

Title Page

**Genetic and Clinical Factors Associated with Chronic Postsurgical Pain after Hernia
Repair, Hysterectomy, and Thoracotomy: A Two-Year Multicenter Cohort Study**

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Abstract

Background:

Chronic postsurgical pain (CPSP) has been linked to many surgical settings. We aimed to analyze functional genetic polymorphisms and clinical factors that might identify CPSP risk after inguinal hernia repair, hysterectomy, and thoracotomy.

Methods:

This prospective multicenter cohort study enrolled 2,929 patients scheduled for inguinal hernia repair, hysterectomy (vaginal or abdominal), or thoracotomy. The main outcome was the incidence of CPSP confirmed by physical examination 4 months after surgery. The secondary outcome was CPSP incidences at 12 and 24 months. We also tested the associations between CPSP and 90 genetic markers plus a series of clinical factors and built a CPSP risk model.

Results:

Within a median of 4.4 months, CPSP had developed in 527 patients (18.0%), in 13.6% after hernia repair, 11.8% after vaginal hysterectomy, 25.1% after abdominal hysterectomy, and 37.6% after thoracotomy. CPSP persisted after a median of 14.6 months and 26.3 months in 6.2% and 4.1%, respectively, after hernia repair; 4.1% and 2.2% after vaginal hysterectomy, 9.9% and 6.7% after abdominal hysterectomy, and 19.1% and 13.2% after thoracotomy. No significant genetic differences between cases and controls were identified. The risk model included six clinical predictors: 1) surgical procedure, 2) age, 3) physical health (Short Form Health Survey-12), 4) mental health (Short Form Health Survey-12), 5) preoperative pain in the surgical field, and 6) preoperative pain in another area. Discrimination was moderate (*c*-statistic, 0.731; 95% confidence interval, 0.705–0.755).

Conclusions:

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3 Until unequivocal genetic predictors of CPSP are understood, we encourage systematic use of
4
5 clinical factors for predicting and managing CPSP risk. (ClinicalTrials.gov NCT01510496)
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INTRODUCTION

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2 Since the discussion of chronic postsurgical pain (CPSP) commenced in 1998,¹ this late
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4 complication has proven to be a frequent cause of persistent pain in the general population²
5
6 and has been linked to a wide range of surgical settings.^{3,4} Risk factors, pathogenesis, and
7
8 preventive strategies continue to be widely debated.³⁻⁶ The main predictors described to date
9
10 are female sex,⁷ age,⁸ psychosocial factors,^{9,10} a history of pain in the region of surgery or
11
12 other sites,^{5,8,11} type of procedure,^{3,4,12} nerve injury,¹³ and postoperative pain intensity.¹⁴
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14 Additionally, genetic polymorphisms have been linked to varying sensitivity to pain,^{15,16}
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16 susceptibility to certain painful conditions,¹⁷ and response to analgesics,¹⁸⁻²⁰ leading some to
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18 suggest that such factors might explain why some patients develop chronic pain and others do
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20 not.^{3,4,21} Studies with sufficient power to confirm the relevance of single nucleotide
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22 polymorphisms (SNPs) have yet to be published, although they are potentially of considerable
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24 interest.

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26 We hypothesized that within patient populations sharing the same surgical contexts and
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28 clinical-demographic risk for CPSP, genetic factors would identify individuals at risk for this
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30 complication. Our aims were to analyze functional genetic polymorphisms related to CPSP
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32 risk or protection and clinical predictors at 4 months after three types of surgery—inguinal
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34 hernia repair, hysterectomy, and thoracotomy. We also sought to determine pain interference
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36 with daily living at 4 months; the incidence of CPSP and pain intensity at 4, 12, and 24
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38 months; and the rate of neuropathic pain in patients with CPSP at 4 months.
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MATERIALS AND METHODS

Study design

This prospective multicenter cohort study enrolled patients scheduled for inguinal hernia repair, hysterectomy (vaginal or abdominal incision), or thoracotomy. Genetic associations in the subgroups of patients with and without CPSP (cases and controls) were compared.

Setting

Twenty-three Spanish hospitals (Appendix 1) recruited patients from January 8, 2009, to December 31, 2010. Follow-up ended on December 31, 2012.

Participants

Candidates for inclusion were scheduled for inpatient or outpatient inguinal hernia repair (men), vaginal or abdominal hysterectomy (for nononcologic reasons or for cervical carcinoma in situ, but excluding other oncologic procedures, or thoracotomy (men) under general, regional, or local anesthesia with sedation (see [table 1 in Supplemental Digital Content 1](#) for patient distribution by diagnostic and surgical codes).

Candidates were excluded if they or their parents or grandparents had been born in the Canary Islands or outside Spain or if they were of Roma ethnicity. Candidates were also excluded if they were under 18 years of age, needed reoperation, had a serious psychological disorder, were undergoing endoscopic or other procedures not requiring incision, or were relatives (parents, grandparents, children, grandchildren, or siblings) of patients already enrolled.

Cases were all patients with CPSP at 4 months; for the gene study a control group was formed by selecting a block-randomized sample of CPSP-free patients from each surgical group.

Outcomes

1 The primary outcome was the incidence of CPSP confirmed by physical examination
2 approximately 4 months after surgery based on the criteria of Macrae and Davies²² published
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4 by the International Association for the Study of Pain. These criteria are as follows: 1) the
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6 pain should have developed after a surgical procedure; 2) the pain should be of a least two
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8 months' duration; 3) other causes for the pain, such as continuing malignancy or chronic
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10 infection, should be excluded; and 4) the possibility that the pain is continuing from a pre-
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12 existing problem should be explored and exclusion attempted. Although these criteria
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14 specified waiting at least two months before diagnosing CPSP, others later proposed waiting
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16 at least three months^{23,24} because of the possibility of persisting inflammatory changes and
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18 neuropathic pain.²⁵ We therefore chose to modify the criteria slightly, cautiously waiting
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20 approximately 4 months before diagnosing CPSP.
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27 The secondary outcomes were 1) the incidence of CPSP reported in telephone interviews at
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29 12 and 24 months; and 2) the percentage of patients with CPSP at 4 months whose pain had
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31 neuropathic characteristics.
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35 **Data Collection**

36 Designated anesthesiologists on each hospital's local research team attended training sessions
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38 on how to complete the clinical questionnaire and diagnose CPSP. Questionnaire variables
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40 and definitions are shown in Supplemental Digital Content 2. The following variables were
41
42 collected before surgery and during hospitalization. Before surgery the anesthesiologist
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44 administered the validated Spanish version²⁶ of the Hospital Anxiety and Depression Scale
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46 (HADS), which has proven useful for diagnosing anxiety or depression in patients without a
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48 prior history of psychiatric problems,²⁷ and version 2 of the Short Form Health Survey-12
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50 (SF-12) questionnaire²⁸ to assess two components (physical and mental) of quality of life.
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57 Also recorded at this time were physical status according to the American Society of
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Anesthesiologists' classification; the presence of prior pain in the area of surgery and in other parts of the body expressed on a verbal numerical rating scale (VNRS) of 0 to 10 (0=no pain, 10=the worst imaginable pain) and history of treatment with analgesics, concomitant diseases; and any history of substance addiction to street drugs, alcohol, or smoking. Surgical variables were procedure, duration, techniques of regional and local anesthesia, doses of opioids and antihyperalgesic agents, and intraoperative complications. For 24 hours after surgery analgesia and postoperative pain (VNRS) were recorded.

Data were collected with a structured telephone questionnaire between 1 and 1.5 months after surgery (see Supplemental Digital Content 2); all the interviews were done by the same investigator (J. Cantillo). Patients who reported pain at that time were telephoned again between 2.5 and 3.5 months after surgery and, if pain was still present, were given an appointment for clinical examination between 3.5 and 4.5 months after surgery; this visit, during which CPSP was diagnosed, took place at the hospital. The examiner at this time was an anesthesiologist expert in pain management who used the following instruments: Brief Pain Inventory (severity, analgesics, and interference with daily living), the Spanish SF-12 questionnaire and the Douleur Neuropathique 4 questionnaire.²⁹ This third instrument assesses whether CPSP could be described as neuropathic, indicated by a positive response to four out of ten items. The physical examination included determining the exact location of pain (noted in the Brief Pain Inventory) followed by testing for hypoesthesia (slight touch with a cotton swab, pinpricking with Von Frey filaments) as well as for dynamic allodynia (brushing) according to items specified in the Douleur Neuropathique 4 questionnaire. These tests were applied on both sides of the body. The patient also reported use of analgesics. Patients whose diagnosis of CPSP was confirmed at this time were interviewed by telephone

again at 12 months and, if pain persisted, again at 24 months. If a patient was lost to follow-up, the National Health Service Death Register was checked.

Ethical Considerations

The study was approved by the clinical research ethics committees of the leading center, Parc de Salut Mar (file reference CEIC-IMAS: 2008/3080/I) and all other centers (Appendix 1).

Patients signed informed consent statements for data collection, DNA analysis, follow-up telephone contact, and a hospital appointment for physical examination. Otherwise, patients received routine care.

Sample size

We targeted examining the presence of strong associations with CPSP, some of which had previously been reported in the literature. Using standard procedures,³⁰ we estimated that a minimum sample of approximately 500 cases and 500 controls was needed to have greater than 90% power to detect a risk allele with an odds ratio (OR) of 1.5 for CPSP in a simple allelic test, assuming an incidence of at least 10% for this late complication and risk allele frequencies of 0.1 or larger.

Based on findings that CPSP develops after 10% of inguinal hernia repair procedures, 10% to 30% of hysterectomies, and 30% to 40% of thoracotomies³ and considering the numbers of these procedures recorded at the 23 participating hospitals in a previous epidemiological study in our area,³¹ we planned to recruit a sample of 600 patients with CPSP in 2 years. A 20% loss to follow-up was expected.

Extraction details for genotyping and single nucleotide polymorphism (SNP) selection

1 DNA extraction was only performed in volunteering patients with confirmed CPSP and in
2 selected control patients without CPSP who were matched to cases by age, surgical speciality,
3 sex, domicile, and hospital recruitment. For each patient, peripheral blood (5 ml) was drawn
4 in the operating room immediately before surgery and placed in ethylene diamine tetraacetic
5 acid-treated tubes. Each blood sample was identified using adhesive barcode labels. Barcode
6 digits were registered twice in succession in the database to avoid misidentification. In
7 addition to the blood samples, each collaborating center also retained the consent forms and
8 questionnaires. Labeled samples were stored in a refrigerator at 4–5 °C until they were
9 shipped to a central laboratory within one week. The blood and questionnaires were then
10 forwarded to the clinical laboratory (Echevarne Clinical Laboratory^{*}), where they were stored
11 in a freezer at –80°C.

12 DNA was extracted with the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany)
13 following the manufacturer's specifications. Genotyping was carried out with the Illumina
14 Golden Gate protocol with VeraCode technology (Illumina[†]) in the National Genotyping
15 Centre (CEGEN, Barcelona, Spain). The selected single nucleotide polymorphisms (SNPs)
16 were genotyped for each patient.

17 A total of 90 SNPs were included in the study (table 1). Eight-seven of the 90 SNPs were
18 selected based on prioritizing functional genetic variants previously associated in the
19 literature with pain sensitivity, chronic pain conditions, and related traits belonging to
20 different genes whose protein products are linked to biological pathways that influence pain
21 sensitivity.^{15,18,20,32-35} Thus, SNPs with no proven influence on gene function at the time were
22 not included. These 87 SNPs had minor allele frequencies in the general Caucasian population
23 ranging of up to 0.4 (National Center for Biotechnology Information[‡]) and a homogeneous

24 * www.echevarne.com (last accessed: November 10, 2014)

25 † www.illumina.com (last accessed: November 10, 2014)

26 ‡ www.ncbi.nlm.nih.gov/snp (last accessed: November 10, 2014)

distribution along the gene and location inside the exons or near them, with a minor allele frequency of 0.1 using data from HapMap.[§] The process was carried out according to the suggestions published by Hoh et al.³⁶ and TagSNPs with $R^2 > 0.8$ were selected according to Carson et al.³⁷ These SNPs are related to two main functional categories:

Type 1: genes encoding proteins that mediate the transmission of pain signals by sensory nerve fibers and by central nervous system pathways that mediate the perception of pain

Type 2: genes encoding proteins that mediate peripheral and central inflammatory responses related to tissue injury

Finally, we included the three significant SNPs detected in the genome-wide association study of acute post-surgical pain in humans by Kim et al.,²⁰ bringing the total number of SNPs to 90.

Statistical Methods

Data are expressed as medians and 10th–90th percentiles. Potential risk factors were evaluated for unadjusted bivariate association with CPSP occurrence based on the t test (continuous variables) or the Fisher exact test or chi-square test (categorical variables).

Bivariate ORs and 95% confidence intervals (CIs) were also calculated. Collinearity between categorical variables was tested with the Cramer V test (between nominal variables) and Kendall's tau-b coefficient (between ordinal variables).

A general lineal mixed model (GLMM) with the variable *recruitment center* as a random factor was constructed using backward stepwise selection with CPSP was the dependent variable. Independent variables were selected for the model on the basis of the investigators' consensus on relevant measurable preoperative variables, the results of previous studies,^{3–7,9,38} the bivariate analysis ($P < 0.05$), and correlation between variables (Kendall's tau-b). At each

[§] www.hapmap.ncbi.nlm.nih.gov (last accessed: November 10, 2014)

step, the likelihood ratio was used to evaluate a potential risk factor. The cutoff for variable removal was set at a significance level of 0.05 and the adjusted ORs and corresponding 95% CIs were calculated.

A bootstrap method was used for internal validation of the subset of factors. A total of 1,000 computer-generated samples, each including 2,834 individuals were derived from the sample by random selection with replacement. Within each bootstrap sample, the β coefficient was calculated using all selected factors. The reliability of predictor variables in the final GLMM was estimated by the 95% CI of the β coefficient in the bootstrap samples. Reliable predictors were retained if the 80% CI of bootstrap samples indicated statistical significance ($P < 0.05$). To assess the model's discrimination and predictive ability we used the *c*-statistic expressed as a percentage (area under the receiver operating characteristic curve). GLMM calibration was assessed by the Hosmer-Lemeshow goodness-of-fit statistic as an estimate of agreement between observed and predicted outcomes.

Statistical Treatment of Genetic Analyses

For each SNP, allele and genotype frequency associations between the CPSP status and the presence of neuropathic pain was tested using SNPator.³⁹ In the genotype analysis, different inheritance models were tested in autosomic SNPs by comparing each genotype against the combination of the remaining two. Chi-square-based Pearson tests were applied to the resulting contingency tables to test for association. Allele frequency associations with pain intensity were also explored using the Wald test implemented in the PLINK suite.⁴⁰

Additional allele frequency testing was performed for CPSP status according to sex and type of surgery.

Haplotype blocks were defined by grouping genotyped SNPs by proximity, disallowing gaps greater than 50 kb. Haplotypes for each individual at each block were estimated using PHASE.⁴¹ For each block, the frequency of each estimated haplotype was compared in cases and controls against the aggregation of all other estimated haplotypes for that block using SNPator.³⁹

We report nominal *P* values for all statistical tests and performed multiple-testing correction by means of a conservative Bonferroni strategy that considered all the tests in our analysis even if they are not independent of each other. Given that we performed allelic and genotypic tests for every marker and haplotypic tests for every gene, for a total of over 400 tests, we used a Bonferroni threshold of 10^{-4} .

Quality Assurance

To evaluate the quality of recruitment and data collection, independent observers audited the medical records of a random sample of 5% of the patients from 6 randomly chosen centers. Thus, 38 patient records (1.3% of the sample) were audited; the 102 items checked encompassed all variables directly involved in the predictive model plus others. This audit found 110 instances of error or missing data (2.8% of the data audited).

RESULTS

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3 For a total of 3,890 recruited patients, we detected protocol violation in 1% cases and 23.7%
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5 were lost to follow-up for the recording of outcome variables. Thus, data for 2,929 patients
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7 (75.3% of those recruited) were analyzed. Eighty-seven patients (3.0%) were lost between the
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9 first follow-up visit and the two-year telephone interview. Figure 1 shows patient flow from
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11 recruitment through 2 years. Table 2 shows patient characteristics according to surgical
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13 procedure. DNA samples for genotyping were available for 2,854 patients (97.4%).
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CPSP: Severity and Life Interference

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22 Figure 2 shows the CPSP incidence after each procedure and each data collection time.
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25 Within a median (10th–90th percentile) of 4.4 months (3.7–5.8), CPSP had developed in 527
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27 patients (18.0%), in 13.6% of patients after hernia repair, 11.8% after vaginal hysterectomy,
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29 25.1% after abdominal hysterectomy, and 37.6% after thoracotomy. The follow-up interviews
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31 to report CPSP were completed at a median of 14.6 months (12.5–16.1) and 26.3 months
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33 (23.8–29.4).
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38 Table 3 shows the incidence of CPSP, including neuropathic pain, and life-interference data
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40 obtained at the follow-up visit distributed by surgical procedure. The thoracotomy group had
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42 the highest incidence of neuropathic pain (55.0%) as assessed by the Douleur Neuropathique
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44 4 questionnaire, and the vaginal hysterectomy group had the lowest (24.5%). The percentages
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46 of patients with a VNRS pain score higher than 3 ranged from 52.7% (thoracotomy) to 38.0%
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48 (hernia repair). CPSP interfered with daily activities (scores of > 3 out of 10, Brief Pain
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50 Inventory) after thoracotomy in 30.5% and after hernia repair in 18%. For patients who still
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52 had CPSP pain at 2 years, the intensity did not decrease, remaining between 3 and 5 on the
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54 VNRS (table 4).
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Genetic Study Exploring CPSP Associations

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3 A total of 1,011 randomly selected samples (35.4% of the 2,854 available) were sent to be
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5 genotyped for 90 SNPs (505 cases, 506 controls); two samples were removed because of low
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7 genotyping success and four additional samples were removed because of incompatibilities
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9 between registered sex and sex imputed from genotypes. Thus, 1,005 samples (502 cases and
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11 503 controls, table 5) were used in subsequent analyses. No significant deviations from
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13 Hardy-Weinberg equilibrium were found, and on comparing cases and controls (table 6), the
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15 subgroups were similar in all except two preoperative clinical variables (mental summary SF-
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17 12 score and preoperative pain in any nonsurgical area). The Bonferroni-corrected analysis
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19 showed no significant genetic differences in allele frequencies between patients with and
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21 without CPSP after any of the interventions studied (Supplemental Digital Content 3, table 1)
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23 and table 7 Nonetheless, some allelic, genotypic, and haplotypic tests did show nominally
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25 significant P values for some SNPs or genes. In particular, two SNPs from *DRD2* in
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27 chromosome 11 (rs12364283 and rs4648317) presented the low P values in some tests but in
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29 no case went beyond a conservative Bonferroni threshold of approximately 10^{-4} .
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Clinical Risk Factors for CPSP

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41 After bivariate analysis of 31 independent variables (table 8), collinearity analysis (rejection
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43 of correlation coefficients higher than 0.25), 18 independent variables entered the GLMM.
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45 These candidate predictors were surgical procedure, body mass index (<24.44, 24.44–28.08,
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47 >28.08), anxiety (HADS score ≥ 8), depression (HADS score ≥ 8), substance addiction,
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49 chronic obstructive pulmonary disease, hypertension, neurologic disease, cancer, preoperative
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51 pain in the surgical area (VNRS score >3), preoperative pain in other areas (pain score >3),
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53 previous experiences of surgery-related pain, family history of surgery-related pain, type of
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55 anesthesia, intraoperative intravenous opioid use, age (<51, 51–64, >64 years), SF-12 physical
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summary (0–33.5, 33.6–55.1, >55.1) and SF-12 mental summary (0–44.8, >44.8). (These cutoffs were determined by distributing the CPSP data in deciles).

Multivariable GLMM selected six CPSP predictors (table 9), which were retained in more than 95% of bootstrap subsamples. The table shows the adjusted ORs for these variables, along with the 95% CIs after bootstrapping. This six-variable mixed model identified over 73% of the patients who developed CPSP, with a *c*-statistic of 0.731 (0.705–0.755). The calibration was good according to the Hosmer-Lemeshow chi-square test ($\chi^2 = 4.02$, $P = 0.855$). According to GLMM-derived β coefficients an individual's risk of CPSP might be calculated as follows: risk of CPSP = $1/(1+e^{-\text{linear predictor}})$ where linear predictor comprising the six independent risk factors was as follows: $-3.37 + 0.50*\text{surgery (abdominal hysterectomy)} + 0.28*\text{surgery (hernia repair)} + 1.88*\text{surgery (thoracotomy)} + 1.13*\text{age (< 51 yrs.)} + 0.48*\text{age (51 to 64 yrs.)} + 0.86*\text{physical SF-12 (<33.5)} + 0.52*\text{physical SF-12 (33.5 to 55.1)} + 0.51*\text{mental SF-12 (< 44.8)} + 0.41*\text{preoperative pain in surgical area (VNRS > 3)} + 0.37*\text{preoperative pain in other area (VNRS > 3)}$.

Supplemental Digital Content 3, table 2, shows the generalized linear mixed model for the five of the six predictors (excluding procedure type) applied to each of the four procedures (treating vaginal and abdominal hysterectomies separately. The *c*-statistics ranged from 0.731 (0.665–0.807) for vaginal hysterectomy) to 0.645 (0.589–0.702) for thoracotomy.

Supplemental Digital Content 3, table 3, shows the generalized linear mixed model for patients with neuropathic CPSP.

DISCUSSION

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3 The overall incidences of CPSP confirmed on physical examination at 4 months are consistent
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5 with previously reported rates for the same procedures^{3,4} with the exception of vaginal
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7 hysterectomy. Previous authors reported similar CPSP rates for vaginal and abdominal
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9 hysterectomy,³⁸ but we observed different CPSP behavior after these procedures and consider
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11 them to be separate settings. The rates had decreased by approximately half one year after
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13 surgery and by two thirds after 2 years, but we found no long-term studies with which to
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15 compare that finding.
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21 Also interesting was our finding of a lower 4-month neuropathic pain rate than reported by
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23 others^{3,4,42}; we attribute this difference to our reliance on exhaustive physical examination for
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25 diagnosis rather than postal questionnaires or patient charts. Finally, over 20% of our CPSP
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27 patients reported moderate–intense pain at the diagnostic visit; that rate was similar to the
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29 18.3% rate recorded in a population-based study of CPSP.² For patients who were still
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31 experiencing pain 2 years later, the intensity had not diminished. We emphasize that pain was
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33 responsible for moderate-intense interference with daily activities for 18–30%, with walking
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35 for 15–29%, and with mood for 10–34%.
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41 The comparison between 502 patients with confirmed CPSP and 503 selected controls
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43 without CPSP showed that a strong effect of genetic profile on this late complication is
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45 unlikely. Under the CPSP diagnostic criteria we applied at four months, and with case–control
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47 sample sizes that rendered a power of approximately 99% for detecting ORs higher than 1.9
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49 in individual allelic tests, we conclude that any potential effects of the tested SNPs would be
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51 weaker than that threshold. We cannot, of course, formally exclude associations with SNPs
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53 that were not selected for tagging in this study.
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Even though none of the studied SNPs survived multiple test correction, we note that the lowest allelic *P* values were for the association between CPSP and the dopamine D2 receptor (*DRD2*) gene SNPs rs12364283 and rs4648317. Both have been associated with enhanced *DRD2* expression⁴³ and several substance addictions—such as nicotine dependence (rs4648317⁴⁴)—as well as with inhibition and impulsivity related to d-amphetamine response effects on stop-task performance and mood (rs12364283⁴⁵). These are but two of many SNPs linked to dopamine pathway dysregulation, which has also been observed in chronic pain unrelated to substance addiction.⁴⁶ Given the weak associations observed for these *DRD2* SNPs, we believe that they might still be candidates for more complex polygenic and multifactorial modelling. One recent study demonstrated an association between the HLA DQB1*03:02 allele and higher CPSP risk after one of the procedures we included (inguinal hernia repair) and after lumbar disk herniation.²¹ We did not analyze HLA DQB1*03:02 because this pathway had not been directly linked to pain pathogenesis, but we think this new finding encourages further exploration of pathways not covered in the present study.

Thus, although we did not find any association between the 90 analyzed SNPs and CPSP, we cannot completely exclude the role of genetics in the development of CPSP, first, because our study was only powered to detect strong associations ($OR > 1.9$); second, because we selected SNPs to cover certain genes and did not exhaustively tag for all variations in every studied gene; and third, because of factors such as incomplete penetrance and variable expressivity of each SNP, epistasis and meiotic and mitotic epigenetic contributors to maintenance of CPSP. We think, however, that our findings do indicate that the positive results reported in other studies should probably be revisited critically until replicated.^{21,47-48}

1 The CPSP risk model identified 73% of the patients with CPSP based on the following
2 clinical predictors: 1) surgical procedure, 2) age, 3) physical health (SF-12 score), 4) mental
3 health (SF-12 score), 5) preoperative pain in the surgical field, and 6) preoperative pain in
4 another area. Although the discriminative power of the model is moderate, to our knowledge
5 it is the first to offer some promise of assessing CPSP risk preoperatively, at least in the
6 surgical settings studied. When we applied five of the six predictors (excluding procedure
7 type) to each of the four procedures (treating vaginal and abdominal hysterectomies
8 separately), we found that the model remained valid in each setting, although its predictive
9 value is more robust in a mixed surgical population.
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23 A clinical scoring system, based on the six easily recorded variables the model identifies
24 therefore merits external validation to test transportability to other settings. In contrast with a
25 recent study by Althaus and colleagues,⁴⁹ who studied CPSP risk in a cohort of 150 patients
26 undergoing a range of surgical procedures, we did not find that the presence of moderate or
27 intense postsurgical pain substantially increased the predictive ability of the model. Thus, this
28 factor was excluded for statistical reasons. However, we also emphasize our interest in
29 identifying predictors available before surgery, such as psychological traits on which
30 clinicians may be able to intervene. Such factors are probably related to patient
31 hypervigilance⁵⁰ and are potentially related to certain gene polymorphisms in the dopamine
32 pathway affecting pain perception.⁵¹ Of the five CPSP predictors identified by Althaus and
33 colleagues, our findings are consistent with two: preoperative pain in the operating field and
34 other preoperative pain. The relevance of preoperative pain in another area of the body is
35 possibly attributable to poor functioning of endogenous pain inhibition mechanisms, as has
36 been demonstrated in patients who develop CPSP after thoracotomy¹⁴ and in several chronic
37 pain settings.⁵²
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Factors related to surgery and anesthetic technique were not predictors of CPSP

(Supplemental Digital Content 3, table 4). The lack of statistical relevance of anesthetic and analgesic variables may be attributable to the certain degree of variability in the execution of techniques in this study reflecting a routine practice setting. In other words, an observational design, even when prospective, may make it difficult to identify factors as predictors if they are subject to small clinical variations. However, we did detect six other clinical risk factors for CPSP, and we think it reasonable to suggest that anesthetic and analgesic factors may be less important to the development of CPSP in clinical circumstances than randomized trials might lead us to believe. Finally, although we detected a higher level of preoperative anxiety in patients with CPSP, anxiety was excluded from the model because it was strongly associated with results for the mental component of the SF-12, which was a stronger predictor.

One major strength of this study was its prospective, population-based, multicenter design with physician-diagnosed CPSP. We collected data for a representative random sample of surgical patients undergoing routine anesthetic procedures in a large genetically homogeneous population. This study was also the first to follow patients for 2 years (range, 22.2–30.0 months) and to prospectively include all the variables considered relevant to chronic pain at the time of design.⁵³⁻⁵⁴

A potential limitation was the large number of data collectors (164 anesthesiologists) in 23 centers; however, we used a structured questionnaire and conducted three training sessions to prevent inconsistent collection that might have led to a center effect.⁵⁵ A second limitation was that we did not use a scale to analyze pain catastrophizing because the predictive value of this factor^{10,56} had not yet been established when our study was designed. This attribute, defined as a tendency to misinterpret and exaggerate situations that may be threatening, has

1 recently been shown to confer risk for CPSP.⁵⁶ A potential limitation with regard to hernia
2 repair was that the type of mesh used for this procedure was not considered as a possible
3 surgery-related risk factor. The final limitation relates to gender in the genetic analysis. We
4 chose to include only men in the hernia repair and thoracotomy groups because of the
5 difficulty in balancing gender in these samples: based on a previous descriptive study of
6 surgical populations in our geographic setting we estimated that women would only account
7 for 28% and 22% of these groups, respectively.³¹ In order to analyze the genetic factor in
8 relation to clinical characteristics within surgical specialties, while enrolling large but not vast
9 numbers of patients, we balanced the all-male thoracotomy and hernia repair groups against
10 the two hysterectomy groups.
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25 We conclude that the lack of unequivocal confirmation of genetic factors predisposing certain
26 patients to CPSP necessitates our continued reliance on scoring clinical factors—particularly
27 procedure, age and preoperative quality of life and experience of pain—to guide interventions
28 or vigilance against the development of this late complication. A surgical team’s
29 understanding of CPSP risk stratification has many applications in large health care systems
30 or the management of individual cases. For benign conditions, high risk should lead to
31 reassessment of surgery and deference to other treatment options,⁵⁷ especially in younger
32 patients with concomitant pain or psychological comorbidity. Our model can facilitate trials
33 of preventive strategies so that ineffective treatments that can have adverse effects or entail
34 inconvenience can be avoided.^{58,59} We encourage the further development of valid,
35 transportable scoring systems to predict CPSP risk based on clinical factors in other surgical
36 settings while the search for genetic and clinical interactions continues through more detailed
37 multifactorial study.
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Table 1. SNPs Genotyped, Their Associated Genes, Chromosomal Locations, and Functions

Gene Name	Chromosomal Location	Gene Function	Gene Symbol	SNP Number
Brain-derived neurotrophic factor	11p14.1	Major regulator of synaptic transmission. It is involved in the activity-dependent pathogenesis of nociceptive pathways that may lead to chronification of pain.	<i>BDNF</i>	rs1048221 rs6265 rs8192466 rs2049046 rs908867
Catechol-O-methyltransferase	22q11.21–q11.23	Catechol O –methyltransferase activity	<i>COMT</i>	rs4646312 rs6269
Dopamine receptor D2	11q23	Dopamine receptor activity	<i>DRD2</i>	rs6277 rs1076560 rs2734837 rs11608185

				rs4936272 rs4648317 rs4322431 rs1799978 rs12364283
Fatty acid amide hydrolase	1p35-p34	Metabolism of the endogenous cannabinoid	<i>FAAH</i>	rs932816 rs4141964 rs2295633
Gamma-aminobutyric acid A receptor, alpha 1	5q34	Neuronal inhibition	<i>GABRA1</i>	rs28364635 rs12658835
Gamma-aminobutyric acid A receptor, alpha 2	4p12	Neuronal inhibition	<i>GABRA2</i>	rs519972 rs7678338 rs7689605 rs10028945
Gamma-aminobutyric acid	5q34	Neuronal inhibition	<i>GABRB2</i>	rs3816596

receptor subunit beta-2				
GTP cyclohydrolase 1	14q22.2	Involved in dopamine synthesis	<i>GCHI</i>	rs10483639 rs7142517 rs752688 rs4411417 rs9671371 rs12147422 rs8004445 rs998259 rs3783641 rs8007267
Glutamate receptor, ionotropic, kainate3	1p34.3	Contribute to excitatory postsynaptic currents in many regions of the CNS	<i>GRIK3</i>	rs6691840
5-Hydroxytryptamine (serotonin) receptor 2C	Xq24	Serotonin receptor activity	<i>HTR2C</i>	rs179997

Interleukin-6 (interferon β 2)	7p21	Cytokine activity; interleukin-6 receptor binding	<i>IL6</i>	rs13447446
Interleukin-10	1q31–q32	Cytokine activity; interleukin-10 receptor binding	<i>IL10</i>	rs1800896
Monoamine oxidase A	Xp11.3	Amine oxidase activity	<i>MAOA</i>	rs3788862 rs2283724 rs1800659 rs979606 rs979605
Melanocortin 4 receptor	18q22	Stimulator of adenylatecyclase	<i>MC4R</i>	rs9966412 rs2229616
Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor	14q13	Involved in immune and proinflammatory responses	<i>NFKBIA</i>	rs8904
Nitric oxide synthase 1	12q24.2	Catalyze the generation of nitric oxide	<i>NOS1</i>	rs9658482

(neuronal)				rs9658478 rs9658279
Opioid receptor, delta 1	1p35.3	Inhibits neurotransmitter release by reducing calcium ion currents and increasing potassium ion conductance	<i>OPRD1</i>	rs1042114 rs533123
Opioid receptor, kappa 1	8q11.2	Receptor for dynorphins	<i>OPRK1</i>	rs702764 rs997917
Opioid receptor, mu 1	6q24-q25	Receptor for endogenous and synthetic opioids	<i>OPRM1</i>	rs1799971 rs563649
Proenkephalin	8q12.1	Involved in pain perception and responses to stress	<i>PENK</i>	rs1975285
Proopiomelanocortin	2p23.3	Hormone activity	<i>POMC</i>	rs28932472 rs934778
Prostaglandin-endoperoxide synthase 2 (prostaglandin	1q31.1	Mediator of inflammation	<i>PTGS2</i>	rs5275

G/Hsynthase and cyclooxygenase)				
Sodium channel, voltage-gated, type IX, alpha	2q24.3	Mediator of inflammation	<i>SCN9A</i>	rs6746030 rs12478318 rs6747673 rs9646771
Solute carrier family 6 (neurotransmitter transporter, noradrenaline member 2	16q12.2	Norepinephrine transporter activity	<i>SCL6A2</i>	rs40434 rs36024 rs36017
Dopamine transporter or DAT1	5p15.3	Dopamine transporter activity	<i>SCL6A3</i>	rs40184 rs6350 rs12516948 rs403636
Solute carrier family 6 (neurotransmitter	17q11.1	Serotonin and monoamine transporter activity	<i>SCL6A4</i>	rs1979572 rs4325622

transporter, serotonin), member 4				rs6352 rs140701 rs6355 rs2066713
Solute carrier organic anion transporter family, member 1A2	12p12.1	Mediates the Na(+)-independent transport of organic anions	<i>SLCO1A2</i>	rs11568563
Solute carrier organic anion transporter family, member 1B3	12p12.2	Mediates the Na(+)-independent uptake of organic anions	<i>SLCO1B3</i>	rs4149117 rs731358
Transcription factor 25	16q24.3	Transcriptional repressor	<i>TCF25</i>	rs3212366
Transforming growth factor, beta 1	19q13.1	Growth factor regulator	<i>TGFB1</i>	rs1800469
Tyrosine hydroxylase	11p15.5	Involved in synthesis of catecholamines	<i>TH</i>	rs3839874
Tumour necrosis factor	6p21.3	Cytokine activity	<i>TNFA</i>	rs1800629

Transient receptor potential cation channel, subfamily A, member 1	8q13	Receptor-activated non-selective cation channel involved in detection of pain	<i>TRPA1</i>	rs11988795
Transient receptor potential cation channel, subfamily V, member 1	17p13.3	Activator of sensory neurons that convey information about noxious stimuli to the CNS	<i>TRPV1</i>	rs8065080
Unknowngene	19p12	The potential function of this hypothetical gene is not known at present. GWAS revealed an association with analgesic onset	<i>LOC400680</i>	rs2562456
Unknowngene	11q23.3	The potential function of this hypothetical gene is not known at present. GWAS found a significant association with analgesic onset.	<i>NR</i>	rs17122021

Unknown gene	1p21.3	The potential function of this hypothetical gene is not known at present. GWAS found a significant association with analgesic onset.	<i>NR</i>	rs6693882
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CNS = Central Nervous System

GWAS = Genome-wide association study

SNP = single nucleotide polymorphism

Table 2. Patient Characteristics according to Surgical Procedure

	Hernia Repair	Vaginal Hysterectomy	Abdominal Hysterectomy	Thoracotomy
Total— N	1761	416	350	402
Age—yr—median (10–90th percentile)	60 (39–76)	63 (45.7–76)	48 (41–63.8)	64 (49–76)
BMI—kg/m ² —median (10–90th percentile)	25.9 (22.3–30.1)	27.1 (22–33.3)	26.4 (21.5–35)	26.8 (21.7–32)
ASA physical status— <i>no. (%)</i>				
1 (normal healthy patient)	543 (30.8)	76 (18.3)	100 (28.6)	54 (13.4)
2 (patient with mild systemic disease)	1,027 (58.3)	307 (73.8)	222 (63.4)	203 (50.4)
3 (patient with severe systemic disease)	187 (10.6)	33 (7.9)	28 (8.0)	143 (35.7)
4 (patient with severe systemic disease that is a constant threat to life)	4 (0.2)	0 (0.0)	0 (0.0)	2 (0.5)
Anxiety—HADS— <i>no. (%)</i>	318 (18.7)	138 (34)	165 (48.4)	118 (30.8)
Depression—HADS— <i>no. (%)</i>	108 (6.3)	47 (11.5)	54 (15.8)	48 (12.6)

Preoperative score on the SF-12

Physical summary—median (10–90th percentile)	49.2 (34.6–56.7)	48.1 (33.1–57.2)	50.5 (31.8–58.6)	48.6 (30.2–57.8)
Mental summary—median (10–90th percentile)	57.2 (42.6–64.2)	52.2 (36.6–62.7)	48.9 (30.6–61.6)	53,5 (35,4–64)
Duration of surgery—min—median (10–90th percentile)	40 (25–74)	85 (50–145)	105 (65–180)	150 (77.4–240)
Hospital stay—days— median (10–90th percentile)	0 (0–1)	3 (2–4)	4 (3–8)	5 (1–11)

ASA = American Society of Anesthesiologists; BMI = body mass index; HADS = Hospital Anxiety and Depression Scale; SF-12 = Short Form Health Survey-12 (version 2, [in Spanish](#)).

Table 3. Chronic Postsurgical Pain and Quality of Life at the Four-Month Follow-up Visit

	Hernia Repair	Vaginal Hysterectomy	Abdominal Hysterectomy	Thoracotomy
Patients — no.	239	49	88	151
DN4 questionnaire	238	49	88	151
Neuropathic pain — (%)	38.7	24.5	44.3	55.0
Brief Pain Inventory questionnaire	237	49	86	150
Pain Severity (%)				
Worst pain in past 24 hours — > 3 (%)	38.0	40.8	52.3	52.7
Average pain in past 24 hours — > 3 (%)	20.6	26.2	23.6	25
Use of pain medication — (%)				
Any pain medication	24.9	38.1	52.8	60.5
Anti-inflammatory and/or acetaminophen	28.3	54.7	68.1	70.5
Minor opioid with or without acetaminophen	1.2	11.9	0.0	9.3

Major opioid	0.0	0.0	0.0	8.4
Anticonvulsant and/or antidepressant	3.6	2.4	1.4	6.7
Other medication	2.4	0.0	1.4	0.8
Percentage of relief provided by drugs in past 24 hours — median (10th–90th percentile)	40 (0–90)	50 (20–100)	50 (21–100)	50 (2–100)
Pain interference — >3 (%)*				
General activity	18.0	26.8	18.1	30.5
Mood	10.2	26.8	34.7	26.3
Walking ability	15.0	29.3	19.4	17.8
Normal work	15.6	31.7	20.8	29.7
Relations with others	9.0	17.1	12.5	17.8
Sleep	4.2	14.6	12.5	25.4
Enjoyment of life	11.4	19.5	18.1	28.0
Four-month SF-12 scores				
Physical summary — median (10th–90th percentile)	47.1 (32.1–55.3)	42.3 (24.6–56.7)	42.3 (30.6–52.9)	35.9 (22.1–52.5)

Mental summary — median (10th–90th percentile)	53.9 (40.7–63.3)	44.8 (27.2–64.0)	44.3 (30.3–60.5)	51.4 (34.6–64.4)
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*Percentages of patients with a “Verbal Numerical Rating Scale” pain score higher than 3

DN4 = Douleur Neuropathique 4 questionnaire; SF-12 = Short Form Health Survey-12 (version 2, in Spanish).

Table 4. Course of CPSP Intensity Reported during Telephone Interviews

	Hernia Repair	Vaginal Hysterectomy	Abdominal Hysterectomy	Thoracotomy
Total—N	266	50	76	116
First phone call*	3 (1–6)	4 (1–6.9)	4 (1–7)	3.5 (1–6)
Total—N	225	49	84	146
Second phone call†	4 (2–6.4)	4 (2–7)	4 (2–6)	3.5 (2–7)
Total—N	105	13	32	70
Third phone call‡	4 (1.6–7)	5 (2–6)	5 (2–7.7)	4 (2–7)
Total—N	71	9	23	47
Fourth phone call§	4 (2–7)	4 (2–7.7)	5 (3–7.6)	4 (2–7)

* 1.3 months after surgery

† 3.3 months after surgery

‡ 14.6 months after surgery

§ 26.3 months after surgery

Data are median (10th–90th percentile). Pain intensity was reported on a verbal numerical rating scale of 0 to 10 (0, no pain, 10, the worst imaginable pain).

CPSP = chronic postsurgical pain

Table 5. Selection of Cases and Controls for Genotyping and Analysis of Associations with CPSP*

	Hernia Repair (n = 1,761)	Vaginal Hysterectomy (n = 416)	Abdominal Hysterectomy (n = 350)	Thoracotomy (n = 402)
Cases, patients with CPSP (n = 527)	239	49	88	151
DNA sample unavailable (n = 22)	13	1	2	6
Selected for analysis (n = 505)	226	48	86	145
Material not valid for analysis (n = 3)	0	0	2	1
Total cases analyzed (n = 502)	226	48	84	144
Controls, patients without CPSP (n = 2402)	1,522	367	262	251
Randomly selected for analysis (n = 523)	232	56	86	149
DNA sample unavailable (n = 17)	4	4	8	1
Selected for analysis (n = 506)	228	47	83	148
Material not valid for analysis (n = 3)	2	0	0	0

Total control patients (n = 503)

226

52

78

147

*CPSP = chronic postsurgical pain.

Table 6 Comparison of Variables of Interest between Cases and Controls in the Genetic Analysis

	Cases (n = 502)	Controls (n = 503)	<i>P</i> Value
	No. (%)	No. (%)	
Surgical speciality			
Hernia repair	226 (50.0)	226 (50.0)	0.938
Vaginal hysterectomy	48 (48.0)	52 (52.0)	
Abdominal hysterectomy	84 (51.9)	78 (48.1)	
Thoracotomy	144 (49.5)	147 (50.5)	
Place of origen*			
Andalusia	108 (47.8)	118 (52.2)	0.763
Aragon	9 (45.0)	11 (55.0)	
Castilla and Leon	24 (57.1)	18 (42.9)	
Castilla–La Mancha	23 (50.0)	23 (50.0)	
Catalonia	239 (51.0)	230 (49.0)	
Valencia	43 (43.4)	56 (56.6)	
Extremadura	18 (50.0)	18 (50.0)	
Galicia	9 (52.9)	8 (47.1)	
Murcia	10 (47.6)	11 (52.4)	
Others	18 (64.3)	10 (35.7)	
ASA			
ASA 1	139 (49.6)	141 (50.4)	0.614
ASA 2	276 (49.0)	287 (51.0)	
ASA 3 or ASA 4	86 (53.4)	75 (46.6)	
Age			

18–51 y	216 (55.4)	174 (44.6)	0.018
> 51–64 y	154 (47.8)	168 (52.2)	
> 64 y	132 (45.1)	161 (54.9)	
Score on the SF-12 (physical summary)			
0–33.5	76 (59.8)	51 (40.2)	0.013
33.6–55.1	336 (49.8)	339 (50.2)	
> 55.1	77 (42.8)	103 (57.2)	
Score on the SF-12 (mental summary)			
0–44.8	146 (59.1)	101 (40.9)	0.001
> 44.8	343 (46.7)	392 (53.3)	
Anxiety (HADS) [n (%)]			
No	311 (47.8)	340 (52.2)	0.100
Yes	177 (53.3)	155 (46.7)	
Depression (HADS) [n (%)]			
No	427 (48.8)	448 (51.2)	0.132
Yes	61 (56.5)	47 (43.5)	
Preoperative pain, surgical area			
VNRS \leq 3	374 (48.7)	394 (51.3)	0.169
VNRS > 3	127 (53.8)	109 (46.2)	
Preoperative pain, other areas			
VNRS \leq 3	369 (47.0)	416 (53.0)	0.001
VNRS > 3	129 (60.0)	86 (40.0)	

ASA = American Society of Anesthesiologists; HADS = Hospital Anxiety and

Depression Score; SF-12 = Short Form **Health Survey**-12, Spanish, version 2; VNRS =

verbal numerical rating scale.

* Locations are Spanish autonomous communities according to the Constitution of 1978; names are given in English when a form is commonly available.

Table 7. Results of Frequency Testing for Risk Alleles for CPSP in All Tested SNPs

Gene	SNP	Chromosome	Position	P Value	Risk Allele	OR (95% CI)
<i>OPRD1</i>	rs1042114	1	29.138.975	0.1636	G	1.20 (0.93–1.55)
<i>OPRD1</i>	rs533123	1	29.141.155	0.9907	C	1.00 (0.80–1.25)
<i>GRIK3</i>	rs6691840	1	37.325.477	0.7091	A	1.04 (0.85–1.27)
<i>FAAH/NSUN4</i>	rs932816	1	46.859.749	0.1251	A	1.16 (0.96–1.41)
<i>FAAH</i>	rs4141964	1	46.865.040	0.8462	G	1.02 (0.85–1.22)
<i>FAAH</i>	rs2295633	1	46.874.383	0.9675	C	1.00 (0.83–1.21)
<i>GWAS*</i>	rs6693882	1	96.145.968	0.2757	A	1.11 (0.92–1.33)
<i>PTGS2</i>	rs5275	1	186.643.058	0.8001	C	1.03 (0.85–1.24)
<i>IL19/IL10</i>	rs1800896	1	206.946.897	0.675	A	1.04 (0.87–1.24)
<i>POMC</i>	rs934778	2	25.389.224	0.7558	T	1.03 (0.86–1.24)
<i>SCN9A</i>	rs6746030	2	167.099.158	0.9196	A	1.01 (0.78–1.32)
<i>SCN9A</i>	rs6747673	2	167.144.974	0.4144	A	1.08 (0.90–1.28)

<i>SCN9A</i>	rs9646771	2	167.163.043	0.6842	C	1.04 (0.86–1.25)
<i>GABRA4</i>	rs7678338	4	46.922.107	0.6507	T	1.05 (0.86–1.27)
<i>GABRA4</i>	rs7689605	4	46.952.029	0.6494	A	1.08 (0.78–1.49)
<i>GABRB1</i>	rs10028945	4	47.428.305	0.8924	A	1.01 (0.84–1.23)
<i>SLC6A3/CLPTM1L</i>	rs12516948	5	1.391.369	0.6565	G	1.04 (0.87–1.24)
<i>SLC6A3</i>	rs40184	5	1.395.077	0.9359	A	1.01 (0.85–1.20)
<i>SLC6A3</i>	rs403636	5	1.438.354	0.1926	G	1.17 (0.92–1.47)
<i>SLC6A3</i>	rs6350	5	1.443.199	0.4853	C	1.13 (0.81–1.57)
<i>GABRB2/GABRA6</i>	rs3816596	5	160.975.332	0.6129	T	1.05 (0.87–1.26)
<i>GABRA1/LOC100287123</i>	rs12658835	5	161.275.302	0.6454	G	1.05 (0.86–1.28)
<i>ATXN1</i>	rs179997	6	16.318.633	0.0473	A	1.20 (1.00–1.44)
<i>TNF/LTA</i>	rs1800629	6	31.543.031	0.3355	G	1.14 (0.87–1.50)
<i>OPRM1</i>	rs1799971	6	154.360.797	0.337	A	1.12 (0.89–1.41)
<i>OPRM1</i>	rs563649	6	154.407.967	0.8261	A	1.04 (0.72–1.50)
<i>OPRK1</i>	rs702764	8	54.142.157	0.7637	T	1.04 (0.81–1.33)

<i>OPRK1</i>	rs997917	8	54.152.378	0.3819	C	1.09 (0.90–1.33)
<i>PENK</i>	rs3839874	8	57.353.827	0.2525	T	1.11 (0.93–1.32)
<i>PENK</i>	rs1975285	8	57.358.682	0.1082	C	1.19 (0.96–1.47)
<i>TRPA1</i>	rs11988795	8	72.949.601	0.8807	C	1.01 (0.84–1.22)
<i>BDNFOS</i>	rs6265	11	27.679.916	0.295	G	1.12 (0.91–1.37)
<i>BDNF</i>	rs2049046	11	27.723.775	0.1426	T	1.14 (0.96–1.36)
<i>KIF18A/BDNF</i>	rs908867	11	27.745.764	0.127	G	1.28 (0.93–1.77)
<i>DRD2</i>	rs6277	11	113.283.459	0.6926	T	1.04 (0.87–1.24)
<i>DRD2</i>	rs1076560	11	113.283.688	0.5758	C	1.08 (0.83–1.41)
<i>DRD2</i>	rs2734837	11	113.286.829	0.7506	G	1.03 (0.85–1.24)
<i>DRD2</i>	rs11608185	11	113.294.976	0.7529	T	1.03 (0.85–1.24)
<i>DRD2</i>	rs4936272	11	113.318.907	0.864	C	1.02 (0.85–1.21)
<i>DRD2</i>	rs4648317	11	113.331.532	0.0186	T	1.35 (1.05–1.74)
<i>DRD2</i>	rs4322431	11	113.332.956	0.3671	T	1.09 (0.90–1.33)
<i>TMPRSS5/DRD2</i>	rs1799978	11	113.346.351	0.8962	A	1.03 (0.69–1.53)

<i>TMPRSS5/DRD2</i>	rs12364283	11	113.346.955	0.0102	G	1.58 (1.11–2.23)
<i>GWAS*</i>	rs17122021	11	118.145.686	0.1005	T	1.17 (0.97–1.40)
<i>SLCO1B3</i>	rs4149117	12	21.011.480	0.5382	G	1.09 (0.84–1.41)
<i>SLCO1A2</i>	rs11568563	12	21.457.434	0.2388	A	1.23 (0.87–1.74)
<i>NFKBIA</i>	rs8904	14	35.871.217	0.0394	T	1.21 (1.01–1.44)
<i>SAMD4A/GCH1</i>	rs10483639	14	55.306.457	0.0713	C	1.24 (0.98–1.57)
<i>SAMD4A/GCH1</i>	rs7142517	14	55.306.804	0.3649	C	1.09 (0.90–1.31)
<i>GCH1</i>	rs752688	14	55.311.569	0.0514	T	1.27 (1.00–1.60)
<i>GCH1</i>	rs4411417	14	55.320.563	0.0458	C	1.27 (1.00–1.62)
<i>GCH1</i>	rs9671371	14	55.328.635	0.1016	T	1.18 (0.97–1.44)
<i>LOC100289044/GCH1</i>	rs12147422	14	55.344.015	0.3107	T	1.17 (0.87–1.57)
<i>LOC100289044/GCH1</i>	rs8004445	14	55.350.666	0.2536	G	1.19 (0.88–1.60)
<i>LOC100289044/GCH1</i>	rs998259	14	55.355.031	0.9864	C	1.00 (0.82–1.22)
<i>GCH1/LOC100289044</i>	rs3783641	14	55.360.139	0.0807	A	1.23 (0.97–1.56)
<i>WDHD1/LOC100289044</i>	rs8007267	14	55.378.991	0.2502	T	1.15 (0.90–1.47)

<i>SLC6A2</i>	rs40434	16	55.699.525	0.139	C	1.15 (0.96–1.38)
<i>SLC6A2</i>	rs36024	16	55.706.391	0.2056	C	1.12 (0.94–1.34)
<i>SLC6A2</i>	rs36017	16	55.718.818	0.141	G	1.14 (0.96–1.36)
<i>TRPV1</i>	rs8065080	17	3.480.447	0.9945	C	1.00 (0.84–1.20)
<i>CCDC55</i>	rs1979572	17	28.511.978	0.7896	C	1.02 (0.86–1.22)
<i>SLC6A4</i>	rs4325622	17	28.526.475	0.9607	T	1.00 (0.84–1.20)
<i>SLC6A4</i>	rs140701	17	28.538.532	0.557	G	1.05 (0.88–1.26)
<i>SLC6A4</i>	rs2066713	17	28.551.665	0.4839	C	1.07 (0.89–1.29)
<i>MC4R/LOC728115</i>	rs9966412	18	58.033.935	0.4191	C	1.11 (0.86–1.44)
<i>GWAS*</i>	rs2562456	19	21.666.210	0.3402	C	1.10 (0.90–1.35)
<i>B9D2/TGFB1</i>	rs1800469	19	41.860.296	0.5785	C	1.05 (0.88–1.27)
<i>COMT</i>	rs4646312	22	19.948.337	0.3568	C	1.09 (0.91–1.30)
<i>COMT</i>	rs6269	22	19.949.952	0.5077	G	1.06 (0.89–1.27)
<i>COMT</i>	rs4680	22	19.951.271	0.6067	G	1.05 (0.88–1.25)
<i>MAOA</i>	rs3788862	X	43.517.364	0.4551	A	1.10 (0.85–1.42)

<i>MAOA</i>	rs2283724	X	43.559.576	0.5271	G	1.08 (0.85–1.37)
<i>MAOA</i>	rs1800659	X	43.574.169	0.8307	C	1.03 (0.80–1.31)
<i>MAOA</i>	rs979606	X	43.601.142	0.8108	G	1.03 (0.80–1.33)
<i>MAOA</i>	rs979605	X	43.601.363	0.7978	T	1.03 (0.80–1.33)

CI = confidence interval; CPSP = chronic postsurgical pain; SNP = single nucleotide polymorphism.

*SNPs selected because they were significant in the genome-wide association study of Kim and colleagues (2009)²⁰

Table 8. Distribution of Independent Variable Results in the Total Study Population of 2,929 Patients and in the 527 Patients with CPSP

	No. of Patients	No. (%) of Patients	<i>P</i> Value
	2,929	with CPSP 527 (18)	
Variables entered into the multiple regression model			
Surgical speciality			
Hernia repair	1,761	239 (13.6)	<0.0001
Vaginal hysterectomy	416	49 (11.8)	
Abdominal hysterectomy	350	88 (25.1)	
Thoracotomy	402	151 (37.6)	
Age			
18–51 y	905	226 (25)	<0.0001
> 51–64 y	919	161 (17.5)	
> 64	1,104	140 (12.7)	
BMI			

< 24.44	864	162 (18.8)	0.334
24.44–28.08	1,151	194 (16.9)	
> 28.08	863	166 (19.2)	
Score on the SF-12 (physical summary)			
0–33.5	284	81 (28.5)	<0.0001
33.6–55.1	1,954	353 (18.1)	
> 55.1	609	80 (13.1)	
Score on the SF-12 (mental summary)			
0–44.8	569	154 (27.1)	<0.0001
> 44.8	2,278	360 (15.8)	
Anxiety (HADS)			
No	2,096	326 (15.6)	<0.0001
Yes	739	187 (25.3)	
Depression (HADS)			
No	2,577	447 (17.3)	0.001

Yes	257	66 (25.7)	
Substance addiction*			
No	1,441	209 (14.5)	<0.0001
Yes	1,477	317 (21.5)	
Diagnosed chronic respiratory disease (COPD)			
No	2,473	415 (16.8)	<0.0001
Yes	449	111 (24.7)	
Hypertension			
No	1,948	375 (19.3)	0.013
Yes	974	151 (15.5)	
Neurologic disease			
No	2,758	486 (17.6)	0.028
Yes	164	40 (24.4)	
Neoplastic disease			
No	2,389	365 (15.3)	<0.0001

Yes	533	161 (30.2)	
Preoperative pain, surgical area			
VNRS ≤ 3	2,356	396 (16.8)	<0.0001
VNRS > 3	559	130 (23.3)	
Preoperative pain, other areas			
VNRS ≤ 3	2,333	388 (16.6)	<0.0001
VNRS > 3	576	134 (23.3)	
Previous experience of pain and surgery			
No	2,099	349 (16.6)	0.001
Yes	816	177 (21.7)	

Family history of pain and surgery			
No	2,578	460 (17.8)	0.019
Yes	214	52 (24.3)	
Type of anesthesia			
Regional or local infiltration	1,684	226 (13.4)	<0.0001
General or combined	1,216	300 (24.7)	
Intraoperative intravenous opioid			
No	1,299	169 (13.0)	<0.0001
Yes	1,598	357 (22.3)	
Other candidate variables not entered into the multiple regression model			
Education			
< 9 y	1,143	174 (15.2)	0.002
≥ 9 y	315	315 (19.9)	
Heart disease			
No	2,628	478 (18.2)	0.431

Yes	294	48 (16.3)	
Peripheral vascular disease			
No	2,706	495 (18.3)	0.147
Yes	216	31 (14.4)	
Chronic kidney disease			
No	2,854	512 (17.9)	0.574
Yes	68	14 (20.6)	
Hepatic disease			
No	2,829	505 (17.9)	0.243
Yes	93	21 (22.6)	
Diabetes mellitus			
No	2,573	463 (18.0)	0.196
Oral medication or diet	297	49 (16.5)	
On insulin	52	14 (26.9)	
Immunocompromised			

No	2,854	512 (17.9)	0.574
Yes	68	14 (20.6)	
Alcohol addiction* > 24 g/d			
No	2,580	451 (17.5)	0.044
Yes	342	75 (21.9)	
Smoking addiction*			
Never	1,536	225 (14.6)	<0.0001
Former smoker	671	150 (22.4)	
Current smoker	715	151 (21.1)	
Street-drug addiction*			
No	2,886	518 (17.9)	0.302
Yes	32	8 (25.0)	
ASA physical status			
1 (normal healthy patient)	770	143 (18.6)	0.008
2 (patient with mild systemic disease)	1,755	291 (16.6)	

3 (patient with severe systemic disease)			
4 (patient with severe systemic disease that is a constant threat to life)	397	92 (23.2)	
Intraoperative intravenous remifentanyl			
No	2,433	420 (17.3)	0.004
Yes	442	102 (23.1)	
Postsurgical pain at 24 h			
VNRS \leq 3	2,547	426 (16.7)	<0.0001
VNRS >3	306	89 (29.1)	

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPSP = chronic postsurgical pain; HADS = Hospital Anxiety and Depression Scale; SF-12 = Short Form Health Survey-12, Spanish version 2; VNRS = verbal numerical rating scale.

* When entered into the model, all types of addiction (smoking, alcohol, and street drugs) were grouped together. Considered separately, substance addiction included alcohol intake >24g/d, current smoking, former smoking, and use of street-drugs (e.g., cannabis, cocaine, heroine).

Table 9. Independent Predictors of Risk for CPSP Identified in the General Linear Mixed Model for Binomial Distribution with the Variable *Recruitment Center* as a Random Factor

	Bivariate Analysis		Multivariable Analysis*	Bootstrap Resampling†
	OR (95% CI)		OR (95% CI)	OR (95% CI)
	N=2834	β-coefficients	N=2,834	
Surgical specialty				
Vaginal hysterectomy	1			
Abdominal hysterectomy	2.4 (1.6–3.6)	0.497	1.6 (1.1–2.5)	1.7 (1.1–2.6)
Hernia repair	1.2 (0.8–1.6)	0.278	1.3 (0.9–1.9)	1.3 (0.9–2.0)
Thoracotomy	4.5 (3.1–6.5)	1.875	6.5 (4.3–9.9)	6.7 (4.5–10.6)
Age				
18–50	2.3 (1.8–2.9)	1.126	3.1 (2.4–4.0)	3.2 (2.4–4.1)
51–64	1.5 (1.2–1.9)	0.476	1.6 (1.2–2.1)	1.6 (1.2–2.1)
> 64	1			

SF-12 score (physical summary)

0–33.5	2.6 (1.8–3.6)	0.862	2.4 (1.6–3.5)	2.4 (1.6–3.6)
33.6–55.1	1.4 (1.1–1.9)	0.517	1.7 (1.3–2.2)	1.7 (1.3–2.3)
> 55.1	1			

SF-12 score (mental summary)

0–44.8	2 (1.6–2.5)	0.513	1.7 (1.3–2.1)	1.7 (1.3–2.1)
> 44.8	1			

Preoperative pain, surgical area

VNRS \leq 3	1			
VNRS > 3	1.5 (1.2–1.9)	0.413	1.5 (1.2–2.0)	1.5 (1.2–2.0)

Preoperative pain, other areas

VNRS \leq 3	1			
VNRS > 3	1.5 (1.2–1.9)	0.366	1.4 (1.1–1.9)	1.4 (1.1–1.9)

CI = confidence interval; CSPS = chronic postsurgical pain; OR = odds ratio; SF-12 = Short Form Health Survey (version 2 in Spanish);

VNRS = verbal numerical rating scale (0–10).

* c -statistic = 0.731; Hosmer-Lemeshow chi-square test (calibration), **chi-squared** = 4.02; P = 0.855.

† A total of 1,000 **bootstrap** subsamples were modelled.

Appendix 1

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5 **A) The GENDOLCAT Study Investigators by Center (n=23). Centers are listed**
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7 **alphabetically; all cities are in Spain. PI refers to principal investigator; SC, steering**
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9 **B) The GENDOLCAT Committees, with contributorships other than principal authors;**
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Design, analysis and interpretation of genetic study:

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Figure Legends

Figure 1. Recruitment flowchart, showing numbers of patients recruited by type of surgery and those lost up until the times of the follow-up visit and phone interviews in the first and second years. **Chronic postsurgical pain (CPSP)** incidences at all data collection moments are included. HR indicates hernia repair; VH, vaginal hysterectomy, AH, abdominal hysterectomy; and T, thoracotomy. * Candidates for the third telephone interview one year after surgery. † Candidates for the fourth (final) telephone interview two years after surgery.

Figure 2. Chronic postsurgical pain incidences 4, 12, and 24 months after surgery.

Figure 1

[Click here to download Figure\(s\): Figure 1 Flowchart.pdf](#)

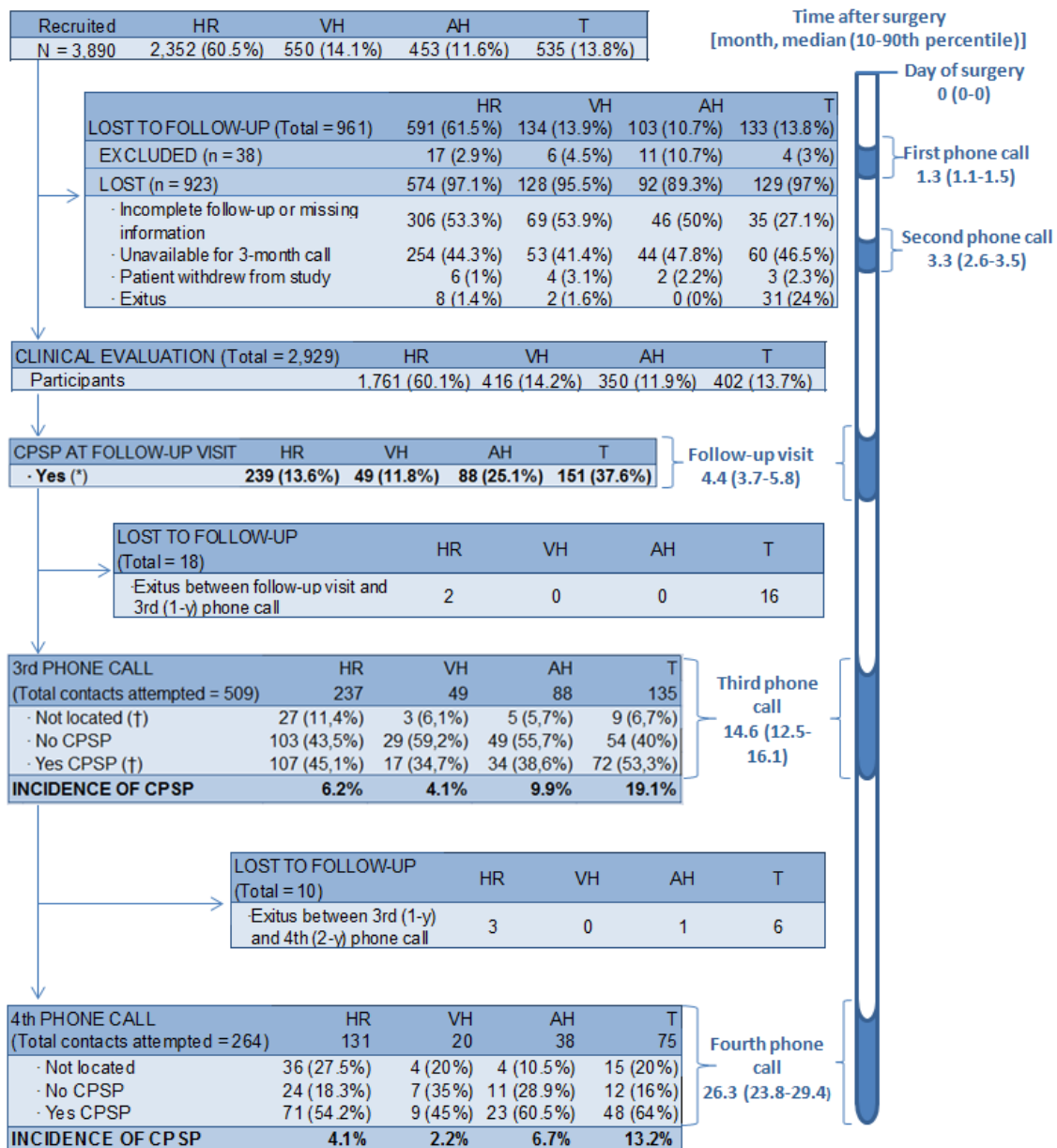


Figure 2

[Click here to download Figure\(s\): Figure 2 Chronic postsurgical pain incidences.pdf](#)

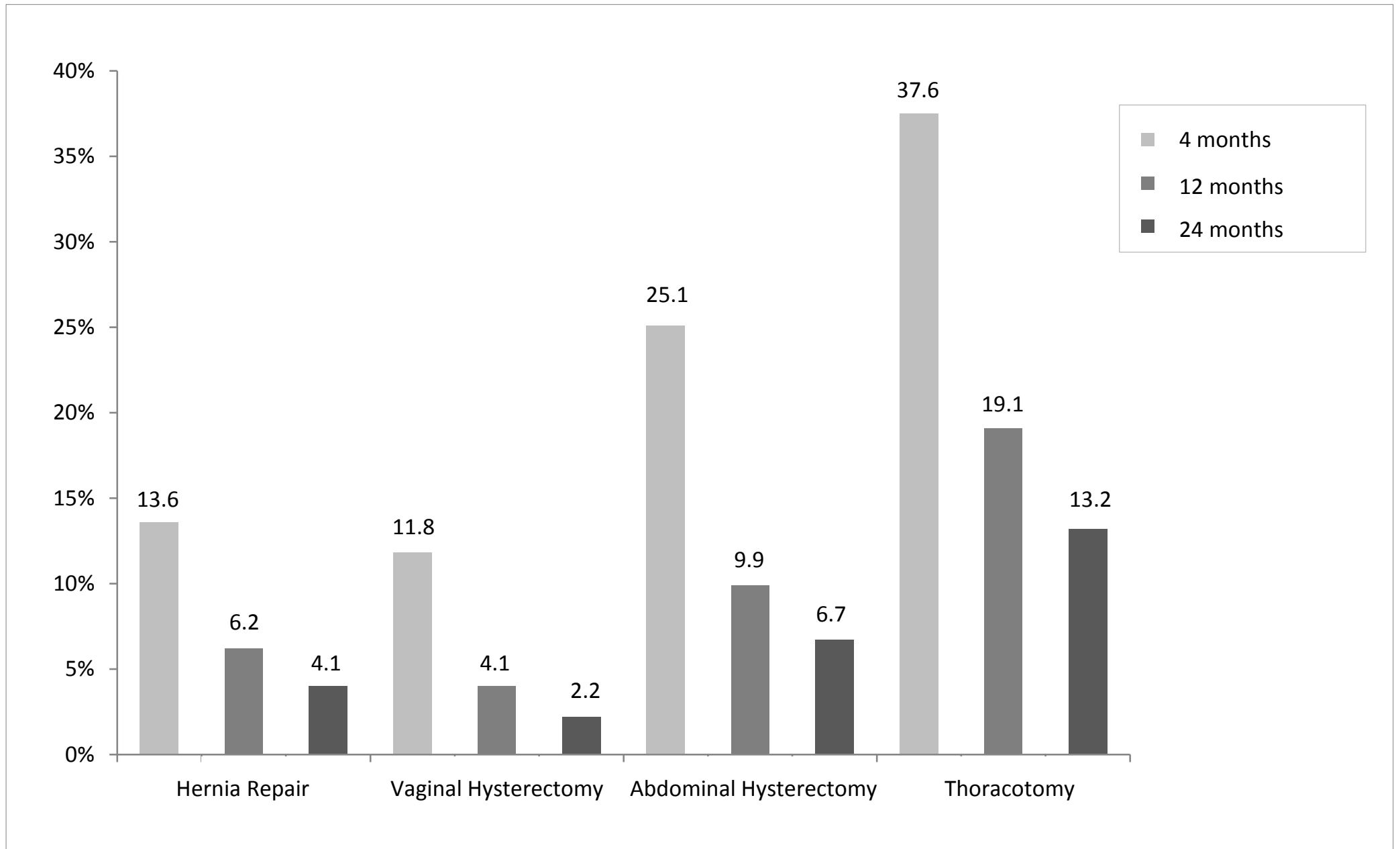


Table 1. Patient Distribution by International Classification of Diseases, Clinical Modification 9 (ICD-9): Diagnostic and Procedure Codes

ICD-9 Diagnostic Codes, Grouped by Type of Surgery Analyzed in the Study

Codes	No. (%)
Hernia repair	1761 (100)
550.90 Unilateral or unspecified inguinal hernia without or gangrene	1480 (84)
550.91 Recurrent unilateral or unspecified inguinal hernia without obstruction or gangrene	92 (5.2)
550.92 Bilateral inguinal hernia without obstruction or gangrene	172 (9.8)
550.93 Recurrent bilateral inguinal hernia without obstruction or gangrene	17 (1)
Vaginal hysterectomy	416 (100)
179 Malignant neoplasm of uterus-part unspecified	3 (0.7)
180 Malignant neoplasm of cervix uteri	9 (2.2)
182 Malignant neoplasm of body of uterus	11 (2.6)
218 Uterine leiomyoma	29 (7)
219 Other benign neoplasm of uterus	33 (7.9)
615 Inflammatory diseases of uterus except cervix	1 (0.2)
618 Genital prolapse	319 (76.7)
629 Other disorders of female genital organs	11 (2.6)
Abdominal hysterectomy abdominal	350 (100)
179 Malignant neoplasm of uterus-part unspecified	21 (6)
180 Malignant neoplasm of cervix uteri	20 (5.7)
182 Malignant neoplasm of body of uterus	25 (7.1)
218 Uterine leiomyoma	185 (52.9)
219 Other benign neoplasm of uterus	62 (17.7)
615 Inflammatory diseases of uterus except cervix	4 (1.1)
618 Genital prolapse	3 (0.9)
629 Other disorders of female genital organs	30 (8.6)
Thoracotomy	402 (100)
162 Malignant neoplasm of trachea bronchus and lung	314 (78.1)
163 Malignant neoplasm of pleura	2 (0.5)
195 Malignant neoplasm of other and ill-defined sites	37 (9.2)
212 Benign neoplasm of respiratory and intrathoracic organs	23 (5.7)
510 Empyema	2 (0.5)
518 Other diseases of lung	19 (4.7)
860 Traumatic pneumothorax and hemothorax	5 (1.2)

ICD-9 Surgical Procedure Codes, Grouped by Type of Surgery Analyzed in the Study

Codes	No. (%)
Hernia repair	1761 (100)
53.00 Unilateral repair of inguinal hernia	62 (3.5)
53.05 Repair of direct inguinal hernia with graft or prosthesis	1528 (86.8)
53.10 Bilateral repair of inguinal hernia	6 (0.3)
53.16 Bilateral repair of inguinal hernia, one direct and one indirect, with graft or prosthesis	9 (0.5)
53.17 Bilateral inguinal hernia repair with graft or prosthesis	150 (8.5)
53.29 Other unilateral femoral herniorrhaphy	5 (0.3)
53.9 Other hernia repair	1 (0.1)
Vaginal hysterectomy	416 (100)
68.59 Other and unspecified vaginal hysterectomy	227 (54.6)
68.7 Radical vaginal hysterectomy	14 (3.4)
68.9 Other and unspecified hysterectomy	11 (2.6)
68.59 Other Vaginal Hysterectomy + 70.5 + Repair of cystocele and rectocele	164 (39.4)
Abdominal hysterectomy	350 (100)
68.39 Other and unspecified subtotal abdominal hysterectomy	43 (12.3)
68.49 Other and unspecified total abdominal hysterectomy	256 (73.1)
68.6 Radical abdominal hysterectomy	41 (11.7)
68.9 Other and unspecified hysterectomy	10 (2.9)
Thoracotomy	402 (100)
32.29 Other local excision or destruction of lesion or tissue of lung	40 (10)
32.3 Segmental resection of lung	58 (14.4)
32.4 Lobectomy of lung	242 (60.2)
32.5 Complete pneumonectomy	32 (8)
33.4 Repair and plastic operation on lung and bronchus	4 (1)
34.02 Exploratory thoracotomy	8 (2)
34.3 Excision or destruction of lesion or tissue of mediastinum	6 (1.5)
34.51 Decortication of lung	5 (1.2)
34.7 Repair of chest wall	1 (0.2)
34.99 Other operations on thorax	6 (1.5)

Supplemental Digital Content 2

Data Collection Questionnaires, Variables, and Definitions

Variables recorded on enrollment

- Diagnosis leading to surgery
- Description of surgical procedure
- Type of surgery: scheduled or emergency
- Sex
- Age in years
- Place of birth (Spanish autonomous community)
- Date of surgery
- Employment status
- Education in years of formal schooling

Variables recorded in the preoperative assessment visit with anesthesiologist

- Weight and height
- Alcohol intake: positive if >24 g/d (>3 glasses of wine, or >3 beers or ≥ 2 glasses of hard liquor)
- Smoking:
 - No
 - Current
 - Ex-smoker (>3 months since last smoke)
- Chronic obstructive pulmonary disease: answer “yes” or “no” to the question “Has any physician told you that you have a chronic respiratory disease?”
- Heart disease declared by the patient, stable or unstable
- Hypertension: answer “yes” if the patient reports this diagnosis or is on an antihypertensive drug
- Peripheral circulatory disease declared by the patient or recorded in the chart
- Neurologic disease declared by the patient or recorded in the chart
- Chronic kidney failure with or without dialysis
- Liver disease declared by the patient, recorded in the chart, or observed (previous jaundice, hepatomegaly or ascites)

- Diabetes mellitus: treated with dietary measures, with oral antidiabetic therapy alone, insulin alone, or an oral antidiabetic agent plus insulin
- Cancer: Karnofsky score $>50\%$ or $\leq 50\%$
- Immunosuppression declared by patient (treatment) or disease recorded in chart
- American Society of Anesthesiologists physical status classification (1-4)

Preoperative pain assessment

- Drugs used for reasons other than pain
 - Benzodiazepines
 - Anticonvulsants: ongoing treatment or only preoperative
 - Antidepressants
 - Corticosteroids
 - Street drugs (cannabis, cocaine, heroine, etc): If cannabis is being used for therapeutic purposes, record “no” or if ≤ 2 cigarettes/d are smoked
- Presence of pain at the site of the intervention or other parts of the body during the 24 hours prior to surgery, with intensity expressed on a verbal numerical rating scale (VNRS) (0=no pain, 10=the worst imaginable pain to 10) (Values > 3 were considered positive in the bivariable and multivariable analyses)¹
- Use of analgesics or other agents for pain: paracetamol, nonsteroidal anti-inflammatory drugs, metamizole, low-dose opioids, strong opioids, antidepressants, anticonvulsants
- Previous experience of intense postoperative pain
- Family history of chronic postoperative pain: grandparents, parents, siblings, children
- Short Form Health Survey-12 (SF-12), for quality of life (version 2; time frame, 4 weeks) (Spanish version)²
- Hospital Anxiety and Depression Scale (Spanish version).³ The 14 items are scored on a 4-point Likert scale. Seven items measuring anxiety and seven measuring depression over the last week provide a total score of between 0 and 21 for each subscale. The cut-off point for anxiety or depression is 8

Intraoperative variables

- Surgical incision
 - Direct inguinal hernia repair:

- Anterior inguinal repair, Liechtenstein mesh hernioplasty
 - Anterior preperitoneal repair, Nyhus or Stoppa technique
 - Repair with plugs (Rutkow/Rutkow-Robbins/Gilbert)
- Femoral hernia repair:
 - Open repair
 - Repair with plugs (Rutkow/Rutkow-Robbins/Gilbert)
 - Meshless repair with suture anchoring (McVay technique)
- Abdominal hysterectomy:
 - Pfannenstiel incision
 - Medial, infraumbilical, or infra-supraumbilical laparotomy
- Vaginal hysterectomy, with or without plasty repair
- Thoracotomy:
 - Unilateral or bilateral
 - Muscle-sparing or not
 - Rib-sparing
 - With resection and/or fracture of a rib
 - With resection and/or fracture of more than one rib
 - Anterior, cartilage-sparing
 - Anterior, with resection of cartilage
 - Anterior, with sternotomy (clamshell incision)
 - Axillary
 - Posterolateral
- Length of incision (except abdominal hysterectomy)
- Nerve-sparing (only in inguinal hernia repair)
- Type of anesthesia (general, including combined with regional anesthesia, or spinal, epidural, plexus nerve block, local)
- Drains
- Opioid doses (fentanyl, remifentanyl, alfentanil, morphine)
- Corticosteroids
- Ondansetron
- Ketamine
- Type of spinal anesthesia: intradural, epidural, combined
- Level of sensory blockade

- Spinal opioid doses (morphine, fentanyl, methadone)
- Type of local anesthetic injected spinally: bupivacaine, mepivacaine, lidocaine, ropivacaine, levobupivacaine, prilocaine
- Results of spinal anesthesia: good, moderate, poor
- Blood loss, in milliliters
- Duration of surgery in minutes (from skin incision to skin closure)
- Destination on discharge from the surgical area: home (major ambulatory surgery), hospital ward (via recovery room), critical care unit, exitus

Postoperative variables

- Pain 24 hours after surgery (VNRS)
- Postoperative length of stay (number of days from the intervention day to discharge)
- Analgesics (oral or parenteral): paracetamol, nonsteroidal anti-inflammatory drugs, metamizole, opioids, tramadol, ketamine, neuroleptics, gabapentinoids
- Infusion and infiltration techniques to manage postoperative pain: epidural or paravertebral infusion, wound infusion, peripheral nerve block
- Surgical wound complications during hospitalization (abscess, fistula, dehiscence, seroma, hematoma)
- Reoperation, using a different incision

Variables recorded at the follow-up visit between 3.5 and 4.5 months

- Date of visit
- Anatomical site of pain
- Brief Pain Inventory (BPI-Spanish version)⁴ (Values > 3 on a scale of 0 to 10 were considered positive indications of interference caused by pain)
- Neuropathic Pain questionnaire (version 4, Douleur Neuropathique 4 [DN4]) (Spanish version)⁵ (cut-off point of 4 out of 10)
- SF-12 questionnaire (version 2, time frame of 4 weeks (Spanish version))
- Analgesic treatments used: paracetamol, non-steroidal anti-inflammatory drug, metamizole, weak opioids, strong opioids, paracetamol-tramadol combination, anticonvulsants, antidepressants, topical analgesic, nerve block, other

Questionnaire for telephone interviews (between 1 and 1.5 months, 2.5 and 3.5 months, at 12 months and at 24 months)

Note the number of days since the operation before the interview.

Ask the patient:

- Do you have (or continue to have) pain related to the operation?

If yes, ask the following questions

- Have you had any problems with the incision?
- Have you had radiotherapy or chemotherapy?
- Have you had to have another operation for any reason, an operation different from the one you had when you joined this study?
- Is the pain you have now like the pain you had after the operation?
- Is the pain continuous or does it come and go?
- If the pain is intermittent, how long does it last? Seconds? Minutes? Hours? Days?
- How bad is the pain on a scale of 0 (meaning no pain at all) to 10 (the worst pain you can imagine)?
- What do you take for your pain?

Allow the patient to express the medication names freely, by active principles or brand names. Classify the replies into the following categories:

- Paracetamol
- Nonsteroidal antiinflammatory drugs
- Metamizole
- Weak opioids
- Strong opioids
- Paracetamol and tramadol in combination
- Anticonvulsant
- Antidepressant
- Topical treatment
- Nerve block
- Other
- Would you say the treatment you're using is effective in relieving your pain? (Not at all? A bit? Somewhat? Pretty well? Very well?)
- Are you still employed or working on your own?

If yes, ask:

- Have you returned to work yet?

Results of the telephone call:

- Exitus
- The patient could not be reached.
- The patient was reached but did not adequately complete the interview.
- The patient was reached and successfully interviewed.

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Supplemental Digital Content 3**Table 1. Genetic Test Results****Results of Allele Frequency Testing With Odds Ratios for CPSP Adjusted for Sex****Male**

SNP	P Value	Risk Allele	Odds Ratio	95% CI
rs1042114	0.0449	G	1.35	1.01–1.81
rs533123	0.4911	C	1.09	0.85–1.4
rs6691840	0.4406	A	1.09	0.87–1.38
rs932816	0.3883	A	1.10	0.88–1.38
rs4141964	0.8819	G	1.01	0.82–1.26
rs2295633	0.9768	C	1.00	0.81–1.24
rs6693882	0.4831	A	1.08	0.87–1.34
rs5275	0.3349	C	1.11	0.89–1.39
rs1800896	0.7223	A	1.03	0.84–1.28
rs6265	0.0329	G	1.30	1.02–1.66
rs2049046	0.1006	T	1.18	0.97–1.46
rs908867	0.3982	G	1.16	0.81–1.68
rs6277	0.7791	T	1.03	0.84–1.27
rs1076560	0.9832	C	1.00	0.74–1.37
rs2734837	0.9373	A	1.01	0.81–1.25
rs11608185	0.9064	C	1.01	0.81–1.26
rs4936272	0.9272	C	1.01	0.82–1.24

rs4648317	0.0404	T	1.36	1.01–1.81
rs4322431	0.3604	T	1.11	0.89–1.39
rs1799978	0.8925	A	1.03	0.64–1.66
rs12364283	0.0573	G	1.47	0.99–2.2
rs17122021	0.0306	T	1.27	1.02–1.57
rs4149117	0.9102	G	1.02	0.75–1.38
rs11568563	0.4042	A	1.19	0.79–1.77
rs8904	0.0308	T	1.25	1.02–1.55
rs10483639	0.0766	C	1.28	0.97–1.7
rs7142517	0.621	C	1.05	0.85–1.31
rs752688	0.0879	T	1.27	0.96–1.69
rs4411417	0.0631	C	1.31	0.98–1.73
rs9671371	0.1585	T	1.18	0.94–1.5
rs12147422	0.1455	T	1.29	0.92–1.81
rs8004445	0.1083	G	1.33	0.94–1.87
rs998259	0.4194	T	1.10	0.87–1.38
rs3783641	0.1748	A	1.21	0.92–1.6
rs8007267	0.2565	T	1.18	0.89–1.58
rs40434	0.1505	C	1.17	0.95–1.44
rs36024	0.3586	C	1.10	0.9–1.35
rs36017	0.4062	G	1.09	0.89–1.34
rs8065080	0.6056	C	1.06	0.86–1.3
rs1979572	0.7951	C	1.03	0.84–1.26
rs4325622	0.8883	C	1.01	0.83–1.24

rs140701	0.5893	G	1.06	0.86–1.3
rs2066713	0.7255	C	1.04	0.84–1.29
rs9966412	0.7198	C	1.06	0.78–1.43
rs2562456	0.9908	T	1.00	0.79–1.27
rs1800469	0.6938	C	1.04	0.84–1.29
rs934778	0.7694	C	1.03	0.83–1.28
rs6746030	0.7984	A	1.04	0.76–1.42
rs6747673	0.2657	A	1.12	0.91–1.38
rs9646771	0.8116	C	1.03	0.83–1.27
rs4646312	0.7426	C	1.03	0.84–1.27
rs6269	0.9745	A	1.00	0.82–1.23
rs4680	0.6193	G	1.05	0.86–1.29
rs7678338	0.5877	T	1.07	0.85–1.34
rs7689605	0.7059	A	1.07	0.74–1.56
rs10028945	0.8413	A	1.02	0.82–1.28
rs12516948	0.5481	A	1.06	0.87–1.31
rs40184	0.5826	A	1.06	0.86–1.3
rs403636	0.578	G	1.08	0.82–1.42
rs6350	0.7908	C	1.05	0.72–1.54
rs3816596	0.1133	T	1.19	0.96–1.47
rs12658835	0.3102	G	1.13	0.89–1.42
rs179997	0.0931	A	1.20	0.97–1.48
rs1800629	0.7464	G	1.05	0.77–1.44
rs1799971	0.877	A	1.02	0.78–1.34

rs563649	0.851	A	1.04	0.68–1.59
rs702764	0.9032	T	1.02	0.76–1.37
rs997917	0.827	C	1.03	0.82–1.29
rs3839874	0.4568	T	1.08	0.88–1.33
rs1975285	0.1264	C	1.21	0.95–1.54
rs11988795	0.6814	C	1.05	0.84–1.3
rs3788862	0.4777	A	1.12	0.81–1.55
rs2283724	0.3758	G	1.15	0.85–1.56
rs1800659	0.8199	C	1.04	0.76–1.42
rs979606	0.7808	G	1.05	0.76–1.44
rs979605	0.7981	T	1.04	0.76–1.44

Female

SNP	<i>P</i> Value	Risk Allele	Odds Ratio	95% CI
rs1042114	0.4777	T	1.22	0.71–2.09
rs533123	0.2344	T	1.32	0.84–2.07
rs6691840	0.5062	C	1.15	0.77–1.72
rs932816	0.1134	A	1.36	0.93–2
rs4141964	0.8969	G	1.02	0.72–1.46
rs2295633	0.9701	C	1.01	0.7–1.44
rs6693882	0.3424	A	1.19	0.83–1.71
rs5275	0.2624	T	1.24	0.85–1.79
rs1800896	0.836	A	1.04	0.73–1.48
rs6265	0.1527	A	1.33	0.9–1.96
rs2049046	0.912	T	1.02	0.72–1.44
rs908867	0.1001	G	1.80	0.89–3.65
rs6277	0.7665	T	1.05	0.74–1.5
rs1076560	0.2939	C	1.32	0.79–2.2
rs2734837	0.4441	G	1.16	0.8–1.67
rs11608185	0.4071	T	1.17	0.81–1.7
rs4936272	0.8405	C	1.04	0.73–1.46
rs4648317	0.2443	T	1.35	0.82–2.22
rs4322431	0.8264	T	1.04	0.71–1.53
rs1799978	0.9657	A	1.02	0.49–2.12
rs12364283	0.0636	G	1.96	0.95–4.02
rs17122021	0.6636	C	1.08	0.75–1.56

rs4149117	0.3099	G	1.31	0.78–2.18
rs11568563	0.3677	A	1.36	0.69–2.67
rs8904	0.6886	T	1.07	0.76–1.52
rs10483639	0.5798	C	1.13	0.73–1.77
rs7142517	0.3528	C	1.19	0.82–1.72
rs752688	0.3529	T	1.23	0.79–1.92
rs4411417	0.4357	C	1.19	0.77–1.86
rs9671371	0.417	T	1.17	0.8–1.72
rs12147422	0.5917	C	1.18	0.64–2.17
rs8004445	0.5917	T	1.18	0.64–2.17
rs998259	0.161	C	1.32	0.89–1.96
rs3783641	0.2708	A	1.28	0.82–1.99
rs8007267	0.7349	T	1.08	0.69–1.7
rs40434	0.6328	C	1.09	0.76–1.56
rs36024	0.3465	C	1.18	0.84–1.66
rs36017	0.1362	G	1.30	0.92–1.83
rs8065080	0.392	T	1.17	0.82–1.65
rs1979572	0.9249	C	1.02	0.72–1.43
rs4325622	0.7257	T	1.06	0.76–1.5
rs140701	0.8004	G	1.05	0.74–1.47
rs2066713	0.4379	C	1.16	0.8–1.67
rs9966412	0.3258	C	1.29	0.77–2.17
rs2562456	0.0596	C	1.47	0.98–2.2
rs1800469	0.6889	C	1.08	0.74–1.57

rs934778	0.2698	T	1.22	0.86–1.74
rs6746030	0.8172	G	1.06	0.65–1.74
rs6747673	0.7852	T	1.05	0.74–1.48
rs9646771	0.6793	C	1.08	0.75–1.55
rs4646312	0.2005	C	1.26	0.89–1.78
rs6269	0.1666	G	1.28	0.9–1.82
rs4680	0.8594	G	1.03	0.73–1.46
rs7678338	0.9765	C	1.01	0.68–1.48
rs7689605	0.7837	A	1.10	0.56–2.17
rs10028945	0.9399	G	1.01	0.7–1.47
rs12516948	0.0607	G	1.39	0.98–1.97
rs40184	0.4379	G	1.15	0.81–1.62
rs403636	0.1104	G	1.44	0.92–2.25
rs6350	0.3448	C	1.39	0.7–2.79
rs3816596	0.0913	C	1.36	0.95–1.96
rs12658835	0.4201	A	1.17	0.8–1.73
rs179997	0.2767	A	1.21	0.86–1.72
rs1800629	0.1789	G	1.44	0.84–2.46
rs1799971	0.1056	A	1.46	0.92–2.3
rs563649	0.9107	A	1.04	0.51–2.11
rs702764	0.6958	T	1.10	0.69–1.76
rs997917	0.1851	C	1.29	0.88–1.89
rs3839874	0.3239	T	1.19	0.84–1.68
rs1975285	0.5818	C	1.13	0.74–1.71

rs11988795	0.6763	T	1.08	0.75–1.57
rs3788862	0.7195	A	1.08	0.71–1.65
rs2283724	0.956	A	1.01	0.68–1.5
rs1800659	0.9196	C	1.02	0.69–1.52
rs979606	0.9499	G	1.01	0.68–1.52
rs979605	0.9138	T	1.02	0.68–1.53

CI = confidence interval; CPSP = chronic postsurgical pain; SNP = single nucleotide polymorphism.

Results of Allele Frequency Testing With Odds Ratios for CPSP Adjusted by Type of Intervention

Hernia Repair

SNP	P Value	Risk Allele	Odds Ratio	95% CI
rs1042114	0.0236	G	1.54	1.06–2.25
rs533123	0.0737	C	1.35	0.97–1.86
rs6691840	0.6271	A	1.07	0.81–1.43
rs932816	0.3894	A	1.13	0.85–1.51
rs4141964	0.4665	G	1.11	0.84–1.45
rs2295633	0.5815	C	1.08	0.82–1.42
rs6693882	0.447	A	1.11	0.85–1.46
rs5275	0.448	C	1.11	0.84–1.47
rs1800896	0.7769	G	1.04	0.8–1.36
rs6265	0.2954	G	1.18	0.86–1.62
rs2049046	0.0846	T	1.26	0.97–1.64
rs908867	0.7426	G	1.08	0.68–1.7
rs6277	0.9769	T	1.00	0.77–1.31
rs1076560	0.9193	A	1.02	0.69–1.52
rs2734837	0.887	A	1.02	0.77–1.35
rs11608185	0.9421	C	1.01	0.77–1.33
rs4936272	0.9972	T	1.00	0.77–1.3
rs4648317	0.0188	T	1.54	1.07–2.22
rs4322431	0.3846	T	1.14	0.85–1.52
rs1799978	0.2826	A	1.43	0.74–2.74

rs12364283	0.0323	G	1.71	1.04–2.82
rs17122021	0.0069	T	1.46	1.11–1.92
rs4149117	0.3494	G	1.20	0.82–1.77
rs11568563	0.6371	A	1.12	0.69–1.82
rs8904	0.0619	T	1.29	0.99–1.68
rs10483639	0.8818	C	1.03	0.72–1.46
rs7142517	0.458	C	1.11	0.84–1.47
rs752688	0.8818	T	1.03	0.72–1.46
rs4411417	0.7637	C	1.06	0.74–1.5
rs9671371	0.6724	T	1.07	0.79–1.44
rs12147422	0.1638	T	1.36	0.88–2.11
rs8004445	0.1638	G	1.36	0.88–2.11
rs998259	0.7293	T	1.05	0.78–1.42
rs3783641	0.6572	T	1.08	0.76–1.53
rs8007267	0.433	C	1.16	0.8–1.67
rs40434	0.068	C	1.29	0.98–1.69
rs36024	0.3791	C	1.13	0.87–1.46
rs36017	0.1429	G	1.22	0.94–1.58
rs8065080	0.8801	T	1.02	0.78–1.33
rs1979572	0.6392	T	1.06	0.82–1.38
rs4325622	0.4272	C	1.11	0.86–1.44
rs140701	0.6907	A	1.05	0.81–1.37
rs2066713	0.8473	C	1.03	0.78–1.36
rs9966412	0.668	T	1.09	0.73–1.62

rs2562456	0.8178	T	1.04	0.76–1.41
rs1800469	0.8683	C	1.02	0.78–1.35
rs934778	0.9155	T	1.02	0.77–1.34
rs6746030	0.9399	G	1.02	0.68–1.51
rs6747673	0.7469	A	1.04	0.8–1.36
rs9646771	0.5801	C	1.08	0.82–1.42
rs4646312	0.7493	C	1.04	0.8–1.36
rs6269	0.873	A	1.02	0.78–1.33
rs4680	0.4535	G	1.11	0.85–1.44
rs7678338	0.119	T	1.26	0.94–1.69
rs7689605	0.0956	A	1.53	0.93–2.51
rs10028945	0.5687	G	1.09	0.82–1.45
rs12516948	0.628	A	1.07	0.82–1.39
rs40184	0.7465	A	1.04	0.8–1.36
rs403636	0.5617	G	1.11	0.78–1.59
rs6350	0.6877	T	1.10	0.69–1.77
rs3816596	0.1785	T	1.20	0.92–1.58
rs12658835	0.8173	G	1.04	0.77–1.4
rs179997	0.0554	A	1.30	0.99–1.71
rs1800629	0.7246	A	1.07	0.72–1.59
rs1799971	0.8182	A	1.04	0.74–1.46
rs563649	0.4823	G	1.23	0.69–2.19
rs702764	0.6628	T	1.09	0.74–1.6
rs997917	0.6567	T	1.07	0.8–1.43

rs3839874	0.8255	C	1.03	0.79–1.34
rs1975285	0.606	C	1.08	0.8–1.48
rs11988795	0.3047	C	1.16	0.88–1.52
rs3788862	0.2316	A	1.28	0.85–1.92
rs2283724	0.197	G	1.29	0.88–1.9
rs1800659	0.3467	C	1.21	0.81–1.8
rs979606	0.5133	G	1.15	0.76–1.72
rs979605	0.5303	T	1.14	0.76–1.72

Vaginal Hysterectomy

SNP	<i>P</i> Value	Risk Allele	Odds Ratio	95% CI
rs1042114	0.8674	G	1.09	0.39-3.03
rs533123	0.8193	C	1.10	0.49-2.44
rs6691840	0.9328	A	1.03	0.53–1.98
rs932816	0.8492	A	1.06	0.57–1.98
rs4141964	0.8795	A	1.05	0.59–1.85
rs2295633	0.9692	C	1.01	0.57–1.8
rs6693882	0.7009	A	1.12	0.63–2
rs5275	0.7815	T	1.09	0.59–2.03
rs1800896	0.326	A	1.33	0.75–2.35
rs6265	0.8248	A	1.07	0.59–1.95
rs2049046	0.3502	T	1.31	0.75–2.28
rs908867	0.0629	G	3.30	0.88–12.37
rs6277	0.541	C	1.19	0.68–2.1
rs1076560	0.9868	A	1.01	0.45–2.27
rs2734837	0.4891	G	1.23	0.68–2.24
rs11608185	0.3135	T	1.36	0.75–2.47
rs4936272	0.7144	T	1.11	0.63–1.95
rs4648317	0.0629	T	2.17	0.95–4.97
rs4322431	0.1314	T	1.63	0.86–3.1
rs1799978	0.8967	G	1.09	0.3–3.88
rs12364283	0.014	G	3.92	1.23–12.46
rs17122021	0.6256	C	1.16	0.64–2.1

rs4149117	0.5246	T	1.30	0.58–2.89
rs11568563	0.4358	C	1.67	0.46–6.1
rs8904	0.7468	T	1.10	0.62–1.93
rs10483639	0.2413	C	1.52	0.75–3.08
rs7142517	0.7815	C	1.09	0.59–2.03
rs752688	0.1552	T	1.66	0.82–3.34
rs4411417	0.2413	C	1.52	0.75–3.08
rs9671371	0.597	T	1.18	0.64–2.15
rs12147422	0.519	T	1.42	0.49–4.15
rs8004445	0.519	G	1.42	0.49–4.15
rs998259	0.6025	C	1.19	0.62–2.3
rs3783641	0.5226	A	1.25	0.63–2.47
rs8007267	0.9203	T	1.04	0.51–2.09
rs40434	0.8411	C	1.06	0.59–1.9
rs36024	0.4307	C	1.25	0.71–2.19
rs36017	0.33	G	1.32	0.76–2.3
rs8065080	0.812	T	1.07	0.61–1.88
rs1979572	0.6834	C	1.12	0.64–1.96
rs4325622	0.6752	T	1.13	0.65–1.96
rs140701	0.5557	G	1.18	0.68–2.06
rs2066713	0.9209	C	1.03	0.56–1.9
rs9966412	0.2202	C	1.68	0.73–3.88
rs2562456	0.7317	C	1.12	0.59–2.13
rs1800469	0.503	T	1.22	0.68–2.19

rs934778	0.4576	C	1.24	0.7–2.19
rs6746030	0.7115	G	1.16	0.53–2.56
rs6747673	0.7887	T	1.08	0.61–1.92
rs9646771	0.9099	T	1.03	0.58–1.85
rs4646312	0.0764	C	1.67	0.95–2.94
rs6269	0.0539	G	1.74	0.99–3.05
rs4680	0.0729	G	1.68	0.95–2.97
rs7678338	0.9435	C	1.02	0.53–1.97
rs7689605	0.5561	G	1.35	0.49–3.71
rs10028945	0.2467	G	1.47	0.76–2.82
rs12516948	0.0115	G	2.06	1.17–3.62
rs40184	0.1268	A	1.55	0.88–2.73
rs403636	0.874	G	1.06	0.49–2.32
rs6350	0.7228	C	1.20	0.43–3.37
rs3816596	0.3529	C	1.32	0.73–2.37
rs12658835	0.9438	G	1.02	0.53–1.96
rs179997	0.294	A	1.35	0.77–2.37
rs1800629	0.3966	G	1.5	0.58–3.85
rs1799971	0.1569	A	1.71	0.81–3.63
rs563649	0.6034	G	1.41	0.39–5.15
rs702764	0.8549	T	1.07	0.51–2.25
rs997917	0.7933	T	1.09	0.59–2
rs3839874	0.2229	T	1.42	0.81–2.48
rs1975285	0.5908	C	1.20	0.62–2.35

rs11988795	0.9778	T	1.01	0.55–1.84
rs3788862	0.3126	A	1.46	0.7–3.08
rs2283724	0.8962	G	1.05	0.53–2.06
rs1800659	0.694	C	1.15	0.58–2.28
rs979606	0.5254	G	1.26	0.62–2.55
rs979605	0.6475	T	1.18	0.58–2.37

Abdominal Hysterectomy

SNP	<i>P</i> Value	Risk Allele	Odds Ratio	95% CI
rs1042114	0.2882	T	1.41	0.75–2.68
rs533123	0.094	T	1.60	0.92–2.78
rs6691840	0.3618	C	1.27	0.76–2.13
rs932816	0.0656	A	1.58	0.97–2.58
rs4141964	0.8076	G	1.06	0.67–1.68
rs2295633	0.9755	T	1.01	0.63–1.6
rs6693882	0.3415	A	1.25	0.79–2
rs5275	0.2132	T	1.34	0.84–2.14
rs1800896	0.5811	G	1.14	0.72–1.79
rs6265	0.0739	A	1.60	0.95–2.7
rs2049046	0.542	A	1.15	0.74–1.77
rs908867	0.5152	G	1.33	0.56–3.18
rs6277	0.4069	T	1.21	0.77–1.89
rs1076560	0.1775	C	1.58	0.81–3.08
rs2734837	0.656	G	1.11	0.69–1.78
rs11608185	0.7742	T	1.07	0.67–1.72
rs4936272	0.6157	C	1.12	0.72–1.73
rs4648317	0.9857	T	1.01	0.53–1.9
rs4322431	0.3985	A	1.23	0.76–1.99
rs1799978	0.8641	A	1.08	0.44–2.67
rs12364283	0.7658	G	1.16	0.44–3.01
rs17122021	0.8146	C	1.06	0.67–1.67

rs4149117	0.0682	G	1.88	0.95–3.73
rs11568563	0.1076	A	1.93	0.86–4.36
rs8904	0.8082	T	1.06	0.68–1.64
rs10483639	0.8326	G	1.06	0.6–1.88
rs7142517	0.309	C	1.27	0.8–2.02
rs752688	0.9358	T	1.02	0.58–1.81
rs4411417	0.9358	C	1.02	0.58–1.81
rs9671371	0.4994	T	1.19	0.72–1.95
rs12147422	0.284	C	1.51	0.71–3.22
rs8004445	0.284	T	1.51	0.71–3.22
rs998259	0.1593	C	1.42	0.87–2.33
rs3783641	0.3389	A	1.32	0.74–2.36
rs8007267	0.6824	T	1.13	0.63–2.04
rs40434	0.6625	C	1.11	0.7–1.73
rs36024	0.5301	C	1.15	0.74–1.78
rs36017	0.2593	G	1.28	0.83–1.99
rs8065080	0.4029	T	1.21	0.77–1.89
rs1979572	0.8393	T	1.05	0.68–1.62
rs4325622	0.9079	T	1.03	0.66–1.58
rs140701	0.8928	A	1.03	0.67–1.59
rs2066713	0.3454	C	1.25	0.79–1.98
rs9966412	0.8023	C	1.09	0.56–2.11
rs2562456	0.0329	C	1.75	1.04–2.94
rs1800469	0.3294	C	1.27	0.78–2.07

rs934778	0.049	T	1.58	1–2.48
rs6746030	0.9857	A	1.01	0.53–1.9
rs6747673	0.9845	T	1.00	0.65–1.56
rs9646771	0.5438	C	1.15	0.73–1.83
rs4646312	0.7682	C	1.07	0.68–1.67
rs6269	0.7732	G	1.07	0.68–1.67
rs4680	0.2706	A	1.28	0.83–1.98
rs7678338	0.9373	T	1.02	0.63–1.65
rs7689605	0.3221	A	1.62	0.62–4.22
rs10028945	0.5277	A	1.16	0.73–1.84
rs12516948	0.64	G	1.11	0.71–1.73
rs40184	0.0279	G	1.63	1.05–2.53
rs403636	0.0557	G	1.71	0.98–2.96
rs6350	0.3665	C	1.54	0.6–3.92
rs3816596	0.1556	C	1.39	0.88–2.21
rs12658835	0.2586	A	1.32	0.81–2.15
rs179997	0.6302	A	1.12	0.71–1.75
rs1800629	0.2718	G	1.44	0.75–2.76
rs1799971	0.3465	A	1.32	0.74–2.35
rs563649	0.6631	A	1.21	0.51–2.84
rs702764	0.7471	T	1.11	0.6–2.04
rs997917	0.0566	C	1.61	0.98–2.63
rs3839874	0.7654	T	1.07	0.69–1.66
rs1975285	0.8153	C	1.07	0.62–1.83

rs11988795	0.5884	T	1.14	0.71–1.84
rs3788862	0.7214	G	1.10	0.66–1.84
rs2283724	0.8101	A	1.06	0.65–1.72
rs1800659	0.8171	T	1.06	0.65–1.72
rs979606	0.6475	A	1.12	0.68–1.84
rs979605	0.786	C	1.07	0.65–1.76

Thoracotomy

SNP	<i>P</i> Value	Risk Allele	Odds Ratio	95% CI
rs1042114	0.7317	G	1.09	0.67–1.76
rs533123	0.2735	T	1.25	0.84–1.86
rs6691840	0.5247	A	1.13	0.77–1.66
rs932816	0.7528	A	1.06	0.75–1.5
rs4141964	0.4986	A	1.13	0.8–1.59
rs2295633	0.5187	T	1.12	0.79–1.59
rs6693882	0.8396	A	1.04	0.73–1.47
rs5275	0.5648	C	1.11	0.77–1.61
rs1800896	0.3566	A	1.17	0.84–1.63
rs6265	0.0386	G	1.49	1.02–2.19
rs2049046	0.6352	T	1.08	0.78–1.5
rs908867	0.3338	G	1.34	0.74–2.46
rs6277	0.6798	T	1.07	0.77–1.5
rs1076560	0.871	C	1.04	0.63–1.72
rs2734837	0.9617	G	1.01	0.71–1.43
rs11608185	0.9207	C	1.02	0.72–1.45
rs4936272	0.8841	C	1.02	0.74–1.42
rs4648317	0.8016	T	1.06	0.65–1.74
rs4322431	0.706	T	1.07	0.75–1.54
rs1799978	0.3281	G	1.42	0.7–2.9
rs12364283	0.796	G	1.09	0.55–2.17
rs17122021	0.9864	C	1.00	0.71–1.43

rs4149117	0.3161	T	1.29	0.79–2.1
rs11568563	0.4098	A	1.36	0.65–2.83
rs8904	0.2625	T	1.21	0.87–1.68
rs10483639	0.0063	C	1.93	1.2–3.11
rs7142517	0.8941	A	1.02	0.73–1.44
rs752688	0.0086	T	1.89	1.17–3.04
rs4411417	0.0078	C	1.90	1.18–3.07
rs9671371	0.0838	T	1.40	0.96–2.04
rs12147422	0.5567	T	1.18	0.68–2.04
rs8004445	0.4064	G	1.27	0.72–2.22
rs998259	0.3923	T	1.17	0.82–1.67
rs3783641	0.0052	A	1.93	1.21–3.07
rs8007267	0.0046	T	1.99	1.23–3.21
rs40434	0.9848	C	1.00	0.72–1.41
rs36024	0.7125	C	1.06	0.77–1.48
rs36017	0.6166	C	1.09	0.78–1.51
rs8065080	0.3106	C	1.19	0.85–1.66
rs1979572	0.3086	C	1.19	0.85–1.65
rs4325622	0.4392	T	1.14	0.82–1.58
rs140701	0.1695	G	1.26	0.91–1.75
rs2066713	0.7555	C	1.06	0.75–1.49
rs9966412	0.2968	C	1.28	0.8–2.04
rs2562456	0.7846	C	1.05	0.72–1.54
rs1800469	0.6806	C	1.07	0.76–1.51

rs934778	0.5505	C	1.11	0.79–1.55
rs6746030	0.6141	A	1.14	0.69–1.87
rs6747673	0.1647	A	1.26	0.91–1.76
rs9646771	0.7584	T	1.06	0.75–1.49
rs4646312	0.9016	C	1.02	0.74–1.42
rs6269	0.8809	G	1.03	0.74–1.43
rs4680	0.8835	A	1.02	0.74–1.42
rs7678338	0.273	C	1.23	0.85–1.78
rs7689605	0.1772	G	1.49	0.83–2.66
rs10028945	0.2999	A	1.21	0.84–1.73
rs12516948	0.7223	A	1.06	0.76–1.48
rs40184	0.6337	A	1.08	0.78–1.5
rs403636	0.8671	G	1.04	0.68–1.58
rs6350	0.3192	C	1.39	0.73–2.64
rs3816596	0.3911	T	1.16	0.83–1.62
rs12658835	0.1841	G	1.28	0.89–1.86
rs179997	0.7695	A	1.05	0.75–1.48
rs1800629	0.3164	G	1.31	0.77–2.21
rs1799971	0.97	G	1.01	0.65–1.56
rs563649	0.2918	A	1.40	0.75–2.65
rs702764	0.7346	C	1.08	0.68–1.72
rs997917	0.3714	C	1.18	0.82–1.69
rs3839874	0.1434	T	1.28	0.92–1.78
rs1975285	0.0698	C	1.44	0.97–2.13

rs11988795	0.5249	T	1.12	0.79–1.6
rs3788862	0.6882	G	1.11	0.66–1.89
rs2283724	0.8181	A	1.06	0.64–1.75
rs1800659	0.3963	T	1.25	0.75–2.07
rs979606	0.6986	A	1.11	0.66–1.86
rs979605	0.6986	C	1.11	0.66–1.86

CI = confidence interval; CPSP = chronic postsurgical pain; SNP = single nucleotide polymorphism.

Results of Risk Genotyping for CPSP

AA+AB / BB

SNP	P Value	Risk Genotype	Odds Ratio	95% CI	N
rs1042114	0.2683	GG+GT	1.18	0.88–1.57	974
rs533123	0.8476	CC+CT	1.03	0.79–1.33	1.000
rs6691840	0.9987	AA+AC	1.00	0.6–1.66	963
rs932816	0.2292	AA+AG	1.16	0.91–1.49	1.000
rs4141964	0.4175	GG	1.11	0.86–1.43	1.004
rs2295633	0.3456	TT	1.20	0.82–1.76	1.000
rs6693882	0.1526	AA+AG	1.25	0.92–1.71	895
rs5275	0.5267	CC+CT	1.08	0.85–1.39	1.004
rs1800896	0.5076	AA+AG	1.12	0.8–1.56	999
rs6265	0.8307	GG	1.03	0.8–1.32	1.004
rs2049046	0.1106	TT	1.28	0.94–1.74	1.005
rs908867	0.1449	GG	1.29	0.92–1.82	1.004
rs6277	0.9953	TT	1.00	0.77–1.29	1.005
rs1076560	0.6963	CC	1.06	0.79–1.42	1.001
rs2734837	0.1971	AA+AG	1.32	0.86–2.03	1.003
rs11608185	0.1691	CC+CT	1.35	0.88–2.08	998
rs4936272	0.2742	CC+CT	1.17	0.88–1.55	1.005
rs4648317	0.3735	CC+CT	1.50	0.61–3.71	1.005
rs4322431	0.6351	TT	1.06	0.83–1.36	1.003
rs1799978	0.1598	AA+AG	-		997
rs12364283	0.5666	AA+AG	1.99	0.18–22.04	1.005

rs17122021	0.0379	TT	1.42	1.02–1.98	921
rs4149117	0.2412	TT	2.03	0.61–6.78	1.005
rs11568563	0.9922	CC	1.01	0.2–5.02	1.002
rs8904	0.2299	TT	1.22	0.88–1.69	1.005
rs10483639	0.1927	CC+CG	1.20	0.91–1.57	1.005
rs7142517	0.4575	CC	1.10	0.86–1.41	1.002
rs752688	0.0293	TT	2.27	1.07–4.85	1.004
rs4411417	0.1469	CC+CT	1.22	0.93–1.61	997
rs9671371	0.0695	TT	1.55	0.96–2.48	1.004
rs12147422	0.3064	TT	1.18	0.86–1.63	1.005
rs8004445	0.794	GG+GT	1.16	0.39–3.47	1.003
rs998259	0.1996	TT	1.38	0.84–2.25	1.001
rs3783641	0.1451	AA+AT	1.22	0.93–1.6	1.004
rs8007267	0.3242	TT	1.48	0.68–3.21	1.004
rs40434	0.0354	CC+CT	1.31	1.02–1.7	1.000
rs36024	0.0866	CC+CT	1.31	0.96–1.8	1.004
rs36017	0.3617	GG	1.14	0.86–1.52	1.004
rs8065080	0.8204	TT	1.03	0.8–1.33	1.002
rs1979572	0.7016	TT	1.06	0.8–1.4	995
rs4325622	0.5322	TT	1.09	0.83–1.44	1.005
rs140701	0.2498	GG	1.17	0.89–1.54	1.002
rs2066713	0.7328	CC+CT	1.07	0.72–1.58	1.003
rs9966412	0.5174	TT	1.32	0.57–3.03	1.003
rs2562456	0.3608	CC+CT	1.13	0.87–1.45	966

rs1800469	0.3747	CC+CT	1.19	0.81–1.75	1.000
rs934778	0.5016	TT	1.09	0.85–1.4	1.002
rs6746030	0.7409	AA+AG	1.05	0.79–1.4	1.004
rs6747673	0.5958	AA+AT	1.09	0.8–1.48	995
rs9646771	0.8517	CC+CT	1.04	0.71–1.52	985
rs4646312	0.5748	TT	1.08	0.83–1.41	1.004
rs6269	0.0192	GG	1.47	1.06–2.04	991
rs4680	0.2331	GG	1.18	0.9–1.56	995
rs7678338	0.8491	CC+CT	1.02	0.8–1.31	996
rs7689605	0.5682	AA+AG	1.11	0.78–1.57	1.005
rs10028945	0.9235	AA+AG	1.01	0.79–1.3	1.005
rs12516948	0.5325	AA+AG	1.11	0.81–1.51	1.001
rs40184	0.9362	AA+AG	1.01	0.77–1.33	1.003
rs403636	0.9868	TT	1.01	0.49–2.08	1.005
rs6350	0.9944	TT	1.01	0.06–16.19	1.001
rs3816596	0.7392	TT	1.07	0.73–1.55	1.004
rs12658835	0.4577	GG	1.20	0.74–1.92	1.000
rs179997	0.4947	AA+AT	1.13	0.79–1.62	1,002
rs1800629	0.1993	GG	1.22	0.9–1.64	992
rs1799971	0.2457	GG	1.57	0.73–3.39	1.004
rs563649	0.8947	AA+AG	1.03	0.7–1.5	1.005
rs702764	0.8461	TT	1.03	0.78–1.36	1.003
rs997917	0.3279	CC+CT	1.13	0.88–1.45	1.003
rs3839874	0.4824	TT	1.12	0.82–1.51	1.001

rs1975285	1	CC+CG	1.00	0.58–1.71	1.000
rs11988795	0.5196	CC+CT	1.14	0.77–1.7	998

AA+BB / AB

SNP	P Value	Risk Genotype	Odds Ratio	95% CI	N
rs1042114	0.5011	GT	1.11	0.82–1.49	974
rs533123	0.7043	CT	1.05	0.81–1.37	1.000
rs6691840	0.6333	AA+CC	1.06	0.82–1.37	963
rs932816	0.6695	AG	1.06	0.82–1.36	1.000
rs4141964	0.1795	AA+GG	1.19	0.92–1.52	1.004
rs2295633	0.1962	CC+TT	1.18	0.92–1.51	1.000
rs6693882	0.3724	AG	1.13	0.87–1.46	895
rs5275	0.3432	CT	1.13	0.88–1.45	1.004
rs1800896	0.6817	AG	1.05	0.82–1.35	999
rs6265	0.375	AG	1.12	0.87–1.46	1.004
rs2049046	0.5915	AA+TT	1.07	0.84–1.37	1.005
rs908867	0.1892	AA+GG	1.27	0.89–1.8	1.004
rs6277	0.593	CT	1.07	0.84–1.37	1.005
rs1076560	0.8658	AA+CC	1.03	0.76–1.38	1.001
rs2734837	0.0534	AG	1.28	1–1.64	1.003
rs11608185	0.0431	CT	1.29	1.01–1.66	998
rs4936272	0.0925	CT	1.4	0.97–1.59	1.005
rs4648317	0.001	CT	1.63	1.21–2.17	1.005
rs4322431	0.8351	AT	1.03	0.8–1.32	1.003

rs1799978	0.7749	AG	1.06	0.7–1.61	997
rs12364283	0.0037	AG	1.73	1.19–2.5	1.005
rs17122021	0.3472	CC+TT	1.13	0.87–1.47	921
rs4149117	0.1966	GG+TT	1.2	0.9–1.63	1.005
rs11568563	0.2017	AA+CC	1.27	0.88–1.85	1.002
rs8904	0.2996	CT	1.14	0.89–1.46	1.005
rs10483639	0.5782	CG	1.08	0.82–1.43	1.005
rs7142517	0.7821	AA+CC	1.04	0.81–1.33	1.002
rs752688	0.5641	CT	1.09	0.82–1.44	1.004
rs4411417	0.5272	CT	1.10	0.83–1.45	997
rs9671371	0.9245	CT	1.01	0.78–1.31	1.004
rs12147422	0.331	CC+TT	1.18	0.85–1.64	1.005
rs8004445	0.2631	GG+TT	1.21	0.87–1.69	1.003
rs998259	0.1733	CC+TT	1.19	0.93–1.54	1.001
rs3783641	0.3512	AT	1.14	0.86–1.51	1.004
rs8007267	0.5378	CT	1.09	0.82–1.45	1.004
rs40434	0.0372	CT	1.30	1.02–1.67	1.000
rs36024	0.3436	CT	1.13	0.88–1.44	1.004
rs36017	0.6142	CG	1.07	0.83–1.36	1.004
rs8065080	0.6548	CC+TT	1.06	0.83–1.36	1.002
rs1979572	0.2942	CC+TT	1.14	0.89–1.46	995
rs4325622	0.2969	CC+TT	1.14	0.89–1.46	1.005
rs140701	0.2046	AA+GG	1.17	0.92–1.51	1.002
rs2066713	0.6162	CC+TT	1.07	0.83–1.37	1.003

rs9966412	0.1594	CC+TT	1.24	0.92–1.68	1.003
rs2562456	0.5129	CT	1.09	0.84–1.41	966
rs1800469	0.6817	CT	1.05	0.82–1.35	1.000
rs934778	0.3662	CC+TT	1.12	0.87–1.44	1.002
rs6746030	0.5739	AG	1.09	0.81–1.46	1.004
rs6747673	0.7742	AA+TT	1.04	0.81–1.33	995
rs9646771	0.7588	CC+TT	1.04	0.81–1.34	985
rs4646312	0.0196	CC+TT	1.34	1.05–1.72	1.004
rs6269	0.007	AA+GG	1.41	1.1–1.81	991
rs4680	0.1527	AA+GG	1.20	0.93–1.54	995
rs7678338	0.3343	CT	1.13	0.88–1.46	996
rs7689605	0.5025	AG	1.13	0.79–1.61	1.005
rs10028945	0.9857	AG	1.00	0.78–1.29	1.005
rs12516948	0.107	AG	1.23	0.96–1.57	1.001
rs40184	0.9752	AG	1.00	0.78–1.29	1.003
rs403636	0.1202	GG+TT	1.24	0.94–1.64	1.005
rs6350	0.4605	CC+TT	1.14	0.8–1.62	1.001
rs3816596	0.8062	CT	1.03	0.81–1.32	1.004
rs12658835	0.8321	AA+GG	1.03	0.8–1.33	1.000
rs179997	0.0755	AA+TT	1.25	0.98–1.61	1.002
rs1800629	0.1224	AA+GG	1.27	0.94–1.73	992
rs1799971	0.0485	AA+GG	1.32	1–1.73	1.004
rs563649	0.973	AG	1.01	0.68–1.49	1.005
rs702764	0.9569	CC+TT	1.01	0.76–1.34	1.003

rs997917	0.3874	CT	1.12	0.87–1.44	1.003
rs3839874	0.6419	CT	1.06	0.83–1.36	1.001
rs1975285	0.0449	CC+GG	1.31	1.01–1.7	1.000
rs11988795	0.5407	CT	1.08	0.84–1.39	998

AB+BB / AA

SNP	P Value	Risk Genotype	Odds Ratio	95% CI	N
rs1042114	0.1826	GG	1.80	0.75–4.34	974
rs533123	0.6398	CT+TT	1.18	0.6–2.31	1.000
rs6691840	0.6369	AA	1.06	0.83–1.37	963
rs932816	0.1799	AA	1.34	0.87–2.05	1.000
rs4141964	0.4207	AA	1.16	0.8–1.69	1.004
rs2295633	0.4989	CC	1.09	0.85–1.4	1.000
rs6693882	0.7143	AA	1.06	0.79–1.42	895
rs5275	0.5882	CT+TT	1.13	0.73–1.75	1.004
rs1800896	0.9286	AA	1.01	0.78–1.31	999
rs6265	0.0343	AG+GG	1.73	1.04–2.88	1.004
rs2049046	0.4	AT+TT	1.12	0.86–1.48	1.005
rs908867	0.4813	AG+GG	1.67	0.4–7.01	1.004
rs6277	0.4447	CT+TT	1.15	0.81–1.63	1.005
rs1076560	0.4003	AC+CC	1.61	0.52–4.96	1.001
rs2734837	0.2395	AG+GG	1.16	0.91–1.49	1.003
rs11608185	0.2222	CT+TT	1.17	0.91–1.5	998
rs4936272	0.3737	CT+TT	1.15	0.85–1.56	1.005

rs4648317	0.0035	CT+TT	1.52	1.15–2.02	1.005
rs4322431	0.207	AT+TT	1.35	0.85–2.14	1.003
rs1799978	0.941	AG+GG	1.02	0.67–1.54	997
rs12364283	0.0053	AG+GG	1.68	1.16–2.42	1.005
rs17122021	0.4718	CT+TT	1.11	0.84–1.45	921
rs4149117	0.3304	GG	1.15	0.87–1.54	1.005
rs11568563	0.2114	AA	1.26	0.88–1.82	1.002
rs8904	0.041	CT+TT	1.31	1.01–1.7	1.005
rs10483639	0.043	CC	2.16	1.01–4.64	1.005
rs7142517	0.4538	AC+CC	1.17	0.78–1.74	1.002
rs752688	0.1628	CT+TT	1.21	0.92–1.59	1.004
rs4411417	0.0297	CC	2.27	1.06–4.84	997
rs9671371	0.2866	CT+TT	1.15	0.89–1.47	1.004
rs12147422	0.7884	CT+TT	1.16	0.39–3.48	1.005
rs8004445	0.2447	GG	1.21	0.88–1.68	1.003
rs998259	0.4981	CC	1.09	0.85–1.4	1.001
rs3783641	0.1669	AA	1.61	0.81–3.19	1.004
rs8007267	0.3414	CT+TT	1.14	0.87–1.5	1.004
rs40434	0.9652	CT+TT	1.01	0.7–1.45	1.000
rs36024	0.6496	CC	1.06	0.81–1.39	1.004
rs36017	0.1395	CG+GG	1.24	0.93–1.64	1.004
rs8065080	0.7511	CC	1.06	0.75–1.49	1.002
rs1979572	0.4098	CC	1.13	0.85–1.5	995
rs4325622	0.5677	CC	1.09	0.81–1.46	1.005

rs140701	0.7955	AA	1.04	0.78–1.39	1.002
rs2066713	0.4743	CC	1.09	0.85–1.4	1.003
rs9966412	0.258	CC	1.18	0.88–1.58	1.003
rs2562456	0.5492	CC	1.19	0.68–2.09	966
rs1800469	0.8669	CC	1.02	0.8–1.31	1.000
rs934778	0.7229	CC	1.07	0.74–1.54	1.002
rs6746030	0.4397	AG+GG	1.50	0.53–4.25	1.004
rs6747673	0.4391	AA	1.11	0.85–1.45	995
rs9646771	0.6637	CC	1.06	0.82–1.36	985
rs4646312	0.0177	CC	1.48	1.07–2.06	1.004
rs6269	0.3373	AA	1.14	0.87–1.5	991
rs4680	0.6717	AA	1.07	0.79–1.44	995
rs7678338	0.1264	CT+TT	1.48	0.89–2.46	996
rs7689605	0.7104	AG+GG	1.33	0.3–5.96	1.005
rs10028945	0.8856	AA	1.03	0.66–1.63	1.005
rs12516948	0.2265	AG+GG	1.18	0.9–1.54	1.001
rs40184	0.9602	AA	1.01	0.75–1.36	1.003
rs403636	0.1328	GG	1.23	0.94–1.6	1.005
rs6350	0.4635	CC	1.14	0.8–1.61	1.001
rs3816596	0.6347	CT+TT	1.06	0.83–1.37	1.004
rs12658835	0.8537	AG+GG	1.02	0.8–1.31	1.000
rs179997	0.0211	AA	1.35	1.05–1.74	1.002
rs1800629	0.4444	AA	1.50	0.53–4.24	992
rs1799971	0.1302	AA	1.23	0.94–1.6	1.004

rs563649	0.6491	AA	1.51	0.25–9.09	1.005
rs702764	0.6171	CT+TT	1.29	0.48–3.49	1.003
rs997917	0.8085	CC	1.06	0.67–1.67	1.003
rs3839874	0.2674	CT+TT	1.16	0.89–1.52	1.001
rs1975285	0.0522	CC	1.29	1–1.66	1.000
rs11988795	0.8385	CT+TT	1.03	0.8–1.32	998

AA / AB / BB

SNP	P Value	Risk Genotype	N
rs1042114	0.3019	GG	974
rs533123	0.8516	CT	1.000
rs6691840	0.8866	AA	963
rs932816	0.2916	AA	1.000
rs4141964	0.3809	AA	1.004
rs2295633	0.3744	TT	1.000
rs6693882	0.3567	AG	895
rs5275	0.6099	CT	1.004
rs1800896	0.7948	AG	999
rs6265	0.0949	AG	1.004
rs2049046	0.2652	TT	1.005
rs908867	0.318	GG	1.004
rs6277	0.7246	CT	1.005
rs1076560	0.6851	CC	1.001
rs2734837	0.1161	AG	1.003

rs11608185	0.0925	CT	998
rs4936272	0.2428	CT	1.005
rs4648317	0.0038	CT	1.005
rs4322431	0.4486	TT	1.003
rs1799978	0.3594	AG	997
rs12364283	0.0129	AG	1.005
rs17122021	0.1159	TT	921
rs4149117	0.2383	TT	1.005
rs11568563	0.4425	AA	1.002
rs8904	0.1075	TT	1.005
rs10483639	0.0953	CC	1.005
rs7142517	0.6548	CC	1.002
rs752688	0.0666	TT	1.004
rs4411417	0.0643	CC	997
rs9671371	0.1699	TT	1.004
rs12147422	0.5926	TT	1.005
rs8004445	0.5081	GG	1.003
rs998259	0.2383	TT	1.001
rs3783641	0.2099	AA	1.004
rs8007267	0.4762	TT	1.004
rs40434	0.0833	CT	1.000
rs36024	0.2289	CT	1.004
rs36017	0.3052	GG	1.004
rs8065080	0.8952	CC	1.002

rs1979572	0.5548	CC	995
rs4325622	0.5804	CC	1.005
rs140701	0.3998	GG	1.002
rs2066713	0.7693	CC	1.003
rs9966412	0.3218	TT	1.003
rs2562456	0.6131	CC	966
rs1800469	0.6681	CT	1.000
rs934778	0.6644	CC	1.002
rs6746030	0.6508	AG	1.004
rs6747673	0.7128	AA	995
rs9646771	0.9085	CC	985
rs4646312	0.0232	CC	1.004
rs6269	0.013	GG	991
rs4680	0.3341	GG	995
rs7678338	0.2533	CT	996
rs7689605	0.7515	AG	1.005
rs10028945	0.9881	AA	1.005
rs12516948	0.2683	AG	1.001
rs40184	0.9965	AA	1.003
rs403636	0.2955	GG	1.005
rs6350	0.7615	CC	1.001
rs3816596	0.8766	TT	1.004
rs12658835	0.758	GG	1.000
rs179997	0.07	AA	1.002

rs1800629	0.2427	AA	992
rs1799971	0.0908	GG	1.004
rs563649	0.9007	AA	1.005
rs702764	0.8788	TT	1.003
rs997917	0.6184	CT	1.003
rs3839874	0.5119	TT	1.001
rs1975285	0.1257	CC	1.000
rs11988795	0.7385	CT	998

CI, confidence interval; CPSP, chronic postsurgical pain; SNP denotes single nucleotide polymorphism.

Haplotype Testing for CPSP

Block	Haplotype	N	P Value	Odds Ratio	95% CI
1	TC	108	0.0118	0.60	0.4–0.9
1	TT	1,605	0.9554	1.01	0.81–1.25
1	GC	293	0.1220	1.22	0.95–1.56
2	AGC	597	0.1255	1.16	0.96–1.41
2	GGC	696	0.1705	0.88	0.73–1.06
2	GAT	690	0.8786	0.99	0.82–1.19
2	GAC	23	0.8489	0.92	0.41–2.1
3	GAC	706	0.6676	0.96	0.8–1.15
3	GTT	335	0.4850	0.92	0.73–1.16
3	GAT	263	0.4255	1.11	0.86–1.44
3	AAC	135	0.3039	1.20	0.85–1.71
3	GTC	447	0.7160	1.04	0.84–1.28
3	ATT	98	0.4306	0.85	0.56–1.28
3	ATC	15	0.4460	0.67	0.24–1.89
3	AAT	9	0.7293	1.26	0.34–4.71
4	TG	1,309	0.9174	1.01	0.84–1.21
4	CG	542	0.6935	0.97	0.79–1.17
4	TA	157	0.6401	1.08	0.78–1.5
5	AGTC	79	0.9373	0.98	0.63–1.54
5	AATC	121	0.0347	0.67	0.46–0.97
5	GAGC	411	0.3026	1.12	0.9–1.39
5	GGGC	308	0.5047	0.92	0.72–1.17

5	GATC	123	0.6094	1.10	0.76–1.58
5	AAGC	250	0.5431	1.09	0.83–1.42
5	AGGC	547	0.5088	1.07	0.88–1.3
5	AGGT	102	0.9671	1.0084	0.68–1.5
5	GAGT	7	0.6971	1.35	0.3–6.03
5	GGGT	20	0.9857	1.01	0.42–2.43
5	AAGT	21	0.0505	0.40	0.15–1.03
5	GGTC	18	0.3523	0.64	0.25–1.65
6	AG	1,536	0.4574	1.08	0.88–1.33
6	GG	348	0.3273	0.89	0.71–1.12
6	AA	124	0.8171	1.04	0.73–1.5
7	TT	1,445	0.3916	0.92	0.76–1.12
7	CC	285	0.7076	0.95	0.74–1.22
7	TC	274	0.1333	1.2	0.94–1.57
8	CC	664	0.8256	1.02	0.85–1.23
8	TC	893	0.2330	1.11	0.93–1.33
8	CG	451	0.0952	0.84	0.68–1.03
9	GAA	156	0.1998	0.81	0.58–1.12
9	GTG	923	0.1205	1.15	0.96–1.37
9	GAG	445	0.9669	1.00	0.81–1.24
9	AAG	476	0.3981	0.92	0.74–1.12
9	AAA	7	0.2605	0.40	0.08–2.08
10	CCGTCTAAA	17	0.2171	1.86	0.68–5.04
10	TCACTCTAA	785	0.6432	1.04	0.87–1.25

10	TCACCCAAA	273	0.7989	0.97	0.75–1.25
10	CCGTCTTAA	38	0.3137	1.39	0.73–2.67
10	CCGTTCTAA	118	0.7377	0.94	0.65–1.36
10	CCGTCCAAA	99	0.4959	0.87	0.58–1.3
10	TCACCTTAG	58	0.0579	1.67	0.98–2.87
10	CCACTCTAA	127	0.3360	0.84	0.58–1.2
10	TCACCTTAA	67	0.2778	0.76	0.47–1.25
10	TCACCCTGA	31	0.3774	0.72	0.35–1.49
10	CAGTCTTAA	18	0.3350	1.59	0.61–4.12
10	CAGTCCAAA	178	0.2967	0.85	0.62–1.16
10	CCGTCCTGA	67	0.8749	1.04	0.64–1.69
10	CCGTCTTAG	50	0.5476	1.19	0.68–2.09
10	CAGTTCTAA	13	0.1686	0.45	0.14–1.45
10	CCATTCTAA	6	0.4080	2.02	0.37–11.05
10	CAGTCTTAG	26	0.2283	1.62	0.73–3.59
11	CCTCTTGCAT	264	0.1644	1.20	0.93–1.56
11	GCCTTTGCTC	170	0.8301	1.04	0.76–1.42
11	GACTCCTCTC	180	0.2994	0.85	0.63–1.16
11	GCCTCTGTTC	126	0.1538	0.77	0.53–1.1
11	GACTCTGTTC	394	0.4457	1.09	0.87–1.36
11	GACTCTGCTC	54	0.0027	0.42	0.23–0.75
11	GCCTCTGCTC	699	0.8593	1.02	0.85–1.22
11	GACTCTGCAT	11	0.7523	1.21	0.37–3.98
11	GCCTTTGCAT	13	0.4120	0.63	0.2–1.93

11	CCTCTTGCAC	32	0.1475	1.69	0.82–3.48
11	GACTCTGCAC	11	0.7523	1.21	0.37–3.98
11	CCTCTTGCTC	14	0.6021	0.75	0.26–2.18
11	CCTCTCTCTC	7	0.6971	1.35	0.3–6.03
12	CCG	514	0.1244	1.17	0.96–1.43
12	TCC	269	0.2401	0.86	0.66–1.11
12	TCG	91	0.0993	1.43	0.93–2.19
12	CCC	233	0.8931	1.02	0.78–1.34
12	TTC	511	0.3848	0.91	0.75–1.12
12	TTG	390	0.4826	0.92	0.74–1.15
13	CTGC	374	0.0549	1.25	1–1.56
13	CTGT	609	0.2731	0.90	0.74–1.09
13	TCAC	907	0.7405	0.97	0.81–1.16
13	TTAC	17	0.7948	1.14	0.44–2.95
13	TCGT	49	0.1835	1.48	0.83–2.63
13	CTAC	18	0.3523	0.64	0.25–1.65
13	TCGC	13	0.7919	0.86	0.29–2.58
13	TTGC	20	0.0751	0.43	0.16–1.12
14	CGG	865	0.3568	1.09	0.91–1.3
14	TAA	936	0.4137	0.93	0.78–1.11
14	TAG	183	0.9832	1.00	0.74–1.35
14	TGG	22	0.4016	0.70	0.3–1.63
15	GATAC	816	0.6090	0.94	0.75–1.19
15	AGCGT	277	0.4368	1.11	0.85–1.45

15	GGCGT	9	0.0953	0.28	0.06–1.37
15	GACGT	43	0.6492	0.87	0.47–1.6
15	AATAC	6	0.4109	2.01	0.37–11.03
15	GGTAC	64	0.5988	1.14	0.69–1.89
15	GACAC	13	0.7848	0.86	0.29–2.57
15	AGCAC	17	0.8020	1.13	0.43–2.95
15	AGTAC	16	0.6193	0.78	0.29–2.1

SNPs Included in Each Block

Block	SNPs
1	rs1042114
	rs533123
2	rs932816
	rs4141964
	rs2295633
3	rs6746030
	rs6747673
	rs9646771
4	rs7678338
	rs7689605
5	rs12516948
	rs40184
	rs403636
	rs6350

6	rs1799971
	rs563649
7	rs702764
	rs997917
8	rs3839874
	rs1975285
9	rs6265
	rs2049046
	rs908867
10	rs6277
	rs1076560
	rs2734837
	rs11608185
	rs4936272
	rs4648317
	rs4322431
	rs1799978
	rs12364283
11	rs10483639
	rs7142517
	rs752688
	rs4411417
	rs9671371
	rs12147422

	rs8004445
	rs998259
	rs3783641
	rs8007267
12	rs40434
	rs36024
	rs36017
13	rs1979572
	rs4325622
	rs140701
	rs2066713
14	rs4646312
	rs6269
	rs4680
15	rs3788862
	rs2283724
	rs1800659
	rs979606
	rs979605

CI = confidence interval; CPSP = chronic postsurgical pain; SNP = single nucleotide polymorphism.

Allele Frequencies Adjusted by Pain Intensity (VNRS >3) at the Follow-up Visit 4.4

Months after Surgery

SNP	Chromosome	Base Pair	Beta	P Value
rs1042114	1	29138975	0.1436	0.3658
rs533123	1	29141155	-0.0049	0.9717
rs6691840	1	37325477	-0.1798	0.1584
rs932816	1	46859749	-0.0627	0.5976
rs4141964	1	46865040	0.0735	0.5196
rs2295633	1	46874383	0.0881	0.446
rs6693882	1	96145968	-0.1598	0.1625
rs5275	1	186643058	0.1054	0.3766
rs1800896	1	206946897	-0.0050	0.9635
rs934778	2	25389224	-0.0044	0.9691
rs6746030	2	167099158	0.1149	0.4832
rs6747673	2	167144974	-0.1950	0.07273
rs9646771	2	167163043	-0.0851	0.4651
rs7678338	4	46922107	0.0368	0.769
rs7689605	4	46952029	-0.1097	0.588
rs10028945	4	47428305	0.0972	0.4209
rs12516948	5	1391369	0.1660	0.1337
rs40184	5	1395077	0.0571	0.6039
rs403636	5	1438354	-0.1028	0.473
rs6350	5	1443199	-0.2814	0.1901
rs3816596	5	160975332	0.0724	0.528

rs12658835	5	161275302	0.2310	0.05935
rs179997	6	16318633	-0.0672	0.556
rs1800629	6	31543031	-0.1915	0.2615
rs1799971	6	154360797	0.0135	0.9256
rs563649	6	154407967	-0.1221	0.5914
rs702764	8	54142157	0.0383	0.8109
rs997917	8	54152378	0.2758	0.02371
rs3839874	8	57353827	-0.1203	0.2646
rs1975285	8	57358682	-0.1324	0.307
rs11988795	8	72949601	0.0006	0.9958
rs6265	11	27679916	-0.0298	0.8117
rs2049046	11	27723775	-0.0443	0.6878
rs908867	11	27745764	-0.2779	0.1625
rs6277	11	113283459	-0.1327	0.2442
rs1076560	11	113283688	-0.1209	0.4683
rs2734837	11	113286829	-0.0697	0.5599
rs11608185	11	113294976	-0.0664	0.5795
rs4936272	11	113318907	0.1021	0.3727
rs4648317	11	113331532	0.1694	0.2861
rs4322431	11	113332956	0.0431	0.7227
rs1799978	11	113346351	-0.0843	0.7334
rs12364283	11	113346955	0.3794	0.0816
rs17122021	11	118145686	0.1389	0.2263
rs4149117	12	21011480	-0.0183	0.9138

rs11568563	12	21457434	-0.1492	0.4865
rs8904	14	35871217	0.2505	0.02274
rs10483639	14	55306457	0.1685	0.2504
rs7142517	14	55306804	-0.0747	0.5209
rs752688	14	55311569	0.1758	0.2288
rs4411417	14	55320563	0.1729	0.2386
rs9671371	14	55328635	0.1223	0.3226
rs12147422	14	55344015	-0.0235	0.8978
rs8004445	14	55350666	-0.0600	0.7433
rs998259	14	55355031	0.0702	0.5731
rs3783641	14	55360139	0.1790	0.2129
rs8007267	14	55378991	0.1130	0.4496
rs40434	16	55699525	0.0651	0.5714
rs36024	16	55706391	-0.1383	0.2149
rs36017	16	55718818	0.1740	0.1109
rs8065080	17	3480447	0.0360	0.7511
rs1979572	17	28511978	0.1274	0.2444
rs4325622	17	28526475	-0.1140	0.297
rs140701	17	28538532	-0.0921	0.3922
rs2066713	17	28551665	-0.0453	0.6924
rs9966412	18	58033935	-0.1453	0.3608
rs2562456	19	21666210	0.1829	0.1684
rs1800469	19	41860296	-0.0681	0.5499
rs4646312	22	19948337	-0.0535	0.6325

rs6269	22	19949952	-0.0682	0.547
rs4680	22	19951271	0.0340	0.7552
rs3788862	23	43517364	0.0700	0.4549
rs2283724	23	43559576	0.1195	0.1819
rs1800659	23	43574169	0.0291	0.7494
rs979606	23	43601142	0.0248	0.7901
rs979605	23	43601363	0.0210	0.8225

CI = confidence interval; CPSP = chronic postsurgical pain; SNP = single nucleotide polymorphism; VNRS = verbal numerical rating scale.

Allele Frequencies, Adjusted by a Presence of Neuropathic CPSP

SNP	P Value	Risk Allele	Odds Ratio	95% CI
rs1042114	0.8897	G	1.03	0.72–1.46
rs533123	0.8027	T	1.04	0.77–1.4
rs6691840	0.6169	A	1.07	0.81–1.41
rs932816	0.6251	G	1.07	0.82–1.39
rs4141964	0.5304	G	1.08	0.84–1.4
rs2295633	0.5956	C	1.07	0.83–1.38
rs6693882	0.1807	A	1.19	0.92–1.54
rs5275	0.8286	C	1.03	0.79–1.33
rs1800896	0.8046	A	1.03	0.81–1.32
rs6265	0.0277	G	1.40	1.04–1.88
rs2049046	0.6052	T	1.07	0.84–1.35
rs908867	0.68	G	1.10	0.7–1.72
rs6277	0.6119	T	1.07	0.83–1.36
rs1076560	0.2484	A	1.22	0.87–1.73
rs2734837	0.924	G	1.01	0.78–1.31
rs11608185	0.9324	C	1.01	0.78–1.31
rs4936272	0.1598	C	1.19	0.93–1.51
rs4648317	0.1806	T	1.25	0.9–1.74
rs4322431	0.6295	A	1.07	0.82–1.39
rs1799978	0.6908	G	1.11	0.66–1.87
rs12364283	0.4576	G	1.19	0.76–1.86
rs17122021	0.0928	T	1.25	0.96–1.61

rs4149117	0.8589	T	1.03	0.73–1.47
rs11568563	0.7625	C	1.07	0.68–1.71
rs8904	0.236	T	1.16	0.91–1.47
rs10483639	0.3388	C	1.17	0.85–1.59
rs7142517	0.8448	A	1.03	0.79–1.32
rs752688	0.4965	T	1.12	0.81–1.53
rs4411417	0.4477	C	1.13	0.82–1.55
rs9671371	0.683	T	1.06	0.81–1.39
rs12147422	0.1676	T	1.36	0.88–2.12
rs8004445	0.0953	G	1.47	0.93–2.33
rs998259	0.0231	T	1.35	1.04–1.76
rs3783641	0.8142	A	1.04	0.76–1.43
rs8007267	0.5512	T	1.10	0.8–1.52
rs40434	0.7857	C	1.03	0.81–1.32
rs36024	0.2467	C	1.15	0.91–1.47
rs36017	0.1061	G	1.22	0.96–1.55
rs8065080	0.7439	T	1.04	0.82–1.33
rs1979572	0.9919	T	1.00	0.79–1.28
rs4325622	0.9495	C	1.01	0.79–1.28
rs140701	0.6488	G	1.06	0.83–1.34
rs2066713	0.6292	C	1.07	0.82–1.38
rs9966412	0.3131	C	1.21	0.84–1.75
rs2562456	0.024	C	1.37	1.04–1.79
rs1800469	0.9271	C	1.01	0.78–1.31

rs934778	0.9363	T	1.01	0.79–1.3
rs6746030	0.3645	G	1.19	0.82–1.73
rs6747673	0.0467	A	1.28	1–1.64
rs9646771	0.7896	T	1.04	0.8–1.33
rs4646312	0.6301	T	1.06	0.83–1.35
rs6269	0.6416	A	1.06	0.83–1.35
rs4680	0.1941	A	1.17	0.92–1.49
rs7678338	0.6203	C	1.07	0.82–1.4
rs7689605	0.9455	A	1.02	0.65–1.58
rs10028945	0.0909	A	1.25	0.97–1.61
rs12516948	0.9967	A	1.00	0.79–1.27
rs40184	0.9521	G	1.01	0.79–1.28
rs403636	0.7584	G	1.05	0.77–1.44
rs6350	0.2968	T	1.26	0.82–1.93
rs3816596	0.2657	T	1.15	0.9–1.47
rs12658835	0.0437	G	1.31	1.01–1.71
rs179997	0.4156	A	1.11	0.86–1.42
rs1800629	0.4587	G	1.15	0.79–1.69
rs1799971	0.6422	A	1.08	0.79–1.48
rs563649	0.4021	G	1.25	0.74–2.14
rs702764	0.5364	C	1.11	0.79–1.56
rs997917	0.0018	C	1.50	1.16–1.94
rs3839874	0.6769	T	1.05	0.83–1.34
rs1975285	0.1267	C	1.26	0.94–1.7

rs11988795	0.8808	T	1.02	0.79–1.32
rs3788862	0.4913	A	1.13	0.8–1.59
rs2283724	0.2074	G	1.23	0.89–1.69
rs1800659	0.8108	C	1.04	0.75–1.45
rs979606	0.5807	G	1.10	0.78–1.54
rs979605	0.8356	T	1.04	0.74–1.46

CI = confidence interval; CPSP = chronic postsurgical pain; SNP = single nucleotide polymorphism.

Genotyping Test for Neuropathic CPSP

AA+AB / BB

SNP	P Value	Risk Genotype	Odds Ratio	95% CI	N
rs1042114	0.9304	GG+GT	1.02	0.68–1.51	857
rs533123	0.9286	TT	1.02	0.71–1.45	881
rs6691840	0.928	AA+AC	1.03	0.52–2.03	847
rs932816	0.8206	GG	1.04	0.74–1.46	882
rs4141964	0.5608	GG	1.11	0.79–1.56	885
rs2295633	0.5145	CC+CT	1.20	0.69–2.08	883
rs6693882	0.4851	AA+AG	1.17	0.76–1.81	791
rs5275	0.4142	CC+CT	1.15	0.82–1.62	885
rs1800896	0.4594	AA+AG	1.20	0.74–1.92	881
rs6265	0.0988	GG	1.34	0.95–1.91	885
rs2049046	0.5886	TT	1.12	0.74–1.68	886
rs908867	0.5441	GG	1.16	0.72–1.88	885
rs6277	0.8363	CC+CT	1.04	0.73–1.48	886
rs1076560	0.1735	AA+AC	1.30	0.89–1.91	882
rs2734837	0.2577	AA+AG	1.44	0.76–2.72	884
rs11608185	0.1058	CC+CT	1.75	0.88–3.46	880
rs4936272	0.0181	CC+CT	1.66	1.09–2.53	886
rs4648317	0.2486	TT	1.85	0.64–5.31	886
rs4322431	0.4118	AA+AT	1.15	0.82–1.62	884
rs1799978	0.4977	AA+AG	-		879
rs12364283	0.5121	GG	2.19	0.2–24.32	886

rs17122021	0.2402	TT	1.30	0.84–2.02	810
rs4149117	0.1683	TT	2.65	0.63–11.21	886
rs11568563	0.9378	CC	1.09	0.12–9.83	885
rs8904	0.4495	TT	1.18	0.77–1.82	886
rs10483639	0.3037	CC+CG	1.21	0.84–1.73	886
rs7142517	0.9462	AA+AC	1.01	0.72–1.42	884
rs752688	0.9379	TT	1.04	0.39–2.8	885
rs4411417	0.4002	CC+CT	1.17	0.81–1.68	878
rs9671371	0.8023	CC+CT	1.09	0.56–2.14	885
rs12147422	0.2998	TT	1.28	0.8–2.04	886
rs8004445	0.1125	GG+GT	—		884
rs998259	0.009	TT	2.11	1.19–3.73	882
rs3783641	0.5931	AA+AT	1.10	0.77–1.59	885
rs8007267	0.6994	TT	1.22	0.45–3.33	885
rs40434	0.2828	CC+CT	1.21	0.85–1.73	882
rs36024	0.1071	CC+CT	1.47	0.92–2.35	885
rs36017	0.4043	GG	1.18	0.8–1.73	885
rs8065080	0.3158	TT	1.19	0.84–1.69	883
rs1979572	0.5649	TT	1.12	0.76–1.65	877
rs4325622	0.4463	TT	1.16	0.8–1.68	886
rs140701	0.4498	GG	1.15	0.8–1.66	883
rs2066713	0.2679	CC+CT	1.38	0.78–2.46	884
rs9966412	0.7768	TT	1.18	0.38–3.59	884
rs2562456	0.0595	CC+CT	1.40	0.99–1.99	851

rs1800469	0.3235	CC+CT	1.33	0.76–2.32	882
rs934778	0.9703	TT	1.01	0.71–1.42	886
rs6746030	0.2795	GG	1.26	0.83–1.9	885
rs6747673	0.1021	AA+AT	1.46	0.93–2.3	878
rs9646771	0.9891	CC+CT	1.00	0.59–1.71	868
rs4646312	0.0567	TT	1.41	0.99–2	886
rs6269	0.2354	GG	1.29	0.85–1.97	872
rs4680	0.8601	AA+AG	1.03	0.71–1.51	877
rs7678338	0.0617	CC+CT	1.38	0.98–1.95	877
rs7689605	0.8833	AA+AG	1.04	0.65–1.66	886
rs10028945	0.3147	AA+AG	1.19	0.85–1.67	886
rs12516948	0.8617	AA+AG	1.04	0.67–1.6	882
rs40184	0.9922	AA+AG	1.00	0.69–1.46	885
rs403636	0.4379	TT	1.41	0.59–3.35	886
rs6350	0.2526	TT	4.40	0.27–70.8	883
rs3816596	0.3891	TT	1.24	0.76–2.02	885
rs12658835	0.0392	GG	1.79	1.02–3.13	882
rs179997	0.8161	AA+AT	1.06	0.65–1.74	885
rs1800629	0.6957	GG	1.09	0.72–1.63	873
rs1799971	0.4855	GG	1.39	0.55–3.54	885
rs563649	0.3426	GG	1.31	0.75–2.3	886
rs702764	0.5399	CC+CT	1.13	0.77–1.64	884
rs997917	0.0057	CC+CT	1.61	1.15–2.27	884
rs3839874	0.9483	CC+CT	1.01	0.67–1.54	885

rs1975285	0.4141	CC+CG	1.40	0.62–3.18	882
rs11988795	0.5951	TT	1.15	0.68–1.95	880

AA+BB / AB

SNP	P Value	Risk Genotype	Odds Ratio	95% CI	N
rs1042114	0.9843	GT	1.00	0.67–1.52	857
rs533123	0.9058	CT	1.02	0.71–1.46	881
rs6691840	0.5826	AA+CC	1.10	0.78–1.57	847
rs932816	0.8567	AG	1.03	0.73–1.46	882
rs4141964	0.7604	AA+GG	1.05	0.75–1.48	885
rs2295633	0.8964	CT	1.02	0.73–1.44	883
rs6693882	0.4818	AA+GG	1.14	0.79–1.64	791
rs5275	0.1708	CT	1.27	0.9–1.78	885
rs1800896	0.4482	AG	1.14	0.81–1.6	881
rs6265	0.535	AA+GG	1.12	0.78–1.6	885
rs2049046	0.8803	AA+TT	1.03	0.73–1.44	886
rs908867	0.4299	AA+GG	1.22	0.74–2.02	885
rs6277	0.272	CT	1.21	0.86–1.7	886
rs1076560	0.1385	AC	1.34	0.91–1.98	882
rs2734837	0.1418	AG	1.29	0.92–1.81	884
rs11608185	0.0721	CT	1.37	0.97–1.92	880
rs4936272	0.03	CT	1.46	1.04–2.07	886
rs4648317	0.4297	CT	1.17	0.79–1.72	886
rs4322431	0.299	AT	1.20	0.85–1.69	884

rs1799978	0.5283	AG	1.19	0.69–2.03	879
rs12364283	0.573	AG	1.15	0.71–1.87	886
rs17122021	0.6063	CT	1.10	0.77–1.58	810
rs4149117	0.6814	GG+TT	1.09	0.73–1.62	886
rs11568563	0.7715	AC	1.08	0.65–1.78	885
rs8904	0.6159	CT	1.09	0.78–1.53	886
rs10483639	0.3209	CG	1.21	0.83–1.75	886
rs7142517	0.8989	AA+CC	1.02	0.73–1.44	884
rs752688	0.4573	CT	1.15	0.79–1.68	885
rs4411417	0.4006	CT	1.17	0.81–1.71	878
rs9671371	0.4301	CT	1.15	0.81–1.63	885
rs12147422	0.5533	CC+TT	1.15	0.72–1.84	886
rs8004445	0.3598	GG+TT	1.25	0.77–2.03	884
rs998259	0.8447	CT	1.04	0.73–1.46	882
rs3783641	0.4088	AT	1.17	0.81–1.7	885
rs8007267	0.6767	CT	1.08	0.74–1.59	885
rs40434	0.0862	CT	1.35	0.96–1.89	882
rs36024	0.3675	CT	1.17	0.83–1.64	885
rs36017	0.3977	CG	1.16	0.82–1.62	885
rs8065080	0.1403	CC+TT	1.29	0.92–1.82	883
rs1979572	0.3223	CC+TT	1.19	0.84–1.68	877
rs4325622	0.1479	CC+TT	1.29	0.91–1.81	886
rs140701	0.4648	AA+GG	1.14	0.81–1.59	883
rs2066713	0.4313	CT	1.15	0.82–1.61	884

rs9966412	0.1734	CC+TT	1.35	0.88–2.08	884
rs2562456	0.3238	CT	1.19	0.84–1.7	851
rs1800469	0.2403	CT	1.23	0.87–1.72	882
rs934778	0.9718	CT	1.01	0.72–1.41	886
rs6746030	0.2346	AA+GG	1.30	0.84–1.99	885
rs6747673	0.8773	AA+TT	1.03	0.73–1.44	878
rs9646771	0.7039	CT	1.07	0.76–1.51	868
rs4646312	0.004	CC+TT	1.65	1.17–2.33	886
rs6269	0.0128	AA+GG	1.55	1.1–2.19	872
rs4680	0.1303	AA+GG	1.30	0.92–1.84	877
rs7678338	0.0016	CT	1.73	1.23–2.44	877
rs7689605	0.8214	AG	1.06	0.65–1.71	886
rs10028945	0.8583	AA+GG	1.03	0.73–1.45	886
rs12516948	0.7874	AG	1.05	0.75–1.47	882
rs40184	0.9184	AG	1.02	0.73–1.43	885
rs403636	0.3283	GG+TT	1.21	0.82–1.78	886
rs6350	0.4277	CT	1.21	0.76–1.92	883
rs3816596	0.7137	CT	1.07	0.76–1.5	885
rs12658835	0.7527	AG	1.06	0.75–1.5	882
rs179997	0.4259	AA+TT	1.15	0.82–1.61	885
rs1800629	0.9747	AG	1.01	0.67–1.52	873
rs1799971	0.2924	AA+GG	1.23	0.84–1.79	885
rs563649	0.301	AA+GG	1.35	0.76–2.41	886
rs702764	0.5835	CT	1.11	0.76–1.64	884

rs997917	0.11	CT	1.32	0.94–1.86	884
rs3839874	0.4889	CT	1.13	0.8–1.58	885
rs1975285	0.2645	CC+GG	1.23	0.85–1.78	882
rs11988795	0.6363	CC+TT	1.09	0.77–1.53	880

AB+BB / AA

SNP	P Value	Risk Genotype	Odds Ratio	95% CI	N
rs1042114	0.8442	GG	1.12	0.37–3.39	857
rs533123	0.6023	CT+TT	1.29	0.49–3.4	881
rs6691840	0.5564	AA	1.11	0.79–1.57	847
rs932816	0.4865	AG+GG	1.25	0.67–2.31	882
rs4141964	0.6818	AG+GG	1.12	0.66–1.89	885
rs2295633	0.7695	CC	1.05	0.75–1.48	883
rs6693882	0.1441	AA	1.34	0.9–1.98	791
rs5275	0.3532	CT+TT	1.35	0.71–2.56	885
rs1800896	0.8293	AG+GG	1.04	0.73–1.48	881
rs6265	0.0379	AG+GG	2.59	1.02–6.59	885
rs2049046	0.7498	AT+TT	1.06	0.73–1.55	886
rs908867	0.4984	AA	1.75	0.34–9.12	885
rs6277	0.2038	CT+TT	1.40	0.83–2.35	886
rs1076560	0.7569	AC+CC	1.27	0.28–5.78	882
rs2734837	0.4261	AG+GG	1.15	0.82–1.62	884
rs11608185	0.3999	CT+TT	1.16	0.82–1.64	880
rs4936272	0.9109	CT+TT	1.02	0.67–1.56	886

rs4648317	0.2577	CT+TT	1.24	0.85–1.81	886
rs4322431	0.7091	AT+TT	1.13	0.59–2.16	884
rs1799978	0.6038	AG+GG	1.15	0.67–1.97	879
rs12364283	0.5036	AG+GG	1.18	0.73–1.9	886
rs17122021	0.1263	CT+TT	1.37	0.91–2.04	810
rs4149117	0.9162	GG	1.02	0.69–1.51	886
rs11568563	0.7624	AC+CC	1.08	0.66–1.76	885
rs8904	0.263	CT+TT	1.23	0.86–1.76	886
rs10483639	0.8576	CC	1.10	0.4–2.96	886
rs7142517	0.7572	AA	1.09	0.64–1.85	884
rs752688	0.4538	CT+TT	1.15	0.8–1.65	885
rs4411417	0.9416	CC	1.04	0.39–2.79	878
rs9671371	0.5242	CT+TT	1.12	0.8–1.57	885
rs12147422	0.1104	CT+TT	-		886
rs8004445	0.177	GG	1.39	0.86–2.24	884
rs998259	0.1283	CT+TT	1.30	0.93–1.83	882
rs3783641	0.4952	AT+TT	1.45	0.5–4.22	885
rs8007267	0.5887	CT+TT	1.11	0.77–1.6	885
rs40434	0.3224	CT+TT	1.31	0.77–2.23	882
rs36024	0.6945	CC	1.08	0.75–1.55	885
rs36017	0.0747	CG+GG	1.45	0.96–2.19	885
rs8065080	0.4763	CC	1.18	0.75–1.86	883
rs1979572	0.5732	CC	1.12	0.76–1.65	877
rs4325622	0.3641	CC	1.20	0.81–1.77	886

rs140701	0.9584	AA	1.01	0.68–1.51	883
rs2066713	0.9455	CT+TT	1.01	0.72–1.42	884
rs9966412	0.2214	CC	1.29	0.86–1.96	884
rs2562456	0.0402	CC	2.00	1.02–3.92	851
rs1800469	0.6013	CT+TT	1.10	0.78–1.54	882
rs934778	0.9148	CT+TT	1.03	0.62–1.71	886
rs6746030	0.7874	AA	1.19	0.33–4.33	885
rs6747673	0.1141	AA	1.33	0.93–1.9	878
rs9646771	0.7055	CT+TT	1.0703	0.75–1.52	868
rs4646312	0.1507	CC	1.36	0.89–2.06	886
rs6269	0.0889	AA	1.36	0.95–1.95	872
rs4680	0.0451	AA	1.48	1.01–2.18	877
rs7678338	0.0139	CT+TT	3.38	1.21–9.47	877
rs7689605	0.7673	AG+GG	1.38	0.16–11.51	886
rs10028945	0.0349	AA	1.77	1.04–3.01	886
rs12516948	0.8866	AG+GG	1.03	0.71–1.48	882
rs40184	0.9102	AG+GG	1.02	0.68–1.54	885
rs403636	0.5147	GG	1.13	0.78–1.63	886
rs6350	0.3465	CT+TT	1.25	0.79–1.97	883
rs3816596	0.342	CT+TT	1.18	0.84–1.67	885
rs12658835	0.1577	AG+GG	1.28	0.91–1.79	882
rs179997	0.324	AA	1.19	0.84–1.68	885
rs1800629	0.1098	AG+GG	—		873
rs1799971	0.4344	AA	1.16	0.8–1.67	885

rs563649	0.7426	AA	1.46	0.15–14.12	886
rs702764	0.7891	CC	1.19	0.33–4.32	884
rs997917	0.0266	CC	1.85	1.07–3.19	884
rs3839874	0.4961	CT+TT	1.14	0.79–1.64	885
rs1975285	0.1433	CC	1.30	0.91–1.85	882
rs11988795	0.8927	CC	1.02	0.73–1.44	880

AA / AB / BB

SNP	P Value	Risk Genotype	N
rs1042114	0.9802	GG	857
rs533123	0.8721	CT	881
rs6691840	0.8385	AA	847
rs932816	0.785	GG	882
rs4141964	0.8217	GG	885
rs2295633	0.8055	CC	883
rs6693882	0.3364	AA	791
rs5275	0.3307	CT	885
rs1800896	0.6739	AG	881
rs6265	0.0671	GG	885
rs2049046	0.8543	TT	886
rs908867	0.5935	AA	885
rs6277	0.3639	CT	886
rs1076560	0.3263	AC	882
rs2734837	0.2596	AG	884

rs11608185	0.1036	CT	880
rs4936272	0.0424	CT	886
rs4648317	0.3482	TT	886
rs4322431	0.5791	AT	884
rs1799978	0.6558	AG	879
rs12364283	0.6823	GG	886
rs17122021	0.2431	TT	810
rs4149117	0.3658	TT	886
rs11568563	0.9551	CC	885
rs8904	0.4942	TT	886
rs10483639	0.5868	CG	886
rs7142517	0.9528	AA	884
rs752688	0.7493	CT	885
rs4411417	0.6932	CT	878
rs9671371	0.7298	CT	885
rs12147422	0.2228	TT	886
rs8004445	0.1728	GG	884
rs998259	0.0241	TT	882
rs3783641	0.5964	AT	885
rs8007267	0.8363	TT	885
rs40434	0.2146	CT	882
rs36024	0.2705	CT	885
rs36017	0.1985	GG	885
rs8065080	0.335	CC	883

rs1979572	0.6127	TT	877
rs4325622	0.3475	CC	886
rs140701	0.7101	GG	883
rs2066713	0.4867	CT	884
rs9966412	0.3898	TT	884
rs2562456	0.045	CC	851
rs1800469	0.4075	CT	882
rs934778	0.9943	TT	886
rs6746030	0.4846	AA	885
rs6747673	0.147	AA	878
rs9646771	0.9227	CT	868
rs4646312	0.0157	CC	886
rs6269	0.045	AA	872
rs4680	0.1158	AA	877
rs7678338	0.0014	CT	877
rs7689605	0.9352	AG	886
rs10028945	0.1001	AA	886
rs12516948	0.9631	AG	882
rs40184	0.9924	AG	885
rs403636	0.4966	TT	886
rs6350	0.3726	TT	883
rs3816596	0.5353	TT	885
rs12658835	0.0874	GG	882
rs179997	0.6129	AA	885

rs1800629	0.2778	GG	873
rs1799971	0.4846	GG	885
rs563649	0.5593	AA	886
rs702764	0.8205	CC	884
rs997917	0.0079	CC	884
rs3839874	0.7515	CT	885
rs1975285	0.3168	CC	882
rs11988795	0.823	TT	880

CI = confidence interval; CPSP = chronic postsurgical pain; SNP = single nucleotide polymorphism.

Table 2. General Linear Mixed Model for four types of surgery

Independent Predictors of Risk for CPSP after Hernia Repair Identified in the General Linear Mixed Model for Binomial Distribution with the Variable Recruitment Center as a Random Factor

	Bivariate Analysis		Multivariable Analysis*		Bootstrap Resampling†
	OR (95% CI)		OR (95% CI)		OR (95% CI)
	N=1,702	β-coefficients	N=1,702		
Age					
18 – 50	3.1 (2.2–4.4)	1.267	3.5 (2.5–5.1)		3.5 (2.5–5.0)
51 – 64	1.9 (1.3–2.7)	0.688	2.0 (1.4–2.9)		1.9 (1.3–2.9)
> 64	1				
SF-12 score (physical summary)					
0 – 33.5	3.2 (1.9–5.5)	1.140	3.1 (1.8–5.6)		3.2 (1.7–5.9)
33.6 – 55.1	1.7 (1.1–2.5)	0.563	1.8 (1.2–2.7)		1.8 (1.2–2.8)
> 55.1	1				

SF-12 score (mental summary)

0 – 44.8	1.8 (1.2–2.5)	0.482	1.6 (1.1–2.4)	1.6 (1.1–2.3)
> 44.8	1			

Preoperative pain, surgical area

VNRS ≤ 3	1			
VNRS > 3	2.0 (1.5–2.7)	0.513	1.7 (1.2–2.3)	1.6 (1.1–2.2)

Preoperative pain, other areas

VNRS ≤ 3	1			
VNRS > 3	1.8 (1.3–2.5)	0.389	1.5 (1.0–2.2)	1.4 (1.0–2.1)

CI = confidence interval; CSPS = chronic postsurgical pain; OR = odds ratio; SF-12, Short Form Health Survey-12 (version 2 in Spanish);

VNRS = verbal numerical rating scale (0–10).

* *c*-statistic (CI 95%) = 0.645 (0.589–0.702); Hosmer-Lemeshow chi-square test = 3.93; *P* = 0.788.

† A total of 1000 bootstrap subsamples were modelled. .

Independent Predictors of Risk for CPSP after Vaginal Hysterectomy Identified in the General Linear Mixed Model for Binomial Distribution with the Variable Recruitment Center as a Random Factor

	Bivariate Analysis		Multivariable Analysis*		Bootstrap Resampling†
	OR (95% CI)		OR (95% CI)		OR (95% CI)
	N=409	β-coefficients	N=409		
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Age					
18 – 50	2.5 (1.2–5.3)	1.010	2.7 (1.2–6.2)		2.4 (1.1-5.2)
51 – 64	1.2 (0.6–2.6)	0.366	1.4 (0.7–3.1)		1.4 (0.6–3.0)
> 64	1				
SF-12 score (physical summary)					
0 – 33.5	2.8 (1.0–7.7)	1.024	2.8 (0.8–9.3)		2.8 (0.8–11.8)
33.6 – 55.1	1.1 (0.5–2.6)	0.196	1.2 (0.5–2.9)		1.2 (0.5–3.8)
> 55.1	1				
SF-12 score (mental summary)					

0 – 44.8	2.5 (1.3–4.5)	0.909	2.5 (1.3–4.9)	2.2 (1.2–4.2)
> 44.8	1			
Preoperative pain, surgical area				
VNRS \leq 3	1			
VNRS > 3	2.0 (1.0–3.9)	0.457	1.6 (0.7–3.5)	1.5 (0.7–3.2)
Preoperative pain, other areas				
VNRS \leq 3	1			
VNRS > 3	1.0 (0.5–1.8)	–0.408	0.7 (0.3–1.4)	0.6 (0.3–1.3)

CI = confidence interval; CSPA = chronic postsurgical pain; OR = odds ratio; SF-12, Short Form Health Survey-12 (version 2 in Spanish);

VNRS = verbal numerical rating scale (0–10).

* *c*-statistic (CI 95%) = 0.645 (0.589–0.702); Hosmer-Lemeshow chi-square test = 3.93; *P* = 0.788.

† A total of 1000 bootstrap subsamples were modelled.

Independent Predictors of Risk for CPSP after Abdominal Hysterectomy Identified in the General Linear Mixed Model for Binomial Distribution with the Variable Recruitment Center as a Random Factor

	Bivariate Analysis	Multivariable Analysis*	Bootstrap Resampling†	
	OR (95% CI)		OR (95% CI)	OR (95% CI)
	N=340	β-coefficients	N=340	
Age				
18 – 50	3.6 (1.1–12.2)	1.501	4.5 (1.3–15.8)	4.5 (1.5–804943805.7)
51 – 64	3.6 (1.0–13.1)	1.360	3.9 (1.0–14.8)	3.9 (1.2–691944174.7)
> 64	1			
SF-12 score (physical summary)				
0 – 33.5	3.7 (1.6–8.8)	1.085	3.0 (1.1–7.7)	3.0 (1.1–8.7)
33.6 – 55.1	1.9 (1.0–3.6)	0.637	1.9 (1.0–3.7)	1.9 (1.0–4.0)
> 55.1	1			
SF-12 score (mental summary)				

0 – 44.8	1.8 (1.1–3.0)	0.475	1.6 (0.9–2.8)	1.6 (0.9–3.0)
> 44.8	1			
Preoperative pain, surgical area				
VNRS ≤ 3	1			
VNRS > 3	1.4 (0.8–2.5)	-0.046	1.0 (0.5–1.7)	1.0 (0.5–1.8)
Preoperative pain, other areas				
VNRS ≤ 3	1			
VNRS > 3	2.6 (1.6–4.3)	0.815	2.3 (1.3–4.0)	2.3 (1.3–4.2)

CI = confidence interval; CSPA = chronic postsurgical pain; OR = odds ratio; SF-12, Short Form Health Survey-12 (version 2 in Spanish);

VNRS = verbal numerical rating scale (0–10).

* *c*-statistic (CI 95%) = 0.645 (0.589–0.702); Hosmer-Lemeshow chi-square test = 3.93; *P* = 0.788.

† A total of 1000 bootstrap subsamples were modelled.

Independent Predictors of Risk for CPSP after Thoracotomy Identified in the General Linear Mixed Model for Binomial Distribution with the Variable Recruitment Center as a Random Factor

	Bivariate Analysis		Multivariable Analysis*		Bootstrap Resampling†
	OR (95% CI)		OR (95% CI)		OR (95% CI)
	N=383	β-coefficients	N=383		
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Age					
18 – 50	3.6 (1.9–6.8)	1.221	3.4 (1.8–6.5)		3.4 (1.7–6.9)
51 – 64	1.1 (0.7–1.7)	0.039	1.0 (0.6–1.7)		1.1 (0.6–1.7)
> 64	1				
SF-12 score (physical summary)					
0 – 33.5	1.2 (0.6–2.5)	0.135	1.1 (0.5–2.5)		1.1 (0.5–2.7)
33.6 – 55.1	1.5 (0.9–2.5)	0.466	1.6 (0.9–2.7)		1.5 (0.9–2.7)
> 55.1	1				
SF-12 score (mental summary)					

0 – 44.8	1.5 (0.9–2.3)	0.376	1.5 (0.9–2.4)	1.4 (0.9–2.4)
> 44.8	1			
Preoperative pain, surgical area				
VNRS ≤ 3	1			
VNRS > 3	2.5 (0.9–7.3)	0.684	2.0 (0.6–6.4)	1.9 (0.5–9.3)
Preoperative pain, other areas				
VNRS ≤ 3	1			
VNRS > 3	1.4 (0.8–2.7)	0.380	1.5 (0.8–2.8)	1.4 (0.7–2.8)

CI = confidence interval; CSPA = chronic postsurgical pain; OR = odds ratio; SF-12, Short Form Health Survey-12 (version 2 in Spanish);

VNRS = verbal numerical rating scale (0–10).

* *c*-statistic (CI 95%) = 0.645 (0.589–0.702); Hosmer-Lemeshow chi-square test = 3.93; *P* = 0.788.

† A total of 1000 bootstrap subsamples were modelled.

Table 3. Independent Predictors of Risk for Neuropathic CPSP Identified in the Logistic Regression Model*

	Bivariate Analysis	Multivariable Analysis*		Bootstrap Resampling
	OR (95% CI)		OR (95% CI)	(1,000 bootstrap subsamples)
	N=2,708	β-coefficients	N=2,708	OR (95% CI)
Surgical specialty				
Vaginal hysterectomy	1			
Abdominal hysterectomy	4.0 (1.9-8.2)	0.974	2.6 (1.2-5.7)	2.6 (1.3-6.7)
Hernia repair	1.6 (0.8-3.1)	0.642	1.9 (0.9-3.8)	1.9 (1.0-4.7)
Thoracotomy	8.6 (4.3-17.0)	2.567	13.0 (6.3-26.8)	13.0 (6.9-34.2)
Age				
18 – 50	2.5 (1.7-3.7)	1.220	3.4 (2.2-5.3)	3.4 (2.2-5.4)
51 – 64	1.6 (1.1-2.5)	0.538	1.7 (1.1-2.7)	1.7 (1.1-2.6)

> 64	1			
SF-12 score (physical summary)				
0 – 33.5	4.6 (2.5–8.3)	1.328	3.8 (2.0–7.1)	3.8 (2.0–8.2)
33.6–55.1	2.0 (1.2–3.4)	0.854	2.3 (1.4–4.0)	2.3 (1.4–4.5)
> 55.1	1			
SF-12 score (mental summary)				
0 – 44.8	2.3 (1.7–3.3)	0.545	1.7 (1.2–2.5)	1.7 (1.1–2.5)
> 44.8	1			
Preoperative pain, surgical area				
VNRS ≤ 3	1			
VNRS > 3	1.5 (1.1–2.2)	0.391	1.5 (1.0–2.2)	1.5 (0.9–2.2)
Preoperative pain, other areas				
VNRS ≤ 3	1			
VNRS > 3	1.7 (1.2–2.4)	0.470	1.6 (1.1–2.4)	1.6 (1.1–2.4)

CI = confidence interval; CSPS = chronic postsurgical pain; OR = odds ratio; SF-12 = Short Form Health Survey-12 (version 2 in Spanish); VNRS = verbal numerical rating scale (0–10).

* *c*-statistic (95% CI) = 0.773 (0.735–0.810); Hosmer-Lemeshow chi-square test = 10.63, *P* = 0.156.

Table 4. Anesthetic and Analgesic Variables by Type of Surgery

Hernia Repair		No. (%) of Patients with CPSP	<i>P</i> Value
Preoperative variables			
Anticonvulsants			
No (n = 1,730)	234 (13.5%)	0.372	
Yes (n = 25)	5 (20.0%)		
Intraoperative variables			
Type of anesthesia			
General anesthesia (n = 241)	28 (11.6%)	0.161	
Combined anesthesia (n = 138)	24 (17.4%)		
Neuroaxial (epidural and spinal) (n = 1,296)	183 (14.1%)		
Plexus nerve block* (n = 12)	2 (16.7%)		
Local (n = 49)	2 (4.1%)		
Ketamine, intravenous			
No (n = 1,721)	238 (13.8%)	0.999	
Yes (n = 12)	1 (8.3%)		
Remifentanil, intravenous			
No (n = 1,563)	215 (13.8%)	0.897	
Yes (n = 170)	24 (14.1%)		
Postoperative period			
Opioids (first 24h according to protocol)			
No (n = 1,557)	205 (13.2%)	0.027	
Yes (n = 165)	32 (19.4%)		

* Plexus nerve block denotes ilioinguinal block, abdominogenital block or transverse abdominis plane block.

CPSP = chronic postsurgical pain.

Vaginal Hysterectomy

	No. (%) of Patients	
	with CPSP	<i>P</i> Value
Preoperative variables		
Anticonvulsants		
No (n = 400)	48 (12.0%)	0.999
Yes (n = 14)	1 (7.1%)	
Intraoperative variables		
Type of anesthesia		
General anesthesia (n = 77)	11 (14.3%)	0.870
Combined anesthesia (n = 20)	2 (10.0%)	
Neuroaxial (epidural and spinal) (n = 317)	36 (11.4%)	
Ketamine, intravenous		
No (n = 406)	45 (11.1%)	0.014
Yes (n = 9)	4 (44.4%)	
Remifentanyl, intravenous		
No (n = 378)	43 (11.4%)	0.420
Yes (n = 37)	6 (16.2%)	
Postoperative period		
Opioids (first 24 h according to protocol)		
No (n = 270)	33 (12.2%)	0.739
Yes (n = 144)	16 (11.1%)	

CPSP = chronic postsurgical pain.

Abdominal Hysterectomy		
	No. (%) of Patients	
	with CPSP	<i>P</i> Value
Preoperative variables		
Anticonvulsants		
No (n = 343)	85 (24.8%)	0.374
Yes (n = 7)	3 (42.9%)	
Intraoperative variables		
Type of anesthesia		
General anesthesia (n = 242)	66 (27.3%)	0.500
Combined anesthesia (n = 100)	20 (20.0%)	
Neuroaxial (epidural and spinal) (n = 7)	2 (28.6%)	
Ketamine, intravenous		
No (n = 336)	83 (24.7%)	0.354
Yes (n = 14)	5 (35.7%)	
Remifentanil, intravenous		
No (n = 256)	67 (26.2%)	0.491
Yes (n = 94)	21 (22.3%)	
Postoperative period		
Opioids (first 24 h according to protocol)		
No (n = 200)	51 (25.5%)	0.944
Yes (n = 147)	37 (25.2%)	

CPSP = chronic postsurgical pain.

Thoracotomy		
	No. (%) of Patients	
	with CPSP	<i>P</i> Value
Preoperative variables		
Anticonvulsants		
No (n = 367)	139 (37.9%)	0.695
Yes (n = 32)	11 (34.4%)	
Intraoperative variables		
Type of anesthesia		
General anesthesia (n = 159)	60 (37.7%)	0.433
Combined anesthesia (n = 239)	89 (37.2%)	
Neuroaxial (epidural and spinal) (n = 1)	1 (100.0%)	
Ketamine, intravenous		
No (n = 386)	144 (37.3%)	0.567
Yes (n = 13)	6 (42.2%)	
Remifentanil, intravenous		
No (n = 258)	99 (38.4%)	0.664
Yes (n = 141)	51 (36.2%)	
Postoperative period		
Opioids (first 24 h according to protocol)		
No (n = 197)	65 (33.0%)	0.058
Yes (n = 199)	84 (42.2%)	

CPSP = chronic postsurgical pain.