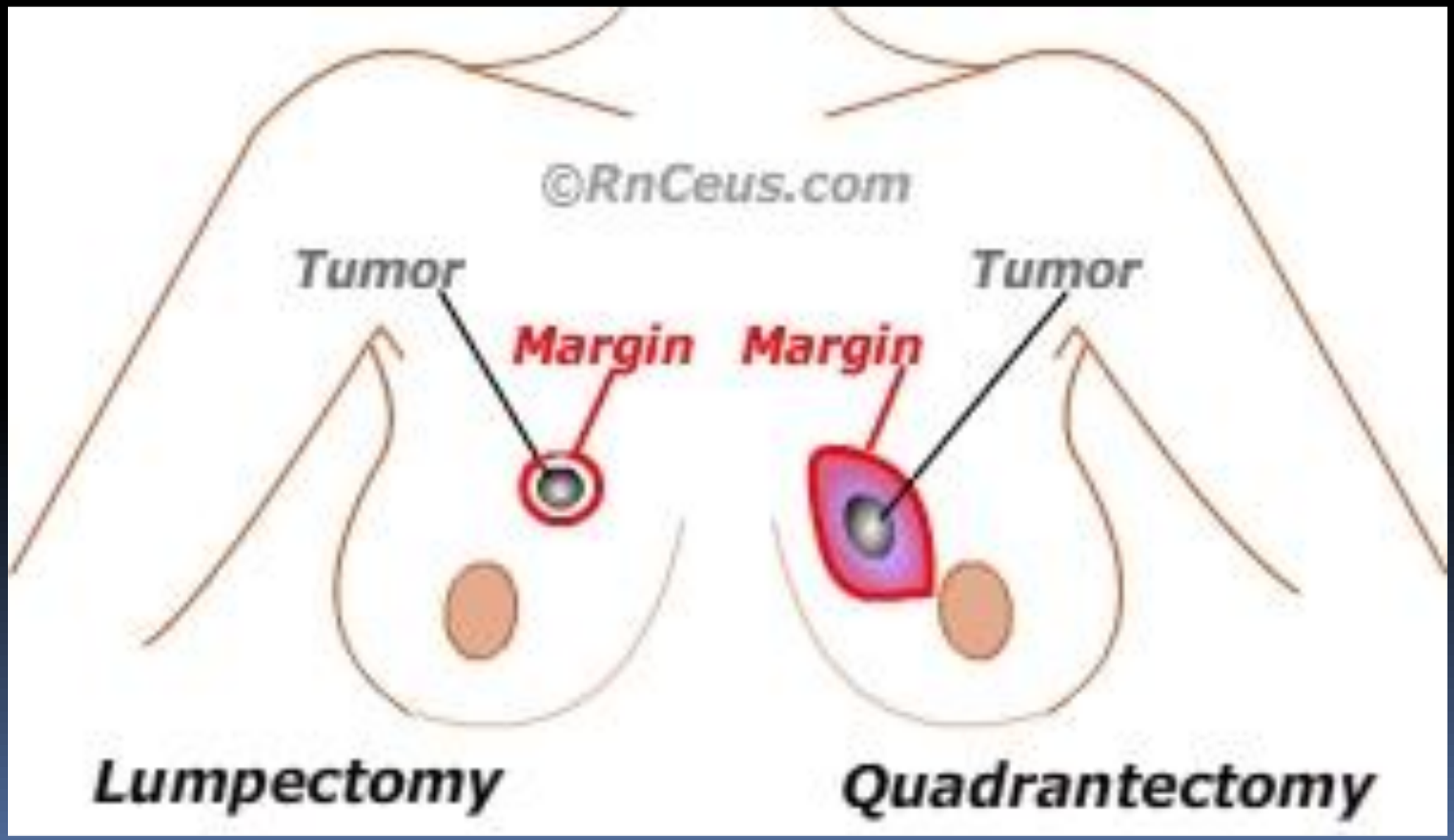
ical mastectomy = quadrantectomy + radiation ther

↓

Breast Conserving Surgery (70% of cases)

SURGERY

Quadrantectomy...lumpectomy + RT



What can a surgeon do to improve QOL?

Tertiary prevention

SURGERY

the answer:

Oncoplastic surgery

SURGERY

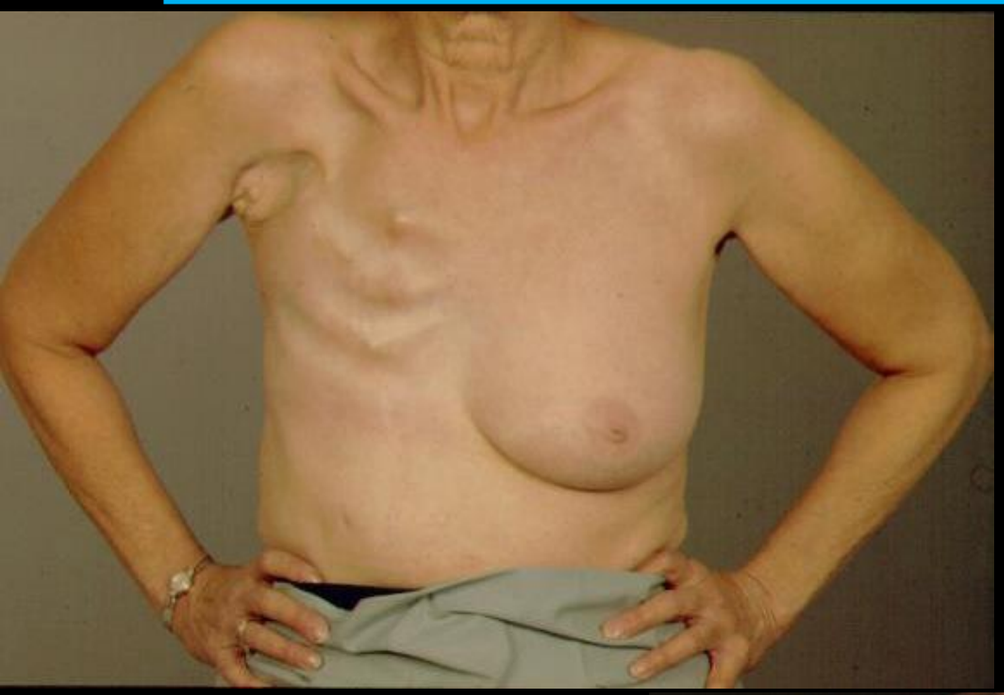
the answer:

Oncoplastic surgery

Latissimus dorsi flap

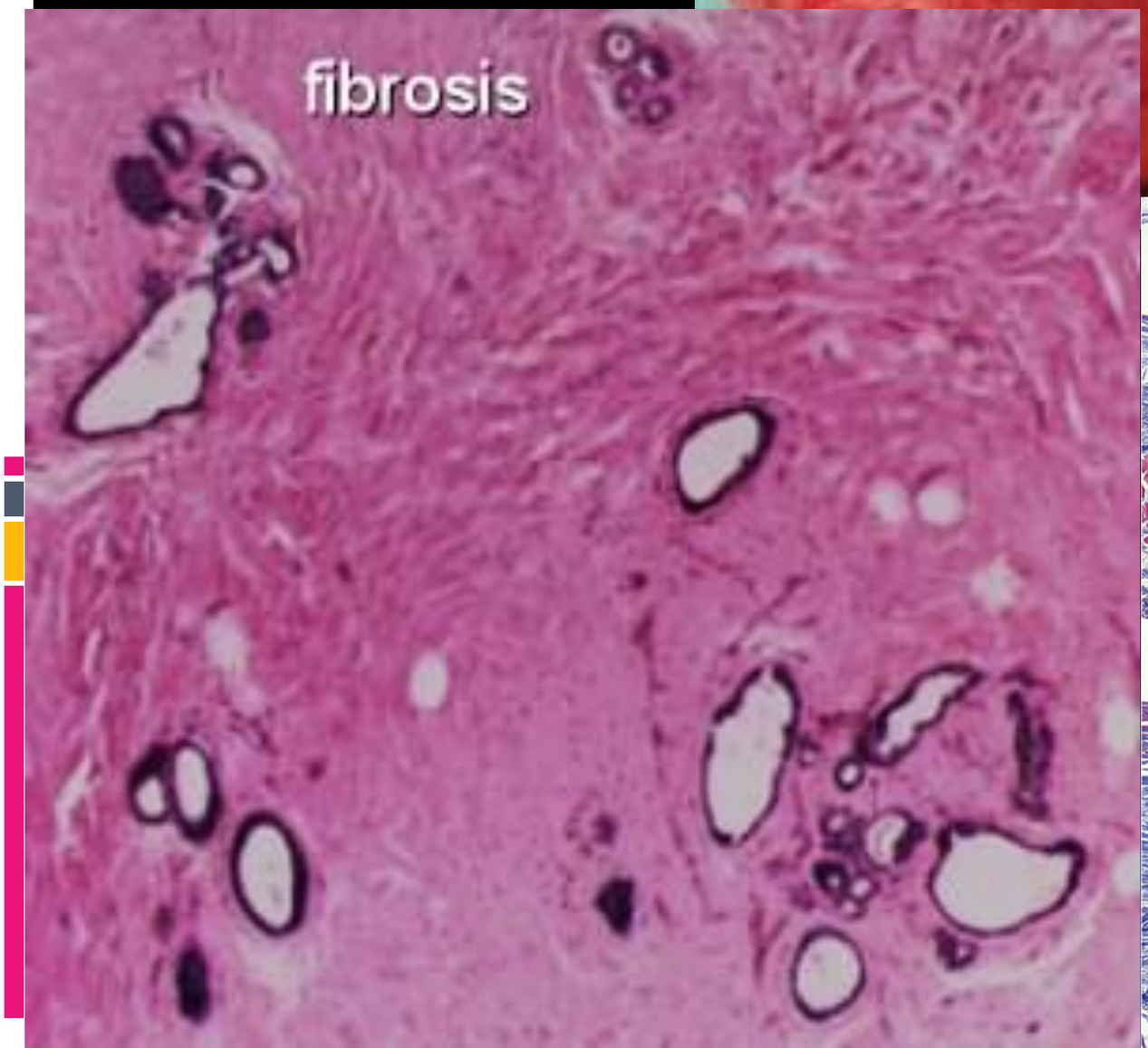
And when mastectomy is needed?
Which is the surgeon's answer?
Tertiary prevention

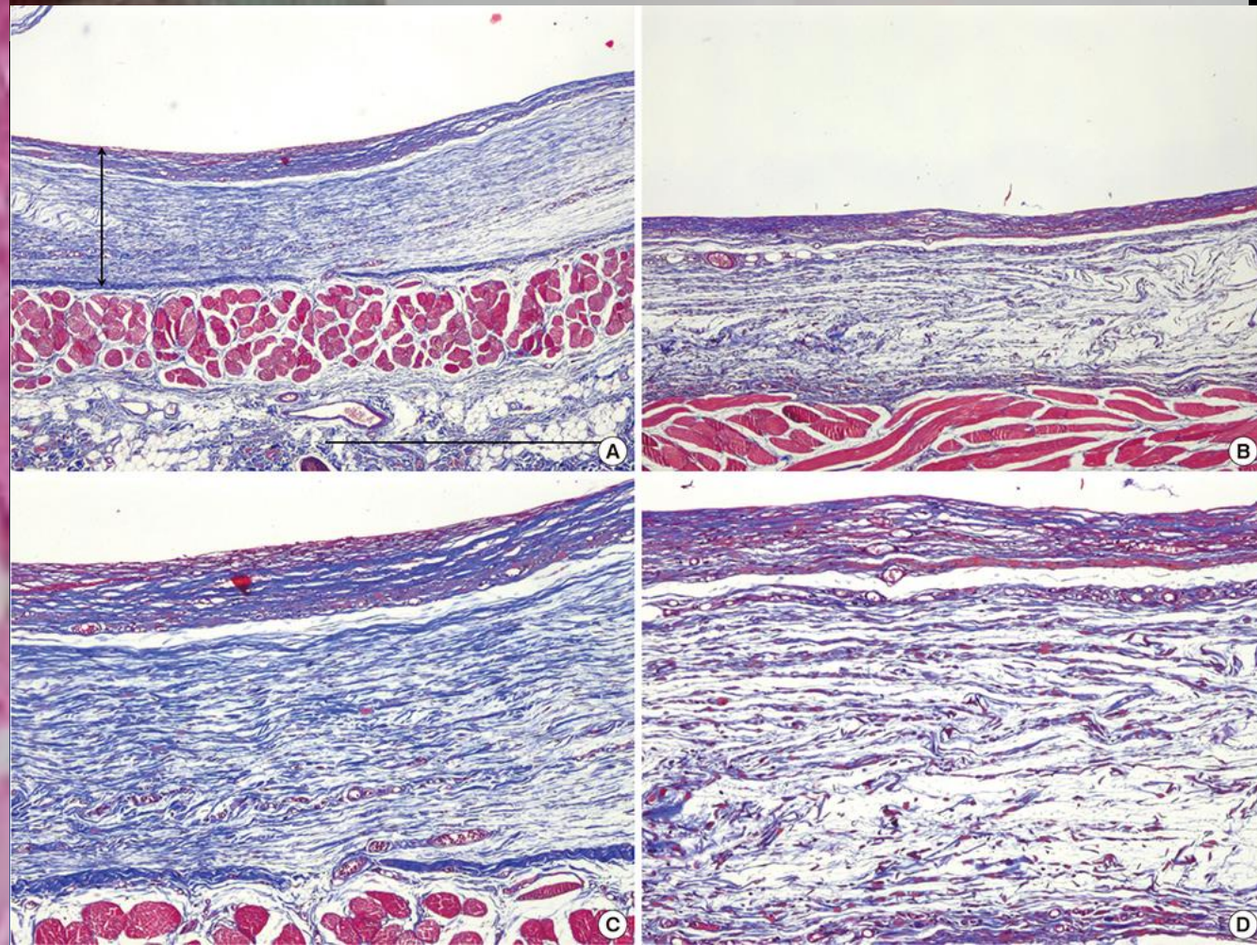
Conservative mastectomies, skin- and nipple sparing mastectomies



BUT… NO MORE ANIMATION DEFORMITIES

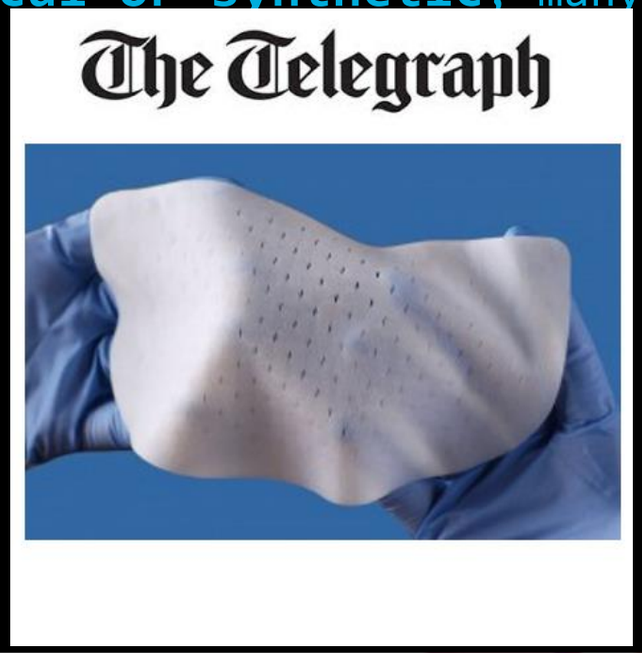
Capsular contracture

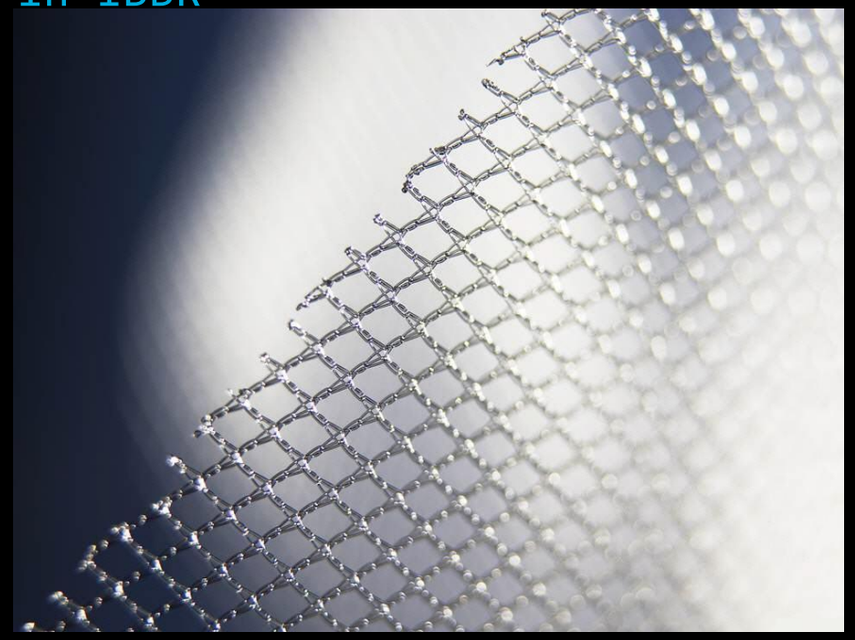


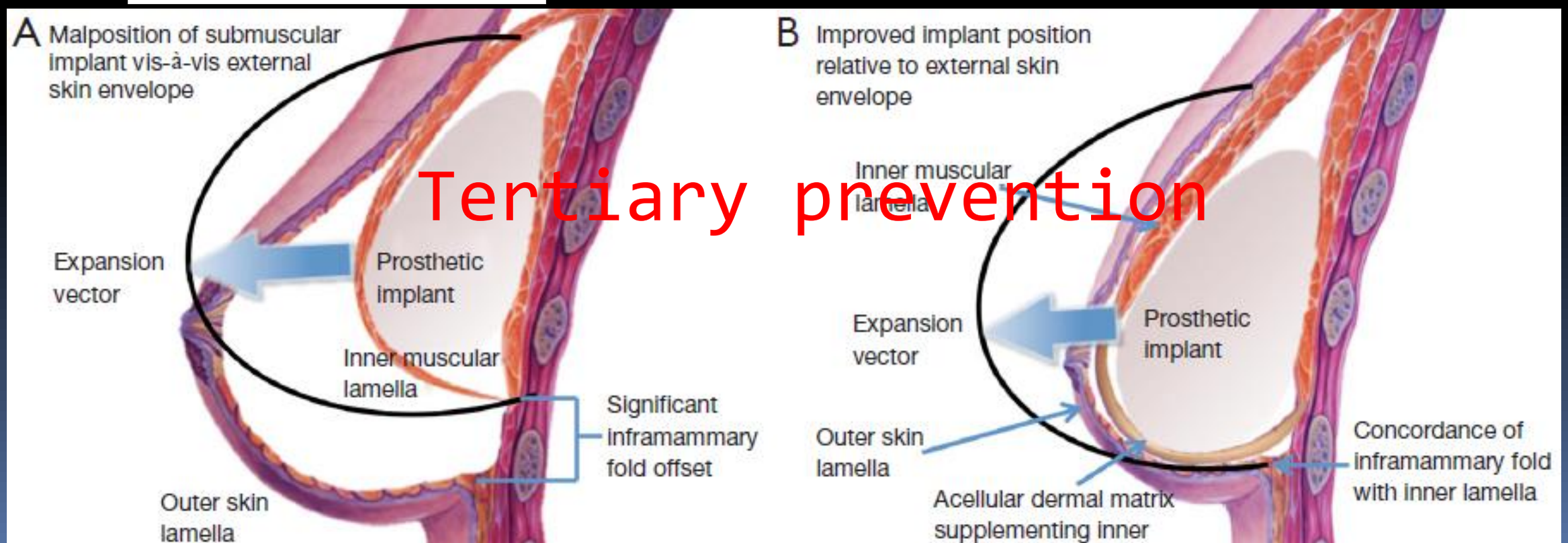


Breast Reconstruction

Finally, with the introduction of **soft tissue replacement devices**, either **biological or synthetic**, many things have changed in IBBR

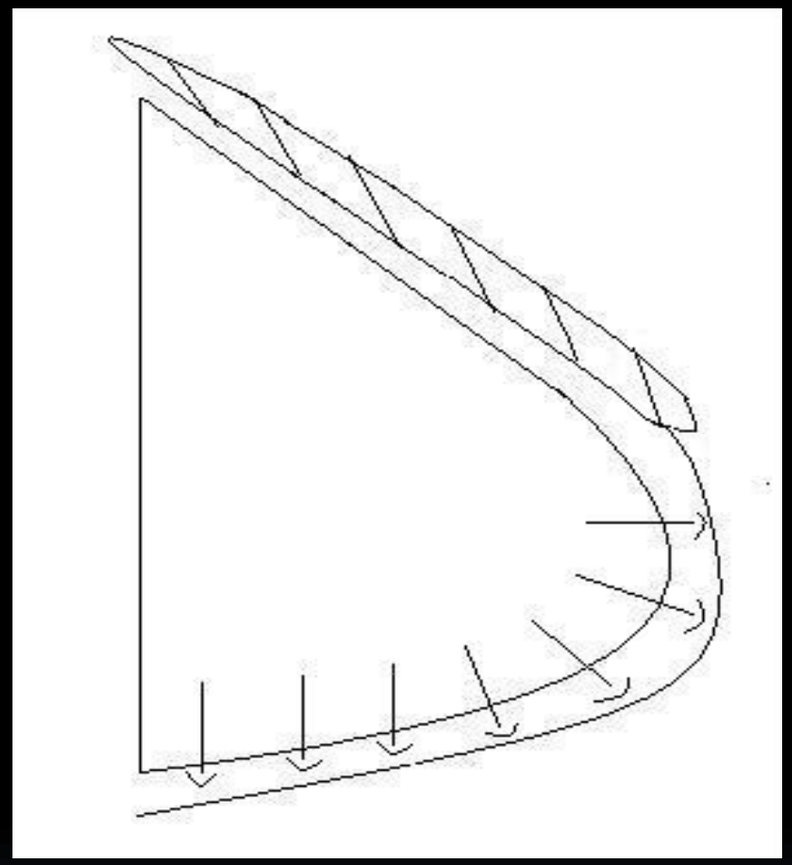




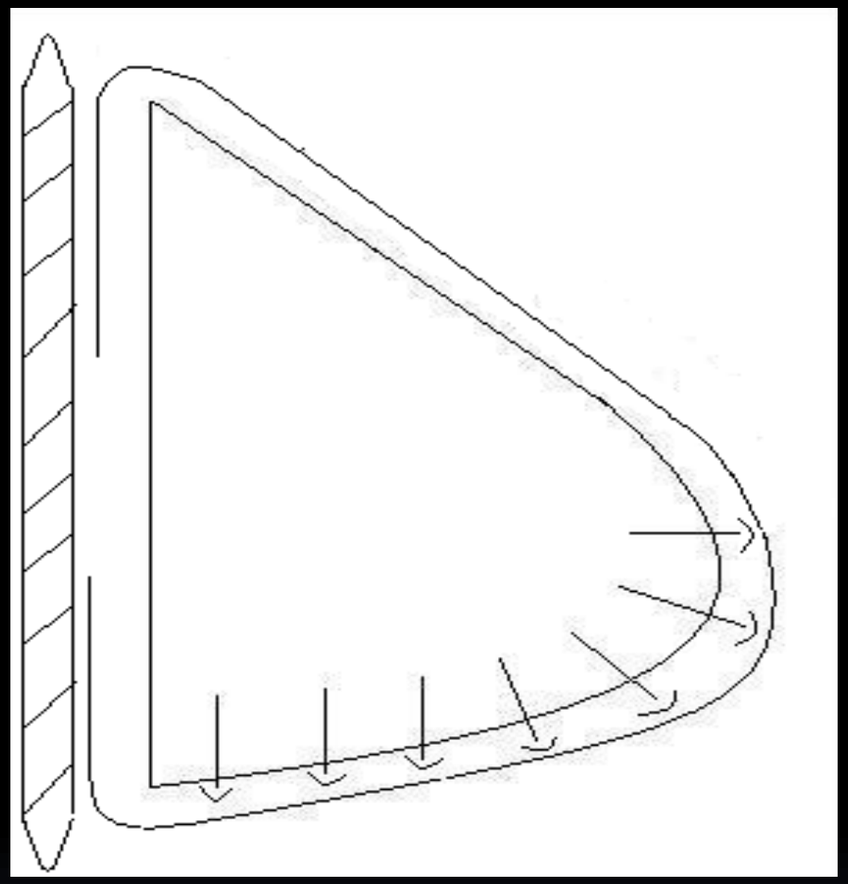


Tertiary prevention

Breast Reconstruction



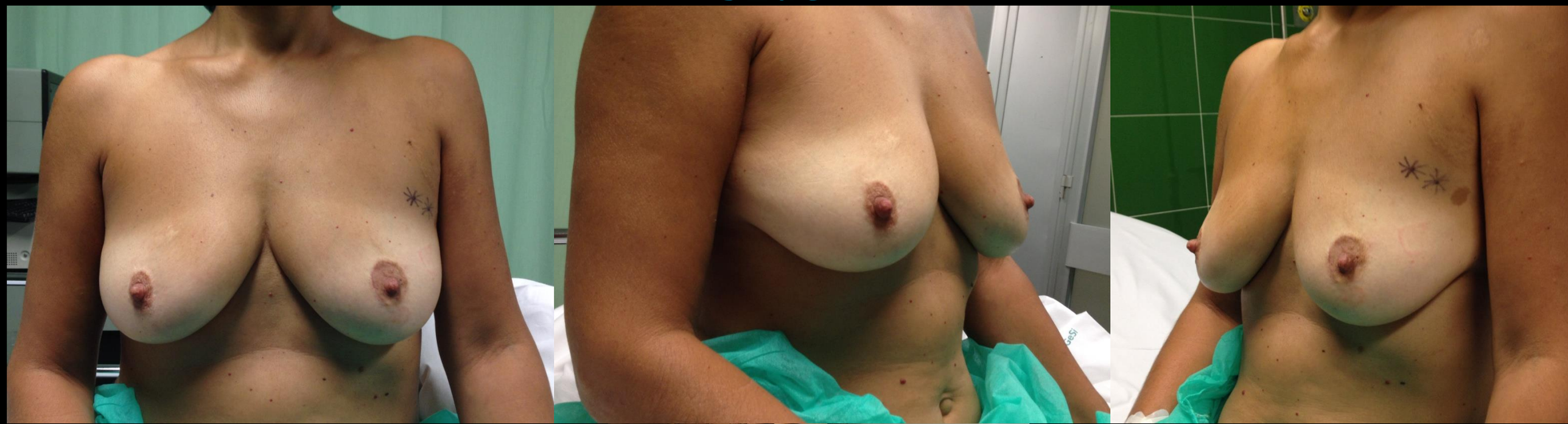
If **Mechanic stress** is on **lower pole**

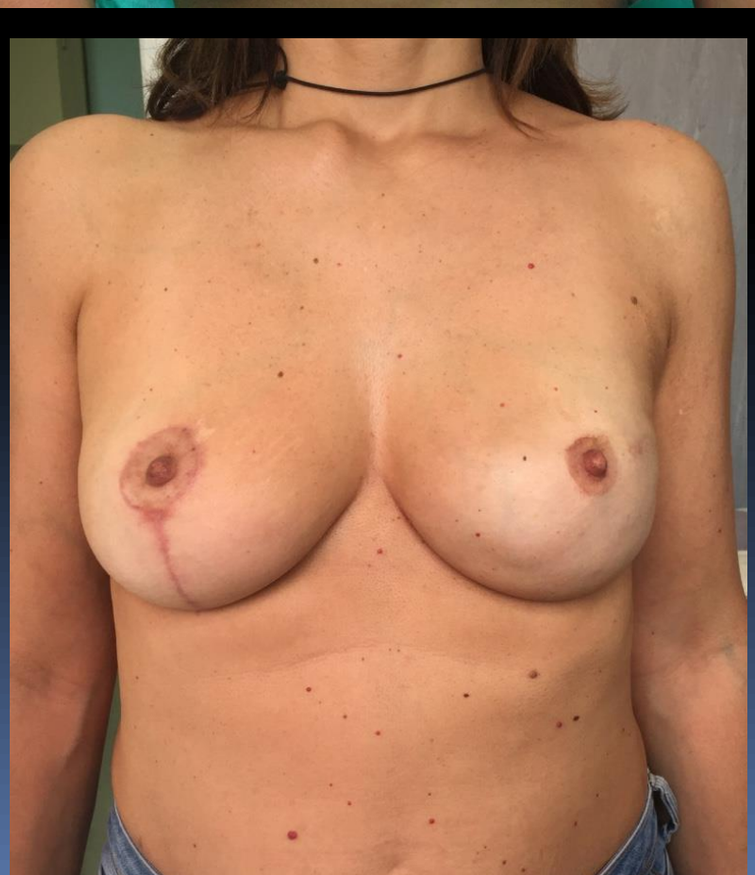


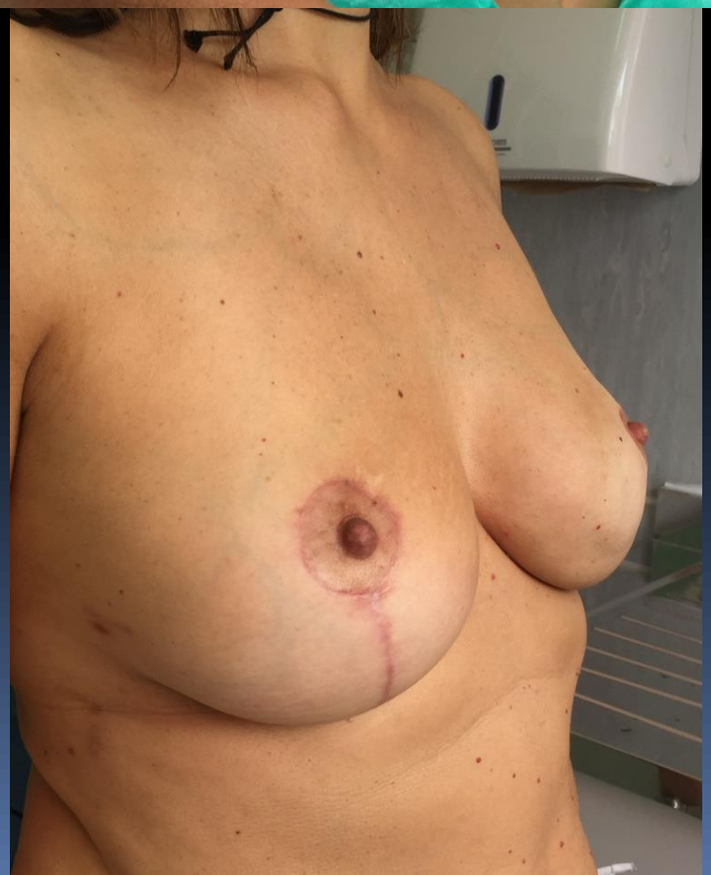
Why not **cover** the **entire implant?**

Pre-Pec Breast Reconstruction

NSM and DTI left side and Lejour mastoplasty on right side



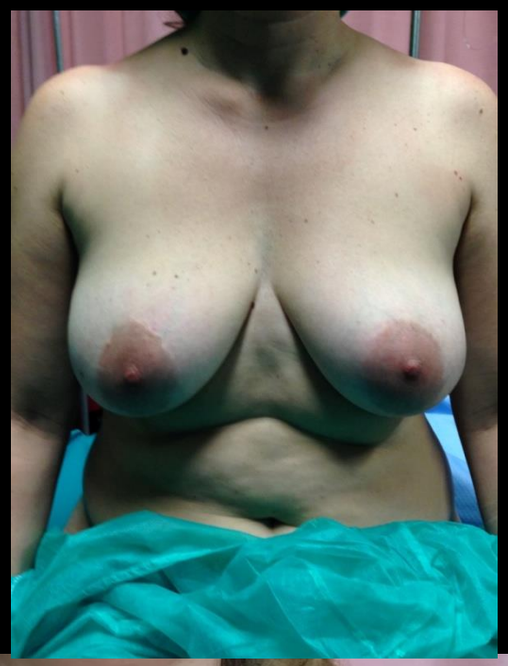




Pre-Pec Breast Reconstruction

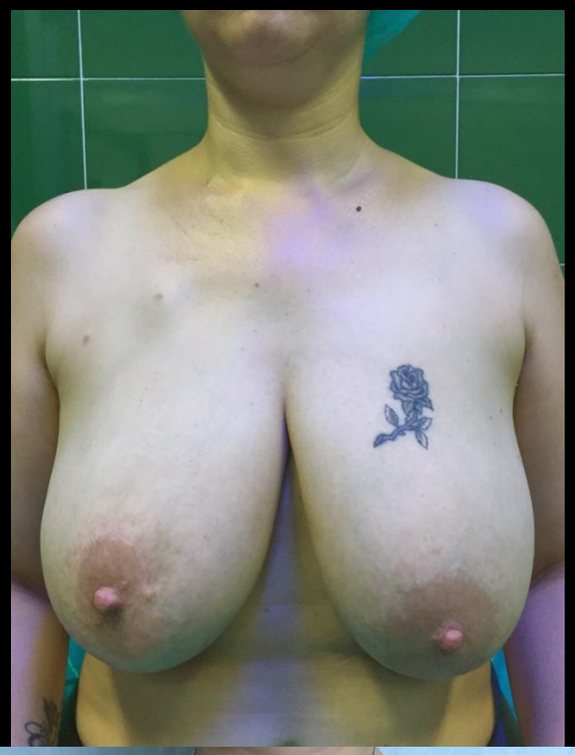
Pre-Pec Breast Reconstruction

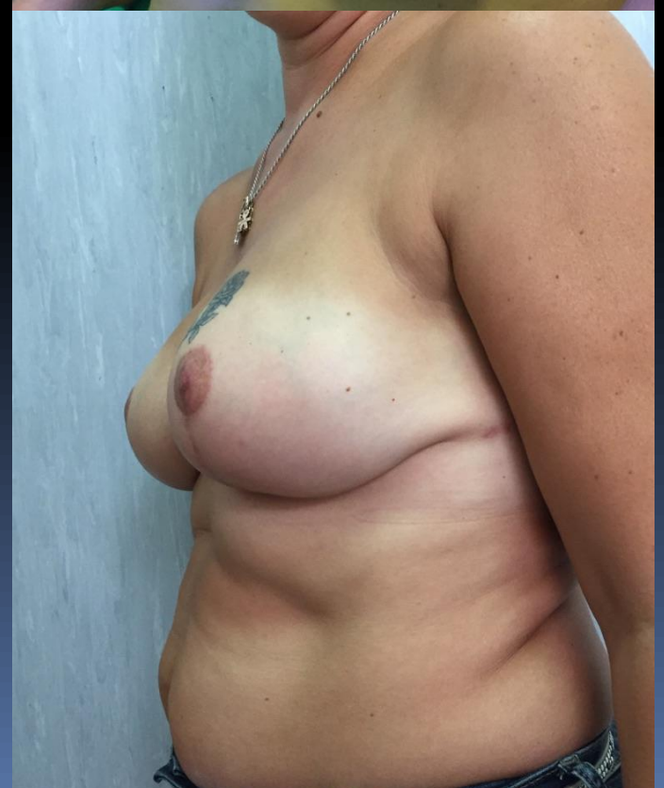
Skin reducing NSM with two-stage TE rec (BRCA)



Pre-Pec Breast Reconstruction

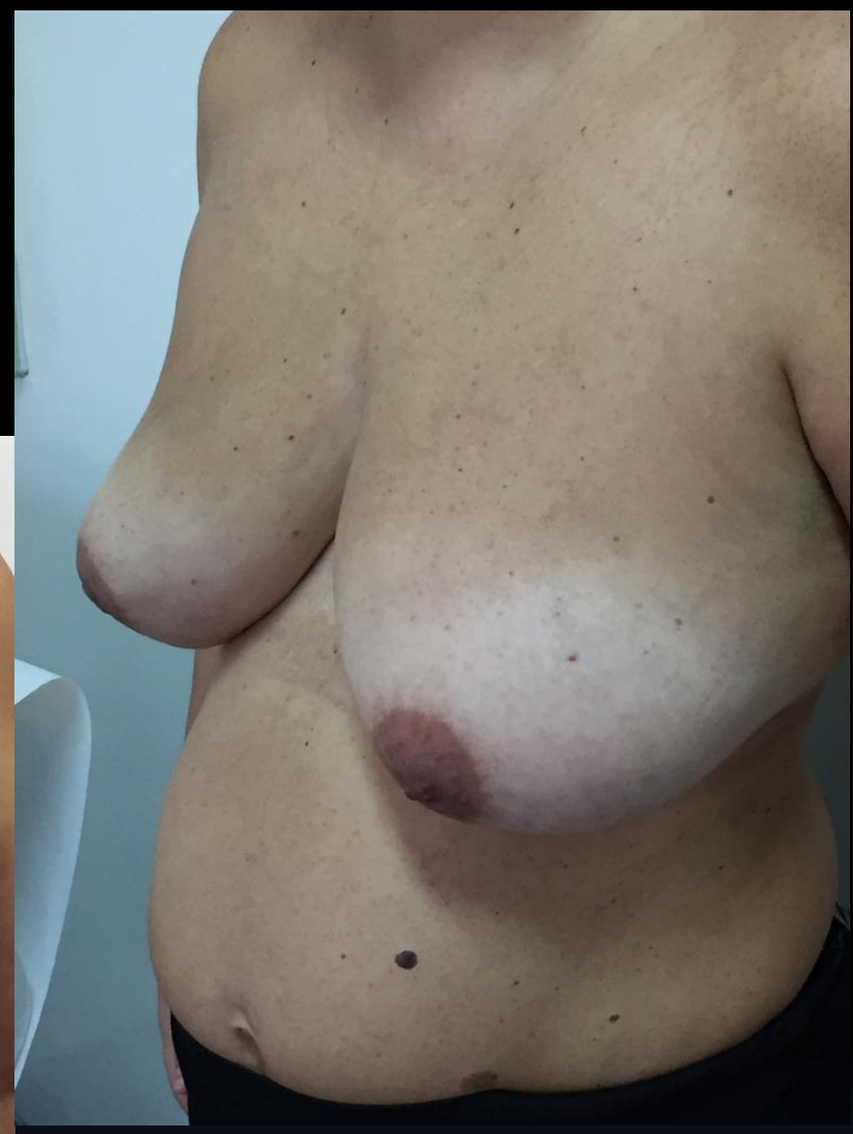
mastectomy with free nipple areola graft (Thorek) and DTI pr



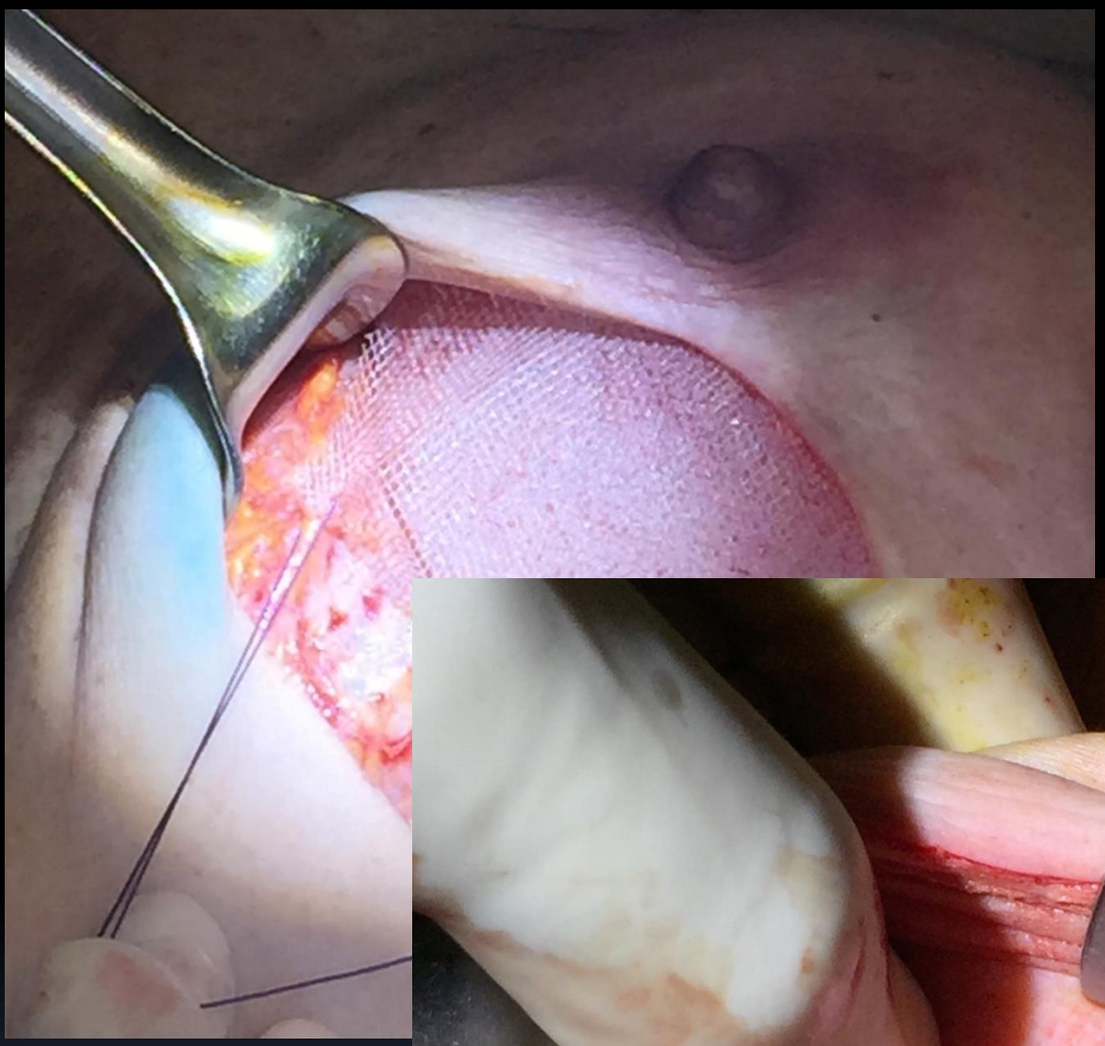


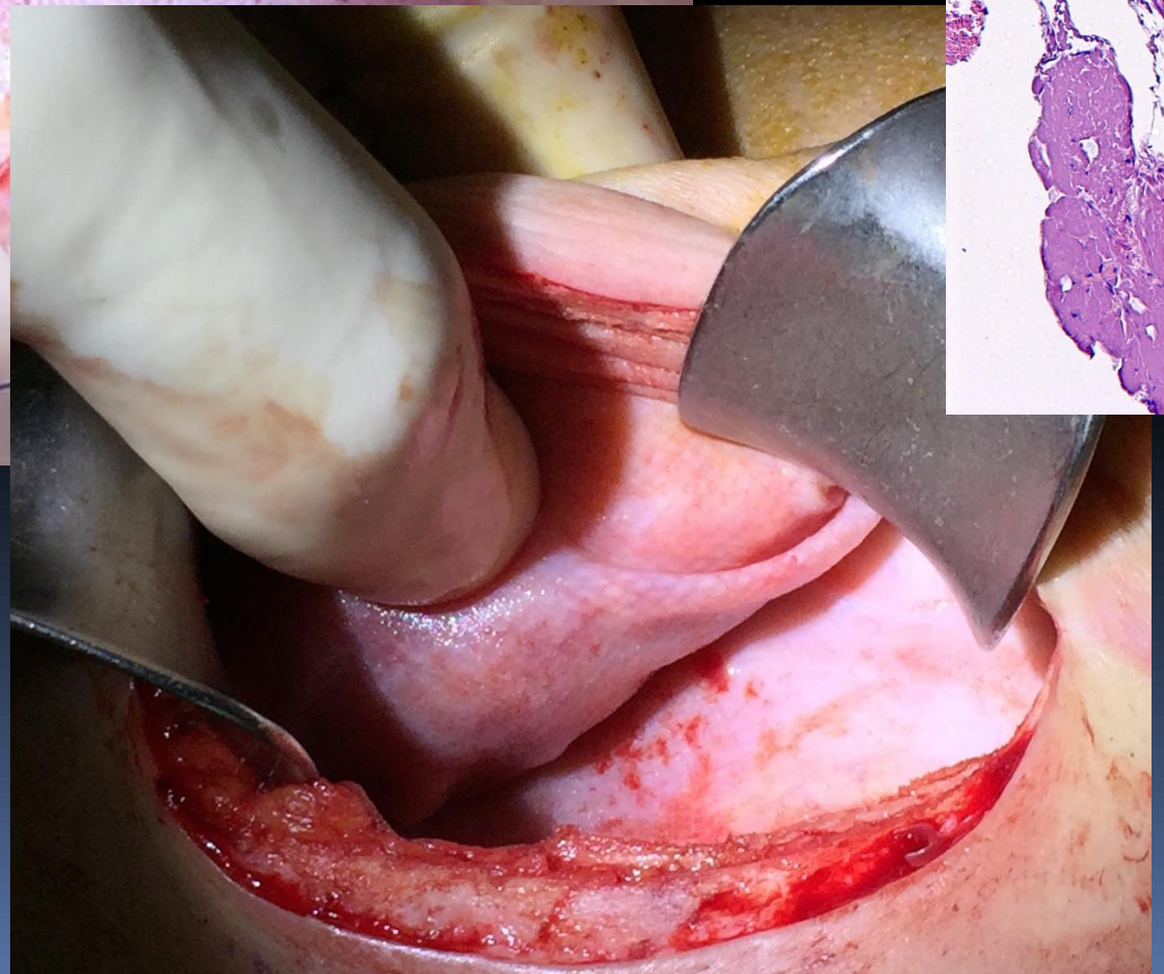
Pre-Pec Breast Reconstruction

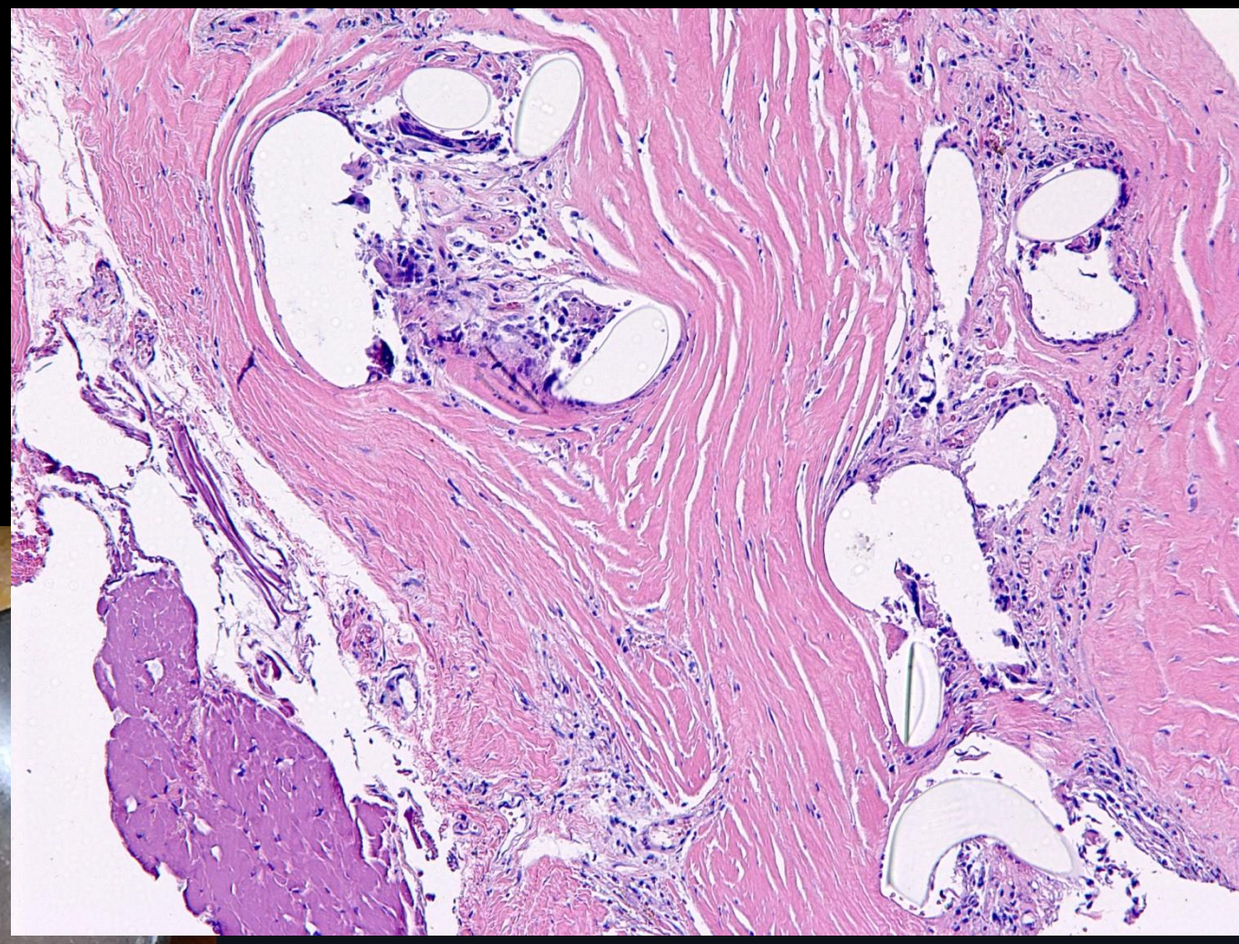
NSM and DTI right side and nothing on left side



Pre-Pec Breast Reconstruction reduces capsular fibrosis





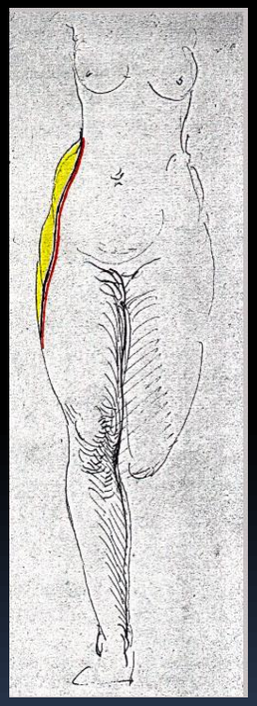


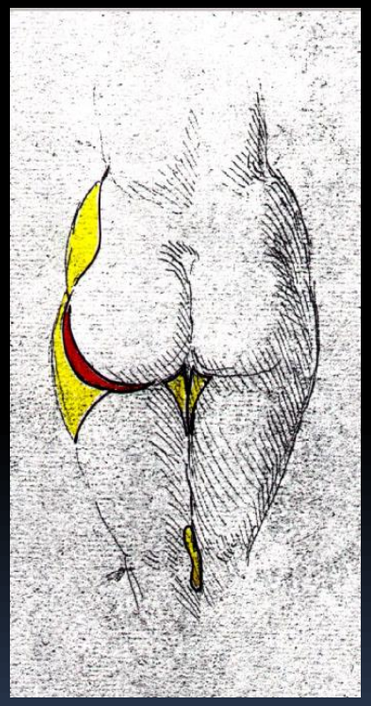
Pre-Pec Breast Reconstruction

- rippling,
- visible implant rim

RECONSTRUCTION AFTER MASTECTOMY

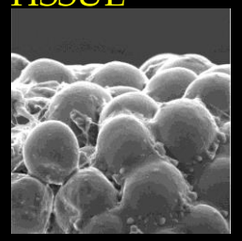
Autologous tissue FAT GRAFT





LIPOSUCTION

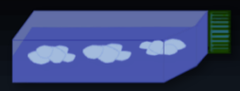
ADIPOSE TISSUE



ADIPOCYTES

SVF

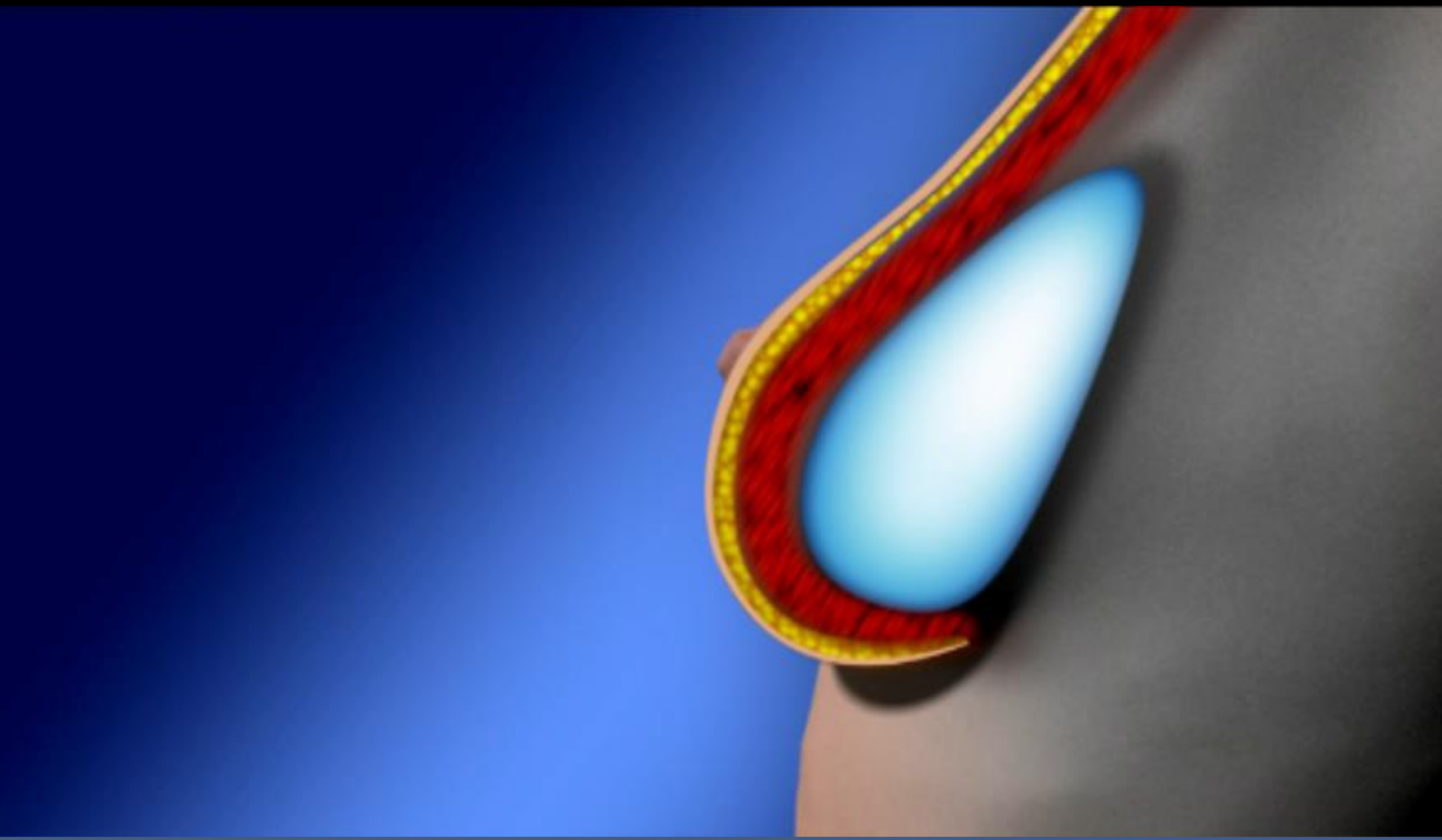
NON ADHERENT CELLS

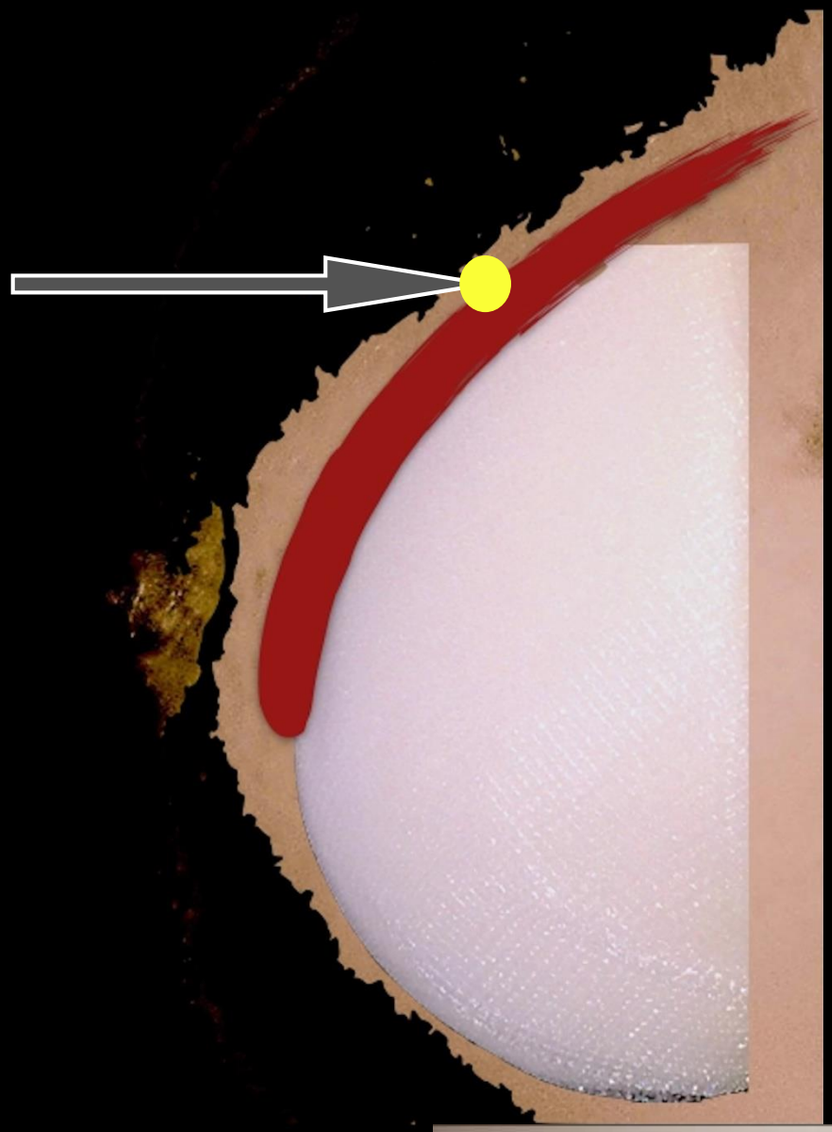


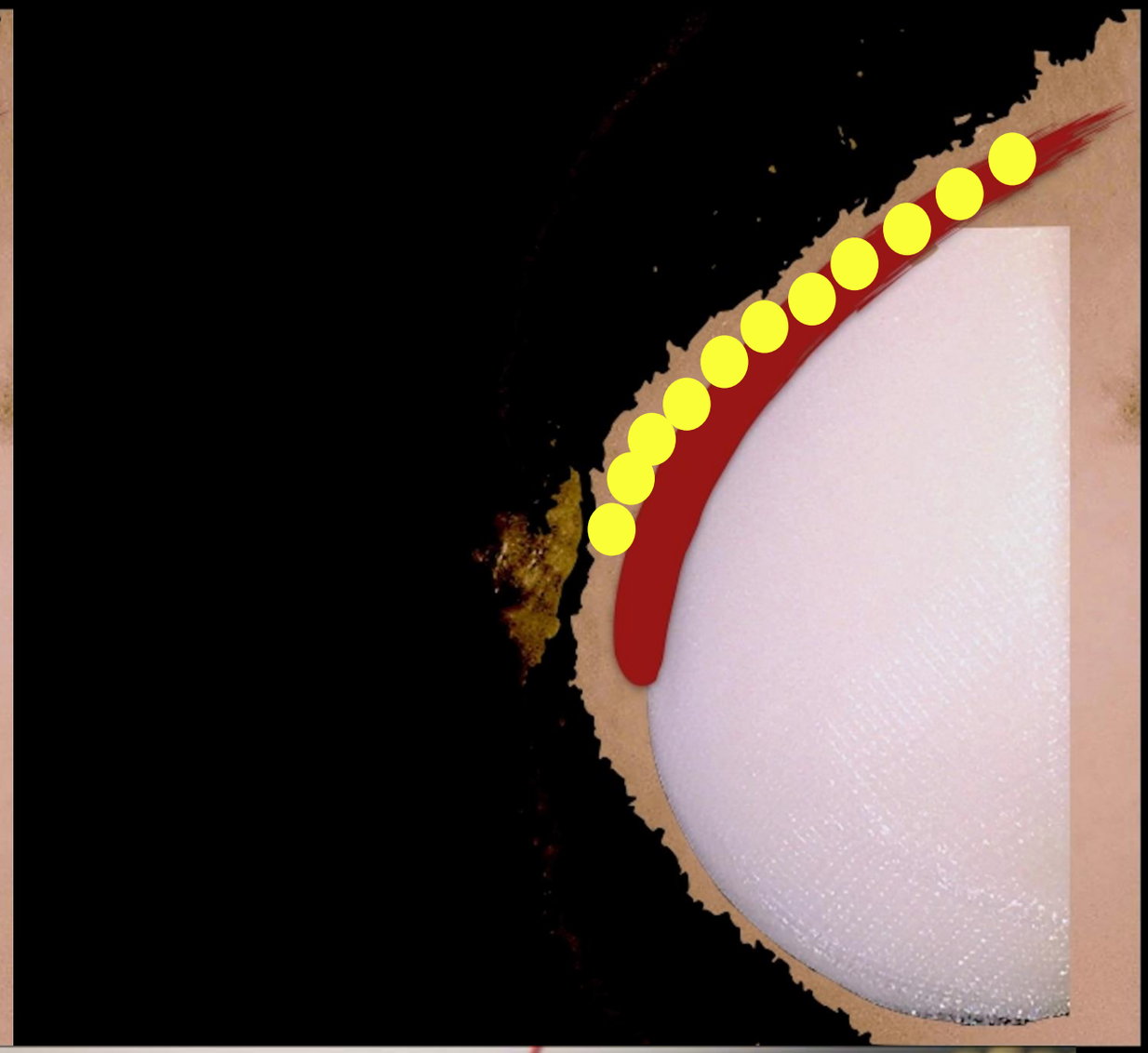
ADSC

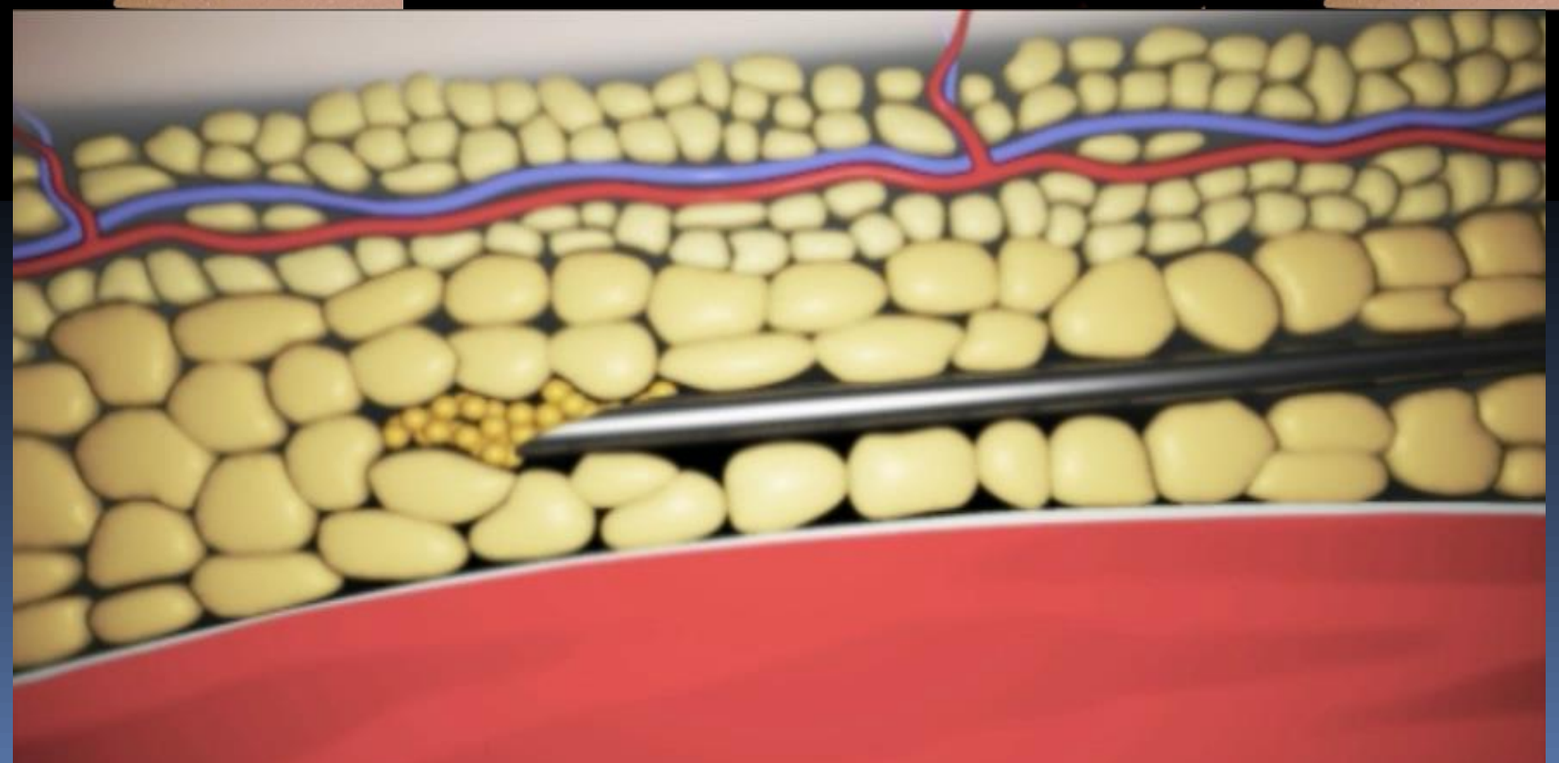
MULTIPOTENT CELLS

- SELECTION BY ADHESION









× Skinny patients

Wound and skin at risk …

LET’S GET BACK… UNDER THE MUSCLE

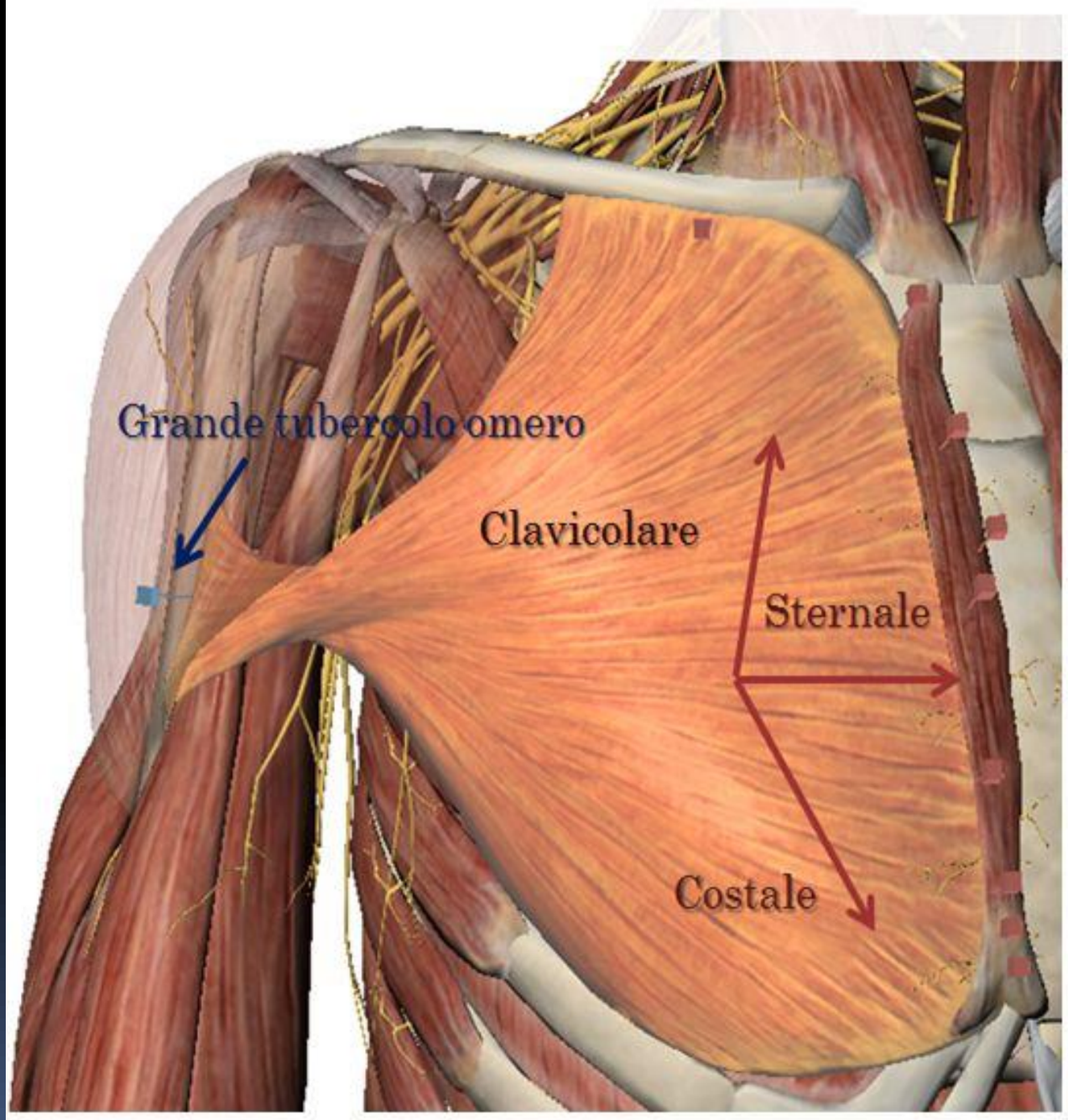
BUT… NO MORE ANIMATION DEFORMITIES

Topics

- ✓Selective Pectoralis Major Muscle Denervation

Selective PMM denervation

GRANDE PETTORALE



- Muscolo superficiale, piatto e convergente posto nella porzione anteriore del torace.
- Costituito di tre fasci che rispecchiano i punti di origine delle lamine muscolari:
  - Fascia clavicolare
  - Fascia sternale
  - Fascia costale.
- I tre fasci convergono in un'unica inserzione sul grande tubercolo dell'omero.

O. Clavicola, sterno e coste

I. Grande tubercolo omero

Selective PMM denervation

Figure 7 Patient with selective C7 brachial plexus injury. (Above) Atrophy of the sternal aspect of the pectoralis major due to an injury of C7 root = injury of middle branch of the pectoral nerve. The clavicular aspect (superior branch = C5-

Journal of Plastic, Reconstructive & Aesthetic Surgery (2012) 65, 1193–1198

ELSEVIER

JPRAS
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www.JPRASurg.com

The anatomy of the pectoral nerves and its significance in breast augmentation, axillary dissection and pectoral muscle flaps

Sylvain David [a,*], Thierry Balaguer [a], Patrick Baque [b], Fernand de Peretti [b], Maxime Valla [a], Elisabeth Lebreton [a], Berengere Chignon-Sicard [a]

Selective PMM denervation

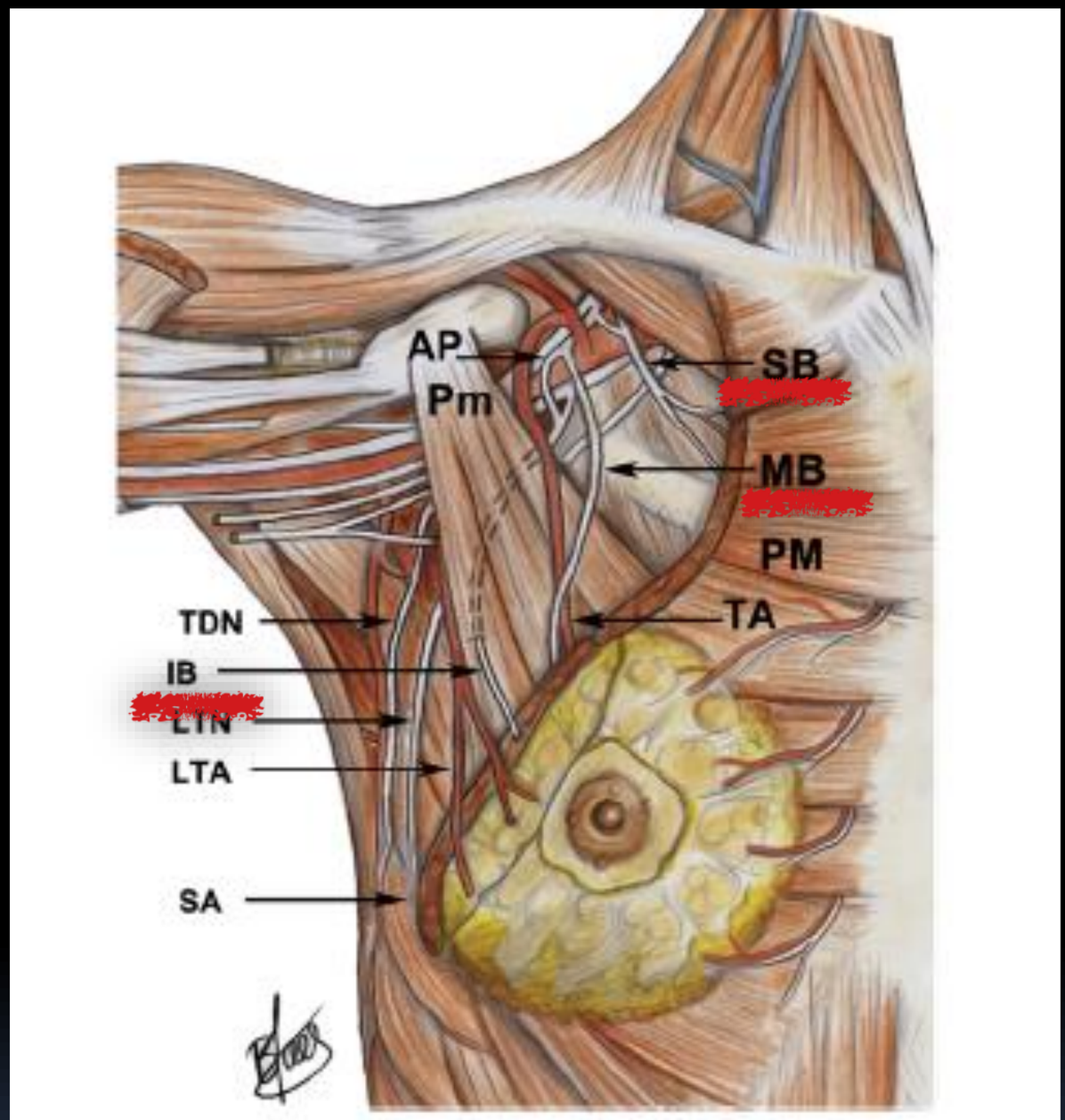

Figure 1 Schematic drawing of right brachial plexus showing the 3 branches of the pectoral nerves. SB, superior branch of the pectoral nerves; MB, middle branch of the pectoral nerves; IB, inferior branch of the pectoral nerves; AP, ansa pectoralis; pM, pectoralis minor; PM, pectoralis major; TA, pectoral branch of the thoraco-acromial artery; LTA, lateral thoracic artery; TDN, thoraco-dorsal nerve; long thoracic nerve; SA, serratus anterior.

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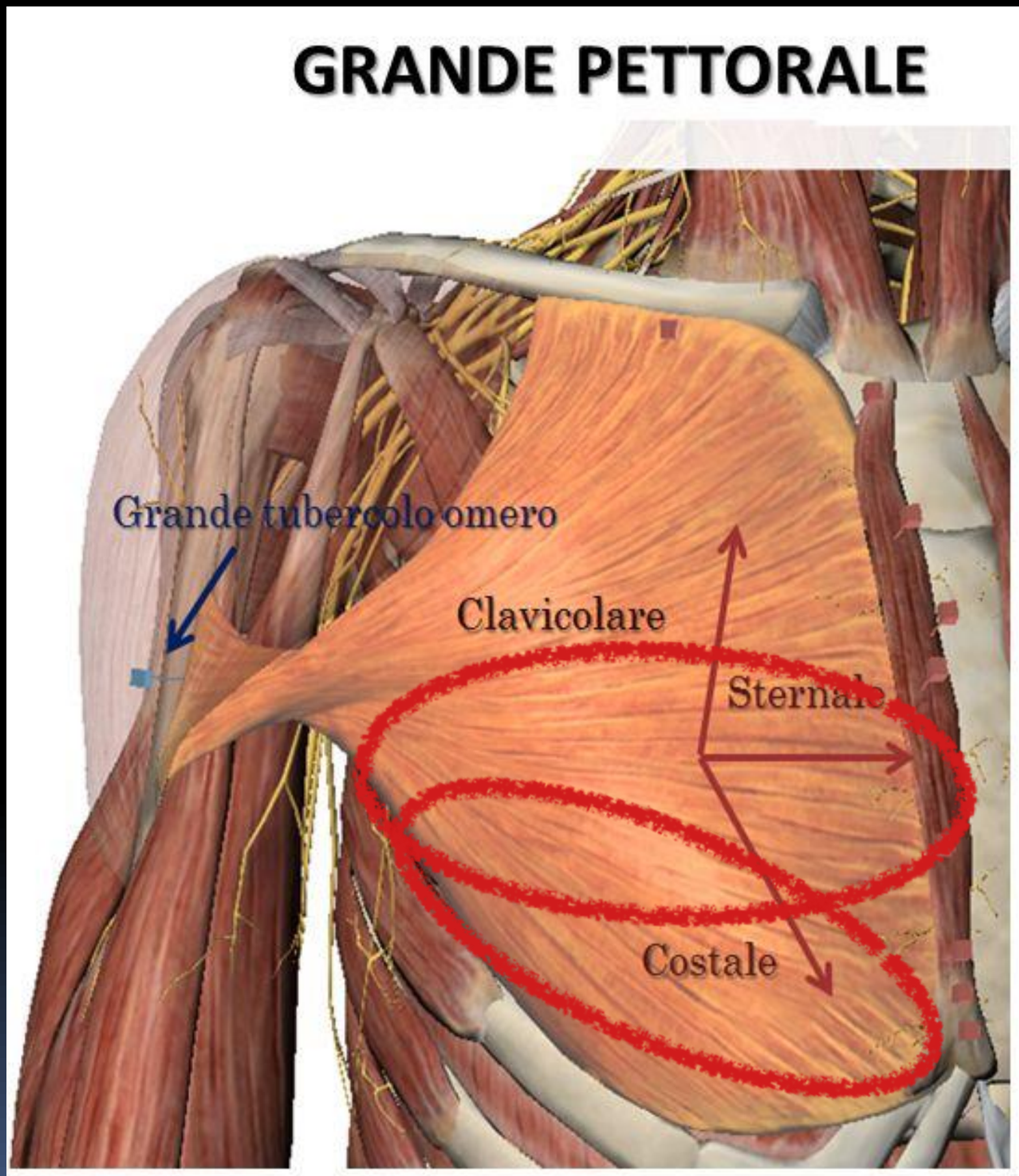

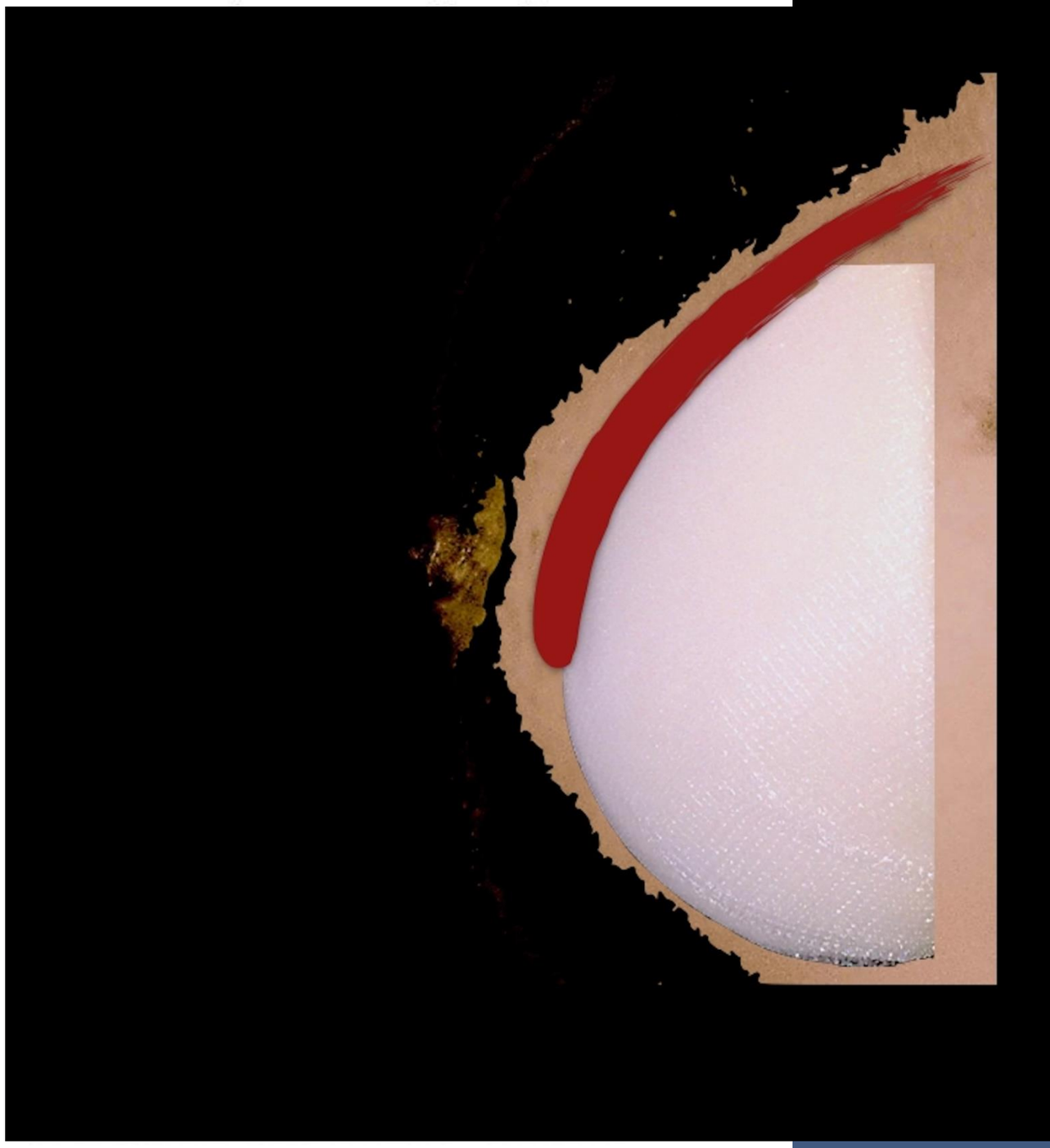

Surgical Technique

Selective pectoralis major muscle denervation in breast reconstruction: a technical modification for more effective and cosmetic results

Marco Bernini[1], Donato Casella[2], Carlo Mariotti[1]

[1]Department of Oncology, Breast Unit Surgery, Careggi University Hospital, Florence, Italy; [2]Breast Unit Surgery, Azienda Sanitaria Toscana Nord-Ovest, Presidio Ospedaliero di Livorno, Livorno, Italy

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Abstract: The use of pectoralis major muscle (PMM) in breast reconstruction has been a mainstay for decades. In recent years, although, a novel approach, the so-called subcutaneous or pre-pectoral breast reconstruction, has been introduced advocating the advantages of sparing the pectoralis muscle. Such advantages include more natural implant ptosis and appearance, significant reduction of capsular contracture and also avoidance of implant animation and animation deformities. These are all drawbacks that the use of muscles in implant coverage inevitably involves overtime. Nonetheless, there are clinical situations which definitely require the use of a muscle coverage either for surgical safety or for a better cosmetic outcome. In such cases a slight and simple modification of the standard technique can be adopted to prevent these drawbacks. While performing the muscular pocket two of the three main nerve trunks of the PMM can be severed, thus leaving innervated only the upper portion of the muscle. The remaining two thirds, basically the part covering a tissue expander (TE) or an implant, will therefore retain a status of a viable soft tissue without any muscular contraction. A significant atrophy will definitely ensue, but a sufficiently vascularized and floppy cushion will cover the prosthetic breast reconstruction device, protecting and masking it.

Keywords: Pectoralis major muscle (PMM) denervation; pre-pectoral breast reconstruction; retro-pectoral breast reconstruction; submuscular breast reconstruction

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Introduction

Implant based breast reconstruction (IBBR) is the most frequent reconstructive choice nowadays. This is true both in the setting of simple mastectomy and even more in case of conservative mastectomies such as nipple sparing mastectomy (NSM) (1,2). In the early era of prosthetic reconstruction, subcutaneous implant placement represented the first attempted technique, as described by Snyderman in 1971 (3). Shortly after, also the first pioneers of tissue expansion, Radovan and Lapin, adopted a subcutaneous placement of their expanders (4,5). By that time, however, most of reconstructions were delayed and in the setting of a previous radical mastectomy with the absence of pectoralis major muscle (PMM). Thanks to the diffusion of modified radical mastectomy and in order to avoid some complications of the subcutaneous techniques, such as prosthesis extrusion, in 1981, Gruber advocated the superiority of a submuscular implant reconstruction over the Snyderman's procedure (6). This principle was also transferred to the tissue expander (TE) approach by Argenta (7). The retro-pectoral approach became the gold standard for more than two decades in the breast reconstructive surgeon armamentarium. Prosthesis coverage by a muscular pocket in order to interpose a viable cushion in case of skin flap/wound dehiscence and in order to avoid a too "visible" implant represented the most commonly used option for

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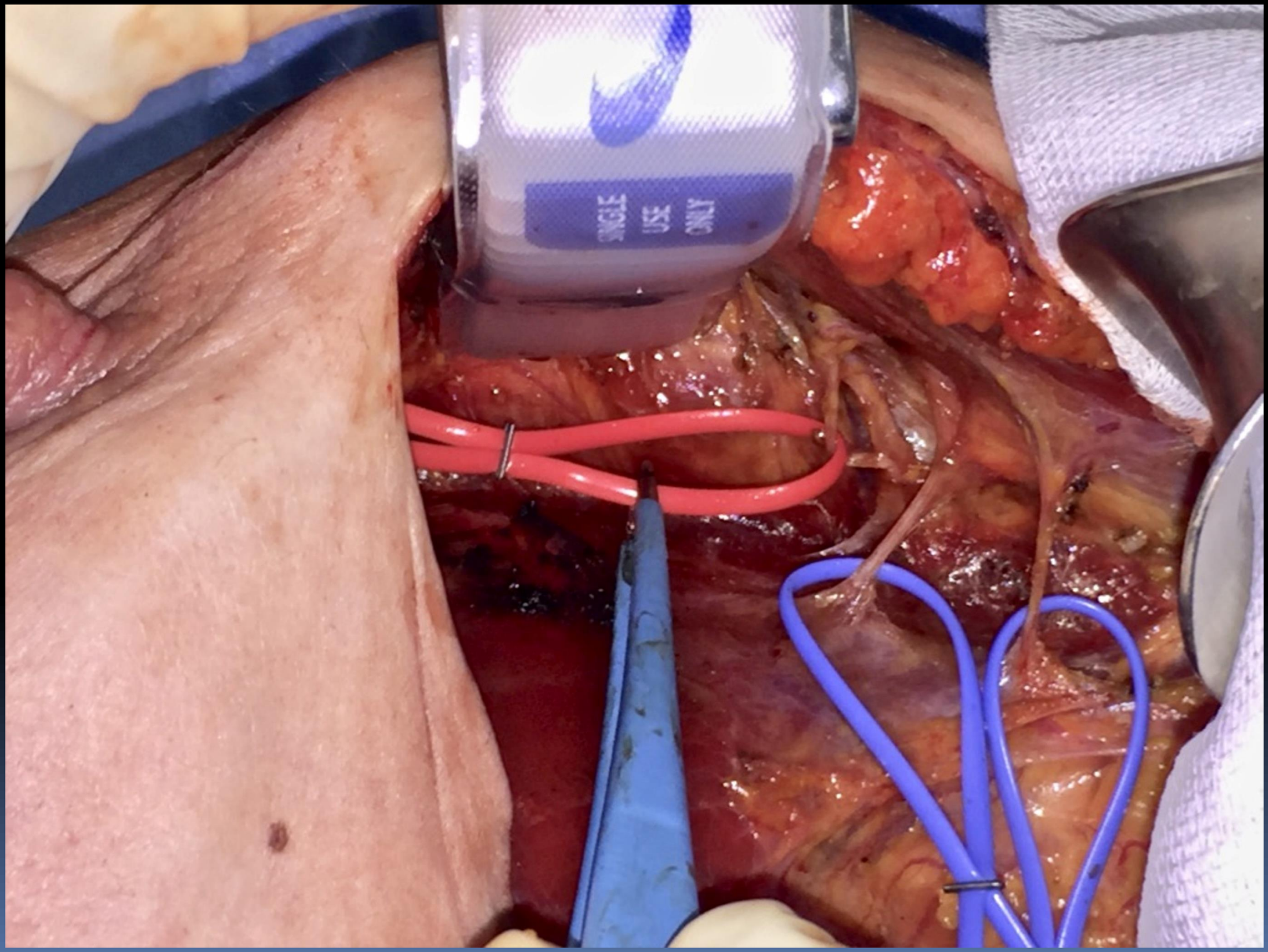
Selective PMM denervation

- *To avoid animation deformities*

- *To reduce pain and discomfort*

Tertiary prevention

Selective PMM denervation



Selective PMM denervation

DTI reconstruction and contralateral augmentation mastop

Selective PMM denervation

DTI reconstruction and contralateral augmentation mastop

Selective PMM denervation

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Selective PMM denervation

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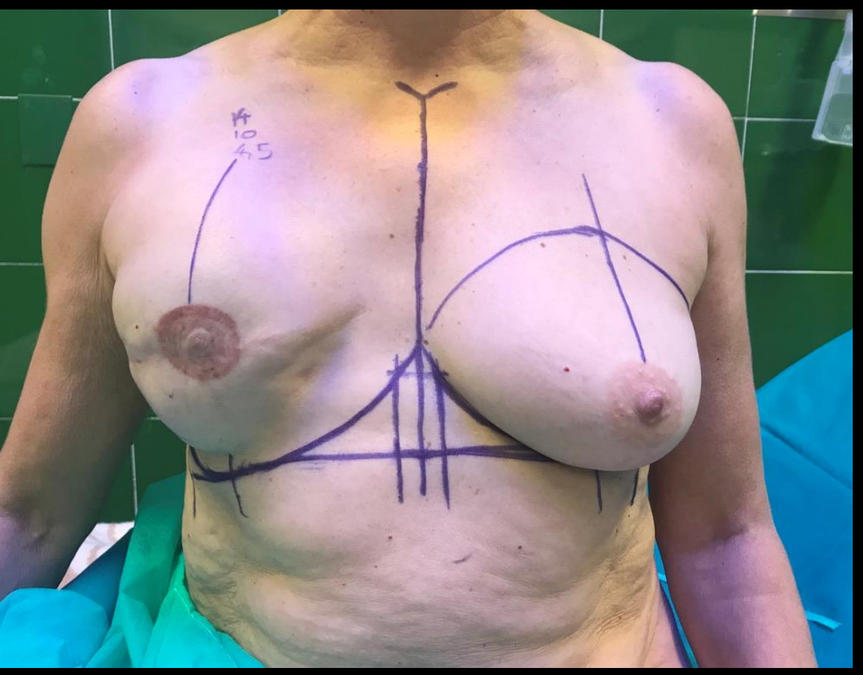
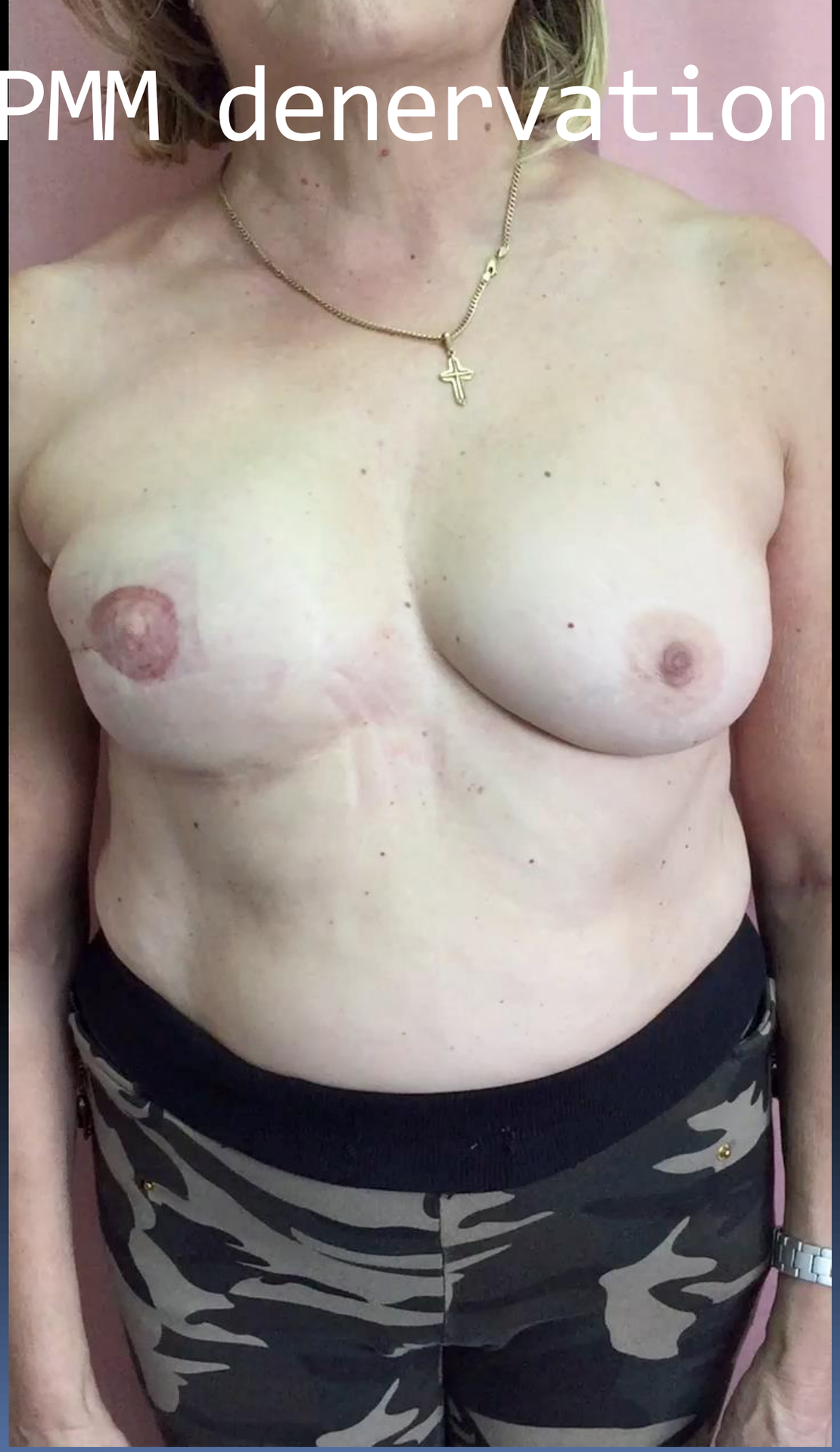
Selective PMM denervation





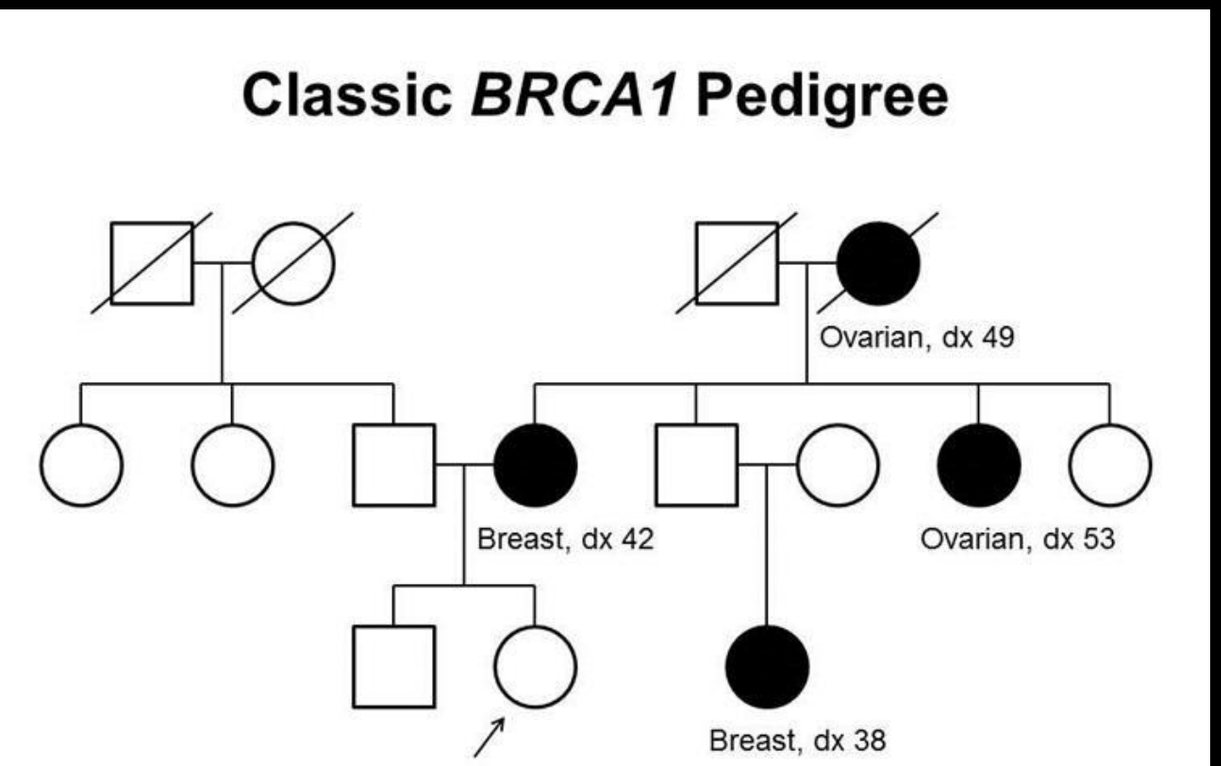
Selective PMM denervation

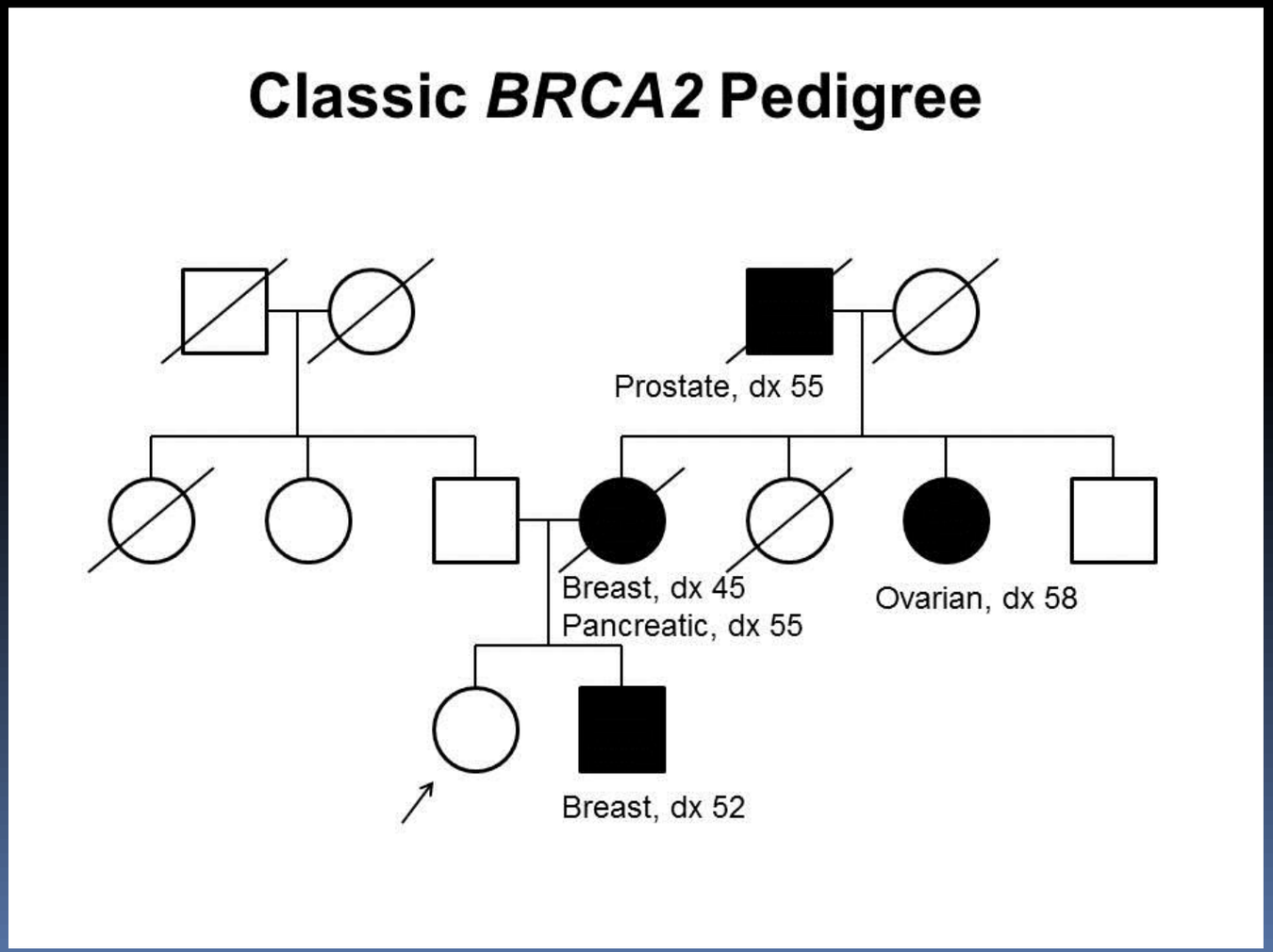
teral capsulotomy, capsulorraphy and selective denervatio

BRCA MUTATION

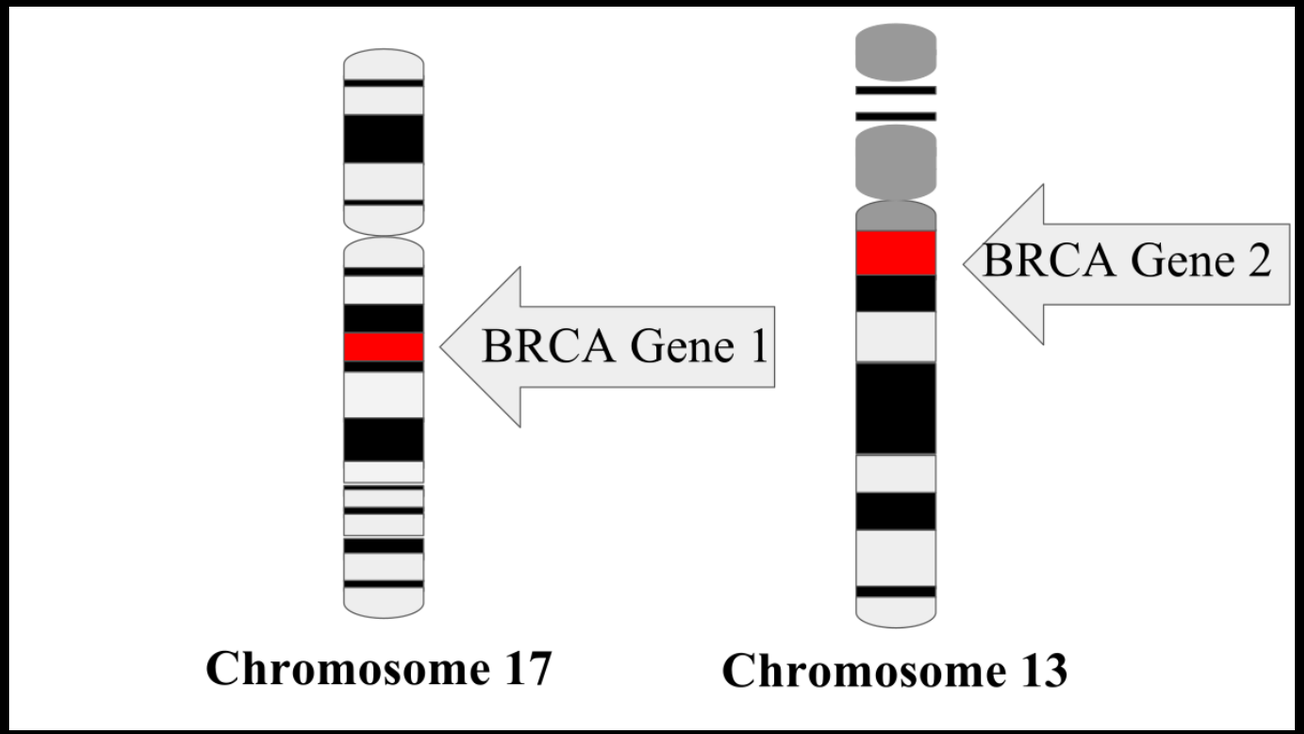
In 1990, Mary-Claire King demonstrated that a single gene on chromosome 17q21, which she later named BRCA1, was responsible for breast and ovarian cancer in many families. Her discovery of BRCA1 revolutionized the study of inherited diseases.

BRCA MUTATION





BRCA MUTATION



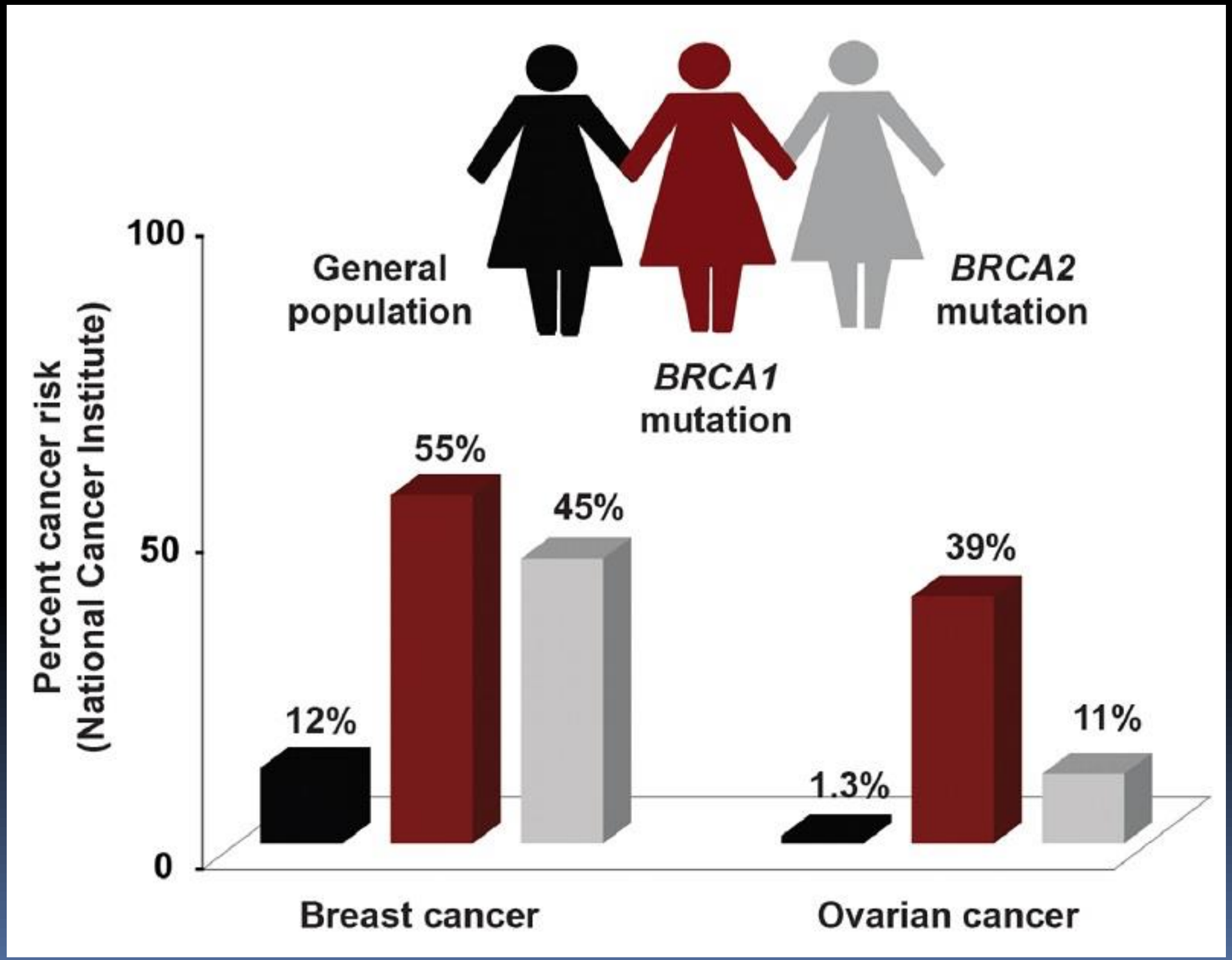
Hereditary breast cancer

- 15-20% of breast cancer are familiar
- 5% are hereditary

Hereditary breast cancer

- BRCA 1-2 mutations
- P-53 mutations, Li-Fraumeni syndrome
- PTEN mutations
- PALB mutation
- STK11/LKB1 locus LOH, Peutz-Jeghers syndrome
- CDH1 (E-cadherin) mutations
- Ataxia Telangiectasia genes mutations

BRCA MUTATION



Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women

Clinical Summary of U.S. Preventive Services Task Force Recommendation

Risk Assessment

Family history factors associated with increased likelihood of potentially harmful BRCA mutations include:

- breast cancer diagnosis before age 50 years,
- bilateral breast cancer,
- family history of breast and ovarian cancer,
- presence of breast cancer in ≥1 male family member,
- multiple cases of breast cancer in the family,
- ≥1 or more family member with 2 primary types of BRCA-related cancer,
- and Ashkenazi Jewish ethnicity.

Several familial risk stratification tools are available to determine the need for in-depth genetic counseling, such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7.

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

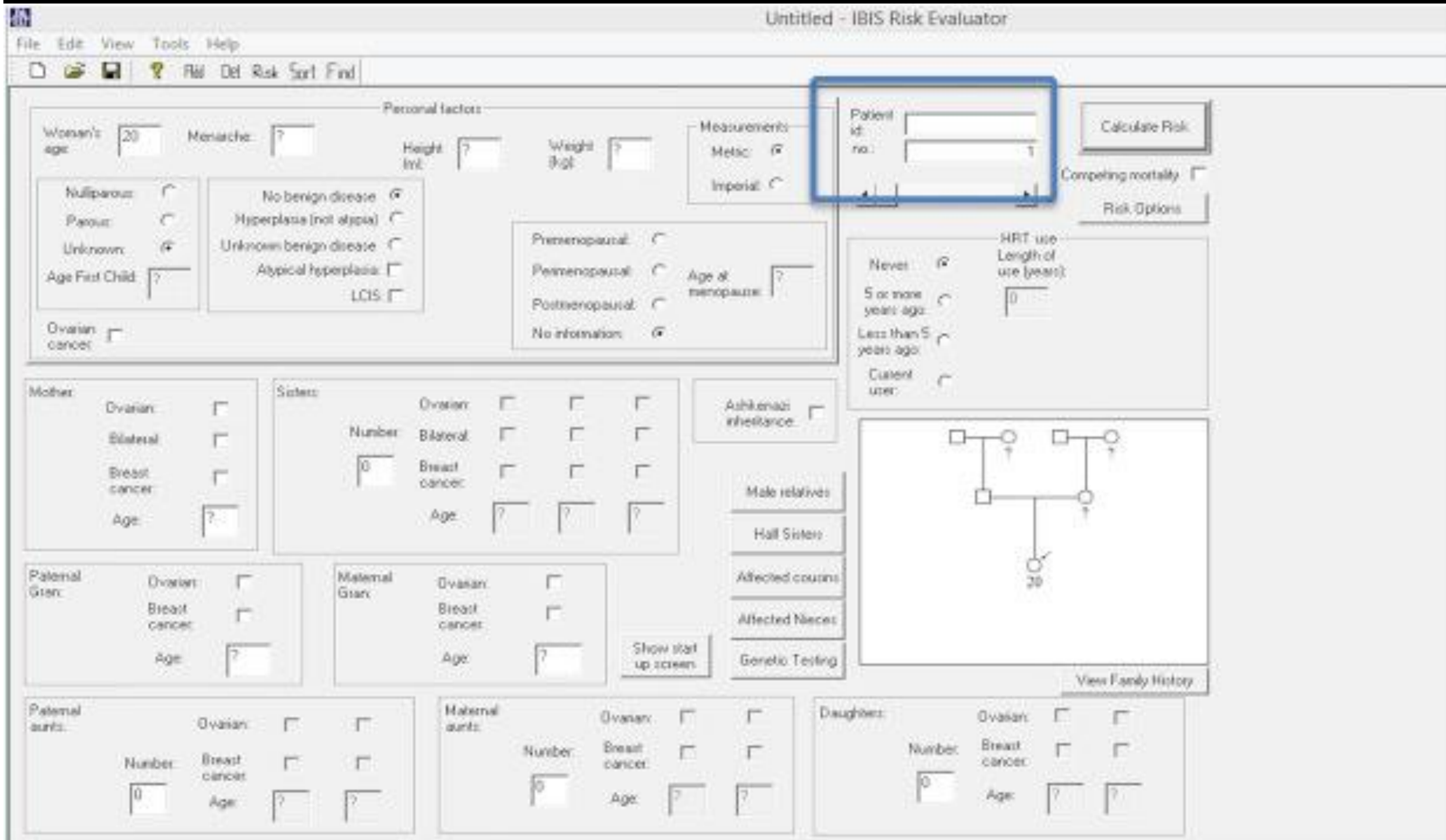
* From reference 13. Developed so that a score of 10 in either column or a combined score of 15 for both columns would be equivalent to a 10% chance of identifying a *BRCA1* or *BRCA2* mutation.
† For relatives in direct lineage.
‡ If *BRCA2* tested.
§ If *BRCA1* tested.

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		

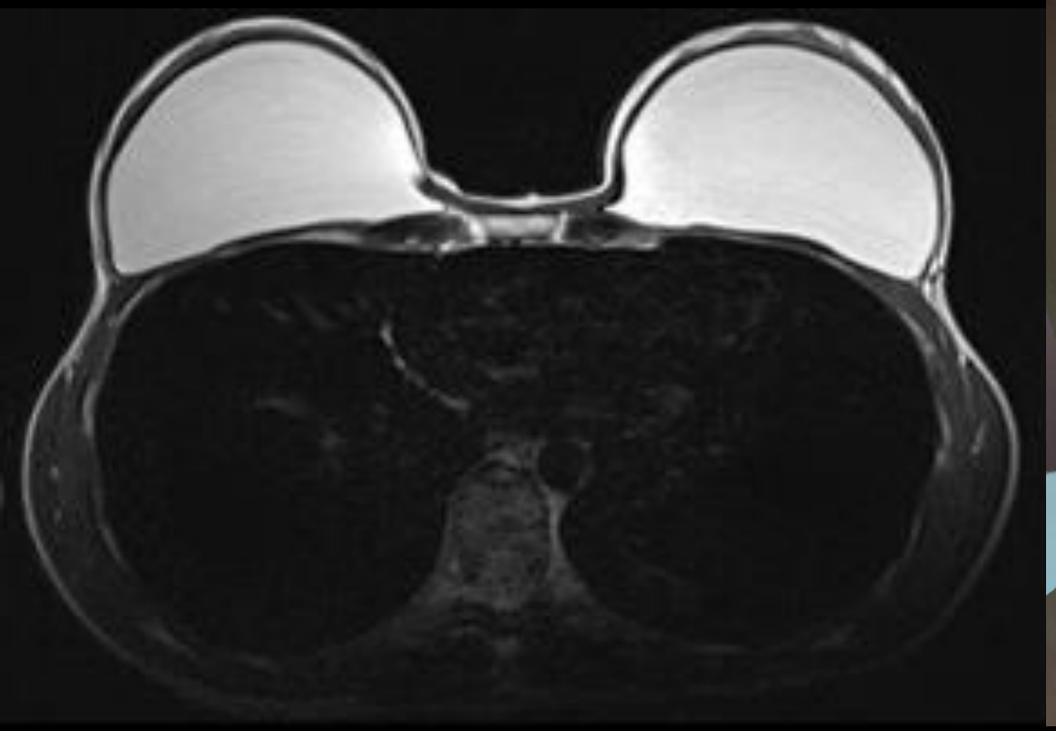
* From reference 16. A patient completes the checklist if she has a family history of breast or ovarian cancer and receives a referral if she checks ≥2 items.

Cuzick and Tyrer model



Options in case of BRCA mutations

- Strict Breast and Ovarian surveillance
- Bilateral salpingo-oophorectomy and bilateral mastectomy



bilateral mastectomy

90-95% risk reduction

berninima@aou-careggi.toscana.it

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