


# Economic Analysis of Noninvasive Tissue Oximetry for Postoperative Monitoring of Deep Inferior Epigastric Perforator Flap Breast Reconstruction: A Review

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## Abstract

**Background.** Postoperative monitoring of deep inferior epigastric perforator (DIEP) flaps for breast reconstruction using noninvasive tissue oximetry enables timely recognition of vascular compromise. This may limit ischemic tissue damage, minimizing postoperative morbidity and healthcare costs. The aim of this review was to provide an economic analysis of tissue oximetry for postoperative monitoring of DIEP flap breast reconstruction. **Methods.** A systematic literature search was conducted utilizing PubMed and Embase. Articles reporting costs related to tissue oximetry following DIEP flap breast reconstruction, costs directly related to DIEP flap surgical procedure, and costs associated with postoperative complications were included. Risk of bias was assessed using different tools depending on study type. **Results.** Six articles were included. Four studies provided an overview of total costs associated with DIEP flap breast reconstruction; two studies focused on whether tissue oximetry could facilitate a decrease in hospital costs. Average overall costs for DIEP flap procedure were estimated at \$28 000, with additional costs up to \$37 530 in case of total flap failure. Tissue oximetry to monitor DIEP flaps could potentially save up to \$1667 per procedure. Moreover, it might eliminate the need for specialized postoperative care. **Conclusion.** Tissue oximetry following DIEP flap breast reconstruction can potentially facilitate a decrease in hospital costs since its readings enable physicians to intervene in an early stage of tissue malperfusion, contributing to minimizing complications. Tissue oximetry may eliminate the need for specialized postoperative care. However, based on the current literature, no firm conclusions can yet be drawn regarding cost-effectiveness of standard implementation.

## Keywords

deep inferior epigastric artery perforator flap, free flap, autologous breast reconstruction, near-infrared spectroscopy, tissue oximetry, cost-effectiveness

## Introduction

The deep inferior epigastric artery perforator (DIEP) flap is one of the most frequently used methods for autologous breast reconstruction.<sup>1-3</sup> Since the introduction of free flap reconstruction and advances in microsurgical techniques, flap viability has improved significantly, with reported success rates around 98%.<sup>4,5,7</sup> Nevertheless, circulatory failure (5-25% of cases) appears as a relatively common complication, necessitating reexploration in 5-7.5% of the procedures and complete flap loss in 1.5-6% of cases.<sup>6-9</sup> Salvage rates are inversely related to the time interval between the onset of critical tissue oxygenation and surgical intervention to restore local tissue perfusion.<sup>8,10</sup> Hence, accurate and continuous monitoring of DIEP flaps is an absolute necessity for timely detection of potential

flap failure, allowing surgical intervention in an early stage.<sup>11,12</sup> In a study by Creech and Miller, the characteristics of the theoretically ideal monitoring technique were defined as harmless to the patient, rapidly responsive,

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accurate, reliable, easy to use, and cost effective.<sup>4,13</sup> Despite the introduction of various new monitoring techniques, to date none of them fulfills all the above mentioned criteria.<sup>4,14</sup> Clinical observation of flap color, temperature, and capillary refill remains the benchmark for assessing flap viability, despite its obvious shortcomings in terms of objectivity and continuity.<sup>14,15</sup>

Tissue oximetry proved to be a versatile clinical monitor with various applications,<sup>16,17</sup> including DIEP flap monitoring.<sup>18</sup> Noninvasive tissue oximetry uses near-infrared spectroscopy (NIRS) to continuously assess regional tissue oxygen saturation (StO<sub>2</sub>) based on the modified Lambert-Beer law.<sup>9,15,19,20</sup> Application of tissue oximetry in free flaps enables early recognition of vascular compromise before clinical symptoms of flap failure become apparent.<sup>4,19,21,22</sup> This may limit the extent of ischemic tissue damage and its detrimental consequences, such as wound problems, including deep tissue infection, and fat necrosis.<sup>3,8</sup> Tissue oximetry has proven to be reliable, sensitive, accurate, and user friendly.<sup>2,4,8</sup> Several clinical studies indicated that tissue oximetry is a viable monitor for this relatively new application. Nevertheless, recent studies report that tissue oximetry could be relatively expensive to implement in clinical practice and it is used in less than 5% of DIEP flap procedures.<sup>4,14,23</sup>

The aim of this review was to provide an economic analysis of tissue oximetry for postoperative monitoring of DIEP flap breast reconstruction and whether inclusion in routine monitoring protocols could be justified.

## Methods

This review was written according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement for reporting systematic reviews.<sup>24</sup>

A systematic literature search was performed utilizing the following databases: National Library of Medicine (PubMed) database and Embase database (via OvidSP) and completed in April 2020. For the PubMed database search, various Medical Subject Heading (MeSH) terms were used in combination with free search terms, as depicted in Table 1. There were no restrictions on language in

this review. Studies conducted other than on human subjects, reviews, and studies published before 2010 were excluded. Detailed search queries are provided in Appendix A.

For the Embase database, the following search strategy was used: (*Deep Inferior Epigastric Perforator flap OR "Mammoplasty" [Mesh] OR "Free Tissue Flaps" [Mesh] OR "Perforator Flap" (Mesh) AND "Near-Infrared" [Mesh] Or Near-infrared spectroscopy OR NIRS OR non-invasive infrared monitoring OR tissue oximetry AND "Cost analysis" [Mesh] OR "Cost-Benefit Analysis" [Mesh] OR Cost-Effectiveness*). The same search filters were used as in the PubMed search.

The literature search was performed by two researchers (AL/VR) independently. Following removal of duplicates, eligibility of the remaining articles was initially determined by screening the title. Subsequently, studies were screened based on the abstract. Remaining studies were screened by reading the full text; those that did not answer the research question concerning the cost-effectiveness of using NIRS following DIEP flap surgery were excluded. In case of disagreement between the aforementioned researchers, a third researcher (NV) was consulted.

From the included studies, the following information was retrieved: the surname of the first author, year of publication, country of origin, objectives, study design, study population, and documented costs.

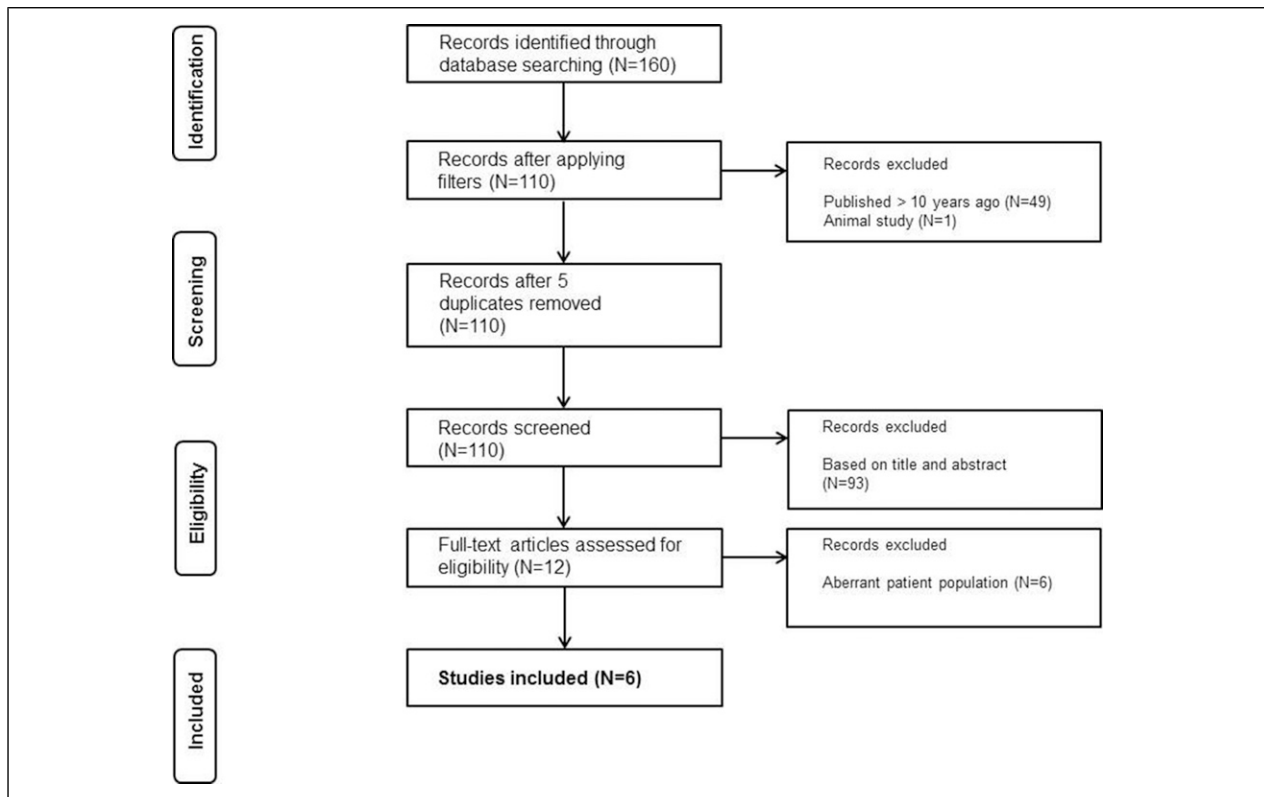
## Results

After conduction of the systematic literature search in the aforementioned databases, 6 of 160 articles were eligible for inclusion. See Figure 1 for the flow chart. Four studies (2 prospective cohort studies and 2 cost analysis studies) reported on costs related to the DIEP flap breast reconstruction. One study (a randomized controlled trial) reported costs related to noninvasive tissue oximetry following DIEP flap surgery. Another study evaluated the use of tissue oximetry to decrease intensive care unit (ICU) monitoring for free flap breast reconstruction. Table 2 shows the study characteristics. All studies were single center trials and were conducted in either Europe or the United States.

**Table 1.** Search Strategy.

Category	MeSH Term	Free Search Term
#1: Population	Mammoplasty, or free tissue flaps, or perforator flap	Breast reconstruction OR Deep Inferior Epigastric Perforator flap OR DIEP-flap OR Microsurgical Free Flap OR Free Flap OR Mammoplasty OR Free Tissue Flaps OR Perforator Flap
#2: Intervention	Spectroscopy or near-infrared	Near-infrared spectroscopy OR NIRS OR noninvasive infrared monitoring OR NIR spectroscopy, tissue oximetry
#3: Comparison	Cost and cost analysis or cost-benefit analyses	Cost OR Cost Analysis OR Cost-Benefit OR Cost-Effectiveness

Abbreviations: DIEP = deep inferior epigastric perforator; MeSH = medical subject headings; NIRS = near-infrared spectroscopy.



**Figure 1.** Flowchart of the used search strategy.

### Risk of Bias Within Studies

Two researchers independently performed the risk of bias assessment using the Cochrane risk of bias tool for randomized controlled trials, the quality assessment tool for observational cohort and cross-sectional studies, and a short checklist of Drummond for bias assessment of the comparative cost analyses.<sup>26-28</sup> Results of both researchers were compared, and inconsistencies were discussed after which a uniform conclusion was made. An overview of the bias assessment is depicted for each tool independently in Tables 3-5 using multiple colors (online version only). The green color depicts the judgment of a low risk of bias, yellow a questionable risk of bias, and red a high risk of bias. Some criteria were not applicable on studies included in this review. Therefore, no score was assigned in these criteria. The 2 comparative cost analysis studies by Tran et al<sup>29</sup> and Matros et al<sup>30</sup> both scored an overall “low risk of bias.” The prospective cohort study of Lagares-Borrego et al<sup>1</sup> and the retrospective observational cohort study of Ricci et al<sup>31</sup> scored a high risk of bias on 1 criterion (1 of 14 criteria) as well as the study of Pelletier et al (1 of 7 criteria).<sup>25</sup> Lastly, the study of Damen et al<sup>32</sup> scored a high risk of bias on one criterion, and a questionable risk of bias on a second criterion (2 of 14 criteria).

### Randomized Controlled Trial

For assessing quality of the randomized controlled trial of Pelletier et al,<sup>25</sup> the Cochrane risk of bias tool was used, which consists of seven categories, as shown in Table 3. The study scored a “high risk of bias” on the criterion “blinding of outcome assessment” because the principal investigator was informed about the choice of department for postoperative stay of the patients.

### Prospective Cohort Studies

The quality assessment tool for observational cohort and cross-sectional studies from the National Heart, Lung, and Blood Institute was used to assess the quality of the included cohort studies (Table 4). The study of Damen et al<sup>32</sup> scored a questionable risk of bias on criterion four (uniform eligibility criteria of subject groups) because one of the surgical reconstructive techniques included in the study was sparsely performed in the chosen time frame (2002-2006). To provide a representative study sample, they extended the inclusion period for this single technique with three years. Furthermore, both prospective cohort studies<sup>1,32</sup> did not provide any justification for their sample size, nor include a statistical power calculation.

**Table 2.** Overview of Study Characteristics.

First Author	Country	Study Design	Objective	Study Population	Duration Data Collection	Type of Documented Costs
Damen <sup>32</sup>	Netherlands	PCS	To comprehensively assess the economic implications of four breast reconstruction techniques from a societal perspective based on real resource use in substantial patient groups	DIAP (N = 104), LD ± SP (N = 116), SP (N = 15), and TE/SP (N = 56)	2002-2009	Unilateral and bilateral DIAP flap reconstructions and cost per hour (personal, anaesthesia, operating room, materials, and sterilization)
Lagares-borrego <sup>1</sup>	Spain	PCS	To compare the economic costs and long-term follow-up outcomes of the DIAP and the E-P method of breast reconstruction, including the cost and clinical outcomes related to the initial reconstruction and associated reoperations due to complications or aesthetic retouches	DIAP (N = 67) and expander/prosthesis (N = 67)	2005-2013	Department and unilateral DIAP flap reconstruction
Matros <sup>30</sup>	USA and Canada	PCEA	To answer the question if autologous tissue reconstructions are cost effective compared to prosthetic techniques when health-related quality of life and patient satisfaction are considered	Implants (N = 309) and DIAP-flap (N = 217)	1-8 years	Unilateral DIAP flap, bilateral DIAP flap, and complications (abdominal wall weakness/hernia, flap loss, fat necrosis, hematoma, and infection)
Pelletier <sup>25</sup>	USA	PRCT	To answer the question if NIRS tissue oximetry monitoring can indirectly lower total hospital costs by eliminating the need for specialized nursing	ICU group (N = 25) and floor group (N = 25)	2006-2010	ICU group and floor group
Ricci <sup>31</sup>	USA	RCS	Evaluating the use of tissue oximetry to decrease intensive unit monitoring for free flap breast reconstructions	DIAP (N = 872), SIEA (N = 2), fTRAM (N = 3), and SGAP (N = 23)	2008-2014	Estimated savings after incorporating tissue oximetry
Tran <sup>29</sup>	USA	CCA	To summarize the available complication data and using it to perform a comparative cost analysis of implant-based vs autologous abdominal-based reconstruction	Two staged TE/ + ADM and DIAP-flaps	2015	Successful surgery and complications

Abbreviations: CCA = comparative cost analysis; DIAP = deep inferior epigastric perforator; fTRAM = free transverse rectus abdominis myocutaneous; ICU = intensive care unit; LD ± SP, pedicled latissimus dorsi flaps with or without implant; NIRS = near-infrared spectroscopy; PCEA = prospective cost-effectiveness analysis; PCS = prospective cohort study; PRCT = prospective randomized controlled trial; RCS = retrospective cohort study; SGAP = superior gluteal artery perforator; SIEA = superficial inferior epigastric artery; SP = silicone prostheses or implants; TE/ + ADM, two-staged tissue expander-implant with a cellular matrix; TE/SP = implants preceded by tissue expansion.

**Table 3.** Cochrane Risk of Bias Tool for Randomized Controlled Trials.

Risk of Bias Category	Pelletier et al <sup>25</sup>
Random sequence generation	LR
Allocation concealment	LR
Selective reporting	LR
Other bias	LR
Blinding of participants and personnel	LR
Blinding of outcome assessment	HR
Incomplete outcome data	LR

Abbreviations: HR = high risk; LR = low risk.

Therefore, both studies were rated as “high risk of bias” on this specific criterion.

### Retrospective Observational Cohort Study

The quality assessment tool for observational cohort and cross-sectional studies from the National Heart, Lung, and Blood Institute was used to assess the quality of the retrospective observational cohort study of Ricci et al<sup>31</sup> (Table 4). The study scored a high risk of bias on criterion 5 (sample size). Due to the type of study, no sample size justification or statistical power calculation was provided.

### Cost Analysis Studies

To assess the quality of the cost analysis studies, the short checklist by Drummond et al was used (Table 5). The study of Tran et al<sup>29</sup> as well as the study of Matros et al had an overall score of “low risk of bias.”<sup>30</sup>

### Economic Analysis of Tissue Oximetry

Total costs for a DIEP flap procedure were calculated based on many elements, including staff costs, costs for medication, and costs for utilizing the operating theatre including all equipment and materials. For comparison purposes, all costs were depicted in American dollars in this study. Partially, due to different healthcare systems, costs of a single DIEP flap procedure showed a widespread variation (Table 6), varying from \$6454 in the Netherlands to \$69 094 in the United States of America and Canada.<sup>29,30,32</sup> Likewise, a widespread variation in costs commencing a successful bilateral DIEP flap surgery was observed, ranging from \$9478 in the Netherlands to \$87 490 in the United States of America and Canada.<sup>29,30,32</sup>

A large variance in overall costs across studies was observed, which can be explained by differences in departmental costs between countries. Costs for the operating theatre including equipment, but excluding costs for personnel, and anesthesia were estimated to be \$46 per hour in the Netherlands, while in Spain, an amount of \$848 per

hour was documented (included costs were not specified in neither articles).<sup>1,32</sup> Furthermore, depending on hospital policy, patients were postoperatively transferred to the ICU, recovery room, or general ward. Due to differences in the extent of specialized nursing care and monitoring, cost for patients staying on the ICU will be higher compared to the ward. As shown in Table 7, mean costs for ICU stay in the Netherlands were estimated to be \$66 per hour, \$220 in Spain, and \$302 in the United States.<sup>1,25,30</sup> On the contrary, cost for staying at the ward varied between \$22 in the Netherlands to \$264 in the United States.<sup>1,25,30</sup>

When complications occurred, previously mentioned costs increased depending on the type and consequences of complication. Table 8 shows an overview of cost related to DIEP flap failure. Concerning minor postoperative complications, additional costs were estimated to extend to \$190 for partial skin necrosis and up to \$19 122 for infections requiring treatment with antibiotics.<sup>29,32</sup> In case of total flap loss, a different type of (autologous) transplant may be considered for the breast reconstruction. Additional costs can amount up to \$37 530.<sup>29</sup> Furthermore, patients with postoperative complications have a prolonged length of hospital stay, resulting in additional expenses varying between \$7000 and \$9000.<sup>1</sup>

The implementation of noninvasive tissue oximetry for completion of standard monitoring routine entails additional costs. For example, as described by Smit et al,<sup>4</sup> costs for a tissue oximetry device account \$16 500, with \$150 for one disposable sensor. Nevertheless, according to Pelletier et al, estimated savings of \$1337.00 per procedure could be obtained when NIRS would be implanted as the standard monitoring tool.<sup>25</sup> In the study of Ricci et al, they incorporated tissue oximetry into standard postoperative monitoring protocol since June 2008. They concluded that the use of tissue oximetry in the postoperative phase reduced the amount of time spent in the intensive care. Patients with continuous oxygen sensor monitoring could be transferred to the ward after 15 hours instead of 24 hours. This resulted in a significant decrease of \$1667 in costs per DIEP flap reconstruction.<sup>31</sup>

### Discussion

This review focused on providing an economic analysis of tissue oximetry for postoperative monitoring of DIEP flap breast reconstruction and whether inclusion in routine monitoring protocols could already be justified based on the current literature.

Since the introduction of autologous breast reconstruction, success rates have improved.<sup>4,6</sup> Nevertheless, circulatory failure for which reexploration is needed occurs in approximately 5-7.5% of the procedures, resulting in a total flap loss of 1.5-6%.<sup>6-9</sup> Costs for DIEP flap surgery

**Table 4.** Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Criterion	Damen et al <sup>32</sup>	Lagares-Borrego et al <sup>1</sup>	Ricci et al <sup>31</sup>	Criterion	Damen et al <sup>32</sup>	Lagares-Borrego et al <sup>1</sup>	Ricci et al <sup>31</sup>
1 Was the research question/objective in this article clearly stated?	LR	LR	LR	8 For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?	LR	LR	LR
2 Was the study population clearly specified and defined?	LR	LR	LR	9 Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	LR	LR	LR
3 Was the participation rate of eligible persons at least 50 percent?	LR	LR	LR	10 Was the exposure(s) assessed more than once over time?	Not applicable	Not applicable	Not applicable
4 Were all subject groups recruited from the same population and uniform eligibility criteria?	QR	LR	LR	11 Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	LR	LR	LR
5 Was a sample size justification, power description or variance, and effect estimates provided?	HR	HR	HR	12 Were the outcome assessors blinded to the exposure status of participants?	Not applicable	Not applicable	Not applicable
6 For the analysis in this article, were the exposure(s) of interest measured prior to the outcome(s) being measured?	LR	LR	LR	13 Follow-up duration?	LR	LR	LR
7 Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	LR	LR	LR	14 Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	LR	LR	LR

Abbreviations: HR = high risk; LR = low risk; QR = questionable risk.

**Table 5.** Assessment of Bias Following the Short Checklist of Drummond et al.

Criterion	Question	Matros et al <sup>30</sup>	Tran et al <sup>29</sup>
1	Is the research question stated?	LR	LR
2	Are the source(s) of effectiveness estimates used clearly stated?	LR	Not applicable
3	Are the primary outcome measure(s) clearly stated?	LR	LR
4	Are the methods for the estimation of quantities and unit costs described?	LR	LR

Abbreviation: LR = low risk.

**Table 6.** Overview DIEP Flap Surgery Related Cost.

DIEP Flap Surgery	Matros et al <sup>30</sup>	Tran et al <sup>29</sup>	Damen et al <sup>32 a</sup>
Successful unilateral DIEP flap surgery	\$69 094	\$10 237	\$6458
Successful bilateral DIEP flap surgery	\$87 490	—	\$9478

Abbreviation: DIEP = deep inferior epigastric perforator.

<sup>a</sup>Euro converted into dollars by means of currency rate on May 01, 2020 (€1 = \$1.10).

**Table 7.** Overview of Specific Departmental Costs per Hour.

Unit	Damen et al <sup>32 a</sup>	Lagares-Borrego et al <sup>1 a</sup>	Pelletier et al <sup>25 a</sup>
Operating room, including equipment	\$46	\$848	—
Ward	\$20 <sup>a</sup> -\$25	\$35	\$264
Intensive care unit	\$66	\$220	\$302

<sup>a</sup>Euro converted into dollars by means of currency rate on May 01, 2020 (€1 = \$1.10).

**Table 8.** Overview of Additional Costs (US Dollar) Related to DIEP Flap Failure.

DIEP Flap Complication	Matros et al <sup>30</sup> (Unilateral Reconstruction)	Matros et al <sup>30</sup> (Bilateral Reconstruction)	Tran et al <sup>29</sup> (Unilateral Reconstruction)
Cellulitis	—	—	\$4374
Seroma	—	—	\$443
Skin necrosis	—	—	\$190
Flap revision for flap loss	—	—	\$7500
Flap revision for partial flap loss	—	—	\$7500
Flap revision for fat necrosis	—	—	\$7500
Flap loss (debridement)	\$26 818	\$8422	—
Flap loss (tissue expander)	\$37 530	\$37 530	—
Fat necrosis (debridement)	\$17 530	\$17 530	—
Hematoma (drainage)	\$34 623	\$8460	—
Infection (antibiotics)	\$19 122	\$19 122	—
Infection (drainage)	\$34 623	\$24 315	—

Abbreviation: DIEP = deep inferior epigastric perforator.

Price determined by the price of the complications minus the price of a successful surgery.

are estimated to amount \$28 000, with a widespread variation between countries.<sup>1,25,30</sup> Additional costs accompanying flap failure can extend to \$37 530.<sup>29</sup> In order to limit or prevent these complications, timely detection of vascular compromise is most essential.

Several studies described the added value of tissue oximetry in postoperative flap monitoring.<sup>9,25</sup> A timely detection of possible flap failure and intervention when applying tissue oximetry in the postoperative setting can

prevent a subset of complications, resulting in an increase in flap salvage rate from 91-99%.<sup>15</sup> In order to benefit from the advantages of continuous monitoring using tissue oximetry, inclusion of the measurement method in the standard monitoring protocols is required. According to Smit et al, costs for a tissue oximetry device account \$16 500, with \$150 for one disposable sensor.<sup>4</sup> Important to note is that when using continuous monitoring, patients may safely be transferred to the ward instead of the ICU in

the early postoperative period.<sup>25</sup> This, in turn, may lead to an estimated saving up to \$1667 per unilateral DIEP flap reconstruction.<sup>31</sup>

When interpreting the results of this review, some limitations need to be taken into account. None of the included articles reported on all types of costs associated with DIEP flap surgery. Given the fact that the included studies were performed in different countries (e.g., Europe and United States) with different healthcare systems, a widespread variation in costs for the surgical procedure can be expected. Therefore, interpretation of the total costs of a DIEP flap procedure was challenging.

The literature objectively describing the benefits vs all costs accompanying application of tissue oximetry in DIEP flap surgery remains scarce. As a result, a true cost-effectiveness analysis could not yet be performed. Further studies are necessary to provide a more specific overview in clinical benefits and costs associated with noninvasive monitoring through tissue oximetry.

In conclusion, tissue oximetry for postoperative monitoring of DIEP flap breast reconstruction can aid in preventing a subset of complications, it can limit the extent of ischemic tissue damage, and can possibly reduce the need for specialized nursing care. This noninvasive tissue monitoring technique can therefore result in a decrease of total costs. However, based on the results of the currently available literature, no firm conclusions can be drawn regarding cost-effectiveness and subsequent endorsement of implementation in standard postoperative protocols.

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## Appendix A: Search Strategies for PubMed

Category	Query
#1: Population	"Mammoplasty"[Mesh] OR "Free Tissue Flaps"[Mesh] OR "Perforator Flap"[Mesh] OR ("mammoplasty"[MeSH Terms] OR "mammoplasty"[All Fields] OR ("breast"[All Fields] AND "reconstruction"[All Fields]) OR "breast reconstruction"[All Fields] OR (Deep[All Fields] AND Inferior[All Fields] AND Epigastric[All Fields] AND ("perforator flap"[MeSH Terms] OR ("perforator"[All Fields] AND "flap"[All Fields]) OR "perforator flap"[All Fields])) OR DIEP-flap[All Fields] OR (("free tissue flaps"[MeSH Terms] OR ("free"[All Fields] AND "tissue"[All Fields] AND "flaps"[All Fields]) OR "free tissue flaps"[All Fields] OR ("flap"[All Fields] AND "free"[All Fields]) OR "flap free"[All Fields]) AND ("tissues"[MeSH Terms] OR "tissues"[All Fields] OR "tissue"[All Fields])) OR (("surgical flaps"[MeSH Terms] OR ("surgical"[All Fields] AND "flaps"[All Fields]) OR "surgical flaps"[All Fields] OR "flap"[All Fields]) AND Microsurgical[All Fields] AND Free[All Fields]) OR ("free tissue flaps"[MeSH Terms] OR ("free"[All Fields] AND "tissue"[All Fields] AND "flaps"[All Fields]) OR "free tissue flaps"[All Fields] OR "free"[All Fields] AND "flap"[All Fields]) OR "free flap"[All Fields])
#2: Intervention	"Spectroscopy, Near-Infrared"[Mesh] OR ("spectroscopy, near-infrared"[MeSH Terms] OR ("spectroscopy"[All Fields] AND "near-infrared"[All Fields]) OR "near-infrared spectroscopy"[All Fields] OR ("near"[All Fields] AND "infrared"[All Fields] AND "spectroscopy"[All Fields]) OR "near infrared spectroscopy"[All Fields] OR near-infrared[All Fields] OR NIRS[All Fields] OR (noninvasive[All Fields] AND infrared[All Fields] AND monitoring[All Fields]) OR ("spectroscopy, near-infrared"[MeSH Terms] OR ("spectroscopy"[All Fields] AND "near-infrared"[All Fields]) OR "near-infrared spectroscopy"[All Fields] OR ("nir"[All Fields] AND "spectroscopy"[All Fields]) OR "nir spectroscopy"[All Fields])
#3: Comparators	"Costs and Cost Analysis"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR ("economics"[Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields] OR ("cost"[All Fields] AND "analysis"[All Fields]) OR "cost analysis"[All Fields]) OR ("cost-benefit analysis"[MeSH Terms] OR ("cost-benefit"[All Fields] AND "analysis"[All Fields]) OR "cost-benefit analysis"[All Fields] OR ("cost"[All Fields] AND "benefit"[All Fields]) OR "cost benefit"[All Fields]) OR ("cost-benefit analysis"[MeSH Terms] OR ("cost-benefit"[All Fields] AND "analysis"[All Fields]) OR "cost-benefit analysis"[All Fields] OR ("cost"[All Fields] AND "effectiveness"[All Fields]) OR "cost-effectiveness"[All Fields])
#1, #2, and #3: PIC	#1 AND #2 AND #3