

SUPPLEMENT

AUTOLOGOUS BREAST RECONSTRUCTION TECHNIQUES AFTER MAMMARY RESECTION: TIME MEASUREMENTS FOR A POTENTIAL RE-EVALUATION OF THE SURGEON FEE



AUTOLOGOUS BREAST RECONSTRUCTION TECHNIQUES AFTER MAMMARY RESECTION: TIME MEASUREMENTS FOR A POTENTIAL RE-EVALUATION OF THE SURGEON FEE

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■ APPENDICES

1 CLINICAL LITERATURE REVIEW

1.1 Search Strategies - Electronic reference databases: Medline (through OVID), EMBASE and the Cochrane Library

Date	2015-02-17		
Database	Medline (OVID)		
Search Strategy	#	Query	Results
	1	exp Breast/	32369
	2	breast?.mp.	359597
	3	mammar*.tw.	59945
	4	1 or 2 or 3	396841
	5	DIEP.tw.	611
	6	"deep inferior epigastric perforator".tw.	465
	7	(flap? adj3 (island or pedicled or surgical)).tw.	6465
	8	flap?.tw.	59940
	9	exp Surgical Flaps/	47936
	10	SGAP.tw.	70
	11	"superior gluteal artery perforator".tw.	88
	12	"deep inferior epigastric perforator".tw.	465
	13	"inferior gluteal artery perforator".tw.	37
	14	"latissimus dorsi".tw.	4676
	15	"superficial inferior epigastric artery".tw.	150
	16	SIEA.tw.	109
	17	LSGAP.tw.	3
	18	TUG.tw.	1236
	19	TRAM.tw.	1859
	20	T-DAP.tw.	2



21	(gracilis adj3 upper).tw.	27
22	"transverse rectus abdominus myocutaneous".tw.	21
23	"superior epigastric artery perforator".tw.	10
24	"thoracodorsal artery perforator".tw.	120
25	exp Free Tissue Flaps/	1535
26	"acellular dermis".tw.	167
27	"acellular dermal matrix".tw.	786
28	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	76993
29	4 and 28	5581
30	exp Abdominal Fat/tr	105
31	exp Tissue Expansion/	1832
32	expander*.ti,ab.	3817
33	(tissue? adj3 (expander? or expansion)).ab,ti.	3124
34	30 or 31 or 32 or 33	6143
35	4 and 34	1184
36	exp Mammoplasty/	8908
37	mamm?plast*.tw.	2923
38	((breast? or mammar*) adj3 reconstruction?).tw.	5595
39	29 or 35 or 36 or 37 or 38	13720
40	limit 39 to systematic reviews	257
41	limit 40 to yr="2005 -Current"	215



Date	2015-02-17		
Database	Embase (Embase.com)		
Search Strategy	#	Query	Results
	1	'breast'/exp	93579
	2	breast*:ab,ti	407314
	3	mammar*:ab,ti	71268
	4	#1 OR #2 OR #3	468696
	5	diep:ab,ti	773
	6	'deep inferior epigastric perforator':ab,ti	494
	7	((flap OR flaps) NEAR/3 (island OR pedicled OR surgical)):ab,ti	7469
	8	flap:ab,ti OR flaps:ab,ti	69478
	9	'surgical flaps'/exp	10168
	10	sgap:ab,ti	85
	11	'superior gluteal artery perforator':ab,ti	95
	12	'deep inferior epigastric perforator':ab,ti	494
	13	'inferior gluteal artery perforator':ab,ti	42
	14	'latissimus dorsi':ab,ti	5401
	15	'superficial inferior epigastric artery':ab,ti	163
	16	siea:ab,ti	130
	17	lsgap:ab,ti	3
	18	tug:ab,ti	1927
	19	tram:ab,ti	2373
	20	't dap':ab,ti	3
	21	(gracilis NEAR/3 upper):ab,ti	22
	22	'transverse rectus abdominus myocutaneous':ab,ti	30
	23	'superior epigastric artery perforator':ab,ti	11
	24	'thoracodorsal artery perforator':ab,ti	116
	25	'free tissue graft'/exp	8635
	26	'acellular dermis':ab,ti	213
	27	'acellular dermal matrix':ab,ti	866



28	'acellular dermal matrix'/exp	730
29	'free tissue graft':ab,ti OR 'free tissue grafts':ab,ti	46
30	'tissue flap'/exp	38173
31	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	83513
32	#4 AND #31	6246
33	'abdominal fat'/exp AND 'transplantation'/exp	286
34	'tissue expansion'/exp	2444
35	expander*:ab,ti	4640
36	(tissue* NEAR/3 (expander* OR expansion)):ab,ti	3722
37	#33 OR #34 OR #35 OR #36	7577
38	#4 AND #37	1446
39	'breast reconstruction'/exp	14965
40	mammoplast*:ab,ti OR mammoplast*:ab,ti	3499
41	((breast* OR mammar*) NEAR/3 reconstruction*):ab,ti	6865
42	#32 OR #38 OR #39 OR #40 OR #41	18161
43	[cochrane review]/lim OR 'systematic review' OR 'meta analyse' OR [meta analysis]/lim OR [systematic review]/lim OR 'meta analyses' OR 'meta analysis'	202160
44	#42 AND #43	259
45	[medline]/lim	21645174
46	#44 NOT #45	86
47	#44 NOT #45 AND [2005-2015]/py	84



Date	2015-02-17		
Database	Cochrane		
Search Strategy	#	Query	Results
	#1	diep:ab,ti	16
	#2	'deep inferior epigastric perforator':ab,ti	15
	#3	((flap or flaps) near/3 (island or pedicled or surgical)):ab,ti	82
	#4	flap:ab,ti or flaps:ab,ti	1958
	#5	MeSH descriptor: [Surgical Flaps] explode all trees	1036
	#6	sgap:ab,ti	1
	#7	'superior gluteal artery perforator':ab,ti	0
	#8	'deep inferior epigastric perforator':ab,ti	15
	#9	'inferior gluteal artery perforator':ab,ti	1
	#10	'latissimus dorsi':ab,ti	77
	#11	'superficial inferior epigastric artery':ab,ti	3
	#12	siea:ab,ti	3
	#13	lsgap:ab,ti	0
	#14	tug:ab,ti	199
	#15	tram:ab,ti	41
	#16	't dap':ab,ti	91
	#17	(gracilis near/3 upper):ab,ti	0
	#18	'transverse rectus abdominus myocutaneous':ab,ti	0
	#19	'superior epigastric artery perforator':ab,ti	0
	#20	'thoracodorsal artery perforator':ab,ti	0
	#21	MeSH descriptor: [Free Tissue Flaps] explode all trees	26
	#22	'acellular dermis':ab,ti	19
	#23	'acellular dermal matrix':ab,ti	106
	#24	MeSH descriptor: [Acellular Dermis] explode all trees	19
	#25	'free tissue graft':ab,ti or 'free tissue grafts':ab,ti	192
	#26	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25	2802



#27	MeSH descriptor: [Abdominal Fat] explode all trees	261
#28	MeSH descriptor: [Tissue Expansion] explode all trees	32
#29	expander*:ab,ti	219
#30	(tissue* near/3 (expander* or expansion)):ab,ti	56
#31	#27 or #28 or #29 or #30	509
#32	MeSH descriptor: [Mammoplasty] explode all trees	254
#33	mammoplast*:ab,ti or mammoplast*:ab,ti	98
#34	((breast* or mammar*) near/3 reconstruction*):ab,ti	206
#35	breast*:ab,ti	22334
#36	mammar*:ab,ti	642
#37	MeSH descriptor: [Breast] explode all trees	627
#38	#35 or #36 or #37	22796
#39	#38 and (#26 or #31)	188
#40	mastectom*:ab,ti or 'post mastectomy':ab,ti or 'post mastectomies':ab,ti or postmastectom*:ab,ti or mammectom*:ab,ti	1441
#41	MeSH descriptor: [Mastectomy] explode all trees	1311
#42	#40 or #41	2097
#43	#42 and (#26 or #31)	115
#44	#32 or #33 or #34 or #39 or #43 Publication Year from 2005 to 2015	283
Notes	Details: Systematic reviews: 2 DARE: 36 HTA: 12 Economic evaluations: 23 RCT (CENTRAL): 141	



1.2 Study selection and quality appraisal

1.2.1 Flow chart for selection procedure

Figure 1 – Flow chart of study selection





1.2.2 Study selection

Table 1 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Losken A, et al. 2014 Ann Plast Surg 72(2):145-9 - A meta-analysis comparing breast conservation therapy alone to the oncoplastic technique	Out of scope
Kelley BP, et al. 2014 Ann Surg Oncol 21(5):1732-8 - A systematic review of morbidity associated with autologous breast reconstruction before and after exposure to radiotherapy: are current practices ideal?	No raw incidence rates per study (arm) provided
Smith SL 2014 J. adv. pract. oncol 5(3):181-7 - Functional morbidity following latissimus dorsi flap breast reconstruction	Narrative review
Song J, et al. 2014 PLoS ONE 9(5):e98225 - Impact of neoadjuvant chemotherapy on immediate breast reconstruction: a meta-analysis	3 of 11 included studies on autologous breast reconstruction; no separate results for autologous breast reconstruction
Wang XL, et al. 2014 Database of Abstracts of Reviews of Effects 1):681-691 - Meta-analysis of the safety and factors contributing to complications of MS-TRAM, DIEP, and SIEA flaps for breast reconstruction	Unreliable data extraction
Endara M, et al. 2013 Plast Reconstr Surg 132(5):1043-54 - Breast reconstruction following nipple-sparing mastectomy: a systematic review of the literature with pooled analysis	Out of scope (Focus on nipple-sparing mastectomy)
Shah C, et al. 2013 Ann Surg Oncol 20(4):1313-22 - Radiation therapy following postmastectomy reconstruction: a systematic review	Narrative review
Egeberg A, et al. 2012 J Plast Reconstr Aesthet Surg 65(11):1474-80 - Comparing the donor-site morbidity using DIEP, SIEA or MS-TRAM flaps for breast reconstructive surgery: a meta-analysis	Out of scope
Gieni M, et al. 2012 Breast 21(3):230-236 - Local breast cancer recurrence after mastectomy and immediate breast reconstruction for invasive cancer: a meta-analysis (Structured abstract)	No separate results for autologous breast reconstruction
Barry M, et al. 2011 Breast Cancer Res Treat 127(1):15-22 - Radiotherapy and breast reconstruction: a meta-analysis	All included studies also adopted in Schaverien et al. 2013
D'Souza N, et al. 2011 Cochrane Database of Systematic Reviews 7):- Immediate versus delayed reconstruction following surgery for breast cancer	1 study included on implants
Potter S, et al. 2011 Ann Surg Oncol 18(3):813-23 - Assessment of cosmesis after breast reconstruction surgery: a systematic review	Evaluation on cosmetic assessment after breast reconstruction
Potter S, et al. 2011 J Natl Cancer Inst 103(1):31-46 - Reporting clinical outcomes of breast reconstruction: a systematic review	Evaluation of quality standards of reports on breast reconstruction



Shridharani SM, et al. 2010 J Reconstr Microsurg 26(5):303-10 - Breast sensation after breast reconstruction: a systematic review	Out of scope
Atisha D, et al. 2009 Ann Plast Surg 63(2):222-30 - A systematic review of abdominal wall function following abdominal flaps for postmastectomy breast reconstruction	Out of scope
Man X, et al. 2009 Plastic and Reconstructive Surgery 124(3):752-764 - Abdominal wall following free TRAM or DIEP flap reconstruction: a meta-analysis and critical review	Out of scope
Sailon AM, et al. 2009 Ann Plast Surg 62(5):560-3 - Free transverse rectus abdominis myocutaneous and deep inferior epigastric perforator flaps for breast reconstruction: a systematic review of flap complication rates and donor-site morbidity	Insufficient raw data to calculate incidence rates and ranges
Javaid M, et al. 2006 Journal of Plastic Reconstructive and Aesthetic Surgery 59(1):16-26 - Radiation effects on the cosmetic outcomes of immediate and delayed autologous breast reconstruction: an argument about timing	No raw data provided



1.3 Quality appraisal of included systematic reviews

Table 2 – Methodological quality of the included systematic reviews (AMSTAR) – Research question 2

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Tsoi et al. 2014 (safety)	Y Registered in Prospero	Y Data were extracted by one reviewer, with accuracy verified by a 2nd reviewer.	Y MEDLINE (1946-Oct 4, 2012), EMBASE (1996-Oct 4, 2012), Cochrane Library (issue 4 of 12, April of 2012), PubMed (for non-MEDLINE records)	Y ProQuest Dissertation and Theses.	N No list of excluded studies	Y	? Newcastle-Ottawa scale; summary score per study	N	NA See report	Y funnel plots	? Only in the form of an acknowledgment; sources of funding of primary studies rarely reported
Wormald et al. 2014	Y	Y Data were extracted by one reviewer, with accuracy verification by others	Y Ovid MEDLINE and Ovid EMBASE (1994 - March 2012)	Y Supplemented by a handsearch for recent/in-press articles	N No list of excluded studies	Y	? Difficult to perform as only case series were retrieved	? As far as possible the authors did	NA See report	Y	? Only for SR, not for primary studies
Khansa et al. 2013	? Unclear if established before conduct of review	N	N	N	N	N	N	N	NA See report	N	? Only for SR, not for primary studies



Table 3 – Methodological quality of the included systematic reviews (AMSTAR) – Research question 3

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Rochlin et al. 2015	? Unclear if established before	? Yes for study selection; no	N	Medline (through Pubmed)	Y "Manual search of reference list	N No list of excluded studies	Y		NA See report	N	? Only for SR, not for primary
Berbers et al. 2014	? Unclear if established before conduct of review	N	N	Pubmed	N	N	N	N	NA See report	N	? Only for SR, not for primary studies
Schaverien et al. 2013	? Unclear if established before conduct of review	? Yes for study selection; no for data extraction	Y	Pubmed (1966 to October 2012), Ovid MEDLINE (1966 to October 2012), EMBASE (1980 to October 2012), and the Cochrane Database of Systematic Reviews (Issue 10, 2012)	N	N	? Only sample size	Y According to STROBE	NA See report	N	? Only for SR, not for primary studies



1.4 Evidence tables of included systematic reviews

1.4.1 *Research question 1: In women who underwent a mastectomy, what is the clinical effectiveness in terms of quality of life in those women who had an autologous breast reconstruction, compared with women who had a breast reconstruction with implants, or a mastectomy without reconstruction?*

Tsoi et al. 2014 (PROs) ¹	
Methods	
• Design	Systematic review
• Source of funding and competing interest	First author is supported through an Award from the Father Sean O'Sullivan Research Centre, St. Joseph's Healthcare Hamilton, and the Canadian Institutes of Health Research Drug Safety and Effectiveness Cross-Disciplinary Training program. Authors had nothing else to disclose Sources of funding of primary studies rarely reported
• Search date	August 26, 2013
• Searched databases	Medline (January 2000 - August 26, 2013), Embase (January 2000 - August 26, 2013), Cochrane Library (January 2000 - August 26, 2013), PubMed (January 2000 - August 26, 2013), Proquest dissertations, theses
• Included study designs	Not specified
• Number of included studies	15
• Statistical analysis	Due to lack of RCTs and heterogeneity in the PROs examined, no formal statistical techniques such as meta-analysis possible
Patient characteristics	
• Eligibility criteria	Papers reporting patient-reported clinical and psychosocial outcomes Sample size >10 patients per study arm
• Exclusion criteria	Studies reporting unsolicited patient feedback Studies in which data could not accurately be extracted
• Patient & disease characteristics	Not reported
Interventions	
• Intervention group	Tissue expander/implant reconstruction (TE/I) N= 500 (patients)
• Control group	Autologous abdominal tissue flaps (ATF): TRAM (free or pedicled)



N= 893 (patients)

Results

- **General satisfaction**
 - Smaller studies: suggesting similar satisfaction vs. larger sample size studies (i.e. >100): recipients of ATF more satisfied up to 2 years post-reconstruction (2 studies), but difference converged by 2nd year
 - Contradictory data on impact of complications on satisfaction (2 studies)
- **Esthetic satisfaction**
 - Smaller studies: suggesting similar esthetic satisfaction vs. larger sample size studies (i.e. >100): recipients of ATF more aesthetically satisfied up to 2 years post-reconstruction (2 studies)
 - Recipients of AFT: satble measures of esthetic reconstruction vs. recipients of TE/I >8 years ago were significantly less satisfied than recipients of TE/I <5 years ago with their breast appearance (adj OR: 0.10, 95% CI: 0.02 - 0.48), softness (adj OR: 0.14, 95% CI: 0.03 - 0.64) and size (adj OR 0.13, 95% CI: 0.03 - 0.62)(1 study)
- **Functional well-being**
 - Contradictory results
- **Social well-being**
 - Immediate reconstruction: no difference between procedures
 - Delayed reconstruction: TE/I recipients reported greater gains (on FACT-B social well-being subscale) than TRAM recipients
 - 2-years post-op:
 - immediate reconstruction group: decline in pedicled TRAM and TE/I vs. increase in free-TRAM group (adjusted for age and pre-op scores; statistically significant difference)
 - delayed reconstruction group: in all groups decline in social well-being
 - No change in sexual life after reconstruction (across different procedure groups)
- **Mental & emotional health**
 - Improvement in both reconstruction groups
 - Body image:
 - 1st & 2nd year: greater adjusted gains in TRAM patients that in TE/I patients (difference was significant in delayed reconstruction patients)
- **Postreconstruction pain**
 - General pain: 1st & 2nd year: no sign difference across reconstructive procedures
 - Abdominal pain & tightness: more reported in TRAM patients than in TE/I patients



- **Willingness to repeat and recommend**
- Comparably high for both procedures

Limitations and other comments

- **Limitations**
 - Only summary score provided for quality appraisal
 - Quality appraisal not taken into account for conclusions
 - Lack of consistent measurement methods, hence pooling of data not possible
 - Variable follow-up duration
 - Selection bias in primary studies very probable
 - Volunteer bias in primary studies very probable
 - Misclassification bias due to self-reporting
 - All included studies were observational, hence results may be influenced by confounders

Winters et al. 2010²

Methods

- **Design** Systematic review
- **Source of funding and competing interest** Supported by Bupa Charitable Giving, Allergan, and University Hospitals Bristol, NHS Foundation Trust—Above and Beyond Charitable Trustees (to first author)
- **Search date** February 2009
- **Searched databases** Medline, Cochrane, Embase, Psychinfo
- **Included study designs** Not specified
- **Number of included studies** 34
- **Statistical analysis** NA

Patient characteristics

- **Eligibility criteria**
 - Articles published in English, between 1978 and 2009
 - Women more than 16 years of age with a diagnosis of breast cancer.
 - Studies that compared outcomes of mastectomy and breast reconstruction (immediate or delayed) or types of immediate or delayed breast reconstruction
 - Only studies using validated questionnaires with reported psychometric properties



<ul style="list-style-type: none"> Exclusion criteria 	<ul style="list-style-type: none"> Studies relating to risk-reducing (prophylactic) surgery, male breast cancer Abstracts (limited extent of methodological) details Studies comparing breast conserving surgery alone or latissimus dorsi miniflap alone Studies with clinician-assessed measures, or patient self-reported symptoms only Studies using ad hoc (single-center, studyspecific) only questionnaires or “modified” questionnaires
<ul style="list-style-type: none"> Patient & disease characteristics 	Not specified
Interventions	
<ul style="list-style-type: none"> Intervention group 	Not specified
<ul style="list-style-type: none"> Control group 	Not specified
Results	
<ul style="list-style-type: none"> HRQoL – mastectomy vs. immediate breast reconstruction 	<ul style="list-style-type: none"> Patients undergoing mastectomy with IBR (both implant only and autologous tissue reconstruction) have lower quality of life scores in the major domains (psychologic, physical, functional, and emotional) compared with women who had mastectomy only (1 prospective study^a) Scores for self concept, body image, emotional problems and sexual functioning – in younger patients (1study^b): <ul style="list-style-type: none"> At 6 months: improvements for IBR recipients compared with either breast conserving surgery or mastectomy only At 12 months after surgery: no differences between IBR recipients compared with either breast conserving surgery or mastectomy only
<ul style="list-style-type: none"> HRQoL – comparison between types of reconstruction 	<ul style="list-style-type: none"> No differences between the types of DBR (lateral thoracodorsal (n=16), latissimus dorsi (n=30), and pedicled TRAM (n=29) (1 RCT) No differences between the types of IBR (4 prosp long studies) DBR: improved body image with autologous TRAM flaps (pedicled or free) compared with implant procedures (2 studies) Physical functioning: worse with TRAM flap reconstruction compared with subpectoral implants; situation deteriorated significantly over a 12-month period postoperatively (P < 0.01) (1 study) No clear relationship between type of breast reconstruction and HRQoL (3 retrospective studies^c)

^a This study benefited from a multivariate analysis correcting for independent variables such as chemotherapy and radiotherapy, although the latter treatment numbers of patients were not recorded. A limitation of this study was its reliance on generic PRO measures, which do not address issues relating to breast reconstruction (i.e. body image).

^b Based on a small sample size (n=21) and post-hoc analysis; “younger” is not defined

^c Limited by study design and small numbers



- Aesthetic satisfaction (using BREAST-Q^d; 1 study, n=219):
 - Short term (≤ 5 years): similar for TE/I recipients and autologous TRAM flap reconstruction recipients
 - Longer term (>8 years): significant attrition in rates of aesthetic satisfaction (appearance, softness, and size) for the TE/I recipients compared with TRAM flap reconstruction recipients

Limitations and other comments

- **Limitations**
 - No patient characteristics specified
 - No treatment characteristics specified
 - Only study design and sample size taken into account in conclusions
 - Likelihood of publication bias not assessed

Lee et al. 2009³

Methods

- **Design** Systematic review
- **Source of funding and competing interest** Authors had nothing to disclose
- **Search date** July 2007
- **Searched databases** Medline, Cochrane, PsychINFO, CINAHL
- **Included study designs** Not specified
- **Number of included studies** 28 (21 cross-sectional surveys and 7 prospective cohort studies)
- **Statistical analysis** “Because of the diversity of outcomes and scales used, a meta-analysis of findings was not considered appropriate.”

Patient characteristics

- **Eligibility criteria** Not specified
- **Exclusion criteria**
 - Articles not in English, not about women, not about breast reconstruction after mastectomy, or published before 1980.
 - Articles that did not assess patient-reported outcomes, or did not compare outcomes of mastectomy with reconstruction with mastectomy only.

^d Validated “reconstruction-specific” patient-reported outcome measure



-
- **Patient & disease characteristics** Not specified

Interventions

- **Intervention group** Not specified
- **Control group** Not specified

Results

See text in report

Limitations and other comments

- **Limitations**
 - No patient characteristics specified
 - No treatment characteristics specified
 - No inclusion criteria specified
 - See text in report for limitations of primary studies
-



1.4.2 Research question 2: What are the adverse outcomes associated with autologous breast reconstruction?

Tsoi et al. 2014 (safety) ⁴	
Methods	
• Design	Systematic review & meta-analysis
• Source of funding and competing interest	First author is supported through an Award from the Father Sean O'Sullivan Research Centre, St. Joseph's Healthcare Hamilton, and the Canadian Institutes of Health Research Drug Safety and Effectiveness Cross-Disciplinary Training program. No declaration of interest Sources of funding of primary studies rarely reported
• Search date	October 4, 2012
• Searched databases	Medline (1946-Oct 4, 2012), Embase (1996-Oct 4, 2012), Cochrane Library (issue 4 of 12, April of 2012), PubMed (for non-medline records)
• Included study designs	All studies, whether randomized or nonrandomized
• Number of included studies	14
• Statistical analysis^e	Pooled analyses using RevMan 5.2; fixed effect model if $I^2 < 30\%$, otherwise random effects model Publication bias assessed with funnel plots
Patient characteristics	
• Eligibility criteria	Studies comparing surgical complications of primary breast reconstruction with tissue expander/implant versus autologous abdominal tissue procedures after total mastectomy for breast cancer in adult women older than 18 y.o. Sample size greater than 10 per study arm
• Exclusion criteria	Articles that evaluated chest wall reconstruction for recurrent disease, volume replacement following breast conservation, or prophylactic surgery
• Patient & disease characteristics	<ul style="list-style-type: none"> • Sample size (i.e. number of reconstructed breasts): range: 38-1542 • Mean age (per treatment arm): range: 43.2-66.6 y.o. • Mean follow-up: range: 6-60.2 months
Interventions	
• Intervention group	Tissue expander/impant reconstruction (TE/I) N= 1931 (breasts)

^e Adhering to the instructions of the Cochrane Handbook on Systematic Reviews not to pool data retrieved from non-randomized studies, the pooled effect estimates are not reported here.⁵ Instead, ranges of reported incidences per study arm are reported. This way, data retrieved from comparative and non-comparative studies added information.



<ul style="list-style-type: none"> Control group 	Autologous abdominal tissue flaps (ATF): TRAM (and variations), DIEP, SIEA N= 1313 (breasts)
Results^f	
<ul style="list-style-type: none"> Major complications^g 	<ul style="list-style-type: none"> With or without return to operation room (8 studies; n^h: ATF: 24-144 – TE/I: 14-79): ATF: 0-49% vs. TE/I: 0-71% Subgroup analysis: necessitating return to operation room (5 studies; n: ATF: 24-56 – TE/I: 18-58): ATF: 0-26% vs. TE/I: 0-39% Subgroup analysis: on irradiated breast (4 studies; n: ATF: 24-41 – TE/I: 14-50): ATF: 0-41% vs. TE/I: 4-71% <p><i>Note:</i></p> <ul style="list-style-type: none"> – Early complications: higher in patients receiving postmastectomy radiotherapy before reconstruction (1 study) – Late complications: higher in patients receiving postmastectomy radiotherapy after reconstruction (1 study)
<ul style="list-style-type: none"> Reconstructive failureⁱ 	<ul style="list-style-type: none"> With or without return to operation room (7 studies; n: ATF: 30-246 – TE/I: 10-334): ATF: 0-3% vs. TE/I: 0-28% Subgroup analysis: necessitating return to operation room (4 studies; n: ATF: 30-246 – TE/I: 18-79): ATF: 0-1% vs. TE/I: 4-28% Subgroup analysis: on irradiated breast (1 study; n: ATF: 30 – TE/I: 18): ATF: 0% vs. TE/I: 11%
<ul style="list-style-type: none"> Surgical-site infection^j 	<ul style="list-style-type: none"> With or without return to operation room (9 studies; n: ATF: 24-246 – TE/I: 10-334): ATF: 0-13% vs. TE/I: 0-35% Subgroup analysis: necessitating return to operation room (2 studies; n: ATF: 43-56 – TE/I: 31-58): ATF: 0-2% vs. TE/I: 0% Subgroup analysis: on irradiated breast (3 studies; n: ATF: 24-35 – TE/I: 18-50): ATF: 0-8% vs TE/I: 4-12%
<ul style="list-style-type: none"> Development of haematoma or seroma 	<ul style="list-style-type: none"> With or without return to operation room (7 studies; n: ATF: 17-246 – TE/I: 10-334): ATF: 0-5% vs. TE/I: 0-10%

^f As pooling of data from non-randomised studies is not recommended, no results of the meta-analyses are reported, only ranges extracted from the primary studies

^g Composite outcome as any complication requiring reoperation, revision surgery, or rehospitalization

^h Sample size range per study arm

ⁱ Reconstructive failure was a pooled variable that incorporated implant failure (defined as extrusion of the prosthesis, implant rupture, implant rippling, implant malposition, implant failure or implant exposure) and flap failure (defined as total flap loss or flap failure); duration of follow-up not specified

^j Excluding donor-site infection; not more specifications provided



	<ul style="list-style-type: none"> Subgroup analysis: on irradiated breast (1 study; n: ATF: 24 – TE/I: 26): ATF: 0% vs. TE/I: 4%
<ul style="list-style-type: none"> Skin/fat necrosis 	<ul style="list-style-type: none"> With or without return to operation room (11 studies; n: ATF: 17-246 – TE/I: 10-334): ATF: 0-24% vs. TE/I: 0-8% Subgroup analysis: necessitating return to operation room (3 studies; n: ATF: 24-43 – TE/I: 18-31): ATF: 8-12% vs. TE/I: 0-6% Subgroup analysis: on irradiated breast (3 studies; n: ATF: 24-35 – TE/I: 18-50): ATF: 8-14% vs. TE/I: 0%
<ul style="list-style-type: none"> Wound dehiscence 	<ul style="list-style-type: none"> With or without return to operation room (6 studies; n: ATF: 24-246 – TE/I: 10-334): ATF: 0-4% vs. TE/I: 4-12% Subgroup analysis: on irradiated breast (2 studies; n: ATF: 24-30 – TE/I: 18-26): ATF: 0% vs. TE/I: 6-12%
<ul style="list-style-type: none"> Venous thrombosis/pulmonary embolism 	<ul style="list-style-type: none"> With or without return to operation room (4 studies; n: ATF: 12-246 – TE/I: 10-334): ATF: 1-8% vs. TE/I: 0-10%
<ul style="list-style-type: none"> Hernia, abdominal bulge rate (only in ATF) 	<ul style="list-style-type: none"> Abdominal bulge: 6% (1 study, breasts reconstructed with TRAM; n:17) Older patients (i.e. ≥60 y.o.) - over a mean of 45.6 months: <ul style="list-style-type: none"> Minor abdominal bulge (i.e. not requiring re-operation): 5% Major abdominal bulge/hernia (i.e. requiring re-operation): 21% Hernia – free TRAM: range: 2.7-6.0% (2 studies) Hernia – free vs. pedicled TRAM: 11.9-7.8% (1 study)
<ul style="list-style-type: none"> Trunk function 	<ul style="list-style-type: none"> Trunk isokinetic peak torque and range of motion, at 24 months after reconstruction (1study): adjusted preoperative trunk flexion significantly lower in TRAM flap recipients than in TE/I recipients <p><i>Notes:</i></p> <ul style="list-style-type: none"> No difference between different TRAM variations
Limitations and other comments	
<ul style="list-style-type: none"> Limitations 	<ul style="list-style-type: none"> All studies were observational Several studies had smaller sample sizes (i.e., <100 participants), with none reporting a power calculation to ensure sufficient power to detect clinically important differences between study groups. All studies relied on convenience sampling, only few used a consecutive sampling strategy Selection bias is highly probable in most studies Fewer than half of the studies adjusted for potential confounders Certain complications were only reported in a few studies



- Outcome reporting may have been impacted by reporting bias as blinding is not possible (scar variation)
- Only one study explicitly addressed loss to follow-up
- Short-term follow-up may not adequately capture all complications relating to each approach to reconstruction
- Not possible to evaluate impact of learning curve of surgeons on outcome
- None of the studies explained how missing data were handled

Wormald et al. 2014⁶

Methods

- **Design** Systematic review & meta-analysis
- **Source of funding and competing interest** No source of funding reported
Declaration of interest present, stating that there are none
- **Search date** March 2012
- **Searched databases** Ovid Medline and Ovid Embase
- **Included study designs** Not specified (only case series were retrieved, 13 consecutive and 4 non-consecutive)
- **Number of included studies** 17 (with a total of 2398 patients)
- **Statistical analysis^e** The unit of investigation was the patient (rather than the flap)
RevMan 5 to calculate relative risk ratios (RR) with 95% CI using the Cochrane Mantel Haenszel test; random effects model due to heterogeneity
Publication bias assessed with funnel plots

Patient characteristics

- **Eligibility criteria**
 - Women over 18 years old undergoing unilateral or bilateral DIEP flap breast reconstruction
 - Only studies with a minimum of 100 patients with unilateral DIEP flap breast reconstruction or a minimum of 50 patients with bilateral DIEP flap breast reconstruction
 - Only studies which reported any adverse outcomes for DIEP flap breast reconstruction including flap related, donor-site or systemic complications
- **Exclusion criteria**
 - Case reports
- **Patient & disease characteristics**
 - Sample size (i.e. number of patients): mean: 141, range: 54-407
 - Mean age: range: 41.9-53.6 y.o.
 - Mean BMI (based on 8 studies): range: 21-28
 - % obese (based on 4 studies): 5-28
 - % active smokers (based on 9 studies): range: 2-26%



- % other medical comorbidity^k (based on 6 studies): range: 7-62
- % previous radiotherapy (based on 6 studies): range: 15-49
- % previous chemotherapy (based on 5 studies): range: 19-88
- % previous abdominal scarring (based on 5 studies): range: 15-74
- Mean follow-up (based on 7 studies): mean: 26 months, range: 14.6-40 months
- Unilateral DIEP reconstruction: 5 studies; bilateral DIEP reconstruction: 3 studies; both unilateral and bilateral DIEP flap breast reconstruction: 8 studies
- Recruitment period: mean: 5.7 years, range: 1-10.5 years

Interventions

- **Intervention group** Bilateral DIEP flap breast reconstruction (Bi-DIEP)
- **Control group** Unilateral DIEP flap breast reconstruction (Uni-DIEP)

Results^l

- **Flap failure**
 - Total flap failure:
 - Uni-DIEP (8 studies): 0-6%
 - Bi-DIEP (6 studies): 0-10%
 - Partial flap failure (3 studies):
 - Uni-DIEP (6 studies): 0-16%
 - Bi-DIEP (4 studies): 0-4%
- **Other flap related adverse outcomes**
 - Breast haematoma:
 - Uni-DIEP (5 studies): 0-10%
 - Bi-DIEP (3 studies): 5-10%
 - Breast seroma:
 - Uni-DIEP (5 studies): 0-6%
 - Bi-DIEP (2 studies): 2-13%
 - Vascular complications:
 - Uni-DIEP (7 studies): 1-20%
 - Bi-DIEP (6 studies): 0-13%
 - Fat necrosis:
 - Uni-DIEP (7 studies): 6-46%
 - Bi-DIEP (6 studies): 2-38%

^k Including diabetes mellitus, hypertension, ischaemic heart disease

^l As pooling of data from non-randomised studies is not recommended, no results of the meta-analyses are reported, only ranges extracted from the primary studies



-
- **Donor site related adverse outcomes**
 - Post-operative abdominal haematoma:
 - Uni-DIEP (4 studies): 0-5%
 - Bi-DIEP (3 studies): 0-4%
 - Post-operative abdominal hernia/bulge:
 - Uni-DIEP (7 studies): 1-10%
 - Bi-DIEP (7 studies): 0-13%
 - Post-operative abdominal seroma:
 - Uni-DIEP (4 studies): 0-6%
 - Bi-DIEP (6 studies): 0-21%
 - **Systemic adverse outcomes**
 - Post-operative infection:
 - Uni-DIEP (studies): 3-24%
 - Bi-DIEP (4 studies): 0-7%
 - Death: none reported
-

Limitations and other comments

- **Limitations**
 - Certain complications could not be pooled, due to paucity of studies
 - Unclear if reconstructions were performed immediate or delayed
 - Inconsistent outcome reporting among primary studies
 - Inaccurate reporting of data
 - All studies were case series
 - Not all primary studies intended to compare unilateral versus bilateral DIEP
 - Selection bias may be present
 - Outcome reporting may have been impacted by reporting bias as blinding is not possible (scar variation)
 - Short-term follow-up may not adequately capture all complications relating to each approach to reconstruction
 - Not possible to evaluate impact of learning curve of surgeons on outcome
 - Not all studies specified duration of follow-up
 - Unclear how missing data were handled
 - Unclear how loss to follow-up was handled
-



1.4.3 Research question 3: What is the impact of radiotherapy on an autologous breast reconstruction?

Rochlin et al. 2015 ⁷	
Methods	
• Design	Systematic review
• Source of funding and competing interest	Last author is a speaker/consultant with LifeCell Corporation No other declaration of interest provided
• Search date	October 2013
• Searched databases	Medline (through Pubmed)
• Included study designs	Any design, but no reviews, comments, editorials or case reports
• Number of included studies	11 (reporting on 337 flaps in 337 patients; 3 comparative and 8 case series; all retrospective)
• Statistical analysis^e	Random effects model because of the heterogeneity of the study populations, using Comprehensive Meta-Analysis Version 2.2
Patient characteristics	
• Eligibility criteria	<ul style="list-style-type: none"> • Clear outline of the total number of patients and type of flap used • Report of the rate, raw data, or percentage of at least one of the following complications: total or partial flap necrosis, fibrosis or contracture, fat necrosis or volume loss, delayed wound healing, and overall complication rate
• Exclusion criteria	<ul style="list-style-type: none"> • Reviews, comments, editorials or case reports • Any study that did not contain the population, treatment, and outcome of interest • Articles reporting techniques or guidelines • Sample smaller than 10 patients
• Patient & disease characteristics	<ul style="list-style-type: none"> • Mean age: range: 42.7-51 y.o. (8 studies) • Smoker: range: 0-16.7% (5 studies) • Adj chemo: range: 13.6-100% (5 studies) • Mean follow-up: range: 18-48 months (7 studies) • Unilateral: range: 65.9-98.8% (3 studies), bilateral: range: 1.2-34.1% (3 studies) • Free TRAM: 56 flaps (16.6%), pedicled TRAM: 91 flaps (27.0%), TRAM without specification whether free or pedicled: 138 (40.9%), DIEP: 52 flaps (15.4%)
Interventions	
• Intervention group	Immediate autologous breast reconstruction (with abdominal wall-based tissue) followed by RT
• Control group	Immediate autologous breast reconstruction (with abdominal wall-based tissue) not followed by RT
Results	



• Total flap loss	RT: 0-7% (8 studies; n: 15-82) vs. no RT: 0% (1 study; n: 14)
• Partial flap loss	RT: 0% (7 studies; n: 15-41) vs. no RT: 0-2% (2 studies; n: 14-149)
• Fat necrosis	RT: 9-34% (6 studies; n: 15-82) vs. no RT: 0-15% (3 studies; n: 14-149)
• Need for revisional surgery	RT: 0-67% (5 studies; n: 22-35) vs. no RT: 19-87% (2 studies; n: 30-149)
• Volume loss	RT: 6-36% (2 studies; n: 35-82)
• Fibrosis and/or contracture	RT: 36-77% (3 studies; n: 30-82) vs. no RT: 0% (2 studies; n: 14-30)
• Infection, haematoma, seroma, erythema, delayed wound healing	"Inconsistently reported"
• Aesthetic outcome	Based on blinded judges: no RT resulted in better aesthetic outcomes (2 studies) Based on self-evaluation, after RT: excellent/good: 77.1%, fair: 17.7%, and poor: 5.2% (3 studies, 96 patients)

Limitations and other comments

- **Limitations**
 - No comprehensive literature search (only Medline through Pubmed)
 - Inconsistencies between data in texts and tables
 - Small sample sizes for most studies
 - All studies were retrospective case series
 - Selection bias may be present
 - Some studies did not specify the number of flaps (hence it was assumed that the number of flaps radiated was equal to the number of patients)
 - No adjustment for confounders
 - No characteristics provided for patients in the no-RT arm of the comparative studies
 - Some studies did not specify duration of follow-up
 - Selected studies varied in study design and method, radiotherapy techniques, mastectomy techniques and types of flaps utilized in immediate reconstruction



Berbers et al. 2014⁸

Methods

• Design	Systematic review & meta-analysis
• Source of funding and competing interest	Authors had no conflict of interest to declare
• Search date	December 2012
• Searched databases	Pubmed
• Included study designs	All study designs apart from case reports
• Number of included studies	37
• Statistical analysis^e	<ul style="list-style-type: none"> • Weighted mean rates (and 95% CI) calculated assigning a weight to each individual study result based on the size of the study population, in relation to the total population for that study group. • A second analysis (to minimise bias from interstudy variability) using only those studies that had direct comparisons (i.e. reconstruction before with after radiotherapy) if there were two or more studies to compare for tht complication • For the total complication rate, and the more serious complications like flap or implant failure, forest plots were made using Revman, comprising data from five of the seven studies that made direct comparisons. • Patient and physician satisfaction on cosmetic outcome analysed per group using forest plots; overall odds ratios (and 95% Cis) were calculated and interpreted while taking into account the number and size of studies providing data.

Patient characteristics

• Eligibility criteria	<ul style="list-style-type: none"> • Articles written in English or Dutch, published between Jan 2000 and December 2012 • Articles reporting on at least 20 patients • Part of a study population could be included if only that part fulfilled the selection criteria • Patients with primary breast cancer
• Exclusion criteria	<ul style="list-style-type: none"> • Case reports • Patients treated for recurrence or secondary breast cancer
• Patient & disease characteristics	None reported

Interventions

• Intervention group	Pre-reconstruction (Sx) radiotherapy (RT) flap (=RT-Sx)
• Control group	Post-reconstruction (Sx) radiotherapy (RT) flap (=Sx-RT)

Results



- | | |
|----------------------------------|---|
| • Total complication rate | RT-Sx: 26-47% (6 studies; n: 15-189) vs. Sx-RT: 9-70% (9 studies; n: 13-78) |
| • Flap failure | RT-Sx: 1-10% (5 studies; n: 53-189) vs. Sx-RT: 7-8% (2 studies; n: 15-53) |

Limitations and other comments

- **Limitations**
 - Inaccurate data extraction of several studies
 - No comprehensive literature search (only pubmed)
 - No list of in- and excluded studies provided
 - No characteristics of included studies provided
 - No patient and disease characteristics of included samples provided, hence no idea on the extent of risk factors present
 - No RCTs available
 - No quality appraisal of included studies
 - Unclear what is considered “an event” in the analyses on patient satisfaction and physician satisfaction
 - Lack of standardised outcome complication parameters
 - Follow-up length was not evaluated
 - No information on the reconstruction types applied (e.g. TRAM, DIEP)
 - Likelihood of publication bias not assessed

Schaverien et al. 2013⁹

Methods

- | | |
|---|---|
| • Design | Systematic review |
| • Source of funding and competing interest | No funding
No conflict of interest to be declared |
| • Search date | October 2012 |
| • Searched databases | Pubmed, Medline, Embase, Cochrane |
| • Included study designs | Specify the type of study: RCT, CCT, case control, case series |
| • Number of included studies | <ul style="list-style-type: none"> • RQ 1: immediate autologous reconstruction and postoperative RT (IBR+RT) vs. immediate autologous reconstruction without RT (IBR): 25 (among which 10 comparative) • RQ 2: immediate autologous reconstruction and postoperative RT (IBR+RT) vs. postoperative RT and DBR (RT+DBR): 16 (among which 14 comparative) <i>Note: some studies counted in both</i> |
| • Statistical analysis | <ul style="list-style-type: none"> • Pooling of data using Review manager version 5 • For dichotomous data, OR with 95% CI were estimated based on the fixed-effects model and according to an intention to treat analysis. • As $I^2 > 50\%$ in both analyses for fat necrosis, OR with 95% CI were estimated based on the random-effects model and according to an intention-to-treat analysis |

Patient characteristics

- | | |
|--|---|
| • Eligibility criteria | <ul style="list-style-type: none"> • Only English language and full text articles • Studies that reported outcomes of autologous breast reconstruction without using a prosthesis |
| • Exclusion criteria | <ul style="list-style-type: none"> • Studies where the data could not be accurately extracted • Studies with patient numbers <10 |
| • Patient & disease characteristics | Not specified |

Interventions – RQ1

- | | |
|-----------------------------|----------|
| • Intervention group | IBR + RT |
| • Control group | IBR |

Results – RQ1

- | | |
|--------------------------------|--|
| • Overall complications | 5 comparative studies: IBR+RT: 26-50% (n: 19-78) vs. IBR: 18-50% (n: 57-371) |
| • Fat necrosis | 6 comparative studies: IBR+RT: 11-34% (n: 19-41) vs. IBR: 0-15% (n: 30-1443) |
| • Revisional surgery | 3 comparative studies: IBR+RT: 12-67% (n: 22-30) vs. IBR: 17-87% (n: 30-149) |

**Interventions – RQ2**

- **Intervention group** IBR + RT
- **Control group** RT + DBR

Results – RQ2

- **Overall complications** 6 comparative studies: RT+DBR: 26-50% (n: 19-78) vs. IBR+RT: 25-58% (n: 15-108)
- **Fat necrosis** 7 comparative studies: RT+DBR: 0-15% (n: 13-36) vs. IBR+RT: 9-24% (n: 11-108)
- **Revisional surgery** 4 comparative studies: RT+DBR: 6-28% (n: 13-36) vs. IBR+RT: 0-18% (n: 11-70)
Note by the review authors: “The higher percentages of revisional surgery in the IBR compared with the DBR group may be related more to the timing of surgery than radiotherapy.”

Limitations and other comments

- **Limitations**
 - Inaccurate data extraction of several studies
 - Insufficient data to determine whether differences existed between different flap types
 - The proportion requiring anastomotic revision was not included in the complication analysis as it was not reported in the majority of studies
 - If reported, there were significant variations in RT treatment variables between and within the studies (e.g. fraction size, fractionation schedule, use of a boost, total dose delivered)
 - The majority of primary studies involved small numbers of patients in single centres with retrospective analysis and variable follow-up periods
 - There was considerable heterogeneity in the types of flaps included, the outcome measures and definitions used
 - Limited report of characteristics of included studies
 - No patient and disease characteristics of included samples provided, hence no idea on the extent of risk factors present
 - No list of in- and excluded studies provided



Title + study ID (+ref endnote)	
Methods	
• Design	
• Source of funding and competing interest	Specify the source of funding: public research funds, government, not governmental organization, healthcare industry or other (give name of organization or corporation) and the presence of declaration of interest (stated/not stated and specify if any)
• Search date	
• Searched databases	
• Included study designs	Specify the type of study: RCT, CCT, case control, case series
• Number of included studies	
• Statistical analysis	Specify the statistical methods used
Patient characteristics	
• Eligibility criteria	State the most relevant inclusion criteria for population (patients and pathology)
• Exclusion criteria	State the most relevant exclusion criteria for population (patients and pathology)
• Patient & disease characteristics	State the most relevant baseline characteristics
Interventions	
• Intervention group	Precise details of the interventions for each group (including dose, length, regimen and timing if relevant)
• Control group	Precise details of the interventions for each group (including dose, length, regimen and timing if relevant)
Results	
• Outcome 1	Summary of the critical and important outcomes within and between groups: effect size (absolute risk reduction, relative risk (reduction), odds ratio) and its precision (p value, CI)
• Outcome 2	
• Outcome 3	
• Outcome 4	
• Outcome 5	
Limitations and other comments	
• Limitations	Comments on limitations of the study (external and internal validity)



2 NATIONAL HOSPITAL STAYS DATABASE (NHDB)

The national hospital stays database (NHDB) merges data from two different sources, one from the hospitals (Minimal Clinical Data – MCD), the other from the national health insurance companies (Hospital Billing Data – HBD).

Registration of Minimal Clinical Data (MCD^m) is mandatory since 1991 for every licensed general hospital in Belgium; psychiatric institutions are excluded, since they have a separate Minimal Psychiatric Data registration (MPD). Mandatory MCD registration means that for each hospitalized patient, information such as year of birth, sex, postal code of domicile and other information such as length of hospital stay (LOS), hospital ward and bed type occupation etc., has to be recorded, along with ICD-9-CMⁿ encoding of all relevant patient diagnoses as well as diagnostic and therapeutic procedures performed. Diagnosis and procedure codes are collected per attended hospital department, each coding for one principal and several secondary diagnoses. This inevitably results in a possible redundancy for certain diagnosis codes, with stay level counts. After stripping of direct patient identifying information, records are biannually sent to the federal Ministry of Health (MoH^o). Here the principal diagnosis of the whole stay is assigned (if not already done by the hospital itself). This principal diagnosis is indeed one of the essential determinants for the APR-DRG-grouper^p software.

The MCD database also contains records of ‘one day’ admissions (i.e. patients not staying overnight in the hospital) and outpatient treatments requiring certain hospital facilities for which NIHDI refunding is provided.

Since 1997 (after two ‘pilot years’, 1995 and 1996) the annually assembled MCD records are afterwards linked to the Hospital Billing Data (HBD), parallel sent by the national health insurance companies (HI) to the NIHDI^q and containing all NIHDI remunerations for each inpatient stay (AZV/SHA^r). Billing records of ‘one day’ stays are collected since 2004 (ADH/HJA^s) and coupling of the latter started in 2006. MCD-HBD linkage is performed by a legally instituted ‘Technical Cell’^s and requires separately sent matching tables containing for each identifiable hospital stay, inter alia, a unique patient pseudonym (UPP) created by two separately executed data hashing operations^t: the first by the hospital or HIC respectively^u and the second by an appointed security advisor of the MOH^{v,w}.

^m MKG = ‘Minimale Klinische Gegevens in Dutch / RCM = Résumé Clinique Minimum’ in French

ⁿ International classification of diseases, clinical modification, version 9 (WHO), translated in a Belgian version (Dutch & French labels).

^o Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu / Service Public Fédéral Santé publique, Sécurité de la Chaîne alimentaire et Environnement

^p All Patient refined Diagnostic Groups, version 15.0 till 2007; since 2008 APR-DRG version 24.0 added.

^q National Institute for Health and Disability Insurance

^r AZV (Dutch) / SHA (French)= billing records of inpatient stays and ADH/HJA = billing records of hospital day-care

^s Law on social provisions, 1996-04-29.

^t Hashing is the transformation of a string of characters into a usually shorter fixed-length value or key that unambiguously represents the original string. It is also used in many encryption algorithms.

^u Both using the same algorithm, applied to the national social security number or, in the absence of such number, the patient’s subscription number to his HIC.

^v Since 2012 both hashing operations are integrated in a web based e-Health platform.

^w All procedures approved by the Belgian Privacy Commission



Linkage process takes at least 2 years to completion and validation. Linkage percentages increased over the years and exceed nowadays 95% overall^x. Consequently, relationships between treated pathology and costs for national health insurance can be studied, at least for inpatient and outpatient hospital care sessions.

It is important to underline that the resulting National Hospital Database (NHDB) is structured as a relational database grouping several separate datasets for the MCD registry as well as for the HBD registry. In 2014 KCE negotiated an annual global transfer of the TCT database^y, after completion and validation of each linkage process by the latter and after re-coding of crucial identification fields (patient and care givers) combined with stripping of certain variables prone to potential contextual identification (postal code and social security status being the most obvious examples). At present KCE has acquired all data for registration years 2008 to 2011. Linkage, by TCT, for the year 2012 is still in progress.

At KCE these annual databases are integrated in one single longitudinal database, with assignment of a unique stay identification number (KCE indices file) over the different years, tertiary validation (leading to some minute exclusions) and addition of 3 useful derivative files, in particular a 'ready to use' file with the pre-calculated 100% stay day remunerations^z. The general data model of this TCT-KCE database is depicted in Figure 2.

The TCT-KCE database contains 15 separate data files, all however connected by the common unique stay identification number:

KCE indices file

Besides the unique stay identification number (primary key) this file provides for each stay:

- The original stay identification number of the TCT source data files (recoded by TCT).
- Registration year
- Primary source registry (day-care vs. inpatient care)
- TCT output registry (linked stay, non-linked MCD or non-linked HBD)
- UPP, if existent (only for linked stays)

Care domains file

This file provides a more detailed break-down of day-care stays, which covers not only classical 'one day' admissions, (medical as well as surgical), but also outpatient haemodialysis, ambulatory hospital care (like plaster ward services, maintenance chemotherapy, IV therapy, ...) as well as ambulatory care provided by the emergency care unit (ECU).

^x Expressed as the fraction of the number of stays in HBD data as denominator; stay counts in HBD are always less than stay counts in MCD data since the latter cover all hospital stays, whether or not they were at the expense of the NIHD. If stay numbers of MCD data are used as denominator, linkage percentages are lower (78% to 85%, depending on the year).

^y Conform legal authorization.

^z Hospital refunding for daily nursing care, main component of the biannually fixed Budget Financial Means (BFM), travels through a dual financing pathway: one (about 20% of the BFM) by means of per stay invoicing of 'per admission' and 'per diem' lump sums, different for each hospital, and the remaining 80% via directly transmitted monthly allowances, independent of hospitalizations. To account for these considerable hospital allowances (not registered in the HBD) per admission and per diem lump sum amounts are substituted by 100% extrapolated per diem amounts.

**Stay insurance file**

Gives all administrative stay data for HBD registration.

Stay hospital file

Gives all administrative stay data for MCD registration.

Stay DRG file

Gives APR-DRG, severity of illness score (SOI), mortality risk index (MI) and principal diagnosis of the hospital stay.

Hospital lump sums file

Assembles for each stay all paid lump sums, per admission (acute bed and burns unit bed occupation) as well as per diem lump sums (acute bed, burns unit bed, chronic care bed and palliative care bed occupation). Patients can transit over different bed types during one stay.

Hospital lump sums extrapolations file

As previously discussed.

Insurance stay select file

Homologue of the care domains file but then specifically applied to inpatient stays, using the hospital lump sums file (breakdown of stay in bed types occupied).

Insurance lab tests file

Contains all remunerations for lab tests

Insurance implants file

Contains all remunerations for reimbursed implants, implantable devices (pacemakers etc.) as well as reimbursed medical disposables (catheters, staplers, etc.)

Insurance medical fees file

Contains all medical and para-medical fees

Insurance pharmaceuticals file

All totally or partially reimbursed pharmaceuticals. Most of them fall under a (partial) lump sum system.

Insurance specifics file

Contains all other bio-materials (blood and derivatives, homo- or allograft tissues, etc.) as well as radio-isotopes. They are separately registered since their reimbursement is usually on a per invoice base.

Hospital diagnoses file

Contains all registered ICD-9-CM diagnoses codes.

Hospital procedures file

Contains all registered ICD-9-CM procedure codes (diagnostic as well as therapeutic).



3 ICD-9-CM PROCEDURE CODES FOR MAMMARY INTERVENTIONS (VERSION DATE: 2015-05-29)

All procedure codes concerning (any) mammary intervention figuring in the entire NHDB for the years 2008-2011 were extracted by executing a 'per stay group by' query filtered on chapter 15 - operations on the integumentary system (code range 85x to 86x) of the ICD-9-CM procedures codes manual and on primarily breast related APR-DRGs (version 15.0) as listed in Table 1. All APR-DRG belong to Major Diagnostic Category (MDC) 9, some surgical (P), others medical (M). Furthermore, some of those APR-DRG (364, 385) are not exclusively for breast disorders, resulting in the need of scoping extracted codes one by one for their application field and frequency (Table 2).

By thus proceeding in an inductive approach we prevent eventually overlooking some codes, not thought of beforehand. This could happen if we set up a selection list by mere deduction. Indeed, referring solely to the official coding instructions manual, hence using only imposed/approved codes, we ignore that hospital encoders – intentionally or not – can interpret their own way code labelling, resulting in inappropriate coding. Even in the presence of a system of coding audits by officials of the federal Ministry of Health (MoH), we have to acknowledge that such auditing, although performed by sampling of 'flashlight' hospital registration records, nevertheless is scant and this for obvious organizational reasons.

Table 4 – Breast related APR-DRG, version 15.0

APR-DRG	Label APR-DRG	Stays 2008-2011	Select
364	Other skin, subcutaneous tissue & breast procedures / MDC 9 - P	136.112	1
363	Breast procedures except mastectomy / MDC 9 - P	81.829	1
385	Other skin & breast disorders / MDC 9 - M	35.512	0
362	Mastectomy procedures / MDC 9 - P	25.452	1
382	Malignant breast disorders / MDC 9 - M	20.803	0
384	Trauma to the skin, subcutaneous tissue & breast / MDC 9 - M	54.508	0

Medical APR-DRG 382, 385 and the (external) trauma related APR-DRG 384 were excluded, since they normally should not contain operation room (OR) procedures.

The resulting procedure codes, along with their frequencies, were flagged for breast involvement or not (Out of scope = 0 or 1) and are listed in Table 2 below.


Table 5 – Frequency table ICD-9-CM procedure codes appearing in 2008-2011 stays of APRRG 362 to 364

DorP	ICD9-P	Code label	Subchapter	Frequency	Out of scope
P	850	Mastotomy	P15.01	1.531	0
P	856	Mastopexy	P15.01	4.235	0
P	857	Total reconstruction of breast	P15.01	585	0
P	863	Other local excision or destruction of lesion or tissue of skin and subcutaneous tissue	P15.02	68.361	0
P	8511	Closed [percutaneous] [needle] biopsy of breast	P15.01	2.644	0
P	8512	Open biopsy of breast	P15.01	4.110	0
P	8519	Other diagnostic procedures on breast	P15.01	462	0
P	8520	Excision or destruction of breast tissue, not otherwise specified	P15.01	772	0
P	8521	Local excision of lesion of breast	P15.01	32.907	0
P	8522	Resection of quadrant of breast	P15.01	5.656	0
P	8523	Subtotal mastectomy	P15.01	5.289	0
P	8524	Excision of ectopic breast tissue	P15.01	247	0
P	8525	Excision of nipple	P15.01	178	0
P	8531	Unilateral reduction mammoplasty	P15.01	2.137	0
P	8532	Bilateral reduction mammoplasty	P15.01	16.020	0
P	8533	Unilateral subcutaneous mamnectomy with synchronous implant	P15.01	250	0
P	8534	Other unilateral subcutaneous mamnectomy	P15.01	1.205	0
P	8535	Bilateral subcutaneous mamnectomy with synchronous implant	P15.01	121	0
P	8536	Other bilateral subcutaneous mamnectomy	P15.01	745	0
P	8541	Unilateral simple mastectomy	P15.01	4.459	0
P	8542	Bilateral simple mastectomy	P15.01	384	0
P	8543	Unilateral extended simple mastectomy	P15.01	10.267	0
P	8544	Bilateral extended simple mastectomy	P15.01	319	0
P	8545	Unilateral radical mastectomy	P15.01	2.081	0
P	8546	Bilateral radical mastectomy	P15.01	76	0
P	8547	Unilateral extended radical mastectomy	P15.01	437	0
P	8548	Bilateral extended radical mastectomy	P15.01	24	0
P	8550	Augmentation mammoplasty, not otherwise specified	P15.01	721	0
P	8551	Unilateral injection into breast for augmentation	P15.01	559	0
P	8552	Bilateral injection into breast for augmentation	P15.01	185	0



P	8553	Unilateral breast implant	P15.01	2.437	0
P	8554	Bilateral breast implant	P15.01	11.130	0
P	8555	Fat graft to breast	P15.01	420	0
P	8570	Total reconstruction of breast, not otherwise specified	P15.01	207	0
P	8571	Latissimus dorsi myo-cutaneous flap	P15.01	502	0
P	8572	Transverse rectus abdominis myo-cutaneous (TRAM) flap, pedicled	P15.01	135	0
P	8573	Transverse rectus abdominis myo-cutaneous (TRAM) flap, free	P15.01	49	0
P	8574	Deep inferior epigastric artery perforator (DIEP) flap, free	P15.01	2.139	0
P	8575	Superficial inferior epigastric artery (SIEA) flap, free	P15.01	46	0
P	8576	Gluteal artery perforator (GAP) flap, free	P15.01	77	0
P	8579	Other total reconstruction of breast	P15.01	151	0
P	8581	Suture of laceration of breast	P15.01	24	0
P	8586	Transposition of nipple	P15.01	341	0
P	8587	Other repair or reconstruction of nipple	P15.01	3.298	0
P	8589	Other mammoplasty	P15.01	3.359	0
P	8591	Aspiration of breast	P15.01	266	0
P	8592	Injection of therapeutic agent into breast	P15.01	118	0
P	8593	Revision of implant of breast	P15.01	1.547	0
P	8594	Removal of implant of breast	P15.01	2.415	0
P	8595	Insertion of breast tissue expander	P15.01	828	0
P	8596	Removal of breast tissue expander	P15.01	542	0
P	8599	Other operations on the breast	P15.01	514	0
P	8601	Aspiration of skin and subcutaneous tissue	P15.02	606	0
P	8602	Injection or tattooing of skin lesion or defect	P15.02	874	0
P	8604	Other incision with drainage of skin and subcutaneous tissue	P15.02	2.055	0
P	8605	Incision with removal of foreign body from skin and subcutaneous tissue	P15.02	1.731	0
P	8606	Insertion of totally implantable infusion pump	P15.02	188	0
P	8607	Insertion of totally implantable vascular access device [VAD]	P15.02	11.667	0
P	8609	Other incision of skin and subcutaneous tissue	P15.02	1.020	0
P	8611	Closed biopsy of skin and subcutaneous tissue	P15.02	1.773	0
P	8619	Other diagnostic procedures on skin and subcutaneous tissue	P15.02	62	0
P	8628	Non-excisional debridement of wound, infection or burn	P15.02	334	0
P	8659	Suture of skin and subcutaneous tissue of other sites	P15.02	1.004	0



P	8683	Size reduction plastic operation	P15.02	9.796	0
P	8684	Relaxation of scar or web contracture of skin	P15.02	3.620	0
P	8687	Fat graft of skin and subcutaneous tissue	P15.02	93	0
P	8689	Other repair and reconstruction of skin and subcutaneous tissue	P15.02	2.790	0
P	8690	Extraction of fat for graft or banking	P15.02	16	0
P	8699	Other operations on skin and subcutaneous tissue	P15.02	220	0
P	8603	Incision of pilonidal sinus or cyst	P15.02	47	1
P	8621	Excision of pilonidal cyst or sinus	P15.02	11.197	1
P	8623	Removal of nail, nail bed, or nail fold	P15.02	8.061	1
P	8624	Chemosurgery of skin	P15.02	162	1
P	8625	Dermabrasion	P15.02	348	1
P	8626	Ligation of dermal appendage	P15.02	15	1
P	8627	Debridement of nail, nail bed, or nail fold	P15.02	928	1
P	8651	Replantation of scalp	P15.02	9	1
P	8664	Hair transplant	P15.02	12	1
P	8681	Repair for facial weakness	P15.02	29	1
P	8682	Facial rhytidectomy	P15.02	2.741	1
P	8685	Correction of syndactyly	P15.02	3	1
P	8686	Onychoplasty	P15.02	1.238	1
P	8692	Electrolysis and other epilation of skin	P15.02	4	1

The resulting final selection list is presented in Table 3. It contains all codes relevant for our analyses. Flags indicating corresponding target intervention involved are added. However, some of the listed codes are not suitable for primary data record selection, since they would induce extraction of unwanted stays. Consequently a flag <1^{ary} select> is added to indicate whether or not the corresponding code is apt for primary selection. The other codes (flag value = 0), nevertheless, are useful for secondary stay classification, e.g. code 8684 - relaxation of scar or web contracture of skin, although certainly not suitable for primary selection (we would end up with getting all stays with any scar treatment irrespective anatomical site), will be useful in searching complications of mammary interventions.



Table 6 – Selection list for ICD-9-CM procedure codes

ICD9-P	Label_En	1ary select	Mamm. resection	Mamm. reconstruction	Secondary intervention	Mamm. complication	Mammoplasty
857	Total reconstruction of breast	1	0	1	0	0	0
8522	Resection of quadrant of breast	1	1	0	0	0	0
8523	Subtotal mastectomy	1	1	0	0	0	0
8531	Unilateral reduction mammoplasty	1	0	0	0	0	1
8533	Unilateral subcutaneous mastectomy with synchronous implant	1	1	1	0	0	0
8534	Other unilateral subcutaneous mastectomy	1	1	0	0	0	0
8535	Bilateral subcutaneous mastectomy with synchronous implant	1	1	0	0	0	0
8536	Other bilateral subcutaneous mastectomy	1	1	0	0	0	0
8541	Unilateral simple mastectomy	1	1	0	0	0	0
8542	Bilateral simple mastectomy	1	1	0	0	0	0
8543	Unilateral extended simple mastectomy	1	1	0	0	0	0
8544	Bilateral extended simple mastectomy	1	1	0	0	0	0
8545	Unilateral radical mastectomy	1	1	0	0	0	0
8546	Bilateral radical mastectomy	1	1	0	0	0	0
8547	Unilateral extended radical mastectomy	1	1	0	0	0	0
8548	Bilateral extended radical mastectomy	1	1	0	0	0	0
8570	Total reconstruction of breast, not otherwise specified	1	0	1	0	0	0
8571	Latissimus dorsi myocutaneous flap	1	0	1	0	0	0
8572	Transverse rectus abdominis myocutaneous (TRAM) flap, pedicled	1	0	1	0	0	0
8573	Transverse rectus abdominis myocutaneous (TRAM) flap, free	1	0	1	0	0	0
8574	Deep inferior epigastric artery perforator (DIEP) flap, free	1	0	1	0	0	0
8575	Superficial inferior epigastric artery (SIEA) flap, free	1	0	1	0	0	0
8576	Gluteal artery perforator (GAP) flap, free	1	0	1	0	0	0
8579	Other total reconstruction of breast	1	0	1	0	0	0
8587	Other repair or reconstruction of nipple	1	0	0	1	0	0
8593	Revision of implant of breast	1	0	0	0	1	0
8594	Removal of implant of breast	1	0	0	0	1	0



8595	Insertion of breast tissue expander	1	0	0	0	0	1
8596	Removal of breast tissue expander	1	0	0	0	0	1
8675	Revision of pedicle or flap graft	1	0	0	0	1	0
850	Mastotomy	0	0	0	0	0	0
856	Mastopexy	0	0	0	0	0	1
863	Other local excision or destruction of lesion or tissue of skin and subcutaneous tissue	0	0	0	0	0	0
8511	Closed [percutaneous] [needle] biopsy of breast	0	0	0	0	0	0
8512	Open biopsy of breast	0	0	0	0	0	0
8519	Other diagnostic procedures on breast	0	0	0	0	0	0
8520	Excision or destruction of breast tissue, not otherwise specified	0	0	0	0	0	0
8521	Local excision of lesion of breast	0	0	0	0	0	0
8524	Excision of ectopic breast tissue	0	0	0	0	0	0
8525	Excision of nipple	0	0	0	0	0	0
8532	Bilateral reduction mammoplasty	0	0	0	0	0	1
8550	Augmentation mammoplasty, not otherwise specified	0	0	0	0	0	1
8551	Unilateral injection into breast for augmentation	0	0	0	0	0	1
8552	Bilateral injection into breast for augmentation	0	0	0	0	0	1
8553	Unilateral breast implant	0	0	0	0	0	1
8554	Bilateral breast implant	0	0	0	0	0	1
8555	Fat graft to breast	0	0	0	1	0	0
8581	Suture of laceration of breast	0	0	0	0	1	0
8586	Transposition of nipple	0	0	0	0	0	1
8589	Other mammoplasty	0	0	0	0	0	1
8591	Aspiration of breast	0	0	0	0	0	0
8592	Injection of therapeutic agent into breast	0	0	0	0	0	0
8599	Other operations on the breast	0	0	0	0	0	0
8601	Aspiration of skin and subcutaneous tissue	0	0	0	0	0	0
8602	Injection or tattooing of skin lesion or defect	0	0	0	1	0	0
8604	Other incision with drainage of skin and subcutaneous tissue	0	0	0	0	1	0
8605	Incision with removal of foreign body from skin and subcutaneous tissue	0	0	0	0	1	0
8606	Insertion of totally implantable infusion pump	0	0	0	0	0	0

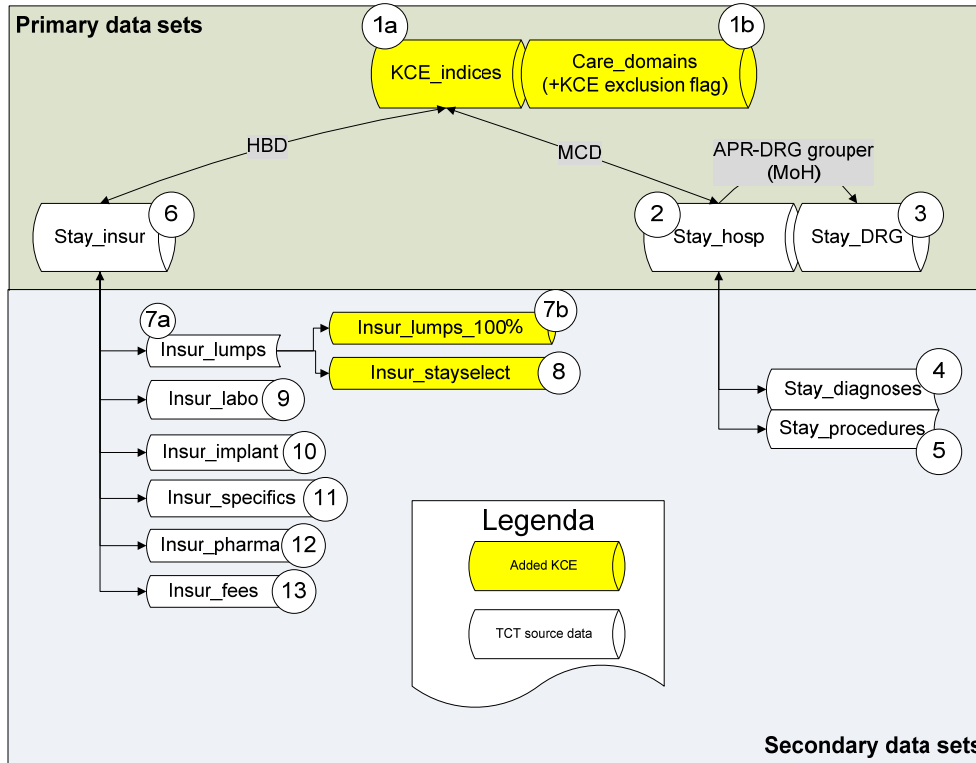


8607	Insertion of totally implantable vascular access device [VAD]	0	0	0	0	0	0
8609	Other incision of skin and subcutaneous tissue	0	0	0	0	0	0
8611	Closed biopsy of skin and subcutaneous tissue	0	0	0	0	0	0
8619	Other diagnostic procedures on skin and subcutaneous tissue	0	0	0	0	0	0
8628	Non-excisional debridement of wound, infection or burn	0	0	0	0	1	0
8659	Suture of skin and subcutaneous tissue of other sites	0	0	0	0	1	0
8683	Size reduction plastic operation	0	0	0	1	0	0
8684	Relaxation of scar or web contracture of skin	0	0	0	0	1	0
8687	Fat graft of skin and subcutaneous tissue	0	0	0	1	0	0
8689	Other repair and reconstruction of skin and subcutaneous tissue	0	0	0	1	0	0
8690	Extraction of fat for graft or banking	0	0	0	0	0	0
8699	Other operations on skin and subcutaneous tissue	0	0	0	0	0	0

Finally, we emphasize that above list only contains codes actually present in NHDB 2008-2011. There is no need to worry about other significant, yet not registered codes.



Figure 2 – KCE data model of the integrated NHDB



Version date: 2015-05-29



4 NIHDI BILLING CODES FOR MAMMARY INTERVENTIONS (VERSION DATE: 2015-05-29)

Billing codes used for hospital refund claims are officially grouped in clinically and anatomically representative sections - articles of the corresponding Royal Decree (RD), in force since 1994-07-24. The codes of interest for present project can be found in articles 14c – plastic surgery and article 14e – thoracic surgery. Coordinated reference texts can be consulted at:

<http://www.inami.fgov.be/nl/nomenclatuur/nomen/Paginas/default.aspx> (Dutch) and

http://www.inami.fgov.be/fr/nomenclature/Pages/default.aspx#Texte_de_la_nomenclature (French)

Most billing codes come in pairs: a code for outpatient billing and a corresponding code for inpatient billing: e.g. 243154_243165 = billing code for appendectomy, 243154 being the code for outpatient ('one day') and 243165 the code for inpatient appendectomy (see also: Format aspects of NIHDI billing codes below).

A more practical grouping system of nomenclature codes consists of classifying them in so-called Rubrics or N-groups, primarily used for NIHDI accountancy purposes. Besides billing codes they also group so-called pseudo-codes, not figuring in the above mentioned RD, but used for other hospital claims – e.g. per admission or per diem lump sums – or for communicating special code related conditions, justifying certain claims.

Primary mammary resections fall under N-group 25 and plastic/reconstructive mammary interventions under N-group 22. Two additional groups – N80 and N82 – contain subsidiary codes, actually intended for refunding costs of implantable prostheses and devices (N82) or reimbursable disposables used during interventions (N80). Strictly spoken they are not necessary for selection since they theoretically require the presence in the claims records of a corresponding intervention code. Nevertheless, they can be very useful e.g. to separate mammary flap reconstructions with prosthesis implant from those without.

Besides this deductive approach, starting from regulatory documents, we performed, as with ICD-9-CM procedure codes, an additional 'per stay group by' query filtered on N-groups N22, N25, N80 and N82 and in primarily breast related APRDRGs (hence only in linked stays) as listed in Table 4 of Appendix 3. The results of this inductive approach – for a total of 167 244 stays found - are presented in Table 1 below.

Table 7 – Frequency table for NIHDI nomenclature codes appearing in 2008-2011 stays of APRDRG 362 to 364

Grp N	Code pair	Short label En	Stays	Stays%
N22	250176_250180	Skin or fascio-cutaneous flap, main intervention	10 428	3.479%
N22	250191_250202	Skin or fascio-cutaneous flap, subsequent intervention	1 133	0.378%
N22	250213_250224	Skin or fascio-cutaneous flap, complete intervention, ≥ 100 cm ²	1 309	0.437%
N22	251274_251285	Dermo-epidermal skin graft < 10 cm ²	190	0.063%
N22	251296_251300	Dermo-epidermal skin graft ≥ 10 cm ² and < 50 cm ²	122	0.041%
N22	251311_251322	Full skin graft ≥ 50 cm ² and < 200 cm ²	191	0.064%
N22	251333_251344	Dermo-epidermal skin graft > 200 cm ²	78	0.026%
N22	251355_251366	Full skin graft ≥ 10 cm ² and < 50 cm ²	182	0.061%
N22	251370_251381	Full skin graft ≥ 50 cm ² and < 200 cm ²	322	0.107%



N22	251576_251580	Mammoplasty by prosthesis	428	0.143%
N22	251591_251602	Removal mammary implant due to complications	1 570	0.524%
N22	251613_251624	Reduction mammoplasty for mammary hypertrophy causing functional impairment	13 417	4.477%
N22	251635_251646	Hetero-lateral reduction mammoplasty for unilateral congenital mammary hypoplasia	191	0.064%
N22	251650_251661	Mammoplasty by prosthesis/tissue expander for congenital hypo- or aplasia or malformation	319	0.106%
N22	251672_251683	Subcutaneous tissue expander implant(s)	275	0.092%
N22	251716_251720	Subcutaneous tissue expander implant(s)	53	0.018%
N22	251731_251742	Excision of tumor of skin or mucosa or other directly accessible lesion followed by plasty or grafting	3 694	1.233%
N22	251753_251764	Resection of malign skin / mucosa cancer with ex tempore frozen section, without closure	91	0.030%
N22	251775_251786	Excision of malign tumor of skin or mucosa with ex tempore frozen sections eventually followed by plasty or grafting	1 879	0.627%
N22	251790_251801	Surgical correction of retracted nipple	739	0.247%
N22	251812_251823	Microsurgical vascular anastomoses, receptor site	47	0.016%
N22	251834_251845	Microsurgical vascular anastomoses, receptor site	431	0.144%
N22	251856_251860	Muscle flap, main intervention	168	0.056%
N22	251871_251882	Muscle flap, subsequent intervention	129	0.043%
N22	251893_251904	Musculo-cutaneous flap, complete intervention	296	0.099%
N22	251915_251926	Preparing simple tissue flap for microsurgical transfer (e.g. muscle)	70	0.023%
N22	251930_251941	Preparing composite tissue flap for microsurgical transfer (e.g. osteo-septo-cutaneous)	418	0.139%
N22	251952_251963	Preparing perforator flap (e.g. DIEP or SGAP), donor site	175	0.058%
N22	252431_252442	Mammary reconstruction by prosthesis for congenital unilateral mammary hypoplasia or deformity or after mutilating intervention on the breast	2 393	0.798%
N22	252453_252464	Mammary reconstruction by pedicled transposition skin flap	290	0.097%
N22	252475_252486	Mammary reconstruction by pedicled transposition skin-muscle flap (Latissimus dorsi)	577	0.193%
N22	252490_252501	Reconstruction areola and nipple	1 632	0.545%
N22	252512_252523	Hetero-lateral remodelling mammoplasty +/- mammary implant or tissue expander	3 917	1.307%
N22	252534_252545	Mammary reconstruction by pedicled transposition (TRAM) flap	88	0.029%
N22	252556_252560	Microsurgical free flap	11	0.004%



N22	252571_252582	Mammary reconstruction with DIEP or SGAP free perforator flap	2 030	0.677%
N22	252593_252604	Mammary reconstruction by prosthesis	263	0.088%
N22	252615_252626	Tattooing of areolar region	7	0.002%
N22	253676_253680	Full skin graft < 10 cm2, except facial	227	0.076%
N25	226936_226940	Axillary curage for breast CA	1 396	0.466%
N25	226951_226962	Urban extended mastectomy	3	0.001%
N25	226973_226984	Halsted-Pathey mastectomy	781	0.261%
N25	226995_227006	Halsted-Pathey mastectomy	2 588	0.864%
N25	227010_227021	Radical extirpation supra-aponeurotic tumefaction	844	0.282%
N25	227032_227043	Mammary resection of tumor of cyst	4 821	1.609%
N25	227054_227065	Partial mastectomy with axillary curage	4 865	1.623%
N25	227076_227080	Incision breast abscess under general anaesthesia	198	0.066%
N25	227091_227102	Surgical mammary biopsy	994	0.332%
N25	227113_227124	Subtotal mastectomy, male	2 972	0.992%
N25	227511_227522	Prosthetic implant with mastectomy (additional code)	273	0.091%
N25	227592_227603	Sentinel adenectomy	496	0.165%
N25	227614_227625	Sentinel adenectomy with ex tempore frozen sections	243	0.081%
N25	227636_227640	Total mastectomy for breast CA	2 429	0.810%
N25	227651_227662	Total mastectomy for breast CA	763	0.255%
N25	227673_227684	Total mastectomy for breast CA	1 754	0.585%
N25	227695_227706	Total mastectomy with axillary curage	7 861	2.623%
N25	227710_227721	Total mastectomy with axillary curage after intra-operative proof of CA on frozen sections	956	0.319%
N25	227732_227743	Partial mastectomy for breast CA	1 662	0.555%
N25	227754_227765	Partial mastectomy	1 979	0.660%
N25	227776_227780	Partial mastectomy with sentinel adenectomy	3 618	1.207%
N25	227791_227802	Partial mastectomy with sentinel adenectomy	9 090	3.033%
N25	227813_227824	Total mastectomy with axillary curage after intra-operative proof of CA on frozen sections	1 865	0.622%
N25	227835_227846	Partial mastectomy with axillary curage	3 844	1.283%



N25	227850_227861	Complete resection benign breast tumor	6 755	2.254%
N25	227872_227883	Mammary tumorectomy	3 974	1.326%
N25	227894_227905	Total mastectomy without proof of CA	787	0.263%
N80	698935_698946	Skin marker	106	0.035%
N80	720893_720904	Transcutaneous access port, vascular, intrathecal or intraperitoneal	7 567	2.525%
N80	720915_720926	PICC catheter	17	0.006%
N80	732432_732443	Disposables with 226936_226940 (axillary curage) endoscopic	356	0.119%
N80	732454_732465	Disposables with 226973_226984 open surgery	393	0.131%
N80	732476_732480	Disposables with 226995_227006 open surgery	1 787	0.596%
N80	732491_732502	Disposables with 227054_227065 open surgery	3 337	1.113%
N80	735475_735486	Disposables with 227592_227603 open surgery	186	0.062%
N80	735490_735501	Disposables with 227614_227625 open surgery	113	0.038%
N80	735512_735523	Disposables with 227636_227640 open surgery	1 031	0.344%
N80	735534_735545	Disposables with 227651_227662 open surgery	357	0.119%
N80	735556_735560	Disposables with 227673_227684 open surgery	836	0.279%
N80	735571_735582	Disposables with 227695_227706 open surgery	3 659	1.221%
N80	735593_735604	Disposables with 227710 - 227721 open surgery	404	0.135%
N80	735615_735626	Disposables with 227732_227743 open surgery	771	0.257%
N80	735630_735641	Disposables with 227754 - 227765 open surgery	989	0.330%
N80	735652_735663	Disposables with 227776 - 227780 open surgery	1 896	0.633%
N80	735674_735685	Disposables with 227791_227802 open surgery	4 409	1.471%
N80	735696_735700	Disposables with 227813 - 227824 open surgery	836	0.279%
N80	735711_735722	Disposables with 227835_227846 open surgery	1 820	0.607%
N80	735733_735744	Disposables with 227054_227065 open surgery	2 318	0.773%
N80	735755_735766	Disposables with 227872_227883 open surgery	1 514	0.505%
N80	735770_735781	Disposables with 227894_227905 open surgery	285	0.095%
N80	736816_736820	Disposables with 226936_226940 endoscopic	68	0.023%
N82	611413_611424	Reservoir for transcutaneous epidural/intrathecal injections	15	0.005%



N82	612371_612382	Mesh implant for repair wall hernia or eventration, per 10 cm ²	478	0.159%
N82	614014_614025	Port-a-Cath	3 680	1.228%
N82	614412_614423	Mammary prosthesis	2 442	0.815%
N82	614434_614445	Implant of temporary tissue expander for breast	697	0.233%
N82	614456_614460	Implant of permanent tissue expander for breast	350	0.117%
N82	614471_614482	Tissue expander, other	50	0.017%
---	Remaining	Not presented (immediately judged irrelevant for present project – N = 374)	6 886	4.12 %

As appears, NIHDI code labelling – although functional for billings – is not necessarily specific for pathology. Some codes, like for instance code pair 251591_251602 – removal mammary implant for complications, have indeed undisputable specificity; others however have not, which forces us to proceed with a contextual appraisal.

From the 473 code pairs appearing in this list 374 could immediately be discarded as evidently not pertinent for our project. The remainder 99 were appraised for their frequency and relevance. If necessary additional focussed queries were executed in order to get insights in underlying related diagnoses by looking at combination frequencies. Such laborious preparatory work allowed us to get to a well-founded judgement on the relevancy of each code pair for present project. The resulting list is presented in Table 8. For future classification purposes codes were assigned to functional main groups and subgroups. As with ICD-9-CM procedure codes a flag <1^{ary} select> was added to indicate whether or not the corresponding code is apt for primary selection.

Table 8 – Selection list for NIHDI nomenclature codes

Grp N	Code pair	Short label En	Subgroup	Main group	1ary_select
N22	251591_251602	Removal mammary implant for complications	Removal mammary implant	Complication	1
N22	252431_252442	Mammary reconstruction by prosthesis	Mammary reconstruction by prosthesis	Mammary reconstruction	1
N22	252453_252464	Mammary reconstruction by pedicled transposition skin flap	Mammary reconstruction by pedicled transposition skin and/or muscle flap	Mammary reconstruction	1
N22	252475_252486	Mammary reconstruction by pedicled transposition skin-muscle flap (Latissimus dorsi)	Mammary reconstruction by pedicled transposition skin and/or muscle flap	Mammary reconstruction	1
N22	252490_252501	Reconstruction areola and nipple	Areola/Nipple	2ary intervention	1
N22	252512_252523	Hetero-lateral remodelling mammoplasty +/- mammary implant or tissue expander	Hetero-lateral remodelling mammoplasty	2ary intervention	1
N22	252534_252545	Mammary reconstruction by pedicled transposition (TRAM) flap	Mammary reconstruction by pedicled transposition skin and/or muscle flap	Mammary reconstruction	1
N22	252556_252560	Mammary reconstruction by microsurgical free flap (non-peforator)	Mammary reconstruction by microsurgical free flap (non-peforator)	Mammary reconstruction	1
N22	252571_252582	Mammary reconstruction with free perforator flap	Mammary reconstruction by perforator flap (DIEP or SGAP)	Mammary reconstruction	1



N22	252593_252604	Mammary reconstruction by prosthesis	Mammary reconstruction by prosthesis	Mammary reconstruction	1
N22	252615_252626	Tattooing areolar region	Areola/Nipple	2ary intervention	1
N22	250176_250180	Skin or fascio-cutaneous flap, main intervention	General skin grafting	Skin grafting	0
N22	250191_250202	Skin or fascio-cutaneous flap, subsequent intervention	General skin grafting	Skin grafting	0
N22	250213_250224	Skin or fascio-cutaneous flap, complete intervention, $\geq 100 \text{ cm}^2$	General skin grafting	Skin grafting	0
N22	251274_251285	Dermo-epidermal skin graft $< 10 \text{ cm}^2$	General skin grafting	Skin grafting	0
N22	251296_251300	Dermo-epidermal skin graft $\geq 10 \text{ cm}^2$ and $< 50 \text{ cm}^2$	General skin grafting	Skin grafting	0
N22	251311_251322	Full skin graft $\geq 50 \text{ cm}^2$ and $< 200 \text{ cm}^2$	General skin grafting	Skin grafting	0
N22	251333_251344	Dermo-epidermal skin graft $> 200 \text{ cm}^2$	General skin grafting	Skin grafting	0
N22	251355_251366	Full skin graft $\geq 10 \text{ cm}^2$ and $< 50 \text{ cm}^2$	General skin grafting	Skin grafting	0
N22	251370_251381	Full skin graft $\geq 50 \text{ cm}^2$ and $< 200 \text{ cm}^2$	General skin grafting	Skin grafting	0
N22	251576_251580	Augmentation mammoplasty by prosthesis	Mammoplasty by prosthesis	Mammoplasties	0
N22	251613_251624	Reduction mammoplasty for mammary hypertrophy	Mammoplasty for reduction	Mammoplasties	0
N22	251635_251646	Hetero-lateral reduction mammoplasty with unilateral congenital mammary hypoplasia	Hetero-lateral mammoplasty for reduction	Mammoplasties	0
N22	251650_251661	Mammoplasty by prosthesis with congenital hypo- or aplasia or malformation	Mammoplasty by prosthesis	Mammoplasties	0
N22	251790_251801	Surgical correction of retracted nipple	Areola/Nipple	2ary intervention	0
N22	251812_251823	Microsurgical vascular anastomoses, donor site	Microsurgical vascular anastomoses	Other reconstruction	0
N22	251834_251845	Microsurgical vascular anastomoses, receptor site	Microsurgical vascular anastomoses	Other reconstruction	0
N22	251856_251860	Muscle flap, main intervention	Pedicled flap	Other reconstruction	0
N22	251871_251882	Muscle flap, subsequent intervention	Pedicled flap	Other reconstruction	0
N22	251893_251904	Musculo-cutaneous flap, complete intervention	General skin grafting	Other reconstruction	0
N22	251915_251926	Microsurgical vascular anastomoses, donor site	Microsurgical vascular anastomoses	Other reconstruction	0
N22	251930_251941	Preparing composite tissue flap for microsurgical transfer (e.g. osteo-septo cutaneous)	Microsurgical vascular anastomoses	Other reconstruction	0
N22	251952_251963	Preparing perforator flap (e.g. DIEP or SGAP), donor site	DIEP or SGAP perforator flap - donor site	Other reconstruction	0
N22	253676_253680	Full skin graft $< 10 \text{ cm}^2$, except facial	General skin grafting	Skin grafting	0
N25	226936_226940	Axillary curage for breast CA	Axillary	1ary mammary resection	1
N25	226951_226962	Urban extended mastectomy	Total mastectomy	1ary mammary resection	1



N25	226973_226984	Halsted-Pathey mastectomy w ex tempore frozen sections	Total mastectomy	1ary mammary resection	1
N25	226995_227006	Halsted-Pathey mastectomy	Total mastectomy	1ary mammary resection	1
N25	227032_227043	Mammary resection of tumor of cyst	Partial mastectomy	1ary mammary resection	1
N25	227054_227065	Partial mastectomy with axillary curage	Partial mastectomy	1ary mammary resection	1
N25	227113_227124	Subtotal mastectomy, male	Partial mastectomy	1ary mammary resection	1
N25	227511_227522	Prosthetic implant with mastectomy (additional code)	Mammary reconstruction by prosthesis	Mammary reconstruction	1
N25	227592_227603	Sentinel adenectomy	Axillary	1ary mammary resection	1
N25	227614_227625	Sentinel adenectomy with ex tempore frozen sections	Axillary	1ary mammary resection	1
N25	227636_227640	Total mastectomy for breast CA	Total mastectomy	1ary mammary resection	1
N25	227651_227662	Total mastectomy for breast CA	Total mastectomy	1ary mammary resection	1
N25	227673_227684	Total mastectomy for breast CA	Total mastectomy	1ary mammary resection	1
N25	227695_227706	Total mastectomy with axillary curage	Total mastectomy	1ary mammary resection	1
N25	227710_227721	Total mastectomy with axillary curage after intra-operative proof of CA by frozen sections on sentinel adenectomy specimen	Total mastectomy	1ary mammary resection	1
N25	227732_227743	Partial mastectomy for breast CA	Partial mastectomy	1ary mammary resection	1
N25	227754_227765	Partial mastectomy after localization procedure	Partial mastectomy	1ary mammary resection	1
N25	227776_227780	Partial mastectomy with sentinel adenectomy	Partial mastectomy	1ary mammary resection	1
N25	227791_227802	Partial mastectomy with sentinel adenectomy	Partial mastectomy	1ary mammary resection	1
N25	227813_227824	Total mastectomy with axillary curage after intra-operative proof of CA on frozen sections	Partial mastectomy	1ary mammary resection	1
N25	227835_227846	Partial mastectomy with axillary curage	Partial mastectomy	1ary mammary resection	1
N25	227850_227861	Complete resection benign breast tumor	Mammary tumorectomy, benign	1ary mammary resection	1
N25	227894_227905	Total mastectomy without proof of CA	Total mastectomy	1ary mammary resection	1
N25	227010_227021	Extirpation supra-fascial tumefaction involving total resection of hosting organ	Total excision NOS (not specific for breast although often used for this organ – code discarded starting 01-01-2009)	1ary mammary resection	0
N25	227076_227080	Incision breast abscess under general anaesthesia	Mastotomy	1ary mammary resection	0
N25	227091_227102	Surgical mammary biopsy	Mastotomy	1ary mammary resection	0
N25	227872_227883	Mammary tumorectomy	Mammary tumorectomy, benign	1ary mammary resection	0
N80	698935_698946	Skin marker	Subsidiary	Subsidiary	0



N80	720893_720904	Trans-cutaneous access port, vascular, intrathecal or intraperitoneal	Reservoir transcutaneous injection (useful to identify chemotherapy patients)	Subsidiary	0
N80	732432_732443	Disposables with 226936_226940 (axillary curage) endoscopic	Axillary	Subsidiary	0
N80	732454_732465	Disposables with 226973_226984 open surgery	Total mastectomy	Subsidiary	0
N80	732476_732480	Disposables with 226995_227006 open surgery	Total mastectomy	Subsidiary	0
N80	732491_732502	Disposables with 227054_227065 open surgery	Partial mastectomy	Subsidiary	0
N80	735475_735486	Disposables with 227592_227603 open surgery	Axillary	Subsidiary	0
N80	735490_735501	Disposables with 227614_227625 open surgery	Axillary	Subsidiary	0
N80	735512_735523	Disposables with 227636_227640 open surgery	Total mastectomy	Subsidiary	0
N80	735534_735545	Disposables with 227651_227662 open surgery	Total mastectomy	Subsidiary	0
N80	735556_735560	Disposables with 227673_227684 open surgery	Partial mastectomy	Subsidiary	0
N80	735571_735582	Disposables with 227695_227706 open surgery	Total mastectomy	Subsidiary	0
N80	735593_735604	Disposables with 227710 - 227721 open surgery	Total mastectomy	Subsidiary	0
N80	735615_735626	Disposables with 227732_227743 open surgery	Partial mastectomy	Subsidiary	0
N80	735630_735641	Disposables with 227754 - 227765 open surgery	Partial mastectomy	Subsidiary	0
N80	735652_735663	Disposables with 227776 - 227780 open surgery	Partial mastectomy	Subsidiary	0
N80	735674_735685	Disposables with 227791_227802 open surgery	Partial mastectomy	Subsidiary	0
N80	735696_735700	Disposables with 227813 - 227824 open surgery	Partial mastectomy	Subsidiary	0
N80	735711_735722	Disposables with 227835_227846 open surgery	Partial mastectomy	Subsidiary	0
N80	735733_735744	Disposables with 227054_227065 open surgery	Mammary tumorectomy, benign	Subsidiary	0
N80	735755_735766	Disposables with 227872_227883 open surgery	Mammary tumorectomy, benign	Subsidiary	0
N80	735770_735781	Disposables with 227894_227905 open surgery	Total mastectomy	Subsidiary	0
N80	736816_736820	Disposables with 226936_226940 endoscopic	Axillary	Subsidiary	0
N82	611413_611424	Reservoir for transcutaneous epidural/intrathecal injections	Reservoir transcutaneous injection	Subsidiary	0
N82	614014_614025	Port-a-Cath	Reservoir transcutaneous injection	Subsidiary	0
N82	614412_614423	Mammary prosthesis	Prosthesis	Subsidiary	0
N82	614434_614445	Tissue expander for breast, temporary	Prosthesis	Subsidiary	0
N82	614456_614460	Tissue expander for breast, permanent	Prosthesis	Subsidiary	0

Mammary resection codes need some extra attention, since in 2008 a NIHDI nomenclature of mammary resections was thoroughly upgraded to current 'state of the art' surgical practice, with obsolete codes being abrogated and new ones being introduced (Figure 1), causing a remarkable drop in annual intervention counts in the NIHDI overall accountancy database (Doc N – Figure 2).



Figure 3 – RIZIV-INAMI billing codes for mammary resections

Code_pair	Short_label_En	Date_start	Date_end	Doc N_2008-2011	Type_intervention
226951_226962	Urban extended mastectomy	1985-04-01	2008-12-01		4 Extended mastectomy
226973_226984	Halsted-Patthey mastectomy w ex tempore frozen sections	1985-04-01	2008-12-01		804 Extended mastectomy
226995_227006	Halsted-Patthey mastectomy	1985-04-01	2008-12-01		2.764 Extended mastectomy
227010_227021	Extirpation suprafascial tumefaction involving total resection of hosting organ (*)	1985-04-01	2008-12-01		1.112 Subtotal mastectomy
227032_227043	Mammary resection of tumor of cyst	1985-04-01	2008-12-01		5.484 Tumorectomy
227054_227065	Partial mastectomy with axillary curage	1985-04-01	2008-12-01		5.013 Partial mastectomy
227113_227124	Subtotal mastectomy, male	1985-04-01	---		4.895 Partial mastectomy
227636_227640	Total mastectomy for breast CA	2008-12-01	---		2.683 Total mastectomy
227651_227662	Total mastectomy for breast CA	2008-12-01	---		828 Total mastectomy
227673_227684	Total mastectomy for breast CA	2008-12-01	---		1.814 Total mastectomy
227695_227706	Total mastectomy with axillary curage	2008-12-01	---		8.234 Total mastectomy
227710_227721	Total mastectomy with axillary curage	2008-12-01	---		988 Total mastectomy
227732_227743	Partial mastectomy for breast CA	2008-12-01	---		2.012 Partial mastectomy
227754_227765	Partial mastectomy + localization procedure	2008-12-01	---		2.174 Partial mastectomy
227776_227780	Partial mastectomy + sentinel adenectomy	2008-12-01	---		3.679 Partial mastectomy
227791_227802	Partial mastectomy + sentinel adenectomy	2008-12-01	---		9.293 Partial mastectomy
227813_227824	Total mastectomy with axillary curage	2008-12-01	---		1.893 Partial mastectomy
227835_227846	Partial mastectomy with axillary curage	2008-12-01	---		3.988 Partial mastectomy
227894_227905	Total mastectomy without proof of CA	2008-12-01	---		1.094 Total mastectomy

**Abrogated end
2008 !**

(*) in its literal description not specific for breast; in practice often related to breast interventions



Figure 4 – Annual NIHDI numbers for mammary resections(Doc N)

Year	N_performed	N_booked
2008	17 319	17 755
2009	13 347	13 696
2010	13 555	13 245
2011	14 535	14 566

Table 9 gives, for each of the NIHDI code pairs, the corresponding target flag(s): value 1 or 0.

Table 9 – Target flags for NIHDI code pairs

Grp N	Code pair	Short label English	Mamm. resection	Mamm. reconstruction	2ary interv.	Complication	Mammo-plasty	Other Mamm. intv.
N22	251576_251580	Augmentation mammoplasty by prosthesis	0	0	0	0	1	0
N22	251591_251602	Removal mammary implant for complications	0	0	0	1	0	0
N22	251613_251624	Reduction mammoplasty for mammary hypertrophy	0	0	0	0	1	0
N22	251635_251646	Hetero-lateral reduction mammoplasty with unilateral congenital mammary hypoplasia	0	0	0	0	1	0
N25	227010_227021	Extirpation supra-aponeurotic tumefaction involving total resection of hosting organ	1	0	0	0	0	0
N22	251650_251661	Mammoplasty by prosthesis with congenital hypo- or aplasia or malformation	0	0	0	0	1	0
N22	251790_251801	Surgical correction of retracted nipple	0	0	0	1	0	0
N25	227076_227080	Incision breast abscess under general anaesthesia	0	0	0	0	0	1
N25	227091_227102	Surgical mammary biopsy	0	0	0	0	0	1
N22	251952_251963	Preparing perforator flap (e.g. DIEP of SGAP), donor site	0	0	0	0	0	0
N22	252431_252442	Mammary reconstruction by prosthesis	0	1	0	0	0	0
N22	252453_252464	Mammary reconstruction by pedicled transposition skin flap	0	1	0	0	0	0
N22	252475_252486	Mammary reconstruction by pedicled transposition skin-muscle flap (Latissimus dorsi)	0	1	0	0	0	0
N22	252490_252501	Reconstruction areola and nipple	0	0	1	0	0	0



N22	252512_252523	Hetero-lateral remodelling mammoplasty +/- mammary implant or tissue expander	0	0	1	0	0	0
N22	252534_252545	Mammary reconstruction by pedicled transposition (TRAM) flap	0	1	0	0	0	0
N22	252571_252582	Mammary reconstruction with free perforator flap	0	1	0	0	0	0
N22	252593_252604	Mammary reconstruction by prosthesis	0	1	0	0	0	0
N22	252615_252626	Tattooing areola	0	0	1	0	0	0
N25	226936_226940	Axillary curage for breast CA	0	0	0	0	0	0
N25	226951_226962	Urban extended mastectomy	1	0	0	0	0	0
N25	226973_226984	Halsted-Pathey mastectomy w ex tempore frozen sections	1	0	0	0	0	0
N25	226995_227006	Halsted-Pathey mastectomy	1	0	0	0	0	0
N25	227032_227043	Mammary resection of tumor of cyst	1	0	0	0	0	0
N25	227054_227065	Partial mastectomy with axillary curage	1	0	0	0	0	0
N25	227872_227883	Mammary tumorectomy	0	0	0	0	0	1
N25	227113_227124	Subtotal mastectomy, male	1	0	0	0	0	0
N22	250176_250180	Skin or fascio-cutaneous flap, main intervention	0	0	0	0	0	0
N22	250191_250202	Skin or fascio-cutaneous flap, subsequent intervention	0	0	0	0	0	0
N22	250213_250224	Skin or fascio-cutaneous flap, complete intervention, ≥ 100 cm ²	0	0	0	0	0	0
N22	251274_251285	Dermo-epidermal skin graft < 10 cm ²	0	0	0	0	0	0
N22	251296_251300	Dermo-epidermal skin graft ≥ 10 cm ² and < 50 cm ²	0	0	0	0	0	0
N22	251311_251322	Full skin graft ≥ 50 cm ² and < 200 cm ²	0	0	0	0	0	0
N22	251333_251344	Dermo-epidermal skin graft > 200 cm ²	0	0	0	0	0	0
N22	251355_251366	Full skin graft ≥ 10 cm ² and < 50 cm ²	0	0	0	0	0	0
N22	251370_251381	Full skin graft ≥ 50 cm ² and < 200 cm ²	0	0	0	0	0	0
N25	227511_227522	Prosthetic implant with mastectomy (additional code)	0	1	0	0	0	0
N25	227592_227603	Sentinel adenectomy	0	0	0	0	0	1
N25	227614_227625	Sentinel adenectomy with ex tempore frozen sections	0	0	0	0	0	1
N25	227636_227640	Total mastectomy for breast CA	1	0	0	0	0	0
N25	227651_227662	Total mastectomy for breast CA	1	0	0	0	0	0



N22	251672_251683	Subcutaneous tissue expander implant(s)	0	0	0	0	0	0
N22	251716_251720	Subcutaneous tissue expander implant(s)	0	0	0	0	0	0
N22	251731_251742	Excision of tumor of skin or mucosa or other directly accessible lesion followed by plasty or grafting	0	0	0	0	0	0
N22	251753_251764	Resection of malign skin / mucosa cancer with ex tempore frozen section, without closure	0	0	0	0	0	0
N22	251775_251786	Excision of malign tumor of skin or mucosa with ex tempore frozen sections eventually followed by plasty or grafting	0	0	0	0	0	0
N25	227673_227684	Total mastectomy for breast CA	1	0	0	0	0	0
N22	251812_251823	Microsurgical vascular anastomoses, donor site	0	0	0	0	0	0
N22	251834_251845	Microsurgical vascular anastomoses, receptor site	0	0	0	0	0	0
N22	251856_251860	Muscle flap, main intervention	0	0	0	0	0	0
N22	251871_251882	Muscle flap, subsequent intervention	0	0	0	0	0	0
N22	251893_251904	Musculo-cutaneous flap, complete intervention	0	0	0	0	0	0
N22	251915_251926	Micro-surgical vascular anastomoses, donor site	0	0	0	0	0	0
N22	251930_251941	Preparing composite tissue flap for microsurgical transfer (e.g. osteo-septo-cutaneous)	0	0	0	0	0	0
N25	227695_227706	Total mastectomy with axillary curage	1	0	0	0	0	0
N25	227710_227721	Total mastectomy with axillary curage after intra-operative proof of CA by frozen sections on sentinel adenectomy specimen	1	0	0	0	0	0
N25	227732_227743	Partial mastectomy for breast CA	1	0	0	0	0	0
N25	227754_227765	Partial mastectomy after localization procedure	1	0	0	0	0	0
N25	227776_227780	Partial mastectomy with sentinel adenectomy	1	0	0	0	0	0
N25	227791_227802	Partial mastectomy with sentinel adenectomy	1	0	0	0	0	0
N25	227813_227824	Total mastectomy with axillary curage after intra-operative proof of CA on frozen sections	1	0	0	0	0	0
N22	252556_252560	Mammary reconstruction by microsurgical free flap (non- perforator)	0	1	0	0	0	0
N25	227835_227846	Partial mastectomy with axillary curage	1	0	0	0	0	0
N25	227850_227861	Complete resection benign breast tumor	0	0	0	0	0	1
N25	227894_227905	Total mastectomy without proof of CA	1	0	0	0	0	0
N22	253676_253680	Full skin graft < 10 cm2, except facial	0	0	0	0	0	0

Format aspects of NIHDI billing codes



NIHDI (RIZIV-INAMI) billing codes are legally established numeric codes representing all medical & paramedical fees, as well as reimbursement codes for medical services and goods that fall under either total or partial reimbursement by the Belgian compulsory health insurance system. Together they form the NIHDI nomenclature. Periodical changes and updates, issued by the RIZIV-INAMI Insurance Committee, are ratified by publishing in the Belgian Official Bulletin (Belgisch Staatsblad – Moniteur Belge).

Based on a Royal Decree, issued in September 1984^{aa} and starting from 01-01-1985, each code comes in a predefined 6-digit format (see table), composed of a 5-digit core number followed by a check-digit in sixth position:

- The 5-digit number starts from 10101 and mounts up to 99999.
- In principle, even 5-digit numbers apply to inpatient billings, the odd ones to outpatient billings^{bb}.
- The check-digit equals the integer residual of the division of the corresponding 5-digit number by seven (modulus 7).
- Following codes result from adding one unit to the preceding 5-digit core number.

As a consequence, most billing codes come in pairs: a code for outpatient billing and a corresponding code for inpatient billing: e.g. 243154_243165 = billing code for appendectomy, 243154 being the code for outpatient ('one day') and 243165 the code for inpatient appendectomy.

Besides legally published nomenclature codes NIHDI uses a lot of a similar codes that are published through periodical circular letters to the national health insurance companies ('pseudo-codes') or in specific billing instructions manuals for health care providers ('instructions codes'^{cc}).

Mathematically 89 889 different codes are available. Throughout the years some codes were rescinded, whereas other, new ones were installed. All codes and their history - creation date, suppression date, Dutch & French labels - are stored in a central database, which is regularly updated by RIZIV-INAMI officials. At present there are 23595 RIZIV-INAMI codes assigned (active = 14 253 or rescinded = 11 781, including pseudo-codes).

Table 10 – Format aspects of NIHDI billing codes

5-digit core number & check-digit → #1 #2 #3 #4 #5 #check			
Components	5 digit core	Check digit	Full code
Algorithms	$N_{1000n} = 10101 \rightarrow 99999$	$N_{1000n} - INT(N_{1n} / 7) \times 7$	$N_{1000n} \times 10 + \text{check digit}$
Start number	10101	0	101010
Increment	$N_{n-1} + 1$		
Endpoint	99999	4	999994
theoretical maximum number of codes =			89 889

^{aa} From historical point of view the RIZIV-INAMI coding system is quite older than 1985: former billing codes were in 4-digit format, without check-digit.

^{bb} For some – technical codes – such distinction between inpatient and outpatient is irrelevant.

^{cc} Instructies voor aflevering van facturatiebestanden op magnetische drager = IMD; instructions relatives à la facturation sur support magnétique = ISM



5 – ICD-9-CM DIAGNOSES FOR MAMMARY INTERVENTIONS (VERSION DATE: 2015-05-29)

As with procedure codes, ICD-9-CM diagnoses codes figuring in the entire National Hospital Database (NHDB) for the years 2008-2011 were extracted by executing a 'group by' query filtered on primarily breast related APRDRGs as listed in Table 1 of Appendix 3. Diagnoses were looked for in the overall diagnoses file but also in the ICD-9-CM procedure file, since the latter contains a variable <related diagnosis> intended to register indications for procedures. Reliability however is questionable since dummy codes occur (6% of all procedures in our extractions for present project).

By thus proceeding in an inductive approach we prevent eventually overlooking codes not thought of beforehand. This could especially be the case for various complication codes, including quite a number that are remarkably general or even unspecific. Such overlooking could occur if a selection list is set up by mere deduction from the bulky Belgian ICD-9-CM reference table. Furthermore, by relying solely on the official coding instructions manual, hence selecting only recommended codes, we ignore that hospital encoders – intentionally or not – can interpret their own way code labelling, resulting in less appropriate or even erroneous coding. Even in the presence of a system of coding audits by officials of the federal Ministry of Health (MoH), we have to acknowledge that such auditing, although performed by sampling of 'flashlight' hospital MCD records and comparing their diagnosis registrations with the actual clinical patient records, nevertheless is scant and this for obvious organizational reasons (manpower in auditors team).

The entire Belgian ICD-9-CM diagnosis code table at present totalizes 15 055 active codes, including E- and V-codes. Fortunately, a great deal of them are totally irrelevant for our inquiry, so we have to apply extra filters to reduce the number of codes left for scrutinizing. This is done by means of preselection of diagnosis subchapters appraised as potentially relevant (taking care not being too restrictive). The selected subchapters are listed in Table 11.

Table 11 – Subchapter filter for ICD-9-CM diagnosis code extraction

Subchapter	Subchapter label (code range)
D02.04	Malignant neoplasm of bone, connective tissue, skin, and breast (170-176)
D02.07	Malignant neoplasm of lymphatic and hematopoietic tissue (200-208)
D02.08	Neuroendocrine tumors (209)
D02.09	Benign neoplasms (210-229)
D02.10	Carcinoma in situ (230-234)
D02.11	Neoplasms of uncertain behaviour (235-238)
D02.12	Neoplasms of unspecified nature (239)
D05.03	Neurotic disorders, personality disorders, and other nonpsychotic mental disorders (300-316)
D10.04	Disorders of breast (610-612)
D12.02	Other inflammatory conditions of skin and subcutaneous tissue (690-698)
D12.03	Other diseases of skin and subcutaneous tissue (700-709)
D14.01	Congenital anomalies (740-759)
D17.13	Late effects of injuries, poisonings, toxic effects, and other external causes (905-909)
D17.24	Complications of surgical and medical care, not elsewhere classified (996-999)
D18.06	Persons with a condition influencing their health status (V40-V49)



D18.07	Persons encountering health services for specific procedures and aftercare (V50-V59)
D18.08	Persons encountering health services in other circumstances (V60-V69)
D18.10	Genetics (V83-V84)
D18.12	Oestrogen receptor status (V86)
D18.13	Other specified personal exposures and history presenting hazards to health (V87)
D18.14	Acquired absence of other organs and tissue (V88)
D18.16	Retained foreign body (V90)
D19.13	Misadventures to patients during surgical and medical care (E870-E876)
D19.14	Surgical and medical procedures as the cause of abnormal reaction of patient or later complication (E878-E879)

With this filter and the restriction of our query to the above mentioned APR-DRG we still obtain a frequency list of 1 295 different codes. Luckily quite a lot of them can be discarded immediately as evidently not pertinent for our project (out of scope). The remainder 86 – within scope - are listed in Table 12.

Table 12 – Frequency table ICD-9-CM diagnosis codes appearing in 2008-2011 stays of APRRG 362 to 364

ICD9-D	Code label English	Subchapter	Frequency
1744	Malignant neoplasm of upper-outer quadrant of female breast	D02.04	22 896
1749	Malignant neoplasm of breast (female), unspecified	D02.04	18 682
1748	Malignant neoplasm of other specified sites of female breast	D02.04	17 015
1742	Malignant neoplasm of upper-inner quadrant of female breast	D02.04	7 292
1745	Malignant neoplasm of lower-outer quadrant of female breast	D02.04	5 501
1743	Malignant neoplasm of lower-inner quadrant of female breast	D02.04	3 648
1741	Malignant neoplasm of central portion of female breast	D02.04	3 471
1740	Malignant neoplasm of nipple and areola of female breast	D02.04	3 214
1746	Malignant neoplasm of axillary tail of female breast	D02.04	458
1759	Malignant neoplasm of other and unspecified sites of male breast	D02.04	383
1750	Malignant neoplasm of nipple and areola of male breast	D02.04	253
217	Benign neoplasm of breast	D02.09	9 171
2330	Carcinoma in situ of breast	D02.10	8 480
2383	Neoplasm of uncertain behaviour of breast	D02.11	269
2393	Neoplasm of unspecified nature of breast	D02.12	218
30250	Trans-sexualism with unspecified sexual history	D05.03	57
30285	Gender identity disorder in adolescents or adults	D05.03	9



3026	Gender identity disorder in children	D05.03	1
30252	Trans-sexualism with homosexual history	D05.03	1
30253	Trans-sexualism with heterosexual history	D05.03	1
6111	Hypertrophy of breast	D10.04	17 941
6101	Diffuse cystic mastopathy	D10.04	4 080
6110	Inflammatory disease of breast	D10.04	3 003
61181	Ptosis of breast	D10.04	2 978
6114	Atrophy of breast	D10.04	2 060
61182	Hypoplasia of breast	D10.04	1 795
6102	Fibro-adenosis of breast	D10.04	1 728
61189	Other specified disorders of breast	D10.04	1 609
6118	Other specified disorders of breast	D10.04	1 602
6121	Disproportion of reconstructed breast	D10.04	1 381
6108	Other specified benign mammary dysplasias	D10.04	1 055
61179	Other signs and symptoms in breast	D10.04	900
6100	Solitary cyst of breast	D10.04	849
6103	Fibrosclerosis of breast	D10.04	731
6104	Mammary duct ectasia	D10.04	645
61183	Capsular contracture of breast implant	D10.04	643
6120	Deformity of reconstructed breast	D10.04	538
6119	Unspecified breast disorder	D10.04	466
6113	Fat necrosis of breast	D10.04	392
61172	Lump or mass in breast	D10.04	297
61171	Mastodynia	D10.04	151
6109	Benign mammary dysplasia, unspecified	D10.04	58
6115	Galactocele	D10.04	12
6112	Fissure of nipple	D10.04	10
7014	Keloid scar	D12.03	2 690
7018	Other specified hypertrophic and atrophic conditions of skin	D12.03	2 556
7094	Foreign body granuloma of skin and subcutaneous tissue	D12.03	1 448



7576	Specified congenital anomalies of breast	D14.01	1 109
7587	Klinefelter's syndrome	D14.01	21
9092	Late effect of radiation	D17.13	2
99654	Mechanical complication due to breast prosthesis	D17.24	2 489
99812	Hematoma complicating a procedure	D17.24	578
99811	Haemorrhage complicating a procedure	D17.24	369
99859	Other postoperative infection	D17.24	97
99679	Other complications due to other internal prosthetic device, implant, and graft	D17.24	95
99889	Other specified complications of procedures not elsewhere classified	D17.24	48
99832	Disruption of external operation (surgical) wound	D17.24	40
99659	Mechanical complication due to other implant and internal device, not elsewhere classified	D17.24	18
9986	Persistent postoperative fistula	D17.24	16
99883	Non-healing surgical wound	D17.24	16
99851	Infected postoperative seroma	D17.24	9
99830	Disruption of wound, unspecified	D17.24	5
V4571	Acquired absence of breast and nipple	D18.06	7 576
V4382	Breast replacement	D18.06	1 317
V423	Skin replaced by transplant	D18.06	269
V4583	Breast implant removal status	D18.06	49
V501	Other plastic surgery for unacceptable cosmetic appearance	D18.07	18 804
V510	Encounter for breast reconstruction following mastectomy	D18.07	5 177
V5849	Other specified aftercare following surgery	D18.07	2 613
V51	Aftercare involving the use of plastic surgery	D18.07	2 128
V518	Other aftercare involving the use of plastic surgery	D18.07	1 208
V5041	Prophylactic breast removal	D18.07	679
V5889	Other specified aftercare	D18.07	574
V5811	Encounter for antineoplastic chemotherapy	D18.07	306
V5877	Aftercare following surgery of the skin and subcutaneous tissue, nec	D18.07	275
V524	Fitting and adjustment of breast prosthesis and implant	D18.07	228
V581	Encounter for chemotherapy and immunotherapy for neoplastic conditions	D18.07	66



V508	Other elective surgery for purposes other than remedying health states	D18.07	29
V580	Encounter for radiotherapy	D18.07	6
V5831	Encounter for change or removal of surgical wound dressing	D18.07	6
V5841	Encounter for planned post-operative wound closure	D18.07	5
V8401	Genetic susceptibility to malignant neoplasm of breast	D18.10	434
V860	Estrogen receptor positive status [ER+]	D18.12	26 107
V861	Estrogen receptor negative status [ER-]	D18.12	5 983
V8741	Personal history of antineoplastic chemotherapy	D18.13	3 976
V9039	Other retained organic fragments	D18.16	6

All codes left were weighed for their frequency as well as their specificity and relevance for extraction of target interventions and their particular complications. They were accordingly flagged for suitability for selection or not (flag 1^{ary} select = 1 or 0). The resulting final selection list is presented in Table 3. Breast cancer diagnosis, for example, although highly specific is not selected as extraction criterion since doing so would confront us with an abundance of irrelevant medical DRG stays (see Appendix 7 on inclusion-exclusion criteria). The same applies to benign mammary disorders.

ICD9-D	Code label En	Subchapter	1ary_select
6120	Deformity of reconstructed breast	D10.04	1
6121	Disproportion of reconstructed breast	D10.04	1
61183	Capsular contracture of breast implant	D10.04	1
99654	Mechanical complication due to breast prosthesis	D17.24	1
V4382	Breast replacement	D18.06	1
V4583	Breast implant removal status	D18.06	1
V5041	Prophylactic breast removal	D18.07	1
V510	Encounter for breast reconstruction following mastectomy	D18.07	1
V524	Fitting and adjustment of breast prosthesis and implant	D18.07	1
217	Benign neoplasm of breast	D02.09	0
1740	Malignant neoplasm of nipple and areola of female breast	D02.04	0
1741	Malignant neoplasm of central portion of female breast	D02.04	0
1742	Malignant neoplasm of upper-inner quadrant of female breast	D02.04	0
1743	Malignant neoplasm of lower-inner quadrant of female breast	D02.04	0
1744	Malignant neoplasm of upper-outer quadrant of female breast	D02.04	0
1745	Malignant neoplasm of lower-outer quadrant of female breast	D02.04	0



1746	Malignant neoplasm of axillary tail of female breast	D02.04	0
1748	Malignant neoplasm of other specified sites of female breast	D02.04	0
1749	Malignant neoplasm of breast (female), unspecified	D02.04	0
1750	Malignant neoplasm of nipple and areola of male breast	D02.04	0
1759	Malignant neoplasm of other and unspecified sites of male breast	D02.04	0
2330	Carcinoma in situ of breast	D02.10	0
2383	Neoplasm of uncertain behaviour of breast	D02.11	0
2393	Neoplasm of unspecified nature of breast	D02.12	0
3026	Gender identity disorder in children	D05.03	0
4570	Post-mastectomy lymphedema syndrome	D07.09	0
6100	Solitary cyst of breast	D10.04	0
6101	Diffuse cystic mastopathy	D10.04	0
6102	Fibro-adenosis of breast	D10.04	0
6103	Fibrosclerosis of breast	D10.04	0
6104	Mammary duct ectasia	D10.04	0
6108	Other specified benign mammary dysplasias	D10.04	0
6109	Benign mammary dysplasia, unspecified	D10.04	0
6110	Inflammatory disease of breast	D10.04	0
6111	Hypertrophy of breast	D10.04	0
6112	Fissure of nipple	D10.04	0
6113	Fat necrosis of breast	D10.04	0
6114	Atrophy of breast	D10.04	0
6115	Galactocele	D10.04	0
6118	Other specified disorders of breast	D10.04	0
6119	Unspecified breast disorder	D10.04	0
7014	Keloid scar	D12.03	0
7018	Other specified hypertrophic and atrophic conditions of skin	D12.03	0
7094	Foreign body granuloma of skin and subcutaneous tissue	D12.03	0
7576	Specified congenital anomalies of breast	D14.01	0
7587	Klinefelter's syndrome	D14.01	0



9092	Late effect of radiation	D17.13	0
9986	Persistent postoperative fistula	D17.24	0
19881	Secondary malignant neoplasm of breast	D02.06	0
30250	Trans-sexualism with unspecified sexual history	D05.03	0
30252	Trans-sexualism with homosexual history	D05.03	0
30253	Trans-sexualism with heterosexual history	D05.03	0
30285	Gender identity disorder in adolescents or adults	D05.03	0
61171	Mastodynia	D10.04	0
61172	Lump or mass in breast	D10.04	0
61179	Other signs and symptoms in breast	D10.04	0
61181	Ptosis of breast	D10.04	0
61182	Hypoplasia of breast	D10.04	0
61189	Other specified disorders of breast	D10.04	0
79381	Mammographic micro-calcification	D16.02	0
99659	Mechanical complication due to other implant and internal device, not elsewhere classified	D17.24	0
99679	Other complications due to other internal prosthetic device, implant, and graft	D17.24	0
99811	Haemorrhage complicating a procedure	D17.24	0
99812	Hematoma complicating a procedure	D17.24	0
99830	Disruption of wound, unspecified	D17.24	0
99832	Disruption of external operation (surgical) wound	D17.24	0
99851	Infected postoperative seroma	D17.24	0
99859	Other postoperative infection	D17.24	0
99883	Non-healing surgical wound	D17.24	0
99889	Other specified complications of procedures not elsewhere classified	D17.24	0
V103	Personal history of malignant neoplasm of breast	D18.03	0
V423	Skin replaced by transplant	D18.06	0
V4571	Acquired absence of breast and nipple	D18.06	0
V501	Other plastic surgery for unacceptable cosmetic appearance	D18.07	0
V508	Other elective surgery for purposes other than remedying health states	D18.07	0
V51	Aftercare involving the use of plastic surgery	D18.07	0



V518	Other aftercare involving the use of plastic surgery	D18.07	0
V580	Encounter for radiotherapy	D18.07	0
V581	Encounter for chemotherapy and immunotherapy for neoplastic conditions	D18.07	0
V5811	Encounter for antineoplastic chemotherapy	D18.07	0
V5831	Encounter for change or removal of surgical wound dressing	D18.07	0
V5841	Encounter for planned post-operative wound closure	D18.07	0
V5849	Other specified aftercare following surgery	D18.07	0
V5877	Aftercare following surgery of the skin and subcutaneous tissue, nec	D18.07	0
V5889	Other specified aftercare	D18.07	0
V8401	Genetic susceptibility to malignant neoplasm of breast	D18.10	0
V860	Oestrogen receptor positive status [ER+]	D18.12	0
V861	Oestrogen receptor negative status [ER-]	D18.12	0
V8741	Personal history of antineoplastic chemotherapy	D18.13	0
V9039	Other retained organic fragments	D18.16	0

Next table gives, for each of the ICD-9-CM diagnosis codes, the corresponding target flag(s): value 1 or 0.

ICD9-D	Code label English	Mamm. resection	Mamm. reconstruction	2ary interv.	Complication
217	Benign neoplasm of breast	0	0	0	0
1740	Malignant neoplasm of nipple and areola of female breast	0	0	0	0
1741	Malignant neoplasm of central portion of female breast	0	0	0	0
1742	Malignant neoplasm of upper-inner quadrant of female breast	0	0	0	0
1743	Malignant neoplasm of lower-inner quadrant of female breast	0	0	0	0
1744	Malignant neoplasm of upper-outer quadrant of female breast	0	0	0	0
1745	Malignant neoplasm of lower-outer quadrant of female breast	0	0	0	0
1746	Malignant neoplasm of axillary tail of female breast	0	0	0	0
1748	Malignant neoplasm of other specified sites of female breast	0	0	0	0
1749	Malignant neoplasm of breast (female), unspecified	0	0	0	0
1750	Malignant neoplasm of nipple and areola of male breast	0	0	0	0
1759	Malignant neoplasm of other and unspecified sites of male breast	0	0	0	0



2330	Carcinoma in situ of breast	0	0	0	0
2383	Neoplasm of uncertain behavior of breast	0	0	0	0
2393	Neoplasm of unspecified nature of breast	0	0	0	0
3026	Gender identity disorder in children	0	0	0	0
4570	Post-mastectomy lymphedema syndrome	1	0	0	0
6100	Solitary cyst of breast	0	0	0	0
6101	Diffuse cystic mastopathy	0	0	0	0
6102	Fibro-adenosis of breast	0	0	0	0
6103	Fibrosclerosis of breast	0	0	0	0
6104	Mammary duct ectasia	0	0	0	0
6108	Other specified benign mammary dysplasias	0	0	0	0
6109	Benign mammary dysplasia, unspecified	0	0	0	0
6110	Inflammatory disease of breast	0	0	0	0
6111	Hypertrophy of breast	0	0	0	0
6112	Fissure of nipple	0	0	0	1
6113	Fat necrosis of breast	0	0	0	1
6114	Atrophy of breast	0	0	0	0
6115	Galactocele	0	0	0	0
6118	Other specified disorders of breast	0	0	0	0
6119	Unspecified breast disorder	0	0	0	0
6120	Deformity of reconstructed breast	0	0	0	1
6121	Disproportion of reconstructed breast	0	0	0	1
7014	Keloid scar	0	0	0	1
7018	Other specified hypertrophic and atrophic conditions of skin	0	0	0	0
7094	Foreign body granuloma of skin and subcutaneous tissue	0	0	0	1
7576	Specified congenital anomalies of breast	0	0	0	0
7587	Klinefelter's syndrome	0	0	0	0
9092	Late effect of radiation	0	0	0	0
9986	Persistent postoperative fistula	0	0	0	1
19881	Secondary malignant neoplasm of breast	0	0	0	0



30250	Trans-sexualism with unspecified sexual history	0	0	0	0
30252	Trans-sexualism with homosexual history	0	0	0	0
30253	Trans-sexualism with heterosexual history	0	0	0	0
30285	Gender identity disorder in adolescents or adults	0	0	0	0
61171	Mastodynia	0	0	0	0
61172	Lump or mass in breast	0	0	0	0
61179	Other signs and symptoms in breast	0	0	0	0
61181	Ptosis of breast	0	0	0	0
61182	Hypoplasia of breast	0	0	0	0
61183	Capsular contracture of breast implant	0	0	0	1
61189	Other specified disorders of breast	0	0	0	0
79381	Mammographic micro-calcification	0	0	0	0
99654	Mechanical complication due to breast prosthesis	0	0	0	1
99659	Mechanical complication due to other implant and internal device, not elsewhere classified	0	0	0	1
99679	Other complications due to other internal prosthetic device, implant, and graft	0	0	0	1
99811	Hemorrhage complicating a procedure	0	0	0	1
99812	Hematoma complicating a procedure	0	0	0	1
99830	Disruption of wound, unspecified	0	0	0	1
99832	Disruption of external operation (surgical) wound	0	0	0	1
99851	Infected postoperative seroma	0	0	0	1
99859	Other postoperative infection	0	0	0	1
99883	Non-healing surgical wound	0	0	0	1
99889	Other specified complications of procedures not elsewhere classified	0	0	0	1
V103	Personal history of malignant neoplasm of breast	0	0	0	0
V423	Skin replaced by transplant	0	0	0	1
V4382	Breast replacement	1	0	0	0
V4571	Acquired absence of breast and nipple	1	1	0	0
V4583	Breast implant removal status	0	0	0	1
V501	Other plastic surgery for unacceptable cosmetic appearance	0	0	0	1



V5041	Prophylactic breast removal	1	0	0	0
V508	Other elective surgery for purposes other than remedying health states	0	0	0	0
V51	Aftercare involving the use of plastic surgery	0	0	0	0
V510	Encounter for breast reconstruction following mastectomy	1	1	0	0
V518	Other aftercare involving the use of plastic surgery	0	0	0	0
V524	Fitting and adjustment of breast prosthesis and implant	0	0	1	0
V580	Encounter for radiotherapy	0	0	0	0
V581	Encounter for chemotherapy and immunotherapy for neoplastic conditions	0	0	0	0
V5811	Encounter for antineoplastic chemotherapy	0	0	0	0
V5831	Encounter for change or removal of surgical wound dressing	0	0	0	0
V5841	Encounter for planned post-operative wound closure	0	0	0	1
V5849	Other specified aftercare following surgery	0	0	0	0
V5877	Aftercare following surgery of the skin and subcutaneous tissue, nec	0	0	0	0
V5889	Other specified aftercare	0	0	0	0
V8401	Genetic susceptibility to malignant neoplasm of breast	0	0	0	0
V860	Oestrogen receptor positive status [ER+]	0	0	0	0
V861	Oestrogen receptor negative status [ER-]	0	0	0	0
V8741	Personal history of antineoplastic chemotherapy	0	0	0	0
V9039	Other retained organic fragments	0	0	0	1



6 INCLUSION-EXCLUSION CRITERIA FOR STAYS AND PATIENTS

Since (1) not all of applied selection codes are fully specific, as discussed in Appendices 2 to 4, and (2) not all source records are complete, superfluous or abortive records need to be excluded. This is done in a cascading series of exclusion operations resulting in the attribution of an increasing exclusion score, to each stay, starting from 1 to even scores 9 (Table 13), score 0 (i.e. non-exclusion) being the default score.

Indeed, records can be classified as abortive either because of absence of HBD data and UPP (non-linkage), either because of absence of MCD data in the presence of HBD data (failed or rejected linkage) and finally because of data flaws rendering them unreliable. Next a number of specific records need to be excluded. For instance, all stays with age at admission under 15 year prove to have a totally different clinical context (congenital breast disorders) quite distinct from older age groups. Likewise all male and (few) transgender stays are also excluded, since they are not in scope for present study (moreover, they show very few reconstructions – N = 32).

Insufficient selection code specificity causes some stays to be extracted in the first round, yet upon closer contextual investigation they can turn out to have had interventions totally out of scope. Consequently such stays are excluded, before going over to patients' UPP assembling. Furthermore, since in the second selection round all other, non-index stays are extracted, some of those can also prove to be totally irrelevant for present study and hence superfluous. For instance, some patients can have stays related to totally different disorders, e.g. an inter-curing cholecystectomy or so, and even if breast pathology related, secondary extraction stays can be irrelevant to present study, e.g. pure chemotherapy stays to give the most prominent example. This last issue, however, deserves some further in depth attention, as we address in appendix 6.

Finally, we keep for inclusion only fully linked, longitudinal data of women age 15 or more.

Table 13 – Overview of inclusion-exclusion scores in primary stays and patients tables

Inclusion-exclusion score	Description	Present in N stays table	Present in N Patients table
0	No exclusion; full inclusion	1 333 676	1 58 522
1	No primary linkage; absent UPP	1 12 269	0 -
2-3	Stays with different sex / birth year for same UPP	0 17	0 -
5	Age at admission <15 yr.	1 938	1 283
6	Male & transgender	1 24 349	1 5 377
7	Primary selection stays irrelevant to the project targets	1 64 303	1 7 228
8	Secondary selection stays irrelevant to the project targets	1 21 846	0 N/A(1)
9	Non-breast CA chemotherapy stays (see appendix 6)	1 4 745	0 N/A(1)

⁽¹⁾ Apply only to subsets of stay records, never to entire patients records



7 FLAGGING CODES AND STAYS FOR BREAST CANCER INVOLVEMENT

Flagging for breast cancer, at first glance, seems quite simple. Indeed, ICD-9-CM breast cancer diagnosis codes are very specific in differentiating mainly topographical types of breast cancer, and many ICD-9-CM procedure codes as well as NIHDI billing codes are, by their labelling, quite easy to checkmark as interventions performed for breast cancer indications.

However, in this study we see flagging for breast cancer in a broader perspective: not only interventions for actual breast cancer, but also cases having or having had a mammary resection in a breast cancer context without actually presenting with an active mammary cancer. The best examples are cases where mammary resection is performed prophylactically, either because of personal antecedents of previous breast cancer, either because of familial predisposition to breast cancer. In the same spirit we also included interventions registered with a labelling ‘uncertain cancer diagnosis’ or ‘unspecified nature of neoplasm’, assuming that such codes would induce a cancer conform surgical treatment. Luckily frequencies of such ‘in dubio’ codes are very low (overall 269 stays for code 2383 and 218 for 2393).

Consequently we looked into the different code selection lists and assigned a flag for breast cancer involvement (value 1) or not (value 0). Results are listed in Tables 13 to 15 (restricted to positive value codes).

Breast cancer codes in ICD-9-CM diagnosis codes

Table 14 lists all breast cancer related diagnosis codes (restricted to positive flag codes; all other codes are to be assumed negative). Moreover, we added a clinical subgroup classification, depending on whether codes relate to primary breast cancer diagnosis, in situ cancer, post-cancer status or prophylaxis (including a specificity marker – last column). For pure data technical reasons we added to these clinical subgroups a hierarchical code (descending order) to enable us to take the most relevant subgroup (least hierarchical code value) in case of stays with multiple breast cancer codes.

Table 14 – ICD-9-CM diagnosis codes related to breast cancer

ICD9-D	Code label English	Subgroup	Code hierarchy	Code specificity
1759	Malignant neoplasm of other and unspecified sites of male breast	Br-CA, 1ary	1	Full
1741	Malignant neoplasm of central portion of female breast	Br-CA, 1ary	1	Full
1742	Malignant neoplasm of upper-inner quadrant of female breast	Br-CA, 1ary	1	Full
1743	Malignant neoplasm of lower-inner quadrant of female breast	Br-CA, 1ary	1	Full
1744	Malignant neoplasm of upper-outer quadrant of female breast	Br-CA, 1ary	1	Full
1745	Malignant neoplasm of lower-outer quadrant of female breast	Br-CA, 1ary	1	Full
1746	Malignant neoplasm of axillary tail of female breast	Br-CA, 1ary	1	Full
1748	Malignant neoplasm of other specified sites of female breast	Br-CA, 1ary	1	Full
1749	Malignant neoplasm of breast (female), unspecified	Br-CA, 1ary	1	Full
1750	Malignant neoplasm of nipple and areola of male breast	Br-CA, 1ary	1	Full
1740	Malignant neoplasm of nipple and areola of female breast	Br-CA, 1ary	1	Full
2330	Carcinoma in situ of breast	Br-CA, in situ	2	Full
19881	Secondary malignant neoplasm of breast	Br-CA, 2ary	3	Full



2383	Neoplasm of uncertain behaviour of breast	Br-CA, uncertain	4	Assumed
2393	Neoplasm of unspecified nature of breast	Br-CA, uncertain	4	Assumed
V8741	Personal history of antineoplastic chemotherapy	Br-CA, post	5	Context
4570	Post-mastectomy lymphedema syndrome	Br-CA, post	5	Full
V103	Personal history of malignant neoplasm of breast	Br-CA, post	5	Full
V580	Encounter for radiotherapy	Br-CA, post	5	Context
V860	Oestrogen receptor positive status [ER+]	Br-CA, post	5	Full
V861	Oestrogen receptor negative status [ER-]	Br-CA, post	5	Full
V5041	Prophylactic breast removal	Prophylaxis	6	Full
V8401	Genetic susceptibility to malignant neoplasm of breast	Prophylaxis	6	Full

Breast cancer flag assignment in ICD-9-CM procedure codes

Table 15 lists all breast cancer related procedure codes (restricted to positive flag codes; all other codes are to be assumed negative). Indeed, all extended or radical mastectomies are by definition for breast cancer.

Table 15 – ICD-9-CM procedure codes related to breast cancer

ICD9-P	Code label English
8543	Unilateral extended simple mastectomy
8544	Bilateral extended simple mastectomy
8545	Unilateral radical mastectomy
8546	Bilateral radical mastectomy
8547	Unilateral extended radical mastectomy
8548	Bilateral extended radical mastectomy

Breast cancer flag assignment NIHDI billing codes

Table 16 lists all breast cancer related NIHDI billing codes (restricted to positive flag codes; all other codes are to be assumed negative). Moreover, we added a clinical subgroup classification, depending on whether mastectomy was partial or total, or whether it involved the axillary region (to resect lymph nodes, usually first station for metastatic spread).

Table 16 – NIHDI billing codes related to breast cancer

Code pair	Short label English	Subgroup
226936_226940	Axillary curage for breast CA	Axillary
227054_227065	Partial mastectomy with axillary curage (different subtypes)	Partial mastectomy
227732_227743		Partial mastectomy



227754_227765		Partial mastectomy
227776_227780		Partial mastectomy
227791_227802		Partial mastectomy
227835_227846		Partial mastectomy
227813_227824		Partial mastectomy
226951_226962	Urban extended mastectomy	Total mastectomy
226973_226984	Halsted-Patney mastectomy	Total mastectomy
226995_227006		Total mastectomy
227636_227640	Total mastectomy for breast CA (different subtypes)	Total mastectomy
227651_227662		Total mastectomy
227673_227684		Total mastectomy
227695_227706	Total mastectomy with axillary curage (different subtypes)	Total mastectomy
227710_227721		Total mastectomy

Contextual check marking for breast cancer

Besides direct and rather straightforward code flagging, we also need to address a far more complicated issue concerning 'contextual' breast cancer flagging. Indeed, in post-mastectomy stays or stays of patients having a breast reconstruction for a mastectomy performed prior to 2008 (i.e. outside present data window) a formal breast cancer diagnosis is not always found in the MCD registrations (we would expect it should, but the ideal world does not exist).

Luckily there are other ways to 'decipher' available data in order to indirectly unveil breast cancer involvement. The most evident way is to look for chemotherapy medication typically used for breast cancer treatment. Loco-regional radiotherapy would be another possible indicator, yet it proves to be less reliable, since this kind of therapy usually is administered on an outpatient base and consequently hospital data records seldom contain such information (as we verified in pre-assessment). For such information ambulatory billing data would be necessary (available in Belgian Cancer Registry – BCR - or databases of National Health Insurers – IMA-AIM). However, assessing those would require a complex and laborious linkage process well as a time consuming authorisation request at the Belgian Privacy Authority.

In most cases, chemotherapy (adjuvant as well as neo-adjuvant treatment) is most effective when combinations of more than one drug are used. Many combinations are being used and it is not clear which single combination is the best. The most common chemo drugs used for early breast cancer include the anthracyclines (such as doxorubicin and epirubicin) and the taxanes (such as paclitaxel and docetaxel). These may be used in combination with certain other drugs, like fluorouracil (5-FU), cyclophosphamide, and carboplatin.

For cancers that are HER2 positive, the targeted drug trastuzumab is often given with one of the taxanes. Pertuzumab can also be combined with trastuzumab and docetaxel for HER2 positive cancers.

Advanced disease, on the other hand, is more often treated with single chemo drugs. Nevertheless, some combinations, such as carboplatin or cisplatin plus gemcitabine are commonly used to treat advanced breast cancer.



Table 17 below lists all commonly used chemotherapeutics and their corresponding ATC-code, by which we can identify them in national hospital stays databases (dataset pharmaceuticals).

Table 17 – Commonly used chemotherapeutics for breast cancer

Early breast CA	ATC	Substance
A. anthracyclines	L01DB01	doxorubicin
	L01DB03	epirubicin
B. taxanes	L01CD01	paclitaxel
	L01CD02	docetaxel
C. combinations of A/B with	L01BC02	5-FU
	L01BC52	5-FU, combinations
	L01AA01	cyclophosphamide
	L01XA02	carboplatin
ANTI-ESTROGENS		
•	L02BA01	tamoxifen
•	L02BA02	toremifene
•	L02BA03	fulvestrant
Advanced breast cancer		
•	L01CD02	docetaxel
•	L01CD01	paclitaxel
•	L01XA01	cisplatin
•	L01XA02	carboplatin
•	L01XA01	vinorelbine
•	L01BC06	capecitabine
•	L01DB01	liposomal doxorubicin
•	L01BC06	gemcitabine
•	L01DB07	mitoxantrone
•	L01DC04	ixabepilone
•	L01XX41	eribulin
Anti HER2/neu protein		
•	L01XC03	trastuzumab (Herceptin®)
•	L01XC13	pertuzumab (Perjeta®)
•	L01XC14	ado-trastuzumab emtansine
•	L01XE07	lapatinib



Anti-oestrogens are – certainly in females – quite specific for adjuvant breast cancer therapy. In fact, they are predominantly prescribed for secondary prophylaxis in oestrogen-receptor positive cases, which means many women take them.

Next, and using table 4 as reference table, we can search for stays having the other ATC pharmaceuticals in their HBD records. If so, we check them for other cancer diagnoses (see Table 18). In absence of the latter, we can assume that chemotherapy was given for breast cancer.

Table 18 – ICD-9-CM code ranges for neoplasm codes

Neoplasm subclasses in ICD-9-CM	3-digit range	L-limit	U-limit
Benign neoplasms	210-229	210	229
Carcinoma in situ	230-234	230	234
Malignant neoplasms, stated or presumed to be primary, of lymphatic and hematopoietic tissue	200-208	200	208
Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphatic and hematopoietic tissue	140-195	140	195
Malignant neoplasms, stated or presumed to be secondary, of specified sites	196-198	196	198
Malignant neoplasms, without specification of site	199	199	199
Neoplasms of uncertain behaviour	235-238	235	238
Neoplasms of unspecified nature	239	239	239
Neuroendocrine tumours	209	209	209



8 EXHAUSTIVENESS WITH EXTRACTION-INCLUSION-EXCLUSION

After extracting records from the NHDB and assigning inclusion-exclusion markers, it always is wise to check how many records are left and especially how many of the target interventions we keep. In other words, we need to evaluate exhaustiveness (representativeness) of our inclusions. This is done by comparing for each target its numbers in the full NHDB database with the numbers left in our extraction database.

This is done code per code, NIHDI codes, as well as ICD-9-CM procedure codes. Results are presented in Table 1 and Table 2. Exhaustiveness is expressed in percentage and lower values of the latter are briefly discussed in a remarks column.

A third table is added, in which we evaluate exhaustiveness for stays in the main breast related APR-DRG.

8.1 Interventions in HBD

Intervention group	Billing codes	N all HBD 2008-2011	N included (only female)	Exhaustiveness	Remarks
<i>Partial mastectomy</i>	227054_227065 227732_227743 227754_227765 227776_227780 227791_227802 227835_227846	26.131	25.960	99,3%	
<i>Total mastectomy</i>	227010_227021 227113_227124 227636_227640 227651_227662 227673_227684 227695_227706 227710_227721 227813_227824 227894_227905	23.685	18.033	76,1%	<i>Males excluded</i>
<i>Extended mastectomy</i>	226951_226962 226973_226984 226995_227006	3.642	3.560	97,7%	
Mammary reconstruction by prosthesis	252431_252442 252593_252604 (*)	4.039	4.007	99,2%	



Mammary reconstruction with microsurgical free perforator flap (DIEP, SGAP, ...)	252571_252582	2.799	2.761	98,6%	
Mammary reconstruction by pedicled transposition skin-muscle flap (Latissimus dorsi)	252475_252486	1.060	1.043	98,4%	
Mammary reconstruction by pedicled transposition skin flap	252453_252464	464	456	98,3%	
Mammary reconstruction by pedicled transposition TRAM flap	252534_252545	134	130	97,0%	
Mammary reconstruction by microsurgical free flap (non-perforator)	252556_252560	25	18	72,0%	<i>Males excluded</i>
Hetero-lateral remodelling mammoplasty	252512_252523	4.848	4.786	98,7%	
Removal mammary implant due to complications	251591_251602	3.455	3.415	98,8%	

* Code switch 2011-08-01

8.2 Interventions in MCD

ICD9-P	Label code	Stays 2008-2011	Stays included	Exhaustiveness	Remarks
8574	Deep inferior epigastric artery perforator (DIEP) flap, free	2.291	2.064	90,1%	
857	Total reconstruction of breast	737	700	95,0%	
8571	Latissimus dorsi myocutaneous flap	599	568	94,8%	
8570	Total reconstruction of breast, not otherwise specified	261	248	95,0%	
8579	Other total reconstruction of breast	176	163	92,6%	
8572	Transverse rectus abdominis myocutaneous (TRAM) flap, pedicled	158	154	97,5%	
8576	Gluteal artery perforator (GAP) flap, free	84	66	78,6%	
8573	Transverse rectus abdominis myocutaneous (TRAM) flap, free	62	54	87,1%	
8575	Superficial inferior epigastric artery (SIEA) flap, free	54	42	77,8%	
8531	Unilateral reduction mammoplasty	2.356	1.766	75,0%	Primary mammoplasties (wo previous reconstruction) not included
8534	Other unilateral subcutaneous mastectomy	1.301	752	57,8%	Males excluded
8536	Other bilateral subcutaneous mastectomy	878	270	30,8%	Males excluded
8533	Unilateral subcutaneous mastectomy with synchronous implant	256	246	96,1%	
8535	Bilateral subcutaneous mastectomy with synchronous implant	125	120	96,0%	



8675	Revision of pedicle or flap graft	2.042	859	42,1%	All pedicle flaps (including non-mammary reconstructions)
8587	Other repair or reconstruction of nipple	3.816	3.384	88,7%	
8594	Removal of implant of breast	3.840	3.230	84,1%	
8593	Revision of implant of breast	2.434	2.005	82,4%	
8595	Insertion of breast tissue expander	939	900	95,8%	
8596	Removal of breast tissue expander	791	746	94,3%	
8543	Unilateral extended simple mastectomy	10.528	10.121	96,1%	
8541	Unilateral simple mastectomy	4.648	4.417	95,0%	
8545	Unilateral radical mastectomy	2.171	2.052	94,5%	
8547	Unilateral extended radical mastectomy	461	438	95,0%	
8542	Bilateral simple mastectomy	413	349	84,5%	
8544	Bilateral extended simple mastectomy	330	319	96,7%	
8546	Bilateral radical mastectomy	84	78	92,9%	
8548	Bilateral extended radical mastectomy	24	22	91,7%	
8522	Resection of quadrant of breast	5.749	5.596	97,3%	
8523	Subtotal mastectomy	5.354	5.193	97,0%	
8554	Bilateral breast implant	12.363	4.038	32,7%	Primary mammoplasties (wo previous reconstruction) not included
8553	Unilateral breast implant	3.182	2.931	92,1%	
8551	Unilateral injection into breast for augmentation	649	584	90,0%	
8555	Fat graft to breast	461	382	82,9%	
8550	Augmentation mammoplasty, not otherwise specified	802	241	30,0%	Primary mammoplasties (wo previous reconstruction) not included
8552	Bilateral injection into breast for augmentation	230	160	69,6%	Primary mammoplasties (wo previous reconstruction) not included



8.3 APR-DRG level

APR-DRG	Full 2008-2011 database			Primary selection Included		Remarks
	All stays	Stays extracted	Exhaustiveness (%)	Stays included	Exhaustiveness (%)	
363	81.829	59.749	51,6%	42.203	70,6%	Non-reconstructive breast interventions excluded
362	25.452	25.447	92,1%	23.449	92,1%	Loss entirely due to linkage failure
364	136.112	13.888	9,0%	12.309	88,6%	DRG not exclusive for breast procedures
382	20.803	5.169	14,4%	3.001	58,1%	Medical APRDRG; no interventions
385	35.512	1.747	3,0%	1.080	61,8%	Medical APRDRG; no interventions

Legenda

- APR-DRG Label APRDRG
- 363 Breast procedures except mastectomy / 9 - P
- 362 Mastectomy procedures / 9 - P
- 364 Other skin, subcutaneous tissue & breast procedures / 9 - P
- 382 Malignant breast disorders / 9 - M
- 385 Other skin & breast disorders / 9 - M



9 GROUPING INTERVENTIONS AND COMPLICATIONS

Since all targeted interventions come in many technical variants, each with different code(s), they need some kind of well thought grouping. Obtaining practical operability without losing clinical relevance is our principal objective and in doing so we considerably simplify future querying. Intervention grouping is presented in Tables 18 to 20.

Based on main surgical characteristics we can group breast reconstructions in three main types:

- Reconstructions by means of a *mammary implant*, i.e. an implantable silicone prosthesis.
- Reconstructions by means of an autologous myo-cutaneous flap with a vascular pedicle that is preserved; such flaps are called *transposition flaps* or *tunneled flaps*.
- Reconstructions by means of an autologous myo-cutaneous flap with a vascular pedicle that is carefully prepared, next cut and then re-implanted on a new axillo-pectoral or intercostal vascular pedicle by means of a micro-vascular surgical anastomosis involving an OR microscope. Such flaps are called *free flaps*.
- The latter two groups have different subtypes, depending on the donor site of the flap.

For complications observations are similar: there is a variety of codes for complications related to the mammary prosthesis implant and an even more variety for those related to the surgical site. Two codes – 6120 and 6121 – finally relate to the overall reconstruction cosmetics. Grouping of complications is presented in Table 19.

Table 19 – Grouping ICD-9-CM codes concerning breast reconstructions

ICD9	Code label English	Group	Remarks
8553	Unilateral breast implant	Plasty_proth	Cover all breast implants, including (augmentation) mammoplasties
8554	Bilateral breast implant	Plasty_proth	Cover all breast implants, including (augmentation) mammoplasties
857	Total reconstruction of breast	Rec_NOS	General code valid in registration year 2008
8570	Total reconstruction of breast, not otherwise specified	Rec_NOS	Introduced since registration year 2009
8571	Latissimus dorsi myocutaneous pedicled flap (*)	Rec_LDF	Introduced since registration year 2009
8572	Transverse rectus abdominis myocutaneous (TRAM) flap, pedicled (*)	Rec_TRAM	Introduced since registration year 2009
8573	Transverse rectus abdominis myocutaneous (TRAM) flap, free (*)	Rec_free	Introduced since registration year 2009
8574	Deep inferior epigastric artery perforator (DIEP) flap, free (*)	Rec_DIEP	Introduced since registration year 2009
8575	Superficial inferior epigastric artery (SIEA) flap, free (*)	Rec_SIEA	Introduced since registration year 2009
8576	Gluteal artery perforator (GAP) flap, free (*)	Rec_GAP	Introduced since registration year 2009
8579	Other total reconstruction of breast	Rec_NOS	Introduced since registration year 2009
8533	Unilateral subcutaneous mastectomy with synchronous implant	Rec_proth	All-in-one intervention
V4571	Acquired absence of breast and nipple	N/A	Status code, covers all cases, including those without subsequent reconstruction



V510	Encounter for breast reconstruction following mastectomy	Rec_NOS	Indicates planned breast reconstruction
6121	Disproportion of reconstructed breast	Rec, post	Indicates previous breast reconstruction
6120	Deformity of reconstructed breast	Rec, post	Indicates previous breast reconstruction

Table 20 – Grouping RIZIV-INAMI codes concerning breast reconstructions

Code_pair	Short label English	Group	Remarks
252431_252442	Mammary reconstruction by prosthesis	Rec_proth	After mutilating intervention on the breast as well as for congenital unilateral mammary hypoplasia or deformity code suppressed per 01/01/2009
252571_252582	Mammary reconstruction with DIEP or SGAP free perforator flap	Rec_DIEP/SGAP	Subdivision in DIEP or GAP to be done based on registered ICD-9-CM procedures codes
252475_252486	Mammary reconstruction by pedicled transposition skin-muscle flap (Latissimus dorsi)	Rec_LDF	
252453_252464	Mammary reconstruction by other pedicled transposition skin flap	Rec_Ped	
227511_227522	Prosthetic implant with mastectomy (immediate reconstruction)	Rec_proth	Subsidiary code: requires actual mastectomy code
252593_252604	Mammary reconstruction by prosthesis	Rec_proth	
252534_252545	Mammary reconstruction by pedicled transposition TRAM flap	Rec_TRAM	
252556_252560	Mammary reconstruction by other microsurgical free flap	Rec_Free	
251576_251580	Mammoplasty by prosthesis	Plasty_proth	Codes involve mammoplasty, not reconstruction (after mammary resection)
251650_251661	Mammoplasty by prosthesis/tissue expander for congenital hypo- or aplasia or malformation	Plasty_proth	Introduced since registration year 2009

Table 21 – Grouping codes for complications

Code	Label English	Group	Subgroup	Subgroup description
6113	Fat necrosis of breast	SSC	Fat_necr	Post-surgery fat necrosis of breast
8675	Revision of pedicle flap	Flap	Flap_rev	Revision of pedicle flap
99889	Other specified complications of procedures, NEC	Other	Other, NEC	Other specified complications, NEC
61183	Capsular contracture of breast implant	Implant	Prosth_contr	Capsular contracture of breast implant
99654	Mechanical complication due to breast prosthesis	Implant	Prosth_mech	Mechanical complication due to breast prosthesis
8594	Removal of implant of breast	Implant	Prosth_rem	Removal of implant of breast



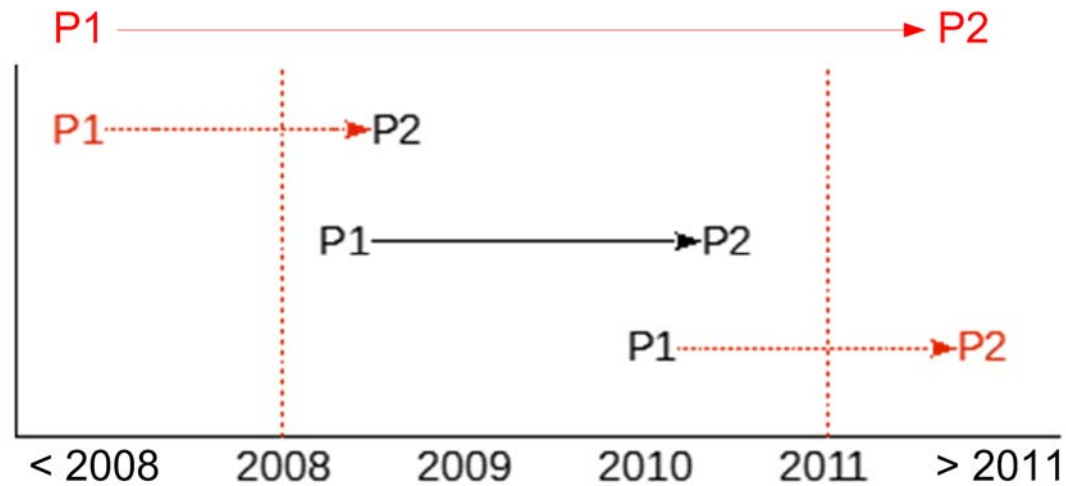
251591_251602	Removal mammary implant due to complications 1	Implant	Prosth_rem	Removal of implant of breast
8593	Revision of implant of breast	Implant	Prosth_rev	Revision of implant of breast
6121	Disproportion of reconstructed breast	Breast	Recon morph	Disproportion/deformity of reconstructed breast
6120	Deformity of reconstructed breast	Breast	Recon morph	Disproportion/deformity of reconstructed breast
99812	Hematoma complicating a procedure	SSC	SS_bleeding	Surgical site hematoma/haemorrhage
99811	Hemorrhage complicating a procedure	SSC	SS_bleeding	Surgical site hematoma/haemorrhage
8604	Other incision with drainage of skin and subcutaneous tissue	SSC	SS_infection	Surgical site infection
99859	Other postoperative infection	SSC	SS_infection	Surgical site infection
9986	Persistent postoperative fistula	SSC	SS_infection	Surgical site infection
8628	Non-excisional debridement of wound, infection or burn	SSC	SS_infection	Surgical site infection
99851	Infected postoperative seroma	SSC	SS_infection	Surgical site infection
8684	Relaxation of scar or web contracture of skin	SSC	SS_tegument	Surgical site skin/subcutis (scar, granuloma, foreign body, defect)
8605	Incision with removal of foreign body from skin and subcutaneous tissue	SSC	SS_tegument	Surgical site skin/subcutis (scar, granuloma, foreign body, defect)
7014	Keloid scar	SSC	SS_tegument	Surgical site skin/subcutis (scar, granuloma, foreign body, defect)
V423	Skin replaced by transplant	SSC	SS_tegument	Surgical site skin/subcutis (scar, granuloma, foreign body, defect)
7094	Foreign body granuloma of skin and subcutaneous tissue	SSC	SS_tegument	Surgical site skin/subcutis (scar, granuloma, foreign body, defect)
99832	Disruption of external operation (surgical) wound	SSC	SW_disrupt	Surgical wound disruption
99883	Non-healing surgical wound	SSC	SW_disrupt	Surgical wound disruption
8659	Suture of skin and subcutaneous tissue of other sites	SSC	SW_disrupt	Surgical wound disruption
V5841	Encounter for planned post-operative wound closure	SSC	SW_disrupt	Surgical wound disruption
99830	Disruption of wound, unspecified	SSC	SW_disrupt	Surgical wound disruption



10 LEAD TIME AND RATIO CALCULATIONS WITH CENSORED DATA

In this appendix we address problems arising from missing data and how we eventually can deal with them, at least in present study. A schematic representation of the problem is given in Figure 1. Such missing data are called censored data and they appear at both sides of our observational window (2008-2011). They are presented in red in the figure. The arrows from P1 to P2 represent lead times (LT). Red arrows indicate LT that cannot be measured.

Figure 1 – Left- and right-censored data



10.1 Intervention lead times

- e.g. P1 = mammary resection = primary index procedure and P2 = mammary reconstruction = secondary index procedure
- P1 and P2 concern a same patient and we want to know how much time elapsed between P1 and P2, i.e. the intervention lead time P1 to P2
- Clinically we know that P2 can follow P1 at very different times, varying from immediate (LT = 0) to several years.
- Our data observation window is 2008-2011, i.e. 4 years, which (epidemiologically) is short.

10.2 Numerators & denominators

- Missing numbers (N) in red
- P1 before 2008 are not traced (*left censored*) →

$$N_{P1all} = N_{P1-2008-2011} + N_{P1<2008}$$



- Idem for P2 after 2011 (*right censored*) →

$$N_{P2all} = N_{P2-2008-2011} + N_{P2>2011}$$

10.3 Lead times statistics

For all LTs:

$$\text{Sum}(LT_{P2}) = \text{Sum}(LT_{P2\ 2008-2011}) + \text{Sum}(LT_{P2 >2011})$$

Average LT = $\text{Sum}(LT_{P2}) / N_{P2}$ ergo:

$$\text{Avg } LT_{all} = \text{Sum}(LT_{P2\ 2008-2011}) + \text{Sum}(LT_{P2 >2011}) / N_{P2\ 2008-2011} + N_{P2 >2011}$$

Missing LT cannot be derived from Doc N. Ergo, we only have (since reduced data window):

$$\text{Avg } LT_{data} = \text{Sum}(LT_{P2\ 2008-2011}) / N_{P2\ 2008-2011}$$

Which is seriously biased: the greater unknown components in numerator and denominator, the higher resulting 'distortion'.

10.4 Fractions and ratios

Similar problem: Ratio P2/P1 = N_{P2all} / N_{P1all} = fraction of women getting a post-resection breast reconstruction

Ergo:

$$\text{Ratio } P2_{all} / P1_{all} = (N_{P2-2008-2011} + N_{P2>2011}) / (N_{P1-2008-2011} + N_{P1<2008})$$

We only have:

$$\text{Ratio } P2 / P1 = N_{P2-2008-2011} / N_{P1-2008-2011}$$

Which also could be biased. Yet, we can (roughly) estimate N_{P2all} and N_{P1all} if:

- we look at sufficiently larger years' series (Doc N) and
- assume that over the years missing numbers per year (of related cases) compensate each other:



Ratios

Reconstruction / Mastectomy – Doc N

Year	Reconstructions	Mastectomies	Ratios	
2000	1 184	9 955	12%	1/8
2001	1 407	10 615	13%	1/8
2002	1 313	10 672	12%	1/8
2003	1 479	11 200	13%	1/8
2004	1 534	11 072	14%	1/7
2005	1 483	11 101	13%	1/7
2006	1 495	11 313	13%	1/8
2007	1 515	11 337	13%	1/7
2008	1 626	11 844	14%	1/7
2009	2 392	13 338	18%	1/6
2010	2 314	13 555	17%	1/6
2011	2 427	14 535	17%	1/6
2012	2 834	14 388	20%	1/5
2013	2 957	14 769	20%	1/5
Total	25 960	169 694	15%	1/7



■ REFERENCES

1. Tsoi B, Ziolkowski NI, Thoma A, Campbell K, O'Reilly D, Goeree R. Systematic review on the patient-reported outcomes of tissue-expander/implant vs autologous abdominal tissue breast reconstruction in postmastectomy breast cancer patients. *J Am Coll Surg*. 2014;218(5):1038-48.
2. Winters ZE, Benson JR, Pusic AL. A systematic review of the clinical evidence to guide treatment recommendations in breast reconstruction based on patient-reported outcome measures and health-related quality of life. *Ann Surg*. 2010;252(6):929-42.
3. Lee C, Sunu C, Pignone M. Patient-reported outcomes of breast reconstruction after mastectomy: a systematic review. *J Am Coll Surg*. 2009;209(1):123-33.
4. Tsoi B, Ziolkowski NI, Thoma A, Campbell K, O'Reilly D, Goeree R. Safety of tissue expander/implant versus autologous abdominal tissue breast reconstruction in postmastectomy breast cancer patients: a systematic review and meta-analysis. *Plast Reconstr Surg*. 2014;133(2):234-49.
5. *Cochrane Handbook for Systematic Reviews of Interventions*. Higgins JPT, Green S, editor.; 2008.
6. Wormald JC, Wade RG, Figus A. The increased risk of adverse outcomes in bilateral deep inferior epigastric artery perforator flap breast reconstruction compared to unilateral reconstruction: a systematic review and meta-analysis. *J Plast Reconstr Aesthet Surg*. 2014;67(2):143-56.
7. Rochlin DH, Jeong AR, Goldberg L, Harris T, Mohan K, Seal S, et al. Postmastectomy radiation therapy and immediate autologous breast reconstruction: Integrating perspectives from surgical oncology, radiation oncology, and plastic and reconstructive surgery. *J Surg Oncol*. 2015;111(3):251-7.
8. Berbers J, van Baardwijk A, Houben R, Heuts E, Smidt M, Keymeulen K, et al. 'Reconstruction: before or after postmastectomy radiotherapy?' A systematic review of the literature. *Eur J Cancer*. 2014;50(16):2752-62.
9. Schaverien MV, Macmillan RD, McCulley SJ. Is immediate autologous breast reconstruction with postoperative radiotherapy good practice?: a systematic review of the literature. *J Plast Reconstr Aesthet Surg*. 2013;66(12):1637-51.