# SWENOTECA TESTIGO
# Quality of life study

## RESEARCH PROTOCOL

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# 2. INVOLVED CENTERS

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## 3. TITLE OF THE STUDY

***SWENOTECA-TESTIGO*** *(**Test**icular Cancer Treatment: Assising Quality of Life in **Go**od Prognosis Metastastic Disease)*

# 4. BACKGROUND

## 4.1 TESTICULAR CANCER

Testicular cancer (seminoma and non-seminoma) is the most common malignancy among young men. Every year, 300 Norwegian and 370 Swedish men are diagnosed with testicular cancer(1). In Germany, the incidence is about 4,000. The Swedish and Norwegian Testicular Cancer Group (SWENOTECA) was founded in 1981 to provide treatment protocols and follow-up schemes of men with germ-cell testicular cancer. The development of treatment for testicular cancer is a medical success-story and today's 5-year survival rates have reached beyond 95% in most European countries(2). Patients with localized disease are recommended surveillance or adjuvant chemotherapy after orchiectomy based on risk factors for recurrence, and the 10-year overall survival rates approach 100% in this group. Remarkably, even among men with metastatic disease the 10-year overall survival is close to 90%(3). The excellent prognosis in men with metastatic disease has primarily been achieved by the introduction of cisplatin in the late 1970s(4). Ever since the mid 1980s, cisplatin in combination with bleomycin and etoposide (BEP) has been the standard treatment in metastatic testicular cancer(5, 6). Historically, radiotherapy has also been widely used for treating patients with small-volume metastatic seminoma and in the adjuvant setting but this treatment option has largely been abandoned due to an increased risk of premature mortality due to second cancers (7).

While the long-term survival in patients with testicular cancer is excellent, the general health and quality of life of these young men may be impaired by treatment-related side-effects. Cisplatin-based chemotherapy is associated with acute risks which can be severe and even life-threatening. These include neutropenic infections, acute thromboembolism, pneumonitis, and pulmonary fibrosis. The late risks of chemotherapy include an increased risk of premature death due to secondary cancers (7). Other long-term complications include cardiovascular disease, neurotoxicity, ototoxicity, and chronic fatigue (8). Consequently, there is an urgent need for refining treatment for men with low-volume metastatic testicular cancer as they might maintain the excellent survival without harmful side-effects from chemotherapy if they undergo surgery instead(9).

## 4.2 RETROPERITONEAL LYMPH NODE DISSECTION

Lymph node metastases are present in about 25% of the patients, and typically occur in the retroperitoneum close to the aorta and caval vein. A retroperitoneal lymph node dissection (RPLND) is sometimes performed to resect these nodes, either in a primary (chemo-naïve) setting or following three or four courses of BEP (post-chemotherapy). A post-chemotherapy RPLND imposes some technical challenges due to the desmoplastic reaction of the tissue following chemotherapy, which in turn entails an increased risk of surgical complications (10). However, a primary RPLND is generally technically less demanding and can often be performed minimally invasively in case of low-stage metastatic disease. Robot-assisted RPLND, with the recognized benefits of minimally invasive surgery in terms of reduced bleeding and shorter hospital stays, is a valid option in referral centers (11).

Since 2017, RPLND is centralized to two centers in Sweden, Karolinska University Hospital Huddinge in Stockholm and Sahlgrenska University Hospital in Gothenburg. In Norway, RPLND is centralized to three centers: Oslo University Hospital in Oslo, Haukeland University

Hospital in Bergen, and St Olav's University Hospital in Trondheim. All patients are discussed at a national multidisciplinary board ahead of surgery. Imaging is reviewed and patients are selected for RPLND depending on type of testicular cancer, clinical stage, and response to possible previous treatment according to clinical guidelines (12). As for the study center in Cologne, patients are referred to this high-volume center from all over Europe to undergo RPLND and treatment plans are discussed in a multidisciplinary meeting.

Regarding lymphatic involvement, patients with metastatic lymph nodes below the diaphragm measuring <2 cm, 2-5 cm, and 5-10 cm, and >10 cm are staged II A, B, C, and D, respectively, according to the Royal Marsden staging system (13). All patients are also stratified into prognosis-groups (good/intermediate/poor) based on tumor marker status and location of metastases according to the IGCCCG system (14).

### 4.3 TREATMENT OF SEMINOMA WITH LIMITED METASTATIC BURDEN

The optimal treatment for patients with stage IIA-B seminoma is under debate. Previously, chemotherapy or radiation were considered standard therapy but concerns regarding toxicity have caused the pendulum to swing towards surgery. A primary RPLND is now recommended in the SWENOTECA guidelines for patients with stage II A-B (<3 cm) seminoma. Studies are ongoing to evaluate the oncological outcome following primary RPLND in this setting. According to these studies, recurrence rates are not entirely insignificant (10-30%) but it seems that chemotherapy can be spared in a major proportion of patients. Of note, proper selection is mandatory(15-17).

## 5. RATIONALE OF THE STUDY

The current SWENOTECA guidelines from 2020 state that patients with seminoma stage IIA-IIB with <3 lymph nodes <30 mm in any dimension should be recommended a primary RPLND rather than the previously considered standard treatment, chemotherapy. The rationale behind this change is to reduce the number of patients at risk of acute and long-term side-effects from chemotherapy. We aim to perform a quality-of-life assessment to determine whether the change from chemotherapy to surgery is justified regarding short- and long-term quality-of-life.

## 6. STUDY DESIGN

### 6.1 METHODS

An explorative study is designed, using questionnaires at different timepoints during and after treatment. Data on diagnosis, treatment received, and complications will be gathered from hospital journals and the SWENOTECA databases. Study participants will be enrolled prospectively at 12 referral centers in Sweden, Norway and Germany.

### 6.2 STUDY POPULATION AND PATIENT GROUPS

Two study-groups are formed to answer the research question. The surgery-group consist of patients >18 years undergoing an open or minimally invasive primary RPLND in Norway, Sweden or in Cologne, Germany, due to seminoma stage II A/B (<30 mm in any dimension). Patients undergoing a primary RPLND due to a retroperitoneal relapse of seminoma are also included. The control-group include patients >18 years scheduled for 3-4 courses of

chemotherapy due to a newly diagnosed good-prognosis metastatic germ cell tumor (nonseminoma or seminoma) at any of the study centers. Patients in the control-group should be chemotherapy naïve at inclusion. Exclusion criteria in both groups include previous chemotherapy (including adjuvant chemotherapy), previous RPLND, and practical considerations such as not being able to read and sign informed consent or understand the questionnaires.

### 6.3 SAMPLE SIZE

The patient cohort will consist of 80 patients in each study-group.

## 7. OBJECTIVES

### 7.1 PRIMARY OBJECTIVE

- To test the hypothesis that patients who undergo surgery (primary RPLND) for low-stage seminoma fare better in terms of patient-reported health-related quality-of-life (HRQOL) compared to patients treated with chemotherapy.

### 7.2 SECONDARY OBJECTIVE

- To compare the incidence and degree of patient-reported fatigue across study-groups during the first three years after initiating treatment.
- To assess effects of treatment on ejaculatory function in both study-groups.
- To compare rate of treatment-related short and long-term complications.
- To assess length of hospital-stay in both study-groups.
- To evaluate progression-free survival (PFS) in both study-groups and describe patterns of recurrence and treatments received.

## 8. ENDPOINTS

| | | |
|---|---|---|
| Primary outcome | 1. | Changes across study-groups in global HRQOL after treatment as measured by the EORTC QLQ-C30 with the testicular cancer-specific supplement EORTC QLQ-TC26. |
| Secondary outcomes | 2. | Differences in fatigue across study-groups as measured by the Fatigue Questionnaire (FQ). |
| | 3. | Differences across study-groups in patient-reported prevalence of retrograde ejaculation as assessed by supplementary questions. |
| | 4. | Rate of doctor-reported complications related to treatment in the study-groups. |
| | 5. | Length of hospital stay during treatment in each study-group. |
| | 6. | Differences in quality adjusted life years across study-groups as measured by the EQ-5D-5L tool |
| | 7. | PFS in both study-groups. * |

*Longer follow-up than 3 years may be allowed for this specific research question.

# 9. ANALYZED CRITERIA

## 9.1 MAIN VARIABLES OF THE PRIMARY ANALYSIS

Data on global HRQOL will be assessed equally in both study-groups using validated questionnaires at baseline (ideally <4 weeks before surgery/chemotherapy), after 3 months, 6 months, 1 year and 3 years (calculated from day of surgery or first day of systemic treatment, respectively). In addition to data from HRQOL questionnaires, stratification variables expected to have an association with the outcome will be assessed (Table 1). Quality-of-life data will be scored and analysed across study-groups using t-test or chi-square. First, mean baseline scores for each group will be calculated. After treatment, the mean change score from baseline will be calculated. Paired sampled t-test will be used for statistical comparison.

**Table 1.** Scheme of assessments for the primary analysis.

| | | Surgery group | | | | | | Control group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | Day of RPLND | 3 m | 6 m | 1 y | 2 y | Baseline | Day 1of Chemotherapy | 3 m | 6 m | 1 y | 2 y |
| Main outcome | HRQOL data (EORTC QLQ C30/TC 26) | x | | x | x | x | x | x | | x | x | x | x |
| Stratification variables | Surgical modality and template | | x | | | | | | | | | | |
| | Use of adjuvant chemotherapy post-operatively | | | x | | | | | | | | | |
| | Choice of primary chemotherapy | | | | | | | | x | | | | |
| | Age | | x | | | | | | x | | | | |
| | Hormone levels | x | | | | x | x | x | | | | x | x |
| | Comorbidity (Charlson score) | x | | x | x | x | x | x | | x | x | x | x |
| | Tobacco use | x | | x | x | x | x | x | | x | x | x | x |
| | Relationship status | x | | x | x | x | x | x | | x | x | x | x |
| | Duration of sick leave | x | | x | x | x | x | x | | x | x | x | x |
| | Occupational status | x | | x | x | x | x | x | | x | x | x | x |
| | Educational level | x | | | | | | x | | | | | |
| | Fatherhood status | x | | | x | x | x | x | | | x | x | x |

EORTC QLQ C30/TC 26
Data from medical charts
Supplementary questionnaire

## 9.2 MAIN VARIABLES OF THE SECONDARY ANALYSIS

The secondary analysis concern domains of HRQOL that are well-known to be important issues for testicular cancer patients. Fatigue will be assessed through the Fatigue Questionnaire (FQ) and ejaculatory function will be assessed by supplementary questions. Health economy will be evaluated through the EQ-5D-5L tool. Timepoints are the same as for the primary analysis. Variables that may be associated with the outcome will be assessed to be able to control for confounding (comorbidity, relationship status, occupational status, educational level, sick leave, smoking habits) (Table 2).

Doctor-reported complications to treatments will be gathered from medical charts and quality registers. The Clavien-Dindo (CD) classification system (18) and the Common Terminology Criteria for Adverse Events (19) will be used for surgically and chemotherapy-treated patients, respectively. Complications will be categorized into short-term (within 90-day following start of treatment) and long-term (from 90 days until 3 years after treatment) in the analysis. Data on oncological outcome after 1 and 3 years will be collected from medical records and quality registers. Survival analyses regarding progression will be performed using the Kaplan-Meier estimator, and comparisons between the study-groups will be made using the log-rank test. A Cox model will be used to adjust for covariates (age, tumor size, clinical stage at diagnosis, and tumor marker status).

**Table 2.** Scheme of assessments for the secondary analyses.

| | | Surgery group | | | | | | Control group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | Day of RPLND | 3 m | 6 m | 1 y | 2 y | Baseline | Day 1 chemotherapy | 3 m | 6 m | 1 y | 2 y |
| Main outcome | HRQOL data (Fatigue) | x | | x | x | x | x | x | | x | x | x | x |
| | Ejaculatory function | x | | | x | x | x | x | | | x | x | x |
| | Surgical complications (Clavien-Dindo) | | | x | x | x | x | | | | | | |
| | Adverse events after systemic treatment (CTCAE) | | | | | | | | | x | | x | x |
| | Recurrence and site | | | | | x | x | | | | | x | x |
| | Health economy | x | | x | x | x | x | x | | x | x | x | x |
| Stratification variables | Age | | x | | | | | | x | | | | |
| | Clinical stage | x | | | | | | x | | | | | |
| | Pathological features of testicular primary | x | | | | | | x | | | | | |
| | Pathological features of RPLND specimen | | | x | | | | | | | | | |
| | Largest axial diameter of retroperitoneal mass | x | | | | | | x | | | | | |
| | Tumor marker status | x | | | x | x | x | x | | | x | x | x |
| | Other treatments received due to recurrence | | | | | x | x | | | | | x | x |
| | Hormone levels | x | | | | x | x | x | | | | x | x |
| | Comorbidity (Charlson score) | x | | x | x | x | x | x | | x | x | x | x |
| | Tobacco use | x | | x | x | x | x | x | | x | x | x | x |
| | Relationship status | x | | x | x | x | x | x | | x | x | x | x |
| | Duration of sick leave | x | | x | x | x | x | x | | x | x | x | x |
| | Occupational status | x | | x | x | x | x | x | | x | x | x | x |
| | Educational level | x | | | | | | x | | | | | |
| | Fatherhood status | x | | | x | x | x | x | | | x | x | x |

Fatigue Questionnaire
Supplementary questionnaire
EQ-5D-5L (health economy)
Data from medical chart

# 10. VISITS AND EXAMINATIONS

## 10.1 RECRUITMENT AND INFORMED CONSENT

Patients scheduled for a primary RPLND as indicated above will be asked for participation in the study (surgery-group) at the first pre-operative visit. The treating urologist and/or study nurse will make sure all necessary information is given to the patient. For the control-group on the other hand, patients are recruited in the oncological department and asked for participation after the decision has been made regarding 3 cycles of BEP/4 cycles of EP due to a good-prognosis nonseminoma or seminoma as indicated above. Obtaining written informed consent is mandatory for all study participants.

## 10.2 FORMS AND ADMINISTRATION OF QUESTIONNAIRES

The questionnaires will be administered at baseline, after 3 months following RPLND/first day of systemic treatment, after 6 months, after 1 year and after 3 years. These timepoints coincide with regular follow-up visits according to guideline recommendations. The questionnaires can easily be distributed and collected at the visit. An alternative to filling in the form at the visit is to receive an SMS with an HTML link to an on-line version of the questionnaire. All forms and the database generated are managed in a secured web application (RedCap). Three validated questionnaires are selected to assess HRQOL in the present study:

1. **EORTC QLQ-C30** is a valid tool that is meant to assess some of the different aspects that depict the quality of life of cancer patients. It is widely understood across language versions (20). It is considered comprehensive and relevant for patients with localized to advanced cancer and includes assessment of general functional health, symptom burden and HRQOL (21).

2. **EORTC QLQ-TC26** is a testicular-cancer specific supplement to EORTC QLQ-C30. It covers treatment related side-effects, physical limitations, sexual activity and function, perspectives on the future, fertility issues, masculinity, body image, and job/educational problems (22).

3. **Fatigue Questionnaire (FQ)** is a validated instrument developed to detect fatigue in epidemiological studies (23). It measures physical fatigue and mental fatigue, and the sum is referred to as total fatigue. The responses are set up as “less than usual”; “same as usual”; “more than usual”; and “much more than usual.”

4. **EQ-5D-5L** is a validated instrument to measure health economy with five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and five response categories for each of the dimensions. It also includes a visual analogue scale to record the patient's self-rated health(24).

In addition to the above-mentioned validated tools, we will use **supplementary questions** to assess relationship status, occupational status, educational level, sick leave, smoking habits, fatherhood attempt and fatherhood success, and retrograde (dry) ejaculation.

### 10.3 HOW TO ENSURE GOOD COMPLIANCE

To ensure completeness of HRQOL data, especially in the surgery-group which is thought to take longer to recruit due to fewer patients, all centers performing RPLND in Sweden and Norway should be participating. The high-volume center of Cologne is expected to contribute with a significant number of patients. Completion of forms are clearly essential for the implementation of the study, and treating doctors and study nurses should emphasize this to patients. Reminders will be sent after 4 weeks in case study participants do not respond to the questions asked. In each study center, a named person is designated to take responsibility for administrating the forms and for the checking of completeness.

### 10.4 GENERALIZABILITY

All Swedish and Norwegian testicular cancer patients will be registered in the SWENOTECA register. Patients included in this study will be linked to the SWENOTECA register and other nationwide register data to pinpoint selection mechanisms such as age, sex, region and other sociodemographic and health related factors. The groups will be compared to investigate selection mechanisms for patients included in the study in relation to all seminoma patients diagnosed in Sweden. This will be important for generalizability measures for the study. Potential differences in progression-free survival between the included and not included patients can also be investigated. Linkage between other nationwide registers also offers availability to long term follow up after completion of the study regarding both outcome, late effects and sociodemographic outcomes.

## 11. ESTIMATED DURATION OF THE STUDY

After completion of ethical approval and study preparation at all centers, recruiting of study participants is expected to begin in spring 2025. Patients will be followed for two years, and we believe that it takes up to three years to include 80 patients in each arm. Hence, recruitment of new study participants is expected to be ongoing until 2028, and long-term follow-up will be completed in 2030. A longer follow-up may be needed to explore potential differences regarding PFS and recurrence patterns why a somewhat longer follow-up may be needed for this specific research questions.

## 12. ETHICAL CONSIDERATIONS

The optimal treatment for low-stage metastatic seminoma is controversial. There is an increasing interest for primary RPLND in patients with low-volume metastatic seminoma to overcome the potential risk of side-effects from chemotherapy in these young men with excellent survival. This assumption, however, needs to be validated. The present study will provide important new insights into different treatments´ effects on quality-of-life. We are aware that some sensitive questions may trigger negative emotions and psychological harm. We also realize that some questions are of intimate character and that there might be a risk of violating personal integrity. However, we believe that the benefits of the study outweigh the potential negative aspects. Risks and benefits of the study will be discussed with study participants ahead of inclusion, and complete information of the procedures will be given orally and in written form. Withdrawal from the study will be possible at any time.

This study will be conducted in compliance with the protocol and in accordance with the ethical principles in the Declaration of Helsinki and in accordance with GCP rules.
It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each patient participating in this study and explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

## 13. COMMUNICATION OF RESULTS

We aim at publishing the main results in a medical journal within the field. In addition, we aim to communicate the results to the medical community through conference papers, in seminars and in popular science sources. The findings will also be taken into consideration in future versions of the SWENOTECA clinical guidelines and communicated to future patients.

# REFERENCES

1. Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff ML, Klint A, et al. NORDCAN--a Nordic tool for cancer information, planning, quality control and research. Acta Oncol. 2010;49(5):725-36.
2. Tandstad T, Dahl O, Cohn-Cedermark G, Cavallin-Stahl E, Stierner U, Solberg A, et al. Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. J Clin Oncol. 2009;27(13):2122-8.
3. Tandstad T, Smaaland R, Solberg A, Bremnes RM, Langberg CW, Laurell A, et al. Management of seminomatous testicular cancer: a binational prospective population-based study from the Swedish norwegian testicular cancer study group. J Clin Oncol. 2011;29(6):719-25.
4. Olofsson SE, Tandstad T, Jerkeman M, Dahl O, Stahl O, Klepp O, et al. Population-based study of treatment guided by tumor marker decline in patients with metastatic nonseminomatous germ cell tumor: a report from the Swedish-Norwegian Testicular Cancer Group. J Clin Oncol. 2011;29(15):2032-9.
5. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol. 1997;15(2):594-603.
6. Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med. 1987;316(23):1435-40.
7. Hellesnes R, Myklebust TA, Fossa SD, Bremnes RM, Karlsdottir A, Kvammen O, et al. Testicular Cancer in the Cisplatin Era: Causes of Death and Mortality Rates in a Population-Based Cohort. J Clin Oncol. 2021;39(32):3561-73.
8. Haugnes HS, Bosl GJ, Boer H, Gietema JA, Brydoy M, Oldenburg J, et al. Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. J Clin Oncol. 2012;30(30):3752-63.
9. Daneshmand S, Cary C, Masterson T, Einhorn L, Adra N, Boorjian SA, et al. Surgery in Early Metastatic Seminoma: A Phase II Trial of Retroperitoneal Lymph Node Dissection for Testicular Seminoma With Limited Retroperitoneal Lymphadenopathy. J Clin Oncol. 2023;41(16):3009-18.
10. Ruf CG, Krampe S, Matthies C, Anheuser P, Nestler T, Simon J, et al. Major complications of post-chemotherapy retroperitoneal lymph node dissection in a contemporary cohort of patients with testicular cancer and a review of the literature. World J Surg Oncol. 2020;18(1):253.
11. Grenabo Bergdahl A. Robotic retroperitoneal lymph node dissection for testicular cancer at a national referral centre. BJUI Compass. 2022.
12. SWENOTECA. SWENOTECA X. 2020.
13. Peckham M. Testicular cancer. Acta Oncol. 1988;27(4):439-53.
14. Kollmannsberger C, Nichols C, Meisner C, Mayer F, Kanz L, Bokemeyer C. Identification of prognostic subgroups among patients with metastatic 'IGCCCG poor-prognosis' germ-cell cancer: an explorative analysis using cart modeling. Ann Oncol. 2000;11(9):1115-20.
15. Heidenreich A, Paffenholz P, Hartmann F, Seelemeyer F, Pfister D. Retroperitoneal Lymph Node Dissection in Clinical Stage IIA/B Metastatic Seminoma: Results of the COlogne Trial of Retroperitoneal Lymphadenectomy In Metastatic Seminoma (COTRIMS). Eur Urol Oncol. 2024;7(1):122-7.

16. Matulewicz RS, Benfante N, Funt SA, Feldman DR, Carver B, Doudt A, et al. Primary Retroperitoneal Lymph Node Dissection for Seminoma Metastatic to the Retroperitoneum. J Urol. 2024;211(1):80-9.
17. Hiester A, Che Y, Lusch A, Kuss O, Niegisch G, Lorch A, et al. Phase 2 Single-arm Trial of Primary Retroperitoneal Lymph Node Dissection in Patients with Seminomatous Testicular Germ Cell Tumors with Clinical Stage IIA/B (PRIMETEST). Eur Urol. 2023;84(1):25-31.
18. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-96.
19. Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst. 2014;106(9).
20. Cocks K, Wells JR, Johnson C, Schmidt H, Koller M, Oerlemans S, et al. Content validity of the EORTC quality of life questionnaire QLQ-C30 for use in cancer. Eur J Cancer. 2023;178:128-38.
21. Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J Clin Epidemiol. 2016;69:79-88.
22. Holzner B, Efficace F, Basso U, Johnson CD, Aaronson NK, Arraras JI, et al. Cross-cultural development of an EORTC questionnaire to assess health-related quality of life in patients with testicular cancer: the EORTC QLQ-TC26. Qual Life Res. 2013;22(2):369-78.
23. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. J Psychosom Res. 1993;37(2):147-53.
24. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.