The consequences of ventral hernia mesh repair

Analyses and interpretation of different aspects of outcome

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1. PREFACE

1.1 Acknowledgments

The present thesis started as a quality improvement project examining medical records of ventral hernia mesh repairs at the Department of Surgery, Akershus University Hospital.

I was put on this project, not by interest, but more because of obedience. Despite reluctance, I was forced to think and reflect on the many aspects of hernia disease. The term herniosis, meaning systemic connective tissue disorder leading to hernia and diverticular disease, kicked me off on a project with connective tissue harvesting during laparotomies to improve our knowledge of incisional hernia etiology. This project terminated due to many reasons. Still I am grateful to the many of my colleagues at the Department of Surgery who enthusiastically participated.

*Professor Ola Røkke, my principal supervisor, forced me into catharsis and renewed thinking, of which I am deeply thankful.

I also would like to express my sincere and deepest gratitude toward all of those who have collaborated, in one way or the other, in the completion of the present studies:

*Professor Ingar Olsen who joined me on the idea of translational research, bringing his expertise in molecular techniques to the operating room, picking mesh samples for further analyses of mesh biofilm microbiology.

*Head of Department of Radiology, Arne Borthne, who kindly offered MRI facilities.

*Stein Harald Holmedal in collaboration with Ole Jacob Grandal in their planning, performance and interpretation of MRI imaging.

*Anne Karin Kristoffersen and Emnet Abesha-Belay for their tirelessly work at the DNA sequencing lab; together with Morten Enersen for his contribution to the article of mesh biofilm.
*Jens Christian Årving and the head of Nedre Romerike Dental Clinic who enabled the periodontal examinations.

*The head of the Department of Surgery who offered study facilities and Merethe Helgeland joining me in the follow-up process keeping records in order.

*Professor Ida Bukholm for reading and commenting on papers and Jūratė Šaltytė Benth for statistical counseling.

I am also indebted to the patients who participated in the studies presented in this thesis.

Last but not least, to those who bites the dust. To my children Nicholas and Matheo: You wouldn`t understand, would you? And to my companion during the last five years, Therese: “You can publish, or you can perish”. Thank you for understanding and participating. The time we could have spent together doing something exciting, is hidden in this thesis as one minute by the word.

To the memory of Charlotte, I will never forget you.
### 1.2 Common expressions and abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>16S rRNA</strong></td>
<td>Bacterial gene</td>
</tr>
<tr>
<td><strong>AAS</strong></td>
<td>Activities assessment scale</td>
</tr>
<tr>
<td><strong>ASA-score</strong></td>
<td>American Society of Anesthesiologists physical status score</td>
</tr>
<tr>
<td><strong>BLAST</strong></td>
<td>Basic Local Alignment Search Tool</td>
</tr>
<tr>
<td><strong>BLAST search</strong></td>
<td>To compare a query sequence with a library or database of sequences, and identify library sequences that resemble the query sequence above a certain threshold</td>
</tr>
<tr>
<td><strong>CI</strong></td>
<td>Confidence Interval</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>Computed Tomography</td>
</tr>
<tr>
<td><strong>EBM-guideline</strong></td>
<td>Evidence Based Medicine guideline</td>
</tr>
<tr>
<td><strong>ePTFE</strong></td>
<td>Expanded Poly TetraFluoroEthylene</td>
</tr>
<tr>
<td><strong>HRQoL</strong></td>
<td>Health related quality of life</td>
</tr>
<tr>
<td><strong>ICD-10</strong></td>
<td>International Classification of Disease, version 10</td>
</tr>
<tr>
<td><strong>IH</strong></td>
<td>Incisional hernia</td>
</tr>
<tr>
<td><strong>IPOM</strong></td>
<td>Intraperitoneal Onlay Mesh</td>
</tr>
<tr>
<td><strong>Laparoscopy</strong></td>
<td>A small insertion through the abdominal wall using fibre-optic camera and instruments to reach the internal organs</td>
</tr>
<tr>
<td><strong>Laparotomy</strong></td>
<td>An incision through the abdominal wall that makes access to the internal organs with the use of hand-instruments only</td>
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<tr>
<td><strong>LOT-R</strong></td>
<td>Life Orientation Test – revised</td>
</tr>
<tr>
<td><strong>LVHR</strong></td>
<td>Laparoscopic ventral hernia repair</td>
</tr>
<tr>
<td><strong>Mesh</strong></td>
<td>A synthetic or biological fabric material to cover a hernia defects</td>
</tr>
<tr>
<td><strong>Molecular techniques</strong></td>
<td>PCR is an example</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td><strong>Neuropathic pain</strong></td>
<td>Chronic pain that is caused by nerve damage and gives off signals that can be burning, aching, exaggerated or numb</td>
</tr>
<tr>
<td><strong>NIH</strong></td>
<td>Non-incisional hernia</td>
</tr>
<tr>
<td><strong>Nociceptive pain</strong></td>
<td>Pain that is physiological due to tissue damage eliciting receptor respons with constant, aching or throbbing sensation</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td>Odds Ratio</td>
</tr>
<tr>
<td><strong>OVHR</strong></td>
<td>Open ventral hernia mesh repair</td>
</tr>
<tr>
<td><strong>PCR</strong></td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>Periodontitis</td>
<td>Inflammatory disease affecting the supportive tissue around the tooth.</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td></td>
<td>The general well-being of individuals.</td>
</tr>
<tr>
<td>QoLHS</td>
<td>Quality of life hernia score</td>
</tr>
<tr>
<td></td>
<td>Self constructed 8-item score to evaluate confidence and satisfaction after ventral hernia mesh repair.</td>
</tr>
<tr>
<td>Hernia recurrence</td>
<td>The occurrence of a hernia in relation to earlier hernioplasty.</td>
</tr>
<tr>
<td>rP</td>
<td>Pearsons rho</td>
</tr>
<tr>
<td></td>
<td>Pearsons rank correlation coefficient.</td>
</tr>
<tr>
<td>Sf-36</td>
<td>Short-form 36</td>
</tr>
<tr>
<td></td>
<td>A health survey with 36 questions</td>
</tr>
<tr>
<td>SSI</td>
<td>Surgical site infection</td>
</tr>
<tr>
<td>VH</td>
<td>Ventral hernia</td>
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<tr>
<td></td>
<td>An orifice or defect in the anterior abdominal wall not covered by muscle or fascia.</td>
</tr>
<tr>
<td>Π</td>
<td>Pi</td>
</tr>
<tr>
<td></td>
<td>Mathematical constant, the ratio of a circle's circumference to its diameter.</td>
</tr>
</tbody>
</table>

### 1.3 Ethical considerations and consents

The follow-up of patients after ventral hernia mesh repair, had no ethical implications because it was considered as part of quality improving measures. Even patients dissatisfied with the hernia repair, met for counselling, not always with the intention of having a new operation. They were pleased with our effort making this recall possible.

The more experimental part of our study, the MRI investigation and the mesh biofilm study, was approved by Norwegian Social Science Data Service (NSD), Regional Committee for Medical and Health Research Ethics (REK-øst) and Norwegian Directorate of Health.

REK-øst nr. 07311 C (MRI study). REK-øst nr. S08838C (Mesh biofilm study)
2. LIST OF PAPERS

I. Langbach O, Bukholm IR, Benth JŠ, Røkke O
   Long term recurrence, pain and patient satisfaction after laparascopic and open ventral hernia mesh repair.

II. Langbach O, Bukholm IR, Benth JŠ, Røkke O
    Long-term quality of life and functionality after ventral hernia mesh repair.

III. Langbach O, Holmedal SH, Grandal OJ, Røkke O
     Adhesions to mesh after ventral hernia mesh repair are detected by MRI, but are not a cause of long term chronic abdominal pain.

IV. Langbach O, Kristoffersen AK, Abesha-Belay E, Enersen M, Røkke O, Olsen I
    Oral, intestinal and skin bacteria in ventral hernia mesh implants.
3. SUMMARY OF PAPERS

A hernia located in the anterior abdominal wall can be spontaneous, caused by abdominal surgery or trauma. If treatment seems appropriate, this includes laparoscopic or open surgery and closure of the defect with mesh prostheses. The surgical treatment objective is to restore the integrity of the abdominal wall, whereas the principal outcome measure should be improved QoL and functionality.

The aim of this thesis was to bring knowledge to different aspects of ventral hernia mesh repair. We compared open and laparoscopic surgical technique with respect to equitable clinical measures concomitantly bringing patient reported outcome to the synthesis.

In paper I we focused on long term recurrence, pain and patient satisfaction after open or laparoscopic mesh repair. There was no difference between these two techniques with respect to these measures. Chronic pain is frequent and is therefore important for explaining dissatisfaction.

In paper II we investigated QoL and functionality long term after open or laparoscopic mesh repair comparing patients presenting with non-recurrent ventral hernia disease. Both surgical techniques reduce chronic pain and physical impairment and improve long-term QoL. Hernia recurrence and persistent pain reduce the beneficial effect of hernia surgery while dispositional optimism seems to modulate QoL reporting and functionality.

By performing MRI, paper III aimed at detecting intra-abdominal adhesions between viscera and the anterior abdominal wall after ventral hernia mesh repair with special attention to any association with pain. Adhesions are common after open and laparoscopic mesh repair, but are not associated with chronic pain.

The purpose of paper IV was to find evidence of bacterial biofilm in mesh implants from the anterior abdominal wall, analyze its bacterial diversity and look for possible resemblance with bacterial biofilm from the periodontal pocket. The results revealed great bacterial diversity
including oral commensals and periodontopathogens. Other sites such as gut and skin however may also provide sources for mesh biofilm.
### 4. THESIS AT A GLANCE

<table>
<thead>
<tr>
<th>Paper</th>
<th>Objective</th>
<th>Patients and Methods</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Laparoscopic (LVHR) vs open mesh (OVHR) repair: -pain -recurrence -satisfaction</td>
<td>LVHR (n=81) OVHR (n=72): -med.records -clinical exam: -recurrence - pain - satisfaction</td>
<td>Recurrence: ns: -LVHR (17.1%) -OVHR (23.3%) Chronic pain: -associated with recurrence after LVHR Satisfaction: -associated with absence of chronic pain and recurrence</td>
<td>LVHR vs. OVHR: -no difference in -recurrence -chronic pain -overall satisfaction</td>
</tr>
<tr>
<td>II</td>
<td>a) Laparoscopic vs open mesh repair: b) Surgical repair (LVHR+OVHR) vs patients with non-treated ventral hernia (Controls): - quality of life - functionality</td>
<td>LVHR (n=81) OVHR (n=72) Controls (n=112) -SF-36 - AAS - LOT - Functionality</td>
<td>a) LVHR = OVHR b) Surgical repair vs Controls: -SF-36: surgery improves physical dimensions -Chromic pain related to impairment - Optimism modulates impairment</td>
<td>a) LVHR = OVHR b) Surgery: - reduces hernia-related pain - improves physical impairment -improves long term QoL. Recurrence and pain reduces the beneficial effects of surgery</td>
</tr>
<tr>
<td>III</td>
<td>a) Can MRI detect adhesions between bowel and mesh/ abdominal wall b) Can adhesions explain abdominal pain after hernia mesh repair?</td>
<td>MR: 124 patients -LVHR (n=64) -OVHR (n=50) -Others (n=10)</td>
<td>MRI detection: - Adhesions: 60% - Mesh shrinkage: 20-50% depending on mesh type -Adhesions and pain not associated</td>
<td>-MRI detects adhesions -adhesions are formed after LVHR and OVHR -adhesions can not explain chronic pain after hernia mesh repair</td>
</tr>
<tr>
<td>IV</td>
<td>a) Can bacteria be detected in implanted mesh? b) May periodontal pockets be an origin of these bacteria?</td>
<td>Mesh sample from 30 implanted ventral mesh + oral subgingival plaques: -PCR -16S rRNA gene sequencing</td>
<td>Bacteria in mesh: -detected in 20/30 -great variety -mean number of taxa: 18.6 (5-56) -oral, enteric and skin -98-100% resemblance bacteria in mesh/plaques in 17 sequences (4.8%)</td>
<td>-Bacteria was detected in implanted mesh -Oral, enteric-and skin bacteria were detected</td>
</tr>
</tbody>
</table>
5. GENERAL INTRODUCTION

5.1 Anatomy of the abdominal wall

The abdominal wall consists of several muscles which together create a complex system providing protection of viscera and functions like movement of the trunk, respiration, defecation and micturition. It is usually divided into posterior, lateral and anterior walls. For descriptive purpose the division is rather in two upper and two lower quadrants.

The anterior abdominal wall is comprised of four muscles: the rectus abdominis, the external and internal abdominal obliquus, and the transversus abdominis. The oblique muscles rotates the trunk and perform lateral flexion of the spine. The transversus abdominis is the main muscle to retain the abdominal content while the rectus muscle mainly take part in ventral flexion of the spine. The rectus sheath is formed by the medial insertion of the three lateral abdominal muscles. The dorsal lamina of the rectus muscle runs from the costae to the arcuate line below the umbilicus of which no dorsal sheath exists below. The two rectus muscles are connected by the linea alba which forms the medial continuation of the rectus sheet (1).

Figure 1. Muscles of the abdominal wall.

Adapted from http://www.pearsonclinical.com/
5.2 Incidence and etiopathogeny of ventral hernias

Incisional hernia after laparotomy has reported incidence rates between 8.9 % and 20 % and represent one of the most common complications after abdominal surgery (2-4) (5). Among these, 80 – 95 % develop within 6 months to 3 years after initial surgery (2). Looking at specific location of entry, Lee reported 29 % after midline laparotomy, 14 % after transverse and 0 % after Phannenstiel incision(6). This is in accordance with others (7). Laparoscopy seems to reduce the risk of hernia development, and incidence rates of 4.7% (3), 4.1% (8) and 2.4% (4) have been reported.

Figure 2. Weak points in the abdominal wall for facial disruptrue and herniation.

Adapted from http://emedicine.medscape.com/article/1923166-overview#a4

A request to the Directory of Health in Norway regarding incidence data on umbilical and ventral hernias, gave the numbers presented in table 1.
Table 1. Incidence of ventral hernia in Norway.

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Disease</th>
<th>Year 2012</th>
<th>Year 2013</th>
<th>Year 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>K420</td>
<td>Primary umbilical hernia with obstruction, without gangrene</td>
<td>419</td>
<td>475</td>
<td>508</td>
</tr>
<tr>
<td>K429</td>
<td>Umbilical hernia without obstruction or gangrene</td>
<td>2538</td>
<td>2707</td>
<td>3102</td>
</tr>
<tr>
<td>K431</td>
<td>Primary incisional hernia with gangrene</td>
<td>22</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>K432</td>
<td>Incisional hernia without obstruction or gangrene</td>
<td>2</td>
<td>573</td>
<td>777</td>
</tr>
<tr>
<td>K439</td>
<td>Other and unspecified ventral hernia without obstruction or gangrene.</td>
<td>3395</td>
<td>3031</td>
<td>3131</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>6376</td>
<td>6809</td>
<td>7545</td>
</tr>
</tbody>
</table>

Data from Norwegian Patient Registry (NPR).

The incidence of ventral and umbilical hernia subclasses beyond what is presented, is probably at a low level, though the exact numbers are uncertain. The prevalence of different types of abdominal wall hernias is discussed by Dabbas et al (9).

The figure shows that inguinal hernia disease, considered a typical male disease, is much more common than ventral hernia disease.

Figure 3. Prevalence data of different types of hernia.

Adapted from Dabbas et al (9).
There are many risk factors for developing incisional hernias, most of all SSI (5, 10-12) and BMI (5, 13, 14). That is also true for trocar site hernias (8). Deep SSI has more impact on the rate of incisional hernia than superficial SSI (15). The thickness of subcutaneous fat could in fact be a stronger predictor of incisional hernia (IH) than BMI itself (16). Many other factors have been implicated as independent predictors of IH, namely smoking (17), COPD (18), steroids (14) and emergency laparotomy (19). The technique of fascial closure with small bites; 4-8 x 4-8 mm rather than big bites, seems to reduce the incidence of IH (12, 20, 21). Non absorbable or slow absorbable monofilament sutures opposed to rapid absorbable sutures reduce the risk of hernia development (22, 23).

Altered collagen metabolism has gained interest over the years explaining both primary (24) and incisional hernias (25). Biopsies from skin and fascia have shown a significantly decreased ratio of type I : III collagen and type I : III procollagen mRNA compared with controls (24-26). The role of matrix metalloproteinase-mediated collagen breakdown in incisional and primary hernias are still under debate (25, 26).

5.3 Ventral hernia classification

Several classifications of abdominal wall hernia have been proposed over the years, but none has gained sufficient interest. European hernia society presented a classification for primary and incisional hernia in 2009 (27). The reason for this new classification was to achieve reliable comparison between future studies on the surgical treatment of ventral hernia disease. The classification distinguishes between non-incisional (usually named primary hernia) and incisional hernias including recurrent hernias in the incisional group.

Key-points in the classification are location and size:
There is no taxonomy for hernias caused by blunt or sharp traumas to the abdominal wall. The size of non-incisional hernias are made by measuring the usually round hernia across its greatest diameter. The size of incisional hernias reached no consensus due to variable shape and lack of a precise formula to calculate size. Therefore the greatest transversal width is recommended with the longitudinal length as an adjunct. In our studies, hernia shape was considered oval and hernia area calculated by the formula: \( \pi/4 \times A \times B \), where A and B are the two diagonals. Multiple hernias in both categories was measured along the largest transversal and longitudinal diameter to encompass all (27).
5.4 Diagnosis of ventral hernia

A ventral hernia can often be verified by a bulge through an opening or defect within the abdominal muscles. However both adipositas, small sized hernias and special location makes clinical diagnosis difficult. Recurrence, pain and eventration can falsify the diagnosis of hernia. The term occult hernia is used when the hernia is symptomatic, but not palpable on physical examination. Benign abdominal wall tumors (lipomas, fibroma, hemangioma) are quite common and can mimic hernias. Less common are primary malignancies and metastases (28). The use of ultrasound will increase the incidence rate of ventral hernias compared to only clinical examination (29). CT scan will further enhance detection rate significantly compared to ultrasound (30). MRI has in contrary to CT the advantage of zero radiation and multiplanar resolution, but evidence is still awaited regarding its sensitivity for hernia detection compared to CT (31). Imaging to detect recurrence can be done with ultrasound, CT or MRI, whereas the latter is suitable for detecting adhesions (32).

5.5 Surgical treatment of ventral hernia

Since the early 1990, two major technical achievements made substantial change to ventral hernia surgery. More and more surgeons began using mesh implants instead of suture repair, creating tension free repairs resulting in significant decrease in hernia recurrence (33). The introduction of laparoscopic mesh repair in 1993 (34) was the beginning of an area of better cosmesis and faster return to normal activities (35).

Today, guidelines and protocols for the treatment of ventral hernia, points to the complexity of hernia disease treatment (32, 36-38). Quoting professor Bittner (32):

“The traditional human subjects clinical research approach to generating EBM guidelines alone is unable to produce improved value for patient care that will be significant and sustainable for our increasingly complex health care system. Specifically, the increasing
variability in ventral/incisional hernia patients and technique options minimizes the value of applying traditional research methods to improve outcomes. We need to change our thinking and learn how to understand and implement research methods designed to address this increasing complexity so we can fully address health care challenges such as ventral/incisional hernia disease.”

5.5.1 Surgical treatment objective in ventral hernia repair.

Ventral hernia strategy in terms of observation or surgical intervention, follows general rules of symptomatology, comorbidity and expected life span. There is no differentiation between non-incisional and incisional hernia. The use of mesh repair is mandatory in order to reduce recurrence. Only very small primary defects (< 1 cm) can be considered for suture repair. It is recommended to approximate the hernia edges with non-absorbable suture and reinforce with a mesh prosthesis to avoid eventration (pseudo hernia). In laparoscopic mesh repair, the mesh is anchored with tackers and/or sutures at the inner lining of the abdomen (IPOM). If the defect is closed by sutures, the term most often used is IPOM +. In open repair, the mesh is usually placed in a retromuscular position and anchored with sutures. In small hernias the mesh can be placed as IPOM. In selected cases of small ventral hernias, the mesh can also be anchored by glue (39)

5.5.2 LVHR vs OVHR

In general ventral hernias with defect sizes smaller than 10 cm, should preferably be treated with laparoscopy. Adhesions of certain magnitude, multiple recurrences, loss of domain and certain anesthiological considerations, may favour open mesh repair. Hybride techniques can often be used to overcome the challenge of laparoscopy. Anterior component separation
(ACS) can be achieved by open approach (40) (41) or by endoscopic approach (42) performing a longitudinal transection of the aponeurosis of the external oblique muscle. Posterior component separation (Transverse abdominis muscle release /TAR) should be considered as an adjunct in very large hernias (43).

5.6 Hernia mesh; structure, types and considerations

In 1958 Usher (44) reported the use of Polypropylene (Marlex) mesh for repair of incisional hernia. In 1962 he published the results of 358 incisional hernia repairs with Marlex mesh (45). 84% were sutured as an onlay graft. The incidence of wound complications was 15% including 6% wound infection. No mesh had to be removed. The recurrence rate in 156 of these cases after 1 year was 10.2%. This substantial effect on recurrence rate, stimulated the research for an optimal mesh with low infection rate, low adhesion formation and high biocompatibility (46). Unfortunately, there are substantial number of reports on seromas, bacterial infections, adhesions, chronic pain and mesh shrinkage (47-49). In 1993 LeBlanc presented his first series of laparoscopic incisional hernia mesh repair with ePTFE. The mean follow-up was 2 months. There were no complications (34).

Picture 1. Hernia mesh anchored by absorbable tacks to the inner lining of the abdomen.
To day there are quiet a number of absorbable synthetic, non-absorbable synthetic and organic material derived meshes available on the market. The different classifications of synthetic meshes, have focused on pore size (50), weight (51, 52) or porosity/ multi or monofilaments (53). Biological meshes are classified according to crosslinking or non-crosslinking of collagen constituents.

**Figure 6. Classification of synthetic hernia meshes by porosity.**

<table>
<thead>
<tr>
<th>Class</th>
<th>Characteristic</th>
<th>Pore size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy weight</td>
<td>&gt; 80g/m²</td>
<td>Small</td>
</tr>
<tr>
<td>Medium weight</td>
<td>50 - 80 g/m²</td>
<td>Medium</td>
</tr>
<tr>
<td>Low weight</td>
<td>&lt; 50g/m²</td>
<td>Large</td>
</tr>
</tbody>
</table>

Adapted from Klinge U. et al. (53)

**Figure 7. Classification of synthetic hernia meshes according to composition.**

1 **Simple.** Prosthetics made of one pure biomaterial.
   PP, PTFE, PGA or PU. Mono or multifilament with same texture on both sides. With or without drugs

2 **Composite.** Prosthetics made of two or more different layers
   One simple layer and the other is non-resorbable (A) or resorbable (B)
   (A) Non-resorbable layer/s (with or without drugs)
       Include e-PTFE, PU, PEU, silicone, and cPP
   (B) Resorbable layer/s include collagen, collagen +
       PEG + glycerol, PDO + ORC, CMC + HA,
       PVP + PEG, O3FA

3 **Combined.** Two materials knitted or woven together.
   (A) Both materials non-resorbable:
       Coated filaments (for example, PP with titanium.
       Two filaments knitted or woven together for example PP + PVDF
   (B) Only one filament resorbable:

Adapted from Coda A. et al (52)
Figure 8. Chemical composition of synthetic hernia meshes.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>PET</td>
<td>Polyester (polyethylene terephthalate)</td>
</tr>
<tr>
<td>PEU</td>
<td>Polyether urethane</td>
</tr>
<tr>
<td>PG</td>
<td>Polyglactin</td>
</tr>
<tr>
<td>PGACL</td>
<td>Polyglycolic acid-caprolactone</td>
</tr>
<tr>
<td>PGCA</td>
<td>Polyglecaprone acid</td>
</tr>
<tr>
<td>PLA</td>
<td>Polylactic acid</td>
</tr>
<tr>
<td>PGA</td>
<td>Polyglycolic acid</td>
</tr>
<tr>
<td>PP</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>cPP</td>
<td>Condensed polypropylene</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>cPTFE</td>
<td>Condensed poltetrafluoroethylene</td>
</tr>
<tr>
<td>ePTFE</td>
<td>Expanded poltetrafluoroethylene</td>
</tr>
<tr>
<td>PVDF</td>
<td>Polyvinylidene fluoride</td>
</tr>
<tr>
<td>PVP</td>
<td>Polyvinylpyrrolidone</td>
</tr>
<tr>
<td>PU</td>
<td>Polyurethane</td>
</tr>
<tr>
<td>CMC</td>
<td>Carboxymethyl cellulose</td>
</tr>
<tr>
<td>HA</td>
<td>Hyaluronic acid</td>
</tr>
<tr>
<td>O3FA</td>
<td>Omega-3 fatty acid</td>
</tr>
<tr>
<td>ORC</td>
<td>Oxidized cellulose regenerated</td>
</tr>
<tr>
<td>PDO</td>
<td>Polydioanone</td>
</tr>
<tr>
<td>PE</td>
<td>Polyethylene</td>
</tr>
<tr>
<td>PEG</td>
<td>Polyethylene glycol</td>
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</tbody>
</table>

Adapted from Coda A. et al (52)

Figure 9. Classification of biological hernia meshes

<table>
<thead>
<tr>
<th>Biological mesh</th>
<th>Source</th>
<th>Manufacturer</th>
<th>Cross linking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alloderm</td>
<td>Human dermis</td>
<td>LifeCell Corp.</td>
<td>No</td>
</tr>
<tr>
<td>Allomax</td>
<td>Human dermis</td>
<td>Davol</td>
<td>No</td>
</tr>
<tr>
<td>Collamend</td>
<td>Porcine dermis</td>
<td>Bard Medical</td>
<td>Collagen and elastin</td>
</tr>
<tr>
<td>FlexHD</td>
<td>Human dermis</td>
<td>Ethicon</td>
<td>No</td>
</tr>
<tr>
<td>FortaGen</td>
<td>Porcine dermis</td>
<td>Organogenesis Inc</td>
<td>Yes (low level)</td>
</tr>
<tr>
<td>Peri-guard</td>
<td>Bovine pericardium</td>
<td>Synovis</td>
<td>Gluteraldehyde</td>
</tr>
<tr>
<td>Permacol</td>
<td>Porcine dermis</td>
<td>Convidien</td>
<td>Yes (disocyanate)</td>
</tr>
<tr>
<td>Strattice</td>
<td>Porcine dermis</td>
<td>LifeCell Corp.</td>
<td>No</td>
</tr>
<tr>
<td>Surgicis</td>
<td>Porcine intestine</td>
<td>Cook</td>
<td>No</td>
</tr>
<tr>
<td>SurgiMend</td>
<td>Fetal bovine dermis</td>
<td>TEI Biosciences</td>
<td>No</td>
</tr>
<tr>
<td>Tutopatch</td>
<td>Bovine pericardium</td>
<td>Tutogen</td>
<td>No</td>
</tr>
<tr>
<td>Veritas</td>
<td>Bovine pericardium</td>
<td>Synovis</td>
<td>No</td>
</tr>
<tr>
<td>XenMatrix</td>
<td>Porcine dermis</td>
<td>Bard Medical</td>
<td>No</td>
</tr>
</tbody>
</table>

Adapted from Smart NJ et al (54)
Prostheses that contains pores larger than 75 micron, permits macrophages and fibroblasts to enter along with angiogenesis and collagen ingrowth, thereby avoiding infection.

Even though a mesh is inert to infection because of large pore size, the use of multifilament suture material can enable infection (50).

The huge amount of hernia meshes available on the market, makes a complete overview and knowledge of the constituents and chemical structure of the different meshes quiet impossible.

In addition there are variables like elasticity and strength of the implant, foreign body reaction, risk of infection, hernia size, abdominal wall architecture to mention few of the many variables that must be considered.

Figure 10. Interaction of mesh related factors on recurrence and pain.
Quoting Bittner (32):” With the number and variety of hernia meshes available for ventral/incisonal hernia repair, this variable alone is sufficient to demonstrate that traditional research mechanisms (i.e., prosopective RCTs) are inadequate to determine the mesh or meshes that have the best value for various patient groups, hernia types, techniques, surgeon skill levels, and so forth.” The huge number of various bio prosthesis are pushed by the industry and widely used despite an insufficient level of high-quality evidence in the literature (55).

5.7 Incidence and surgical activity in Norway

Ventral hernia mesh repair is common in Norway. Data from the Directory of Health in Norway, shows the numbers presented in Table 2. The register doesn’t differentiate between incisional and non-incisional hernias nor the exact location of the hernia. This makes any robust statement on the diversity of ventral hernia surgery obscure.

Table 2. Repair of ventral hernia in Norway.

<table>
<thead>
<tr>
<th>NOMESCO</th>
<th>Procedure</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2012</td>
</tr>
<tr>
<td>JAD10</td>
<td>Repair of incisional hernia</td>
<td>319</td>
</tr>
<tr>
<td>JAD11</td>
<td>Laparoscopic repair of incisional hernia</td>
<td>509</td>
</tr>
<tr>
<td>JAF10</td>
<td>Repair of umbilical hernia</td>
<td>1082</td>
</tr>
<tr>
<td>JAF11</td>
<td>Laparoscopic repair of umbilical hernia</td>
<td>255</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2165</td>
</tr>
</tbody>
</table>

Data from Norwegian Patient Registry (NPR).

5.8 Complications

Postoperative and late complications are still on the table for ongoing research. Laparoscopic hernia mesh repair shows better outcome in terms of overall complications, superficial and
deep infections compared to open mesh repair (56). Mesh related complications is thought to be far less than 5 % per year (57).

Side effects, complications and failure to cure are terms that implement negative outcome after surgery. Postoperative pain and recurrence are usually not considered regular complications. Even Clavien-Dindo chart for classification of postoperative complications, doesn’t encompass these conditions.

5.9 Pain

Pain after ventral hernia mesh repair is common and gradually diminish, but are not resolved for many patients, even after 6 months. Cutting through the abdomen wall or stretching of the abdominal can result in injury to the thoragic lateral cutaneous nerve or the ilioniguinal or iliohypogastric nerves (58). Preoperative pain seems to predict postoperative pain (59). The type of mesh fixation (60-62) is also important, though any conclusive statement regarding suture and/or tackers cannot be made. Chronic pain can be caused by nerve damage or because of mesh related factors.

5.10 Recurrence

Recurrence rates after LVHR and OVHR varies considerable and are related to surgical methods and skills, patient characteristics and length of follow up (63). Obesity and hernia size are among factors considered to be important. Recurrence rate seems to have reached peak incidence level after 2 years, with few additional recurrences appearing after that (64). Furthermore, it is generally agreed that follow-up of at least 3 years is necessary to detect the majority of recurrences (65).
5.11 Quality of life

Quality of life is a multidimensional and dynamic concept encompassing positive and negative features of life. There is no exact definition of this concept. It harbours elements of satisfaction, physical and psychological state, independency, cultural perspectives, values and personal expectations, educational level and many more (66). Felce and Perry (67) propose the concepts of Objective Life Conditions, Subjective feelings of Well-being and Personal Values and Aspirations that closely interacts. Each of these concepts contains five elements; that of physical well-being, material well-being, social well-being, development and activity and emotional well-being.

Health-related quality of life has evolved since the early 80s to encompass those elements of QoL that is related to physical or mental health. Often the term QoL is used in most hernia papers instead of HRQoL.

Improved quality of life and adequate abdominal wall functionality should be the principal outcome measure in hernia surgery rather than the absence of recurrence (68, 69).

5.12 Microbiology and abdominal wall implants

Bacteria capable of forming biofilm are responsible for mesh colonization and eventually mesh infection. Infection after mesh implantation can be a serious problem and rates around 6 - 10 % have been hernia repairs (70-72). Bacteria can colonize the mesh during surgery or postoperatively due to surgical drains, catheters and tubes leading to subsequent biofilm formation on the mesh.

There are currently no data available for the minimum bacterial inoculum required for bacterial adhesion to mesh used for abdominal hernia repair (73). The composition and structure of synthetic mesh seems to be the key to facilitate bacterial adherence (46).
The methods of detecting bacteria from these meshes, has been traditional cultivating methods and microscopy. We therefore know very little about the true composition of mesh biofilm, and literally nothing about the consequences of such biofilm for the integrity of the mesh. Coagulase-negative staphylococci, *Staphylococcus aureus*, *Streptococcus* spp., anaerobic bacteria and enteric gram negative bacteria have often been cultured from infected meshes (46, 74, 75). Biofilm consists of bacterial colonies embedded in a polysaccharide matrix (76). Bacteria within biofilms form complex communities that interact via quorum sensing thereby regulating the formation and growth of biofilm. The outermost bacteria are metabolically active, while the innermost bacteria are protected from the host defense system and antibiotics (77).

5.13 Periodontitis

Periodontal diseases are chronic infections resulting in variable degrees of connective tissue breakdown and bone loss around the teeth, and they are considered a heterogenous disease group caused by the complex actions and interactions of the subgingival biofilm microbiota and modified by the host immune system. These infections are polymicrobial due to the strong indications of several bacterial species taking part in the initiation and progression of the disease. It is well-established that untreated advanced periodontal disease constitutes a chronic source of bacterial dissemination which can result in hematogenous spread to other parts of the body. Severe forms of periodontitis affect approximately 10-20% of the world’s population (78). More than 600 different bacteria can be detected in the oral cavity (79). Studies have shown that bacterial species considered as commensals in the oral cavity may be associated with systemic diseases, e.g., endocarditis (80). The subgingival biofilm is dominated by obligate and facultative anaerobic bacteria. Most related to the progression of periodontal disease are
the obligate anaerobic, Gram-negative species *Porphyromonas gingivalis*, *Tannerella forsythia* and *Tannerella denticola* (Red Complex Bacteria). *Fusobacterium nucleatum* and *Prevotella* spp. are also considered important (81). These species are part of the normal oral microbiota and are not considered as exogenous pathogens. In periodontal healthy individuals, there is a predominance of *Streptococcus* species (82).

**Picture 2. Dental X-ray showing severe alveolar breakdown due to periodontitis.**

5.13.1 **Periodontitis and systemic disease**

Evidence exist that relates periodontal disease to several types of systemic diseases. There is a low–to–moderate association between periodontitis and coronary artery disease (83).

Periodontal pathogens have been identified in atherosclerotic plaques (84–86) with *B. forsythus*, *P. gingivalis* and *A. actinomycetemcomitans* representing 74% of all species (86).

Periodontal disease and hyperglycemia/diabetes mellitus are associated. Diabetes increase the prevalence and severity of periodontitis. On the other hand, periodontitis seems to affect diabetes through systemic release of cytokines and inflammatory mediators. Chemokines, a large family of cytokines, have implications on the progression of both diabetes and periodontal disease (87).
A meta-analysis found significant (p< 0.01) higher antibody titer against *P. gingivalis* in patients with rheumatoid arthritis compared to patients with periodontal healthy controls and systemically healthy patients with periodontal disease (88).

6. AIMS OF THE STUDY

1. To compare laparoscopic and open mesh repair for incisional and non-incisional hernias in terms of complications, recurrence, pain and patient satisfaction with the outcome.

2. To investigate QoL after LVHR and OVHR on long-term follow-up and compare QoL measures with those of patients presenting with non-recurrent ventral hernia disease.

3. To evaluate to what extent MRI is able to detect the mesh implant and adhesions to the bowel after LVHR and OVHR. In addition we wanted to find if adhesions could explain chronic pain after VHR.

4. To find evidence for bacterial biofilm in mesh implants, analyze its bacterial diversity, and look for possible resemblance with biofilm from the periodontal area.

7. MATERIALS AND METHODS

In paper I and II we conducted a observational follow-up study of all patients undergoing mesh repair for incisional and non-incisional hernia at Akershus University Hospital, Norway between March 2000 and June 2010. Both the hernia population and the participating surgeons reflects the “world of hernia” appearing at a medium-sized regional hospital in Norway and reflecting a change from solely open repairs to more and more laparoscopic repairs.

The clinical data were partly extracted from electronic medical journals retrospectively (n=115 /75.2%) or registered prospectively (n=38 /24.8%). Follow-up examinations were
carried out by one surgeon and one study nurse. The recorded hernia operation is referred to as the index mesh repair.

We enrolled 194 consecutive patients, of whom 94 had been treated with laparoscopic mesh repair and 100 with open mesh repair including 11 conversions. Of these, 27 patients had died and 12 patients failed to attend their follow-up appointment without providing an explanation. One hundred and fifty-three (78.9%) patients attended their follow-up appointment and two patients (1.0%) were interviewed by telephone. The patients not attending follow-up, was older with significantly higher Charlson Index score at the time of hernia surgery.

Table 3. Baseline characteristics VHR

<table>
<thead>
<tr>
<th>Variable</th>
<th>Follow-up</th>
<th>No follow-up</th>
<th>p value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age y. mean (+/-SD)</td>
<td>n=155</td>
<td>n=39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male(%)</td>
<td>56.8(+/-13.4)</td>
<td>61.1(+/-14.9)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Preop. BMI (kg/m2). mean (+/-SD)</td>
<td>68(43.9)</td>
<td>21(53.8)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Charlson Index .mean (+/-SD)</td>
<td>30.2(+/-5.8)</td>
<td>29.4(+/-6.8)</td>
<td>0.43</td>
<td>excl 3 missing</td>
</tr>
<tr>
<td>Type of hernia (%)</td>
<td></td>
<td></td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Incisional(secondary)</td>
<td>114(73.5)</td>
<td>33(84.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-incisional(primary)</td>
<td>30(19.4)</td>
<td>4(10.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incisional(primary)</td>
<td>11(7.1)</td>
<td>2(5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative complications(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor ( I+II)</td>
<td>40(25.8)</td>
<td>15(38.5)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Major (III+IV)</td>
<td>15 (9.7)</td>
<td>5(12.8)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Lethal ( V)</td>
<td>0</td>
<td>1 (2.6)</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Of the patients who attended their follow-up appointment, 82 (52.9%) had received a laparoscopic mesh repair while 73 (47.1%) patients had undergone open mesh repair, including 11 conversions from laparoscopic surgery due to intestinal injuries or technical problems. These 11 patients are included under open surgical procedures in tables and text, i.e. as per protocol.

Median follow-up was 48 months (9–88 months) after LVHR and 52 months
(12–115 months) after OVHR. Postoperative complications were classified according to Dindo (89) and recorded as minor (Clavien I + IIIa) or major (Clavien IIIb + IV). Late complications (30 days after surgery) were recorded using medical records.

The choice of laparoscopic vs open mesh repair, was not associated with comorbidity condition (p = 0.61) or Charlson Index (p = 0.41), but mostly based on the surgeons own preference and experience.

The operative technique for LVHR and OVHR is described in SUPPLEMENTARY.

The anterior sheet was not routinely closed. In OVHR the mesh was positioned in a retromuscular position with modifications in smaller hernias. The mesh was anchored with running non-resorbable transfascial sutures. In LVHR the mesh was anchored with tacks and/or non-resorbable transfascial sutures on the inner side of the abdominal wall (IPOM).

The adhesion score in OVHR could not be established due to deficient reporting.

Adhesions were graded according to Mazuji et al. (90).

Questionnaires for quality of life and functionality assessment were presented all patients before recall. One hundred and twelve consecutive patients referred to our hospital with non-recurrent ventral hernia disease, were presented with the same questionnaires and examined by the same surgeon and nurse. Clinical examination focused on pain by palpating the abdominal wall in nine areas.

**Figure 11.** Sectoral map of the abdominal wall.
7.1 Clinical assessment tools and questionnaires.

Pain was assessed by a 100-mm visual analogue scale (VAS) ruler anchored by word descriptors at each end to calculate the patient’s impression of pain (91). At examination, we asked about maximum abdominal wall pain for the last 30 days and maximum abdominal wall pain relative to sedentary- and work-level activities. We palpated the abdomen according to 9 sectors (Figure S1). Grading of pain was done according to Jensen (91): no pain \( \leq 5 \) mm, mild pain 6–43 mm, moderate pain 44–71 mm and severe pain \( \geq 72 \) mm. Chronic pain was defined as regular episodes of pain \( > 30 \) mm over the last 30 days (92).

Comorbidity was scored using the Charlson Comorbidity Index (CCI) (93). One point is given for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, stroke or transient ischemic attack, and diabetes. Two points are given for hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, any tumor, leukemia and lymphoma. Three points are given for moderate or severe liver disease, and six points are given for a metastatic solid tumor and acquired immune deficiency syndrome.

SF-36 (94) short form is a generic multi-dimensional scale that measures patient-reported health status and functioning. It consists of 36 questions (items). This generates 8 domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). In addition to these are the physical component score (PCS) and the mental component score (MCS). The subscales are transformed into values ranging from poorest health (0) to best possible health (100). Internal consistency (Cronbach’s alpha) for 10 domains of SF-36 in our study was 0.92. A lower limit for Cronbach’s alpha of 0.7 is recommended. Its reliability has
been tested in several trials (95, 96). The scores for both groups have been related to the Norwegian general population for comparison (97).

**Activities Assessment Scale (AAS)** consists of 13 items with 3 subscales: The activities are named sedentary (questions 1–4), ambulatory (questions 6–8) and work activities (questions 11–13) (98). The AAS scores are transformed according to the original study (98) using the formula:

\[
\text{Transformed scale} = \frac{(\text{actual raw score} - \text{lowest possible raw score})}{\text{possible raw score range}} \times 100; \quad \text{``0 %'' if no pain-related activity impairment and ``100 %'' for maximum impairment.}
\]

Though the questionnaire can be reduced leaving questions 5, 9 and 10 (sedentary activity level), we chose to address all 13 questions to the patients. Sexual activity was replaced with bending over activity to tailor the questionnaire to our target population. We also adopted the construct of Aasvang (95), who set a cutoff value of 8.3% on the transformed scale for those having substantial functional impairment 6 months after groin hernia therapy.

To improve sensitivity, the grading was done as follows (95): 0 = no impairment, 0–8.3 = minimal impairment, 8.3–30.3 = moderate impairment and >30.3 = severe impairment.

Internal consistency of AAS in our study was 0.84.

**Life Orientation Test—Revised (LOT-R)** has been used prospectively and in cross-sectional studies to estimate the implication of dispositional optimism on outcome after surgery, trauma and treatment for cancer disease among others. LOT-R divides personality traits into pessimistic and optimistic categories. Ten items compose the questionnaire where four are fillers. It consists of a 5-point scale, from 0 (strongly disagree) to 4 (strongly agree). Before scoring, the negative traits are flipped. The six actual items are summed to give a score ranging from 0 to 24, where high scores reflect optimism. The exact cutoff
between optimist and pessimist is set at LOT-R total of 18 (99). Others have used the following gradation (100): high optimism (19–24), moderate optimism (14–18) and low optimism (0–13). This type of personality trait is found to be relatively stable (101). In validation studies, the internal consistency was 0.78 (102) compared to 0.77 in our study.

Quality of life after hernia surgery (QoLHS): This 8 item questionnaire was constructed by the group to give some simple questions to patients in the study group in order to examine their opinion on the preoperative information and the outcome of surgery including satisfaction. This questionnaire has not been validated before, but was subjected to appropriate validity tests, including internal consistency, validity and responsiveness of a questionnaire. (96, 103, 104). Cronbach’s alfa was calculated to 0.79 for all items and 0.77 and 0.71 for components 1 and 2 respectively.

Comp I: Item 3, 6, 7, 8
Comp II: Item 1, 2, 4, 5

Component I showed a ceiling effect in which 41.2 of the patients achieved the highest possible score.
Component II showed a ceiling effect in which 45.6 % of the patients achieved the highest possible score.

7.2 MRI examination.

All patients from the original cohort that attended for follow-up or telephone interview were kindly asked to participate in the study. The MRI examination was finally performed in 50 (43.9 %) after OVHR and 64 (56.1 %) after LVHR. 41 (26.5%) patients were excluded. To increase the number of diagnostic MRI examinations, another 10 patients after VHR were included. In these patients data from medical records were not available. A total of 124 MRI examinations was performed.
A nine-segment map was used as location reference of the abdominal wall (Figure 11). Two experienced radiologists were informed about every patient's ventral hernia repair, but blinded to other clinical and per-operative findings. Criteria for detection of adhesions were restriction of visceral movement between bowel and adjacent abdominal wall or surgical mesh. The adhesions were classified according to the location and involved structures and other unrelated abdominal pathology was also recorded. Adhesions between different bowel loops or other organs were not evaluated.

Mesh detection and mesh size alteration was registered. The abdominal wall was investigated for recurrences, seroma and atrophy.
7.3 Collection and analyses of plaque and mesh bacteria.

36 patients with painful recurrence after former ventral hernia mesh repair were enrolled with the intention of periodontal examination before new hernia repair surgery. Five patients refused either dental examination or surgery, and in one patient no mesh was detected during surgery. In the final cohort of 30 patients, recurrences were verified by MRI or CT-scan in 25 cases. Information about former hernia surgery was extracted from medical records available.

**Mesh Sample Collection:** A small piece of incorporated mesh (1x1 cm) was collected, either during LVHR or OVHR for recurrence. The piece was arbitrary excised with scissors where the mesh was most easily accessible. The samples were immediately placed in an empty sterile glass container, transported on ice, and stored at 80°C. In one patient (ID=15), we could not find the implanted mesh and chose to set up a blindfold sample by taking a small piece of mesh directly from the sterile package and stored it at 80°C.

**Periodontal examination and microbial sampling:** The periodontal examination was conducted by an experienced dentist (JCÅ). Gingivitis was assessed by bleeding on probing (BOP) (105). Periodontitis was defined as the presence of one or more teeth with at least one site with probing depth ≥4 mm and BOP (106). Any severity grading of periodontal disease was beyond the scope of our interest. Periodontal pockets were measured in four sites for each tooth. Subgingival plaque specimens were collected from each pocket ≥4 mm by insertion of several sterile paper points (pooled samples) to the bottom of the pocket for 10 s. In pockets <4 mm, the same procedure was repeated, but only froma representative site of the first molar. If the first molar was missing, the second premolar was chosen, and then the first premolar. The collected plaque samples for each patient were pooled in a 1.5 mL microcentrifuge tube containing 1 mL sterile phosphate-buffered saline and stored at 80 °C. The alveolar bone loss was analyzed by periapical digital radiographs taken by an experienced dentist (JCÅ) and
analyzed by an experienced periodontist (ME). The distance between the cementum-enamel junction and limbus alveolaris was recorded. Due to lack of a protocol for standardization of radiographic recordings, differential diagnosis of bone loss was not possible. The aim of this assessment was left with the detection of alveolar bone loss indicative of periodontal disease.

**DNA extraction and PCR:** DNA extractions of samples from mesh and subgingival plaque were performed using the MasterPure DNA isolation kit from Epicentre (MCD85201, Epicentre Biotechnologies, Madison, WI). 16S rRNA gene fragments from bacterial DNA were amplified with PCR using universal eubacterial primers, forward primer 334f (5’-CCAGACTCCTACGGGAGGCAGC- 3’), and reverse primer 939r (5’-TTGTGCGGGCCCCCGTCAATTC-3’) (107) targeting the V3-V5 hypervariable region.

PCR reactions were performed with 32 cycles in 25 mL mixture of Accuprime supermix II (Invitrogen, Carlsbad, CA) in an Applied Biosystem (Foster City, CA) PCR cycler.

**Cloning and sequencing:** PCR products were ligated to the pCR4-TOPO vector and transformed into Escherichia coli DH5a cells using the TOPO-TA cloning kit according to the manufacturer’s instructions (Invitrogen). From each sample, 96 clones were picked. The partial sequencing of the clones was performed with BigDye Terminator v1.1 (Applied Biosystem) and M13 forward sequencing primer on ABI 3730. All sequences were trimmed for elimination of vector sequences and adjusted for quality values by using Sequencher 5.0 (Gene Codes Corporation, Ann Arbor, MI).

**Identification of 16S rRNA gene sequences:** We performed a BLAST search, comparing the consensus sequences with known sequences against the Ribosomal Database Project (RDP, update 10) (108) and the Human Oral Microbiome Database (HOMD) (www.homd.org/). Alignment of the nucleotide sequences was conducted with Clustalw2 with the default program settings (www.ebi.ac.uk/Tools/msa/clustalw2/). A phylogenetic tree was generated by the neighbor-joining method, using the Clustal W 2.0 program. The Molecular
Evolutionary Genetics Analysis (MEGA) software (version 5.2) was used to visualize sequence differences and to generate dendrograms (109). The nucleotide sequences from mesh and plaque analysis have been submitted to NCIB with GenBank accession numbers (Supplementary Table 1).

7.4 Statistical analysis.

The analysis in all paper were performed on a per – protocol basis. Patient, hernia characteristics and questionnaires scores are given as means and standard deviations (± SD) supplemented by median with range or frequencies and percentages, as appropriate. Interquartile range instead of standard deviations was used postoperative stay. Categorical variables were compared by the $\chi^2$-test and the Fisher exact test as appropriate. Comparison of symmetrically distributed continuous variables was performed using Student’s t-test while the Mann-Whitney nonparametric test was applied in the case of skewed distribution. Comparison of median values were performed using the Median test. Univariate analysis at the $P < 0.1$ level of appropriate variables were conducted and included in multivariate analysis. The result were presented as odds ratios (ORs) with a 95% CI estimated by the multivariate model unless otherwise stated. Pearson’s correlations test or Spearman’s rank correlation test were used to establish association between certain variables. Principal Component analysis were performed to evaluated the dimensionality of the QoLHS questionnaire and Cronbachs alfa was calculated on all QoL questionnaires to measure internal consistency. Principal component analysis was also carried out to illustrate the loading of bacteria on mesh insertion technique. General linear models (two-way ANOVA) was used to assess the influence of optimism and hernia surgery on AAS and the influence of optimism and gender on AAS.
The Shannon-Weaver index of diversity ($H'$) was used to determine the diversity of bacteria present in the subgingival pockets and mesh samples by the following equation (108).

$$H' = - \sum_{i=1}^{s} p_i \ln (p_i)$$

where $s$ is the number of species (species richness) and $p_i$ is the proportion of species in sample $i$. $H'$ was compared for subjects by the Mann-Whitney U test. All the tests were two-tailed with a level of significance of 0.05 ($P < 0.05$). The analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL United States).

8. SUMMARY OF PAPERS AND INDIVIDUAL MAIN CONCLUSIONS

8.1 Paper I

Findings:

We investigated the outcome of LVHR and OVHR after 48 and 52 months respectively. The primary outcome variables were postoperative complications, recurrence, pain and satisfaction.

Postoperative complications:

The prevalence of minor and major complications after LVHR and OVHR were not different. Wound infection and seroma were more pronounced after OVHR.

LVHR was more time-consuming compared to OVHR.

Predictors of postoperative complications:

- Operative time > 108 min. Only LVHR
- Intestinal adhesions.
- Incisional hernia
Recurrence rate:
- 14 (17.1%) after LVHR.
- 17 (23.3%) after OVHR

Predictors of recurrence:
- Higher BMI, number of trocars and length of postoperative stay. Only LVHR
- Smoking. Only OVHR

Pain:
- Pain reported and pain on palpation, LVHR ~ OVHR
- Pain without recurrence, LVHR (18.3%) ~ OVHR (15.4%)

Predictors for pain:
- Recurrence
- Late complications.

Satisfaction with the result:
- Satisfied, 60.5% after LVHR. 49.3% after OVHR

Predictors for satisfaction:
- Absence of chronic pain
- Absence of recurrence. Only OVHR.

Discussion of results:
Even though our recurrence rates were high after both LVHR and OVHR, the mean follow-up time was longer than in many other studies. The great variation of follow-up time among different studies could affect recurrence rates (110). There are also other factors to consider: Our study involved mandatory examination of all patients. Patients who report no symptoms of recurrence in mailed questionnaires can easily be misdiagnosed. Finally, we need to consider that relatively small numbers of patients are followed-up in some of the previously conducted studies (111). Late complications are usually due to the consequences of mesh
implantation. Bowel obstruction (112, 113), sinus tract formation (114) and foreign body reaction with seroma, migration of mesh and pain (115), are most prevalent reported and seems to be time-dependent.

Recurrence is associated with pain, but even without recurrence, 13 patients (18.3%) and eight patients (15.4%) reported chronic pain after LVHR and OVHR respectively. Several factors can generate (chronic) abdominal wall pain. We didn`t discriminate between the most common pain form; neuropathic and nociceptive pain. Nerve entrapment of the abdominal cutaneous nerves is thought to be the most important mechanism in neuropathic pain sensation (116), while nociceptive pain is often caused by inflammation and injury to the tissue caused by the mesh placement (117). Transection or blunt dissection of nerves also results in neuropathic or sensory disturbance, while the fixation with transfascial sutures causes nociceptive pain sensation (118).

The lack of symptoms from the anterior abdominal wall, doesn`t always imply that the patients are satisfied with the hernia surgery. Only 66.2% and 60.7% were satisfied, after laparoscopic and open hernia surgery respectively, even without recurrence. In our study, absence of chronic pain was the most important factor for satisfaction after LVHR. Recurrence (119) and chronic pain (92, 119, 120) are predictors for dissatisfaction. Old age at hernia surgery also predicted satisfaction, while clinical recurrence was predictive for discontent only in the crude model. Longer follow-up was associated with discontent in our study and could be due to increased rate of recurrence, though this is not proven.

Chronic pain and clinical recurrence was associated with discontent after OVHR.

**Conclusion:**

There was no difference in long term recurrence, pain and overall patient satisfaction after OVHR and LVHR. The frequency of recurrence was relatively high. The
absence of chronic pain, also frequent without recurrence, is the most important factor for patient satisfaction.

8.2 Paper II

Findings:

Quality of life and functionality on long-term follow-up, was compared using validated instruments. The expected normal value for each domain of the SF-36 score based on the scores published for the general Norwegian population stratified by age and sex (97) was recorded for each patient in the study. The scores for the surgery and non-surgery groups were then calculated and compared. There was no significant difference between the ‘‘normalized SF-36 values’’ of the two groups in any domain.

SF-36:

- All domains: LVHR ~ OVHR
- Physical dimensions of life: Surgery group better than non-surgery group.
- Physical dimensions of life, GH and BP: Significantly lower scores in women.

Predictors of SF-36 scores.

- Clinical recurrence detoriates QoL after LVHR and OVHR.
- Incisional VHR: Physcial dimensions of life, VT and SF improves.

AAS:

- Physical dimensions of life in SF-36 in accordance with AAS transformed scale
  
  LVHR ~ OVHR

  Surgery group ~ Non-surgery group.

  No difference between genders in both groups.

- Physical impairment less prevalent after VHR
- Bending over most disabling activity in non-surgery group, but also prevalent after VHR without recurrence.

**Pain:**
- Chronic pain and physical impairment closely related in surgery and non-surgery group.
- Chronic pain more pronounced and frequent in the non-surgery group.

**LOT:**
- Optimism improves functionality after VHR.
- Optimistic patients report less pain after VHR.

**Discussion of results:**
The lower scores on all SF-36 domains seen in women are consistent with the scores from USA (121), UK (122) and Canada (123). The reason for women's perception of inferior quality of life is multifactorial. Lower level of education, at least in the older age group, lower level of physical activity, chronic morbidity and more frequent use of health services, cultural and biological factors (124).

The cohort evaluated after VHR, showed significantly higher scores on the physical domains (PF), physical function restrictions (RP) and bodily pain (BP), compared to the non-surgery group, but only after incisional hernia repair. There were no differences between laparoscopic and open mesh repair on any domain.

Other reports are not consistent. There are, however, problems with the interpretation of results from previous studies due to the fact that few papers encompass SF-36 norm-based scores (125). There are also mixed populations of incisional and non-incisional hernias without further separate analysis (120). An incisional hernia encompasses former surgery with its consequence on abdominal wall pain and physical activity, adhesion formation and intestinal function. This paradigm cannot easily be exploited when SF-36 covers both
incisional and non-incisional hernia repairs for analysis (61). Despite hernia mesh repair, 75% reported moderate and severe physical impairment, even without recurrence. In our study excluding recurrence, nearly 20% reported movement limitations (bending over, stretching, climbing stairs) caused by abdominal wall symptoms. This is in accordance with other reports using SF-36 and CCS, respectively (68, 119). The burden of comorbidity, seemed to affect the physical domains in SF-36 only in the surgery group. Healthy patients compared to non-healthy patients, had significant less impairment in the surgery group. In the non-surgery group, this lack of association could imply the importance of hernia itself as the main factor for impairment. The difference between groups seen in our results must be interpreted with caution due to the observational analytic approach not reflecting true (longitudinal) change in the estimates of interest. Non-disease related stressful events such as unemployment, divorce, etc., could for instance hamper the SF-36 scores and make interpretation difficult (126). In our study, there was no difference between optimistic and pessimistic patients reporting abdominal wall pain and pain on palpation when having a hernia. After hernia repair and excluding recurrence, there was significantly less abdominal wall pain given an optimistic trait. In the non-surgery group, pain was not associated with dispositional traits. The reason for this difference between the groups could be due to the burden of having a hernia and that the condition itself offsets any optimistic trait. One could also argue that better health generates optimism or is it that lack of optimism gives worse perception of health? This question has not been definitively answered (127).

**Conclusion:**

Laparoscopic and open ventral hernia mesh repair reduce chronic pain and physical impairment and improve long-term QoL. Hernia recurrence and persistent pain reduce the beneficial effect of hernia surgery. Dispositional optimism can modulate QoL reporting.
8.3 Paper III

Findings:

- MRI could detect between 50 and 100% of implanted meshes.
- Mesh shrinkage was 30% for all meshes pooled together.
- Adhesions between bowel and abdominal wall/mesh in 59% of the cohort.
  No difference between LVHR and OVHR.
- No detection of adhesions between omentum and abdominal wall.
- Adhesions are not related to chronic pain.
- Validation by laparoscopy:
  Sensitivity 70%. Specificity 75%. Positive predictive value 78%.

Predictors for adhesions:

- Charlson Comorbidity Index
- Mesh area.

Discussion of results:

Intra-abdominal adhesions may have deleterious effects, like intestinal obstruction, chronic pain and reduced QoL (128). Adhesions also seems to be associated with vague abdominal pain and discomfort (129).

The detection of intra abdominal adhesions by MRI was first described by Lienemann et al (130). Several further publications on the same topic have shown promise (131, 132) and impressive accuracy (132). A proportion of patients will seek medical assistance due to abdominal pain after former laparotomies. Non-invasive imaging by planar X-ray, CT or MRI are used in an attempt to detect abrupt change in bowel caliber from distension to a collapsed distal region (133, 134). Radiographic imaging will detect the site of obstruction, but not the cause, though an adhesion is most likely (135). Improved non-invasive diagnostic methods should strive to diagnose adhesions in symptomatic patients with and without obstruction
before appropriate surgery is justified (135). The assessment of cine-MR images can be challenging and limited by patients compliance, high inter-operator variability and excessive reporting time (136). Our effort to detect inter-visceral adhesions was abandoned due to the challenge of having patients making deep breaths for 20-25 minutes during the MRI-scan period. The study was therefore not designed to detect adhesions between bowel loops, or between urinary bladder or between female internal genitals and bowel loops. The movement of abdominal wall muscles could be affected by health condition, age, abdominal wall pain and stiffness caused by mesh implant. In some previous reports, a MRI-slice-thickness of 5-15 mm has been used (128). To increase patient compliance, the MRI-slice thickness of 15 mm was selected to reduce the scan-time, which in theory could overestimate the presence of adhesions.

Adhesions between bowel and abdominal wall or mesh was easily detected, opposed to adhesions of omentum. In previous studies with intraoperative validation of the MRI’s ability to detect adhesions, a prevalence of 96 %, an accuracy of 90%, a sensitivity of 93%, a positive predictive value of 96%, and a specificity of 25 % were found explained by the low number of individuals without adhesions (137). In our small series of 18 patients with MRI before laparoscopy, we found a sensitivity of 70%, specificity of 75 %, positive predictive value of 78% and negative predictive value of 67%. Thus, MRI underestimated the presence of adhesions.

Transabdominal ultrasound can be compared to cine-MRI in detection of intraabdominal adhesions with the same sensitivity and specificity, but its diagnostic power diminish in obese subjects (138).

This study was unable to find any association between adhesions and pain. This is in accordance with a study by Swank et al. (139) who randomized patients with chronic abdominal pain and adhesions to either laparoscopy with adhesiolysis or laparoscopy alone.
There was no difference between the groups, except for more complications after adhesiolysis. On the contrary, Demco et al. (140) performed laparoscopy in 20 sedated but awake patients and a systematic traction of adhesions was performed which induced pain depending on the type of adhesions.

Ultrasound has been used to deline mesh implants of the abdominal wall, but scanning of the thin prosthetic mesh can be challenging (141). Only ePTFE meshes are detected by CT and because of radiation exposure, CT is not appropriate for routine follow-up (142).

There are reports that questions the visibility of many mesh implants by MRI (142-144). Materials with a density similar to that of human tissue (isoattenuating), are not visible on MRI (145). Hydrophobic implants (ePTFE) tends to be more visible because it doesn’t permit collagen tissue ingrowth (131). To overcome the problem of visualizing the meshes, contrast agents like superparamagnetic iron oxides (143) or gadolinium chelate (146) can be incorporated in the mesh structure. All IPOM meshes are coated with an absorbable protein film (coating) that can be detected by MRI, but because of resorption this film will only be visible in 3-4 weeks (147, 148).

Polyester (Parietex Composix) and Polypropylene meshes have density similar to adjacent muscle and are generally either invisible or poorly invisible. Indirect evidence for the presence of these meshes can be recognized to the intense inflammatory response incorporating the mesh (145). To enhance early detectability of the resorbable coating, the use of a contrast agent (amid proton transfer) have been suggested (149).

On the other hand, Zinther et al reported that polyester mesh (Intramesh W3) in all 30 patients 5 y 7 m after LVHR was visible. Also Polypropylene mesh (Bard Composix) was visible in 10 patients after laparoscopic inguinal hernia repair (150).
In a study by Burgmans et al after TEP with inter rater assessment, mesh was detected in 59 of 67 (88%) groins. Different mesh implants like Polypropylene with coating (Ultrapro, Bard 3D, Physiomesh) and Polyester with coating (Parietex) was used (151).

The patients in our study was given no intravenous contrast agent. The meshes was visible as a thin black line and effort was made to avoid false interpretation of scar and fibrous tissue.

**Figure 13. Detection rates on MRI according to mesh type. *p< 0.05**

<table>
<thead>
<tr>
<th>Mesh</th>
<th>Biomaterial</th>
<th>Classcode</th>
<th>Detection (%)</th>
<th>Schrinkage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietex comp</td>
<td>PET + collagen/PEG/glycerol</td>
<td>2B</td>
<td>35/38 (92)</td>
<td></td>
</tr>
<tr>
<td>Polypropylene</td>
<td>PP monofil</td>
<td>1</td>
<td>12/21 (57)</td>
<td>+1</td>
</tr>
<tr>
<td>Bard comp</td>
<td>PP monofil + hydrogel coating</td>
<td>2B</td>
<td>14/18 (78)</td>
<td>-36 *</td>
</tr>
<tr>
<td>Goretex DM</td>
<td>e-PTFE with 2 layers</td>
<td>2A</td>
<td>13/17 (72)</td>
<td>-23</td>
</tr>
<tr>
<td>Proceed</td>
<td>PP + PDO + ORC</td>
<td>2B</td>
<td>7/7 (100)</td>
<td>-37</td>
</tr>
<tr>
<td>Marlex</td>
<td>PP monofil</td>
<td>1</td>
<td>3/6 (50)</td>
<td>-72</td>
</tr>
<tr>
<td>TiMESH</td>
<td>PP monofil + Ti coating</td>
<td>3A</td>
<td>3/3 (100)</td>
<td>-52 *</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td>1/4 (25)</td>
<td></td>
</tr>
</tbody>
</table>

In our series the shrinkage of of Parietex composix, Bard Composite and TiMESH was significant. The time from VHR to MRI scan was 5 years (SD ± 1y 11 m / range 1y 4 m – 11y 5 m). Köhler et al.(143) used iron-loaded PVDF-mesh to enhance visibility and found a mean decrease in surface are of 19.1%. Mesh shrinkage seems to reach a plateau after 3 months (143). The use of ironloaded meshes makes more accurate diagnosis of mesh position, folding and shrinkage (143, 152).

**Conclusion**: There is no difference between the tendency to form adhesions after LVHR and OVHR. The area covered by the mesh is associated with formation of adhesions. Adhesions between bowel and abdominal wall cannot explain chronic pain after LVHR or OVHR.
**Picture 3.** Adhesions between small intestine and IPOM mesh.

**Picture 4.** Adhesions between omentum and IPOM mesh with tackers.
8.4 Paper IV

Findings:

- The mean time from index hernia mesh repair to mesh sample collection was 3.9 y.
- Positive 16S rRNA gene PCR products were obtained from 20 meshes (66.7%).
- 70.6% and 61.5% of the meshes after OVHR and LVHR respectively revealed 16S rRNA gene products.
- Periodontitis was detected in 10 patients (33.3%).
- Six patients with periodontitis had positive 16S rRNA gene PCR products from mesh.

Mesh bacteria: 90 different taxa were detected from a total of 357 different sequences. The mean number of taxa in mesh samples was 18.69 SD ± 12.7. The most abundant species in all mesh samples were *Propionibacterium acnes*, *Streptococcus australis*, and *Streptococcus* spp. Also *Fretibacterium* spp., *Propionibacterium* spp., and *Sphingomonas* spp were abundant.

Typical oral bacterial taxa were more abundant than typical skin taxa and enteric taxa.

Putative periodontopathogens found in mesh samples were *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotea* spp., and *Treponema* spp., which comprised 9.8% of the taxa. Among typical skin bacteria detected were *Staphylococcus* spp. including *S. aureus*, *S. epidermidis*, *S. caprae*, and *S. warneri* which contributed to 6.4% of all taxa. *Enterobacter* spp., *Enterococcus* spp., *E. coli*, and *Klyvera ascorbate* comprised 7.0% of all taxa.

Plaque bacteria: 197 different taxa from a total of 1,008 different sequences.

Streptococcaceae, Fusobacteriaceae, Veillonellaceae, and Prevotellaceae accounted for nearly half of all families.

Associations:

- Mesh bacterial diversity not associated with periodontitis (P =0.57) or gingivitis.
- Mesh bacterial diversity not associated with elevated CRP or leukocyte count.
- Periodontal disease was not associated with the detection of 16S RNA gene products
- Perioperative antibiotics reduces the extent of typical skin bacteria, enterics and bacterial diversity.
- Resemblance >99.5% between certain mesh and plaque bacteria in 8 patients.

Predictors of mesh bacterial diversity:
- Subgingival plaque bacterial diversity.

Discussion:
The striking association between plaque and mesh bacterial diversity could be coincidental or a reflection of a direct haematogenous route. In contrary to other investigations (153), the prevalence of red complex bacteria and A. actinomycetemcomitans in subgingival plaque samples was very low. None of the six patients with periodontal disease revealed these bacteria. In univariate analysis, neither periodontal disease nor BOP was associated with mesh bacterial diversity or detection of oral bacteria in mesh. Association statistics covering large numbers of diverse bacteria, often fails in exploring causal relationships with symptoms or disease. Literally, all patients were diagnosed with BOP. The impact of periodontal disease on association statistics was obviously negligible. Bacteriemia following toothbrushing or periodontal disease could in fact nourish the mesh biofilm by time and explain the abundance of oral bacteria both after OVHR and LVHR (154). Some oral bacteria are more equipped for hematogenous spread than others. F.nucleatum destroys the endothelial cell junction and make blood vessels more permable permitting also neighboring bacteria to escape hematogenously and replicate at distant locations (155, 156).

Antibiotic prophylaxis with amoxicillin before single tooth extraction decreased the overall incidence of bacteremia by 61% (154). In our series, there was an overall 43.4% incidence reduction of all mesh harboring taxa after perioperative antibiotics.

Mesh characteristics (46, 52), including hydrophobicity, electrostatic charge, number of filaments in yarn, and chemical composition, have influenced the infection rate (157).
There are several reports on PP mesh infection as the most common reason for mesh explantation (158). Engelsman et al. (46) suggested that both PP and Polyester meshes have clinical comparable rates of infection. ePTFE is associated with relatively high risk of infection (159) and most often has to be removed when mesh related infection occurs (70). In our series, there was no significant difference in bacterial diversity between the mesh types.

We don't know if mesh biofilm can generate pain and discomfort. Proteolytic bacterial enzymes could possibly interfere with tissue ingrowth increasing the potential of relapse. When mesh biocompatibility is low, a barrier of fibro-connective tissue prevents the host immune system to migrate to the biomaterial surface. The chemical composition of the mesh, the wettability and charge of the surface of the mesh, affects the composition of the conditioning film (46). Loosening of hip prostheses has for example been related to bacteria in the synovial fluid without any biochemical or clinical signs of infection (160). An established mesh infection on the other hand, can definitely promote hernia recurrence (161). Biological meshes have evolved during the recent years claiming excellence in contaminated and potential contaminated areas. Experimental data (162, 163) has revealed that no cross-linking gives better biological response with tissue incorporation and revasculatriaztion compared to cross-linked meshes. Clinical studies are however relatively few with poorly described methodology (54). The ability to resist infection and promote tissue integration is still controversial and must further be explored and validated (164).

**Conclusion:** There was great bacterial diversity in mesh implants including typical oral commensals and periodontopathogens, enterics and skin bacteria. Mesh can be reached by bacteria in several ways, including hematogenous spread from an oral site, but also from gut and skin.
9. GENERAL DISCUSSION

Favourable outcome of hernia surgery is often measured by the absence of recurrence and pain (165). Improved quality of life and optimized patient function are however measures that encompass a better judgment of patients outcome (166). Most papers suggest that LVHR results in a shorter hospital stay, fewer wound complications and better cosmetic results compared to OVHR (167). According to a Cochrane report comparing LVHR and OVHR, other outcomes of interest can be mentioned (65):

- Duration of surgery
- Enterotomy
- Local seroma or hematoma
- Local infection
- Reoperation.
- Acute pain on day 1,2 and 3
- Length of hospital stay
- Necessity for and duration of intensive care unit (ICU) stay after surgery.
- Time until return to normal activities or work.
- Quality of life.
- Chronic pain (>6 months after surgery).
- Patient satisfaction and cosmetic appearance.
- Costs of therapy (with or without out-of-hospital costs).

9.1 Statistical considerations

Intention – to – treat analysis is superior to per – protocol analysis because all patients are originally allocated after randomization and therefore don’t call for bias. Per-protocol analysis compares treatment groups that includes only patients who completed the original allocation (168).

The studies in paper 1 and 2 is of explorative character and no adjustments were therefore made for multiple hypothesis testing.

For postoperative stay, we have chosen interquartile range instead of standard deviation due to some instances of extreme values (169).
9.2 Study design.

**Paper I** is partly a retrospective and partly a prospective cohort study of patients treated for ventral hernia with either laparoscopic or open mesh repair. The search in our electronic patient system was based on preoperative diagnosis and operative procedure according to the ICD10 classification. An follow-up rate greater than 80 % is considered optimal for conclusion of treatment efficacy in RCT’s (170, 171). In epidemiological cohorts, some authors find rates for follow-up at 50 – 80% being acceptable, but the validity is not thoroughly tested (170).

In our study the clinical follow-up rate was 79 %. Loss to follow-up in clinical studies is common and can seriously limit their conclusions (110).

Obvious limitations that calls for carefull interpretation of the results, are the relatively small cohort, the retrospective analysis of records, the heterogeneity of ventral hernia types and the lack of a scheduled timeline for follow-up.

**Paper II** is a case-control study examining treatment efficacy using generic a QoL questionnaire, functionality questionnaire and a psychometric test. The study population (cases) and the follow-up rate is the same as in paper 1. The controls represent consecutive patients from referral list with untreated ventral hernia.

The cases and controls are not matched for age, sex or type of ventral hernia. The effect of VHR on Qol and functionality, therefor have to be interpreted with caution.

**Paper III** contains the study-population of paper 1, except for those who were reluctant or excused due to medical conditions. In addition, 10 consecutive and willing patients from the referral list, with former VHR, were included.

The interpretation of MR images are subjected to variability. Like in clinical medicine, there is no single established validated grading scale for various radiographic findings (172). The performance by any observer is an important source for inconsistency in imaging-based
diagnosis. Our two radiologist were both fellowship-trained attending physicians with 10 and 8 years of MRI experience. The subjects were examined concomitantly and in a random order. The radiologists were blinded to the repair technique and the mesh type that was used. The MRI criteria for diagnosis of adhesion detection and mapping was distortion of adjacent organs, a preserved visceral slide of adjacent structures in the same direction with missing separation between them, and a missing normal excursion along the peritoneal layer within the section orientation (137).

The first 10 subjects were evaluated to establish inter rater agreement. Unfortunately, the rest of the MRI interpretations were done without calculation of inter rater or intra rater agreement. The examination were structured according to a predefined checklist, but diagnostic criteria was not established on a “synoptic checklist” (173). Double reading of radiographs would significantly enhanced the diagnostic value (174).

Cohens kappa with 95 % confidence limits has been used to measure inter rater agreement. Kappa values below 0.4 represent poor agreement, 0.4 – 0.75 indicate fair to good agreement and values of 0.75 and higher represent excellent agreement (175). Others have also stressed the incorporation of congruent classifications for better interpretation of inter rater agreement (176). Among published MRI studies on the detection of intra abdominal adhesions, there are quite few incorporating inter rater and intra rater agreement.

Paper IV incorportated patients from paper 1 with recurrence in addition to patients from referral list with former VHR and recurrence.

The limitations of the Sanger technique and the lack of blood and stool samples for bacterial analysis, makes any robust conclusion of bacterial ancestry impossible.
9.3 Adverse effects.

Any surgical procedure has a risk of adverse effects. Failure to cure, complications and side effects/sequela. Complications after surgery are prone to fall in the opinion of the surgeon unless there exist an objective classification system that can be used and is validated (89). One can argue the need of a more disease specific complication form than that presented. Our results reflects the postoperative state before discharge, and we have no recordings of late complications besides those of such a magnitude as to be recorded by the patients readmission to the hospital or the patients own information at recall.

The consequence of applying a new surgical approach carries the risk of pitfalls. Some of our LVHR patients certainly was subjected to surgical enthusiasm and heroism in decision making defining the surgical treatment objective. Some complications and recurrences could be due to the lack of technical skills and experience in laparoscopic ventral hernia mesh repair. We analyzed each surgeons experience in both LVHR and OVHR, but found no class association to complications or recurrence rate (p = 0.18).

9.4 Comorbidity

Comorbidity is often measured in terms of ASA score. The grading criteria is subjective; ie. grading of “severe” disease is left to the interpretation of the anesthesiologist (177). Poor inter-rater reliability has also been demonstrated for certain disease populations (178). Because of this, any association between ASA score and complications can be coincidental. Charlson Comorbidity Index (CCI) is disease specific and not influenced by subjective interpretation. It has however a general construct that may fail to include or inadequately weight patient comorbidity that increase the likelihood of major complications seen in specific surgical procedures. There are very few papers on VHR encompassing CCI.
There is need for further research to create a tailored comorbidity score. It seems that a risk assessment tool as CCI is unable to predict functional outcome (179).

9.5 Quality of life.

The effectiveness of health-care interventions, is most often measured in terms of quality-adjusted life years. Quality-adjusted life years combine the quality and quantity of life into a one-dimensional outcome (180). The search for scales to measure patient reported outcome, has generated at least 60 unique measurement scales on well-being (generic scales) (181) and more than 200 disease specific scales (182). These scales are based on patients self-reports that assess functional status, emotional well-being and subjective perceptions of health.

There is no core curriculum to be extracted from previous studies on VHR and Qol. The reason for this is the heterogeneity of many studies, the variety of assessment tools used, the different surgical approaches, the variation in hernia size, the extent of follow-up, the variation in pain assessment and the lack of uniformity in assessing recurrence (183).

9.5.1. Requirements of health questionnaires.

The use of questionnaires/scales in clinical research has been discussed thoroughly by the Scientific advisory committee of the medical Outcomes trust: Conceptual and measurement model, validity, reliability, responsiveness, interpretability, respondent and administrative burden, alternative forms and cultural and language adaptions (184). Some adaptions have been made by others putting forward the following criteria (185): Content validity, internal consistency, criterion validity, construct validity, reproducibility, responsiveness, floor and ceiling effects and interpretability. The most fundamental requirement/fourth requirement for scales used as measures of outcome is that they must detect equally both improvement and deterioration in the population under study. To do this a
single state scale must have a sufficient range to encompass the spectrum of the phenomenon in the population (186).

The dimensionality of a scale is measured by principal component analysis to see if all items in a scale display substantial loadings on a single factor. Than it is justified to add the score to produce a single scale score. If a test is uni-dimensional; ie all the items measure a common structure, than it will display internal consistency (187)

Internal consistency means that the items in the questionnaire are correlated and are measuring the same concept. Cronbach’s alfa of 0.70 – 0.95 implies good internal consistency (96, 185).

Validity of a questionnaire means its ability to measure its target questions. Content validity examines the extent to which the concepts of interest are comprehensively represented by the items in the questionnaire (188). Construct validity measures the relationship between different questionnaires when it comes to specific and congruent types of questions (189). Because variables such as pain, disability and QoL are not measurable with standard measures, one examines the convergent validity or discriminant validity of the questionnaires to see if the scores are related to those of other instruments measuring the same construct (189). Acceptable convergent validity means rP ≥ 60 and acceptable discriminant validity means rP ≤ 0.30. Concurrent validity (criterion and predictive validity) refers to the degree to which the operationalization correlates with other measures of the same construct that are measured at the same time. If compared to a ” gold standard”, rP must be at least 0.7 (185).

Responsiveness refers to a questionnaires ability to detect change over time (189) and is considered a very important aspects of the instrument (190). It is measured by the area under the receiver operating curve (ROC curve) (191) or the group’s mean change in score divided by the standard deviation of the change in score (189). Due to our design for capturing QoL reporting, this aspect becomes irrelevant.
Reproducibility (test retest validity) of a questionnaire means that repeated measurements in stable subjects provide similar results (185). Unfortunately we didn’t take such measures, but all patients were helped to clarify any problems with questions. Further, the patients were forced to recall some past experience and put this impression on a rating scale (Sf-36, satisfaction). The use of a cohort relying on recollection, has certainly features that favours a more positive outcome compared to prospective data (192). Patient’s assessment of outcome is important. Some researchers have suggested multidimensional assessment including domains of importance to the patient; namely complications, symptoms, function and QoL. This can easily generate scales of unproportional length and magnitude reducing patient compliance (193, 194).

Floor and ceiling effects refers to extreme scores at both ends of the scale. It is present if more than 15 % of the cohort achieved the lowest or highest possible score, respectively (195). The responsiveness of the scale will therefore be weakened because changes observed cannot be measured (185).

Interpretability: Four out of 155 Sf 36 questionnaires were completely blank, and in the fifth there were 2 missing items. In two cases out of 155, the AAS questionnaires were blank on all 13 items but without any other missing items for the rest of the group. Five cases out of 155 LOT questionnaires were blank on all items and with only one item put in for the sixth case. For the “QoLHS” there were three cases with complete blank questionnaires.

9.5.2 Generic vs disease specific questionnaires.

Generic QoL scales should be used for comparing outcomes across different populations and intervention while disease-specific scales are better suited for assessing the responsiveness of treatment for a particular disease (196). Generic scales can be applicable to a broad range of
diseases. For those diseases that affect a narrow spectrum of the patients well-beeing, a generic instrument seems to insensitive to measure changes brought about by treatment (197). The effect of VHR can certainly be evaluated by a disease specific scale, but the hernia may not always represent unilateral dysfunction. Heniford et al (103) has developed Carolina Confort Scale (CCS) for the use in inguinal and ventral hernia. It is a 5 point Likert construct consisting of 8 Domains and 23 items with worst possible score of 115. It does not provide normative data based on the general (US) population. It has only physical attributes except for “Activity of daily living” and fails to address social impact and patient satisfaction. Even though CCS total score correlates well with both the physical and mental scores of the SF-36, the correlation coefficients are in the lower range of a moderate relationship (103). One could argue that the use of instruments tapered with many and bothersome questions, may not be the desirable. The use of core outcome measures seems to be more favourable due to their limited number of questions (192, 198).

Pietersma et al (199) evaluated seven common generic scales by using the Delphi-procedure (200). Mental and social domains were considered more important than physical domains by the raters (199). In longitudinal generic scale studies, the group can improve on average as a result of treatment, but individual variation in deterioration, stability or improvement may be overlooked (195). There is also a problem with Likert scaling methods where a specific score cannot be etiologically interpreted because this could mean numerous of combinations. There are 2850 combinations to reach a score of 70 in SF-36, although not all combinations are observed in a given sample (195). Crosby et al (201) present anchor-based and distribution based methods for capturing clinical meaningful change in health related quality of life. SF-36 is an example of an anchor-based global rating scale. The problem with this scale is recall-bias and influence of former events and current mood state. Also reliability and validity can be questioned because of recall-bias (202). A more severe health status is not equivalent
to impairment in QoL. These health factors are likely to be at least moderately correlated across a given sample, but can be quite discordant in individual cases (201).

Pain related to the hernia itself or pain after VHR, can be evaluated with the questionnaires already mentioned. The McGill Pain Questionnaire uses descriptive terms to assess pain. The word descriptors are transformed to numbers. The numbers must be interpreted individually and are not based on normative values from the general population (203). The Patient-Reported Outcomes Measurement Information System (PROMIS) measures key symptoms and health categorized in 5 domains including pain. The assessment of pain and its interference with patient’s behavior and social functioning is compared to normative data from the general US population (204).

In our study the most disabling symptom reported, was not always from the abdominal wall.

Table 4. Abdominal wall pain and other pain locations in surgery group (n=153)

<table>
<thead>
<tr>
<th>Abdominal wall pain main problem (%)</th>
<th>no</th>
<th>119 (77.8)</th>
<th>yes</th>
<th>34 (22.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main health problem (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td></td>
<td>32 (20.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hernia and/or abd.wall pain</td>
<td></td>
<td>34 (22.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>muscle/back/neck pain</td>
<td></td>
<td>31 (20.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip/knee</td>
<td></td>
<td>13 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>congestive heart disease</td>
<td></td>
<td>13 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pain and/or fatigue from cancer</td>
<td></td>
<td>2 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pain or discomfort multiple regions</td>
<td></td>
<td>13 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chronic obstructive pulm disease</td>
<td></td>
<td>9 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neurologic disorders</td>
<td></td>
<td>2 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>others</td>
<td></td>
<td>3 (2.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9.5.3 Patients satisfaction with outcome.

Satisfaction with outcome after surgery has a complexity not fully understood. It harbours emotional elements, but also expectations for speed and quality of recovery and also for the final result (127). Satisfaction after hernia surgery has been advocated as the sole primary goal (197).

The question of treatment expectancy has been studied and there where weak correlation between positive expectancy and optimism, but non between positive outcome and optimism. The same relationship was found between expectancy and anxiety both in a positive or negative manner (205). Due to editorials and the need for shortening of the final manuscript, the results from the QoLHS questionnaire were not presented in the final manuscript of Paper I.

Satisfaction was not predefined to just encompass the absence of discomfort or pain which could be misinterpreted in the paper. We did in fact give no rules for interpretation of the phrase, but made it clear to the patients to also include any complaints including bulging and cosmesis.

QoLHS had acceptable internal consistency, floor and ceiling effects. For both components respectively and QoLHS- sumscore, there were moderately strong inversely correlation to VAS and Transformed scale. The strongest association between SF 36 and QoLHS , was seen between Component I and Social Function sum score of the SF-36 and Component II and Bodily pain sum score. There were also strong correlation between Physical domains in SF 36 and QoLHS – sumscore. Concurrent validity revealed moderately strong correlations between “QoLHS” - sumscore. for all the SF-36 domains , Transformed scale and VAS.
Table 5. Correlation (rP) between QoLHS, SF-36 and AAS.

<table>
<thead>
<tr>
<th>QoLHS</th>
<th>SF36 PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
<th>AAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comp 1</td>
<td>0.48</td>
<td>0.44</td>
<td>0.40</td>
<td>0.43</td>
<td>0.44</td>
<td>0.52</td>
<td>0.49</td>
<td>0.41</td>
<td>-0.44</td>
</tr>
<tr>
<td>Comp 2</td>
<td>0.34</td>
<td>0.39</td>
<td>0.46</td>
<td>0.29</td>
<td>0.32</td>
<td>0.37</td>
<td>0.41</td>
<td>0.35</td>
<td>-0.32</td>
</tr>
<tr>
<td>Sumscore</td>
<td>0.49</td>
<td>0.49</td>
<td>0.50</td>
<td>0.44</td>
<td>0.46</td>
<td>0.53</td>
<td>0.54</td>
<td>0.45</td>
<td>-0.46</td>
</tr>
</tbody>
</table>

9.6 Life Orientation Test.

Personality is thought of as a stable characteristic like age and gender which are not malleable or situation-dependent. It has been identified as a major factor predicting QoL in different diseases (206). Optimism is considered to balance negative outcomes with the use of adaptive coping strategies, motivation to overcome adversity and a more realistic and positive oriented life perspective (207). Testing 84 studies there were strong evidence for optimism as a significant predictor of physical health outcome. The author also found stronger relationship to subjective measures to assess health compared to objective measures (208). Others have also elucidated the importance of preoperative information to provide more realistic expectations and thereby overcoming the influence of dispostional pessimistic trait (209). Furthermore high expectations to a surgical procedure may reflect general optimism and better perception of the result (127).

Bourne et al reported 86 % declaration of successful outcome after total hip arthroplasty, while only 55 % felt their expectations were met (210).

The correlation (Spearmans rho) between LOT and successful operation ( r = 0.302) in our cohort, contrasts LOT and satisfaction after operation ( r = 0.066). This may reflect that an optimistic trait gives a higher degree of success report, while satisfaction after surgery is far more complex (127).
9.7 Bacteriological considerations.

Until quiet recently, scientist have known that the diversity of microbial life is very great, but have had difficulty gaining access to the global diversity or the diversity in discrete ecosystems (211). With the evolvement of Sanger sequencing and later High Throughput Sequencing (HTS)/(NextGeneration Sequencing), there has become a revolution in the field of microbiological analysis. The DNA sequencing method used in our study is clone-based. 16S rRNA PCR products were cloned into a vector followed by Sanger dideoxy sequencing. Next- Generation Sequencing (NGS) techniques like Roche 454 pyrosequencing, has the ability to identify previously unknown DNA sequences and provide reads as long as the individual sequences in Sanger technique in addition to much higher amount of reads giving deeper and more profound analysis (212). A typical Sanger sequencing would generate $10^2$ sequences (600 – 900 bp of length) in contrast to HTS which can potentially generate $10^6$ – $10^9$ sequences (100 – 700 bp) per run (213). This could in fact increase the detection of contaminated meshes, reveal greater bacterial diversity together with more precise interpretation of bacterial ancestry. However, this technique was not available in our laboratory when we started our project. One could also argue that a small piece of mesh only reflects a glimpse of the entire biofilm covering all or some parts of the mesh.

The detection of specific taxa and calculation of bacterial diversity from the same echo system give different results due to methodological reasons. DNA extraction techniques, the use of specific or universal primers and PCR conditions may vary (84, 214). But even by using similar PCR-based techniques with the same specific primers, variation in detection rates of different species are observed. By using nested PCR sequencing and bacterial specific primers, even sparse bacterial DNA can be detected (215). The detection of bacterial DNA should be checked by scanning electronic microscopy (SEM) in order to confirm the presence of bacteria and not only genetic material. Microbial-specific DNA that are detected can
originate from living or dead microorganisms or from fragments after cell phagocytosis (216). Bacterial translocation across the intestinal wall can occur in 5-15% of normal individuals (217-219). Bacterial DNA seen in blood of healthy individuals, can be considered normal or as transmission from skin to blood during venipuncture despite meticulous hygiene (220). One could also argue that the detection of bacterial DNA is illusive and does not prove the existent of viable bacteria. In the mesenteric lymph node system any bacterial DNA will go further if the bacteria has survived the barriers of phagocytic activity proving that bacterial DNA from intestinal bacteria detected in mesh, most likely represent living bacteria from the intestine. More precision would be possible if a set of functional genes were used to ensure that the bacterial DNA located corresponds to a germ with an infective capacity (221). Due to lack of both blood and stool samples for 16S rRNA analysis, we cannot estimate the magnitude of periodontal or intestinal ancestry. Our eubacterial primer doesn’t contain the V2 region necessary for detection of some streptococci. The small fraction of the 16S rRNA gene sequences subjected to analysis in our study only suggest a role of periodontitis as a pathogenic factor explaining mesh biofilm constituents.

10. INNOVATION POTENTIALS AND PERSPECTIVES

Paper I

Recurrence can be considered a failure to cure and can be minimized with adequate treatment planning, experience and thoughtful surgical repair. At follow-up, all patients must be examined individually supplied with diagnostic imaging if necessary, to reveal the true incidence of abdominal wall complications and recurrence. Chronic abdominal wall pain must be considered an adverse effect of ventral hernia mesh repair and must be of more concern. This study hopefully will sensitize the hernia surgeon to pain determinants after ventral hernia repair.
Paper II
The outcome of ventral hernia mesh repair should be evaluated with validated QoL questionnaires encompassing a disease specific scoring system rather than generic questionnaires pay. The need of normative data from the general population is still awaited for full acceptance of the questionnaire of choice. By using one generic (Sf-36), one disease specific (AAS) in adjunct with satisfaction with the result and dispositional testing, the elements of patient reported outcome seems rather complex. The research should strive for more comprehensive assessment tools to bring better knowledge to the outcome of ventral hernia mesh repair.

Paper III
Abdominal pain after VHR without recurrence is most likely due to the fixation of the mesh and the mesh it self. Adhesions to mesh are common, even to meshes with antiadhesive barriers. Our study could not find any evidence for abdominal pain caused by adhesions. MRI is capable of delining adhesions between intestine and abdominal wall that are helpful in decision making and treatment planning before definitive ventral hernia mesh repair. Also the evaluation of mesh shrinkage of new fabrics and fixation methods is important regarding the question of fascial closure and overlap.

Paper IV
This is the first paper utilizing 16S rRNA gene sequencing to characterize bacterial biofilm in mesh implants of the abdominal wall. Hereby documenting great bacterial diversity, the implication for relapse, dormant infection, pain and immunological consequences must be addressed and further elucidated.

With next generation sequencing, mesh biofilm can be characterized more thoroughly. Hopefully, hernia mesh implants will become more inert and biocompatible with better overall outcome for the individual.
11. CONCLUDING REMARKS

This thesis looks into the physical, radiological and bacteriological consequences of ventral hernia mesh repair. The principal outcome of improved well-being for the individual, are governed by many factors of which most still will be on the table for ongoing research.
12. REFERENCES


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205. Younger J, Gandhi V, Hubbard E, Mackey S. Development of the Stanford Expectations


13. SUPPLEMENTARY

13.1 Operative technique OVHR and LVHR.

OVHR:
In open mesh repair, the incision was made over the hernia thus exposing the hernia content. The hernia sac was removed if possible. The peritoneum or posterior rectus sheet was dissected from the rectus muscle. The posterior sheet was not routinely closed with running absorbable sutures. The mesh was anchored in a retromuscular position with running non-resorbable transfascial sutures and seeking to achieve a 5 cm overlap. The anterior rectus sheet was not routinely closed. Neither intraperitoneal onlay mesh technique with Kugel patch nor mesh plug repair was applied. For small umbilical and epigastric hernias, the mesh was placed as described, but with minor modifications. Drains were used as per the surgeon’s preferences.

LVHR:
The access to the abdominal cavity was established with open introduction of a 12 mm trocar. Capnoperitoneum was established with a pressure of 12 mmHg. Two or three additional abdominal trocars 5 or 10 mm, were positioned on the surgeon’s side or on the contralateral side if appropriate. Adhesions were detached with scissors and occasionally with LigaSure® or ultracision. Fatty tissue on the inner abdominal wall was removed. The hernia sac was not routinely removed. The defect was measured. The mesh was introduced through the 12 mm trocar and placed over the defect with a minimum of 5 cm hernia overlap using tacks or transfascial non-absorbable sutures according to the surgeon’s preferences. The mesh did not necessarily cover the entire scar with a 5 cm overlap.
13.2 Nucleotide sequences with submission and accession numbers (Paper IV)

Table S1. The nucleotide sequences from mesh and plaque samples with submission number and accession number in GenBank

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<td>SUB1607043</td>
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<td>7</td>
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<td>9</td>
<td>KX376686-KX376699</td>
<td>SUB1607034</td>
</tr>
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<td>11</td>
<td>KX376621-KX376651</td>
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Plaque ID

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</table>
### 13.3 Bacterial taxa detected in mesh samples

#### Table S2. Bacterial taxa detected in mesh samples. Corresponding taxon detected in plaque is labelled “y”

<table>
<thead>
<tr>
<th>Phylum</th>
<th>Family</th>
<th>Taxa in mesh</th>
<th>Taxa in plaque</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Actinobacteria</strong></td>
<td><em>Actinomycetaceae</em></td>
<td><em>Actinobaculum</em> spp.</td>
<td>y</td>
<td>1</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Actinomyces naeslundii II</em></td>
<td>y</td>
<td>1</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Actinomyces odontolyticus</em></td>
<td>y</td>
<td>2</td>
<td>(0.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Actinomyces oris</em></td>
<td>y</td>
<td>1</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Actinomyces spp.</em></td>
<td>y</td>
<td>9</td>
<td>(2.52)</td>
</tr>
<tr>
<td><strong>Coriobacteriaceae</strong></td>
<td></td>
<td><em>Atopobium</em> spp.</td>
<td>y</td>
<td>3</td>
<td>(0.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Atopobium vaginae</em></td>
<td></td>
<td>3</td>
<td>(0.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Olsenella</em> spp.</td>
<td></td>
<td>3</td>
<td>(0.84)</td>
</tr>
<tr>
<td><strong>Corynebacteriaceae</strong></td>
<td></td>
<td><em>Corynebacterium diphtheriae</em></td>
<td></td>
<td>6</td>
<td>(1.68)</td>
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<tr>
<td></td>
<td></td>
<td><em>Corynebacterium matruchotii</em></td>
<td>y</td>
<td>3</td>
<td>(0.84)</td>
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<tr>
<td></td>
<td></td>
<td><em>Corynebacterium mucificiens</em></td>
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<td>(0.84)</td>
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<tr>
<td></td>
<td></td>
<td><em>Corynebacterium spp.</em></td>
<td></td>
<td>2</td>
<td>(0.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Corynebacterium urealticum</em></td>
<td>y</td>
<td>1</td>
<td>(0.28)</td>
</tr>
<tr>
<td><strong>Micrococcaceae</strong></td>
<td></td>
<td><em>Kocuria</em> spp.</td>
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<td>1</td>
<td>(0.28)</td>
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<tr>
<td></td>
<td></td>
<td><em>Microbacterium</em> spp.</td>
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<td>1</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Rothia aeria</em></td>
<td>y</td>
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<tr>
<td><strong>Propionibacteriaceae</strong></td>
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<td><em>Propionibacterium acnes</em></td>
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<td></td>
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<td>(0.28)</td>
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<td></td>
<td><em>pseudoalcaligenes</em></td>
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<td><strong>Bacteroidetes</strong></td>
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<td><em>Bacteroidales</em> spp.</td>
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<td>1</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td><em>Flavobacteriaceae</em></td>
<td><em>Capnocytophaga</em> sputigena</td>
<td>y</td>
<td>1</td>
<td>(0.28)</td>
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<tr>
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<td>3</td>
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</tr>
<tr>
<td><strong>Prevotellaceae</strong></td>
<td></td>
<td><em>Prevotella</em> histicola</td>
<td>y</td>
<td>2</td>
<td>(0.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Prevotella</em> maculosa</td>
<td>y</td>
<td>2</td>
<td>(0.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Prevotella oris</em></td>
<td>y</td>
<td>3</td>
<td>(0.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Prevotella</em> spp.</td>
<td>y</td>
<td>8</td>
<td>(2.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Prevotella veroralis</em></td>
<td>y</td>
<td>3</td>
<td>(0.84)</td>
</tr>
<tr>
<td><strong>Firmicutes</strong></td>
<td><em>Aerococcaceae</em></td>
<td><em>Abiotrophia</em> defectiva</td>
<td>y</td>
<td>2</td>
<td>(0.56)</td>
</tr>
<tr>
<td></td>
<td><em>Clostridiales</em></td>
<td><em>Clostridiales</em> spp.</td>
<td>y</td>
<td>3</td>
<td>(0.84)</td>
</tr>
<tr>
<td></td>
<td><em>Enterococcaceae</em></td>
<td><em>Enterococcus</em> casseliflavus</td>
<td>y</td>
<td>1</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Enterococcus</em> faecalis</td>
<td></td>
<td>1</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Enterococcus italicus</em></td>
<td>y</td>
<td>1</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td><em>Peptostreptococcaceae</em></td>
<td><em>Filifactor</em> alocis</td>
<td>y</td>
<td>1</td>
<td>(0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Finegoldia</em> magna</td>
<td></td>
<td>3</td>
<td>(0.84)</td>
</tr>
<tr>
<td><strong>Staphylococcaceae</strong></td>
<td></td>
<td><em>Staphylococcus</em> aureus</td>
<td>y</td>
<td>6</td>
<td>(1.68)</td>
</tr>
<tr>
<td>Family</td>
<td>Species</td>
<td>Count</td>
<td>Relative Abundance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------------------</td>
<td>-------</td>
<td>--------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Staphylococcaceae</strong></td>
<td>Staphylococcus caprae</td>
<td>y</td>
<td>6 (1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staphylococcus epidermidis</td>
<td>y</td>
<td>6 (1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Staphylococcus warneri</td>
<td></td>
<td>5 (1.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactococcus lactis</td>
<td></td>
<td>7 (1.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus anginosus</td>
<td>y</td>
<td>2 (0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus australis</td>
<td>y</td>
<td>14 (3.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus constellatus</td>
<td>y</td>
<td>2 (0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus cristatus</td>
<td>y</td>
<td>6 (1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus gordonii</td>
<td>y</td>
<td>2 (0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus infantis</td>
<td>y</td>
<td>4 (1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus mitis</td>
<td>y</td>
<td>4 (1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus mitis bv 2</td>
<td>y</td>
<td>10 (2.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus oligofermentans</td>
<td>y</td>
<td>6 (1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus oralis</td>
<td>y</td>
<td>8 (2.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus parasanguinis I</td>
<td>y</td>
<td>1 (0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus parasanguinis II</td>
<td>y</td>
<td>6 (1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus peroris</td>
<td>y</td>
<td>2 (0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus salivarius</td>
<td>y</td>
<td>3 (0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus sanguinis</td>
<td>y</td>
<td>3 (0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus sinensis</td>
<td>y</td>
<td>6 (1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus spp.</td>
<td>y</td>
<td>14 (3.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Streptococcus vestibularis</td>
<td>y</td>
<td>2 (0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Veillonellaceae</strong></td>
<td>Veillonella disppar</td>
<td>y</td>
<td>5 (1.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Veillonella parvula</td>
<td>y</td>
<td>6 (1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fusobacteria</strong></td>
<td>Fusobacterium nucleatum ss vin</td>
<td>y</td>
<td>3 (0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fusobacterium spp.</td>
<td>y</td>
<td>1 (0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proteobacteria</strong></td>
<td>Lautropia mirabilis</td>
<td></td>
<td>6 (1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ralstonia pickettii</td>
<td></td>
<td>6 (1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ralstonia spp.</td>
<td></td>
<td>4 (1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Caulobacteraceae</strong></td>
<td>Brevundimonas diminuta</td>
<td></td>
<td>1 (0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comamonadaceae</strong></td>
<td>Delftia acidovorans</td>
<td></td>
<td>2 (0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td>Enterobacter cancerogenus</td>
<td></td>
<td>5 (1.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enterobacter hormaechei</td>
<td>y</td>
<td>7 (1.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enterobacter sakazakii</td>
<td></td>
<td>2 (0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Escherichia coli</td>
<td></td>
<td>4 (1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Klebsiella pneumoniae</td>
<td>y</td>
<td>1 (0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kluyvera ascorbata</td>
<td></td>
<td>4 (1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yersinia pestis</td>
<td></td>
<td>4 (1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moraxellaceae</strong></td>
<td>Acinetobacter baumannii</td>
<td>y</td>
<td>3 (0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acinetobacter spp.</td>
<td>y</td>
<td>1 (0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moraxella osloensis</td>
<td>y</td>
<td>3 (0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neisseriaceae</strong></td>
<td>Eikenella correodens</td>
<td>y</td>
<td>2 (0.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kingella denitrificans</td>
<td></td>
<td>1 (0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kingella oralis</td>
<td>y</td>
<td>1 (0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kingella spp.</td>
<td></td>
<td>1 (0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pasteurellaceae</strong></td>
<td>Terrahaemophilus</td>
<td>y</td>
<td>1 (0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family</td>
<td>Genus</td>
<td>Species</td>
<td>Count</td>
<td>Score</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>----------------------------------</td>
<td>-------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Pseudomonadaceae</td>
<td>Pseudomonas</td>
<td>fluorescens</td>
<td>3</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pseudomonas</td>
<td>pseudoalcaligenes</td>
<td>2</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Sphingomonadaceae</td>
<td>Sphingomonas</td>
<td>spp.</td>
<td>12</td>
<td>3.36</td>
<td></td>
</tr>
<tr>
<td>Xanthomonadaceae</td>
<td>Stenotrophomonas</td>
<td>maltophilia</td>
<td>2</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Spirochaetes</td>
<td>Spirochaetaceae</td>
<td>Treponema spp.</td>
<td>y</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Synergistetes</td>
<td>Synergistetes</td>
<td>Fretibacterium spp.</td>
<td>y</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>60</td>
<td>357</td>
<td></td>
</tr>
</tbody>
</table>

14. APPENDIX

14.1 ASA-score

**Figure S1.** American Society of Anesthesiologist’s (ASA) Physical Status Classification

<table>
<thead>
<tr>
<th>ASA I</th>
<th>A normally healthy patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA II</td>
<td>A patient with mild systemic disease</td>
</tr>
<tr>
<td>ASA III</td>
<td>A patient with severe systemic disease that is not incapacitating</td>
</tr>
<tr>
<td>ASA IV</td>
<td>A patient with an incapacitating systemic disease that is a constant threat to life</td>
</tr>
<tr>
<td>ASA V</td>
<td>A moribund patient who is not expected to survive for 24 hours with or without operation</td>
</tr>
</tbody>
</table>

Adopted from Owens et al (222)
**Din Helse og Trivsel**

**INTRODUKSJON:** Dette spørreskjemaet handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål. Takk for at du fyller ut dette spørreskjemaet.

For hvert av de følgende spørsmålene vennligst sett et (X) i den ene luken som best beskriver ditt svar.

1. **Stort sett, vil du si at din helse er:**
   - [ ] Utmerket
   - [ ] Meget god
   - [ ] God
   - [ ] Nokså god
   - [ ] Dårlig

2. **Sammenlignet med for ett år siden**, hvordan vil du si at din helse stort sett er **nå**?
   - [ ] Mye bedre nå enn for ett år siden
   - [ ] Litt bedre nå enn for ett år siden
   - [ ] Omtrent den samme som for ett år siden
   - [ ] Litt dårligere nå enn for ett år siden
   - [ ] Mye dårligere nå enn for ett år siden

3. **De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå?** Hvis ja, hvor mye?

   a. Anstrengende aktiviteter som å løpe, løfte tungt gjenstander, delta i anstrengende idrett
   - [ ] Ja, begrenser meg mye
   - [ ] Ja, begrenser meg litt
   - [ ] Nei, begrenser meg ikke i det hele tatt

   b. Moderate aktiviteter som å flytte et bord, støvsume, gå en tur eller drive med hagearbeid
   - [ ]

   c. Løfte eller bære en handlekurv
   - [ ]

   d. Gå opp trappen flere etasjer
   - [ ]

   e. Gå opp trappen en etasje
   - [ ]

   f. Bøy deg eller sitte på huk
   - [ ]

   g. Gå mer enn to kilometer
   - [ ]

   h. Gå noen hundre meter
   - [ ]

   i. Gå hundre meter
   - [ ]

   j. Vaske eller kle på deg
   - [ ]
4. I løpet av de siste 4 ukene, hvor ofte har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

   a. Du har måttet redusere tiden du har brukt på arbeid eller på andre gjøremål  
   b. Du har utrettet mindre enn du hadde ønsket  
   c. Du har vært hindret i å utføre visse typer arbeid eller gjøremål  
   d. Du har hatt problemer med å gjennomføre arbeidet eller andre gjøremål (for eksempel fordi det krevede ekstra anstrengelser)  

5. I løpet av de 4 siste ukene, hvor ofte har du hatt noen av de følgende problemer i ditt arbeid eller andre av dine daglige gjøremål på grunn av følelsesmessige problemer (som for eksempel å være deprimert eller engstelig)?

   a. Du har måttet redusere tiden du har brukt på arbeid eller på andre gjøremål  
   b. Du har utrettet mindre enn du hadde ønsket  
   c. Du har utført arbeidet eller andre gjøremål mindre grundig enn vanlig  

6. I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

   Ikke i det hele tatt    Litt    En del    Mye    Svært mye  

7. Hvor sterke krepslige smerter har du hatt i løpet av de siste 4 ukene?

   Ingen    Meget svake    Svake    Moderate    Sterke    Meget sterke  

8. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

   Ikke i det hele tatt    Litt    En del    Mye    Svært mye
9. Disse spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste 4 ukene har du:

<table>
<thead>
<tr>
<th></th>
<th>Hele tiden</th>
<th>Mye av tiden</th>
<th>En del av tiden</th>
<th>Litt av tiden</th>
<th>Ikke i det hele tatt</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Felt deg full av in?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Felt deg veldig nervøs?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Vært så langt nede at ingenting har kunnet munter deg opp?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Felt deg rolig og harmonisk?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Hatt mye overskudd?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Felt deg nedfor og deprimert?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Felt deg sliten?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h. Felt deg glad?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Felt deg trett?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. I løpet av de siste 4 ukene, hvor ofte har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?

<table>
<thead>
<tr>
<th></th>
<th>Hele tiden</th>
<th>Mye av tiden</th>
<th>En del av tiden</th>
<th>Litt av tiden</th>
<th>Ikke i det hele tatt</th>
</tr>
</thead>
</table>

11. Hvor RIKTIG eller GAL er hvert av de følgende påstander for deg?

<table>
<thead>
<tr>
<th></th>
<th>Helt riktig</th>
<th>Delvis riktig</th>
<th>Vet ikke</th>
<th>Delvis gal</th>
<th>Helt gal</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Det virker som om jeg blir syk litt lettere enn andre</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Jeg er like frisk som de fleste jeg kjenner</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Jeg tror at helsen min vil forverres</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Jeg har utmerket helse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

_Takk for at du fylte ut dette spørreskjemaet!_
### Activities assessment scale

<table>
<thead>
<tr>
<th>Pasient ID</th>
<th>Life orientation test</th>
<th>Life orientation test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dato</td>
<td>Life orientation test</td>
<td>Life orientation test</td>
</tr>
</tbody>
</table>

Angi hvor store problemer det har vært å utføre følgende aktiviteter de siste 30 dagene

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikke vanskelig</td>
<td>Litt vanskelig</td>
<td>Ganske vanskelig</td>
<td>Svært vanskelig</td>
<td>Umulig å gjøre</td>
<td>Ikke gjort</td>
<td></td>
</tr>
</tbody>
</table>

- Ligg i sengen
- Sitte i en stol
- Komme seg ut av sengen eller opp av stolen
- Strekke seg etter noe på bordet eller på en hylle
- Bøyse seg
- Løfte 1-3 kg
- Gå omkring i hjemmet
- Å gå i trapper
- Å gå utendørs eller gå på arbeid
- Delta i svært lette aktiviteter som se på TV, diskusjoner, spille kort etc
- Delta i lette fysiske aktiviteter som matlaging, støvtørk, besøke venner
- Delta i moderate fysiske aktiviteter som bilvask, gå en liten tur etc
- Delta i harde fysiske aktiviteter som vektøvning, løping etc
For hvert punkt setter du et kryss i den ruten som passer best slik du for tiden opplever deg selv. Utsagnene her er skrevet i jeg form og du setter et kryss alt etter hvor enig/uenig du er. Vennligst svar på hvert spørsmål så ærlig du kan.

<table>
<thead>
<tr>
<th>Helt enig</th>
<th>Nokså enig</th>
<th>Både/og</th>
<th>Nokså uenig</th>
<th>Svært uenig</th>
</tr>
</thead>
</table>

1) I usikre tider forventer jeg alltid det beste.

2) Det er lett for meg å slappe av.

3) Hvis noe kan gå galt for meg, så gjør det det.

4) Jeg er alltid optimistisk i forhold til min fremtid.

5) Jeg trives med mine venner.

6) Det er viktig for meg å være beskjæftiget.

7) Jeg forventer nesten aldri at gode ting skal skje meg.

8) Jeg blir lett opprørt.

9) Jeg forventer sjelden at gode ting skal skje.

10) Når alt kommer til alt forventer jeg at det skal skje flere gode ting enn dårlige ting med meg.
Skjema livskvalitet ved etterkontroll av pasienter operert for brokk.

1. Var det å operere brokket som du hadde forventet:

2. Har du noen gang angret på at du opererte brokket?

3. Synes du at du fikk nok informasjon om hva en brokkoperasjon ville innebære?

4. Har du hatt plager etter brokkoperasjonen?


6. Hvordan vil du karakterisere din evne til fysisk aktivitet etter brokkoperasjonen


8. Alt i alt; er du fornøyd med resultatet etter operasjonen?
   1. Nei  2. Ja

Component I: Item 3, 6, 7, 8

Component II: Item 1, 2, 4, 5
14.6 Charlson Comorbidity scoring system

One Point

- □ Myocardial infarction (history, not ECG changes only)
- □ Congestive heart failure
- □ Peripheral disease (includes aortic aneurysm ≥ 6 cm)
- □ Cerebrovascular disease: CVA with mild or no residua or TIA
- □ Dementia
- □ Chronic pulmonary disease
- □ Connective tissue disease
- □ Peptic ulcer disease
- □ Mild liver disease (without portal hypertension, includes chronic hepatitis)
- □ Diabetes without end-organ damage (excludes diet-controlled alone)

Two Points

- □ Hemiplegia
- □ Moderate or severe renal disease
- □ Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
- □ Tumor without metastasis (exclude if > 5 y from diagnosis)
- □ Leukemia (acute or chronic)
- □ Lymphoma

Three Points

- □ Moderate or severe liver disease

Six Points

- □ Metastatic solid tumor
- □ AIDS (not just HIV positive)

Age 50 – 59: 1 point, Age 60-69: 2 points, Age 70 -79: 3 points and age 80-89: 4 points.
14.7 Dindo Clavien scoring on postoperative complications

Grade I: Very mild deviation from a normal postoperative course without the need of any medical or other therapeutic intervention besides regularly used regimes with antipyretic, antiemetics, analcetics, electrolytes, diuretics but also including wounds opened bedside.

Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications
Blood transfusions and total parenteral nutrition are also included

Grade III: Requiring surgical, endoscopic or radiological intervention
Grade IIIa: Intervention not under general anesthesia
Grade IIIb: Intervention under general anesthesia

Grade IV: Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa: Single organ dysfunction (including dialysis)
Grade IVb: Multiorgan dysfunction

Grade V: Death of a patient
15. ERRATUM

Paper I:

Unfortunately in table 14 in the published manuscript, the term “age>60” is misplaced for clinical recurrence (adjusted model) which is correct.

Paper III:

The reference (16) is wrong. The correct citation is Lang et al.
16. PAPERS I-IV