Computer-Assisted Navigation for Total Knee Arthroplasty

Tec

Assessment
Program
Volume 22, No. 10
February 2008

Executive Summary

Background

Total knee replacement, or total knee arthroplasty (TKA), has achieved widespread success for the treatment of degenerative arthritis. However, a small percentage of patients who undergo TKA experience poor outcomes, often requiring TKA revision surgery. Improper alignment of the prosthetic implants has been proposed as one reason for poor outcomes following TKA. Computer-assisted navigation for TKA is a refinement of conventional TKA that is intended to improve the accuracy of implant alignment.

Objective

To determine whether computer-assisted navigation improves the accuracy of implant alignment for TKA, and whether the amount of improvement in alignment results in meaningful improvements in health outcomes, such as pain, function, or revision surgery.

Search Strategy

A MEDLINE® search was conducted for the periods of January 1980 to August 2007. For randomized, controlled trials evaluating implant alignment, the following search was used: ((computer or navigation OR navigated) AND total AND knee) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH® Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH® Terms] OR therapeutic use[MeSH® Subheading]). For studies of the relationship between alignment and clinical outcomes the keywords (“total knee arthroplasty” OR “TKA” OR “total knee replacement”) were cross-referenced with the terms (“alignment” OR “malalignment” OR “revision”).

Selection Criteria

For evaluation of the accuracy of implant alignment, selection criteria were: 1) randomized, controlled trials (RCTs) with at least 25 patients per treatment arm, 2) used tricompartmental knee replacement done by the open approach, and 3) compared alignment of prosthetic implants between groups. For the association of malalignment with clinical outcomes, selection criteria were: 1) cohort studies that evaluated postoperative alignment as a predictor of future poor outcomes, such as the need for revision surgery; 2) case-control studies that evaluated differences in alignment between patients with poor outcomes and patients with good outcomes; and 3) case series of patients with poor outcomes following TKA that reported the percentage of patients who had component malalignment.

Main Results

For the outcome of overall limb alignment, 4 of 7 trials reported a statistically significant reduction in the number of patients with malalignment for the computer-assisted navigation group. A fixed-effect, inverse-variance-weighted pooling of data from these 7 trials suggests that malalignment of greater

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than 3 degrees will be avoided in approximately 15.5% of patients (95% CI: 9.4–21.7% when computer-assisted navigation is used; number needed to treat of 6.45 to avoid one instance of malalignment [95% CI: 4.61–10.69]). A similar pattern of results was reported for other measures of alignment (e.g., alignment of tibial components alone or alignment of femoral component alone).

Operating time was compared between groups in 7 of the reports from the RCTs, and 5 of the 7 reported significantly increased operating room times for the computer-assisted navigation group. The increase in time ranged from 5–34 minutes. Five trials compared the amount of blood loss between groups, and 2 of the 5 reported a statistically significant decrease in blood loss for the computer-assisted navigation group. The difference in blood loss in those two trials was approximately 100–200 mL. None of the trials meeting the article selection criteria reported on other postoperative complications such as thromboembolism or fat embolism.

Seven publications included comparisons of functional outcomes, including 3 that followed patients for up to 2–3 years. In these studies, there were no differences between groups on any of the functional status outcomes. These data establish that there are not large differences in functional outcomes between conventional TKA and TKA performed with computer-assisted navigation at 2–3 years of follow-up. However, none of these trials was adequately powered to detect small differences that might be expected on these functional outcome measures.

For the question of whether improper alignment leads to meaningful differences in clinically relevant outcomes, 5 cohort studies were identified. One of these evaluated postoperative alignment prospectively as a risk factor for revision surgery using multivariate analysis. This study reported a strong relationship between malalignment and outcomes, with malalignment of greater than 3 degrees associated with a greater than 17-fold risk for revision surgery. However, a number of methodologic limitations reduce confidence in the validity of these reported results. First, the study covered a long time period from 1983–2000 and thus was subject to maturation effects arising from changes in TKA surgery over this period. There were only a relatively small number of patients undergoing revision surgery (n=41), thereby limiting the power to evaluate the many potential predictors of revision surgery. Finally, the analysis was done using data-mining techniques and iterative modeling that likely resulted in an overestimate of the true predictive ability of malalignment.

The other 4 cohort studies divided patients into groups based on postoperative alignment (e.g., varus, neutral, and valgus alignment) and compared revision rates among the group. In 3 of the 4 studies, there was a significantly increased revision rate for the group of patients who had varus postoperative alignment. Two small case-control studies compared rotational alignment among patients with poor outcomes and those with good outcomes. Both studies reported significant differences in rotational alignment between groups, with excess internal rotation noted in the group of patients with poor outcome. Four case series of patients undergoing TKA revisions were identified: these studies were consistent in reporting that approximately 10% of patients had evidence for implant malalignment (range: 9.4–12%).

Author's Conclusions and Comments

The RCTs allow conclusions on postoperative alignment outcomes. These RCTs are relatively consistent in demonstrating a reduction in alignment outliers for the computer-assisted navigation group across different studies and different measures of alignment. It is possible to conclude that approximately 15.5% of patients may avoid malalignment of more than 3 degrees in overall limb alignment when computer-assisted navigation is used. It is also possible to conclude that computer-assisted navigation is associated with longer operating times. The evidence on blood loss is less certain, in that some studies report a small reduction in blood loss, but others do not.

There is no direct evidence to evaluate whether long-term functional outcomes are improved by computer-assisted navigation. The RCTs that report on short- to intermediate-term functional outcomes do not report improvements associated with computer-assisted navigation. This establishes that there is not a large difference in functional outcomes associated with computer-assisted navigation over a 2- to 3-year follow-up period. However, these small RCTs are inadequately powered and have an insufficient length of follow-up to detect the smaller differences in functional status scores that might be expected from computer-assisted navigation when evaluating the entire population of patients undergoing the procedure. Since the vast majority of patients do well following TKA and only a small minority has poor outcomes, larger RCTs with longer follow-up will be required to demonstrate improved outcomes as measured by standardized knee rating scores.

The available evidence on the relationship between malalignment and clinical outcomes consists of observational studies of various designs. Only one of these observational studies was a prospective cohort study that used postoperative alignment as a predictor of future poor outcomes in a multivariate analysis, and this study had only a relatively small number of outcomes (n=41). This study did show a strong relationship between malalignment and poor outcomes. Four other cohort studies, which were generally much older studies, reported that outcomes were worse for patients who had postoperative varus alignment.

The case-control studies and case series that evaluated the association of alignment with outcomes represent weak study designs to answer the specific questions. These studies did not use postoperative malalignment to predict outcomes, but rather evaluated alignment at the time of the poor outcomes. The case-control studies did report an association between rotational malalignment and clinical outcomes, and the case series suggested that approximately 10% of patients undergoing TKA revision surgery have malalignment at the time of revision surgery.

Thus, while RCTs suggest that approximately 15.5% of patients may avoid malalignment of greater than 3 degrees by this analysis, it is not possible to conclude that all these patients benefit from computer-assisted navigation. The threshold definition for malalignment is derived from older studies. It is not certain that this threshold is the most clinically relevant definition of malalignment in the current era of TKA. There have been many advances in TKA that might mitigate the impact of malalignment seen in earlier studies. In addition, there is a lack of clinical studies that define the threshold for malalignment, and there may be an interaction between alignment and other risks for poor outcome, such as obesity.

The positive associations reported across different types of observational studies suggest that there is a relationship between malalignment and poor outcomes. However, as a result of deficiencies in the available evidence, it is not possible to test this hypothesis or to determine whether the degree of improvement in alignment reported in the RCTs leads to meaningful improvements in health outcomes, such as pain, function, or revision surgery. Therefore, it is not possible to conclude that the use of computer-assisted navigation with TKA leads to improved health outcomes.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the use of computer-assisted navigation for total knee arthroplasty (TKA) meets the Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

TKA is a surgical procedure that is not subject to U.S. Food and Drug Administration (FDA) regulations. Several systems for computer-assisted navigation have been cleared for marketing by the FDA via the 510(k) process (e.g., PiGalileo™ Computer-Assisted Orthopedic Surgery System, PLUS Orthopedics; OrthoPilot® Navigation System, Braun; Navitrack® Navigation System, ORTHOsoft).

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The evidence is sufficient to conclude that the use of computer-assisted navigation with TKA results in more accurate implant alignment. This conclusion is derived from RCT evidence comparing TKA using computer-assisted navigation with conventional TKA and reporting on the number of patients in each group with malalignment. Approximately 15.5% of patients may avoid malalignment of greater than 3 degrees in overall limb alignment with the use of computer-assisted navigation.

The evidence is not sufficient to conclude that the improvement in alignment associated with computer-assisted navigation leads to meaningful differences in health outcomes, such as pain, function, and revision surgery. Long-term evidence from RCTs is not available to answer this question. Observational studies that evaluate the association between alignment and clinical outcomes consistently report an association between malalignment and poor outcomes. However, these studies have a variety of methodologic limitations and, by their nature, are hypothesis generating. Thus, the evidence is not sufficient to determine that the degree of improvement in alignment reported in the RCTs leads to a meaningful benefit in health outcome.

3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives.

Evidence is not sufficient to permit conclusions as to whether computer-assisted navigation improves the net health outcome or is as beneficial as conventional alignment techniques.

5. The improvement must be attainable outside the investigational settings.

It cannot be determined whether any improvement is attainable outside the investigational setting since the evidence is not sufficient to permit conclusions on the effect of computer-assisted navigation on health outcomes.

For the above reasons, the use of computer-assisted navigation for total knee arthroplasty does not meet the TEC criteria.

Contents

Published in cooperation with Kaiser Foundation Health Plan and Southern California Permanente Medical Group.

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Assessment Objective

The objective of this Assessment is to determine whether the use of computer-assisted navigation for total knee arthroplasty (TKA) leads to improvement in health outcomes. TKA is a common surgical procedure with a high success rate. However, a small percentage of patients have poor outcomes following TKA, and some of these poor outcomes may be related to component malalignment.

Computer-assisted navigation is a refinement of TKA that is intended to improve the ability of the surgeon to properly align the prosthetic implants. In conventional TKA, alignment of the prosthetic implants is done manually with the assistance of intramedullary and/or extramedullary rods. Computer-assisted navigation utilizes computer models that incorporate anatomic landmarks and patient kinematics to determine the correct placement of the implants.

Improvement in implant alignment following TKA is the proximal outcome that will be examined for this Assessment. However, this is an intermediate outcome and improvement in this outcome is not sufficient to conclude that patient outcomes are improved. In order to conclude that patient outcomes are improved, it is necessary to determine that the amount of improvement in alignment leads to meaningful differences in clinical outcomes. These clinical outcomes include symptoms such as pain, functional status, and the need for TKA revision surgery.

Background

Total knee replacement, or TKA is primarily a treatment for degenerative arthritis of the knees, either osteoarthritis or rheumatoid arthritis (Campbell's Operative Orthopaedics 2003). Degenerative arthritis leads to pain and limitations in function that are progressive in severity over time. Conservative treatment, including anti-inflammatory medications, activity modification, and assistive devices, may either fail to control symptoms adequately or may not permit the patient to participate in his/her desired level of activities. The indications for TKA are pain or activity limitations that are not responsive to conservative treatments (Campbell's Operative Orthopaedics 2003).

TKA has been proven effective in reducing pain and improving function for patients with late-stage arthritis (NIH Consensus Conference 2003; Rasanen et al. 2007). An Agency for Healthcare Research and Quality (AHRQ) evidence report (Kane et al. 2003) concluded that there was a large magnitude of benefit following TKA. A quantitative meta-analysis done as part of this evidence report found that the average improvement on global knee scores (0–100 scale) was 30.8 (95% CI: 26.6–35.0) for the Knee Score (KS) and 28.3 (95% CI: 25.3–31.2) for the Hospital of Special Surgery (HSS) knee scale. TKA is also a relatively safe operation with low rates of serious complications and few contraindications. Complications occur in approximately 5% of patients (Kane et al. 2003) and are primarily knee-related or thromboembolic events.

As a result of the success of TKA, and the increase in the aging population, the incidence of TKA is increasing rapidly. Currently, there are approximately 500,000 TKAs performed annually (Kurtz 2007). A recent study based on data from the Nationwide Inpatient Sample and the National Hospital Discharge Survey estimated that this number will increase to over 3.5 million by the year 2030. This represents a 678% increase in the total number of TKAs over this time period.

The success rate for primary TKA is high, with overall survivorship for implanted knees greater than 90% at 10–15 years (Lonner et al. 1999). However, some patients continue to have pain or limitations in function following surgery. Other patients initially do well, but later develop pain and/or other symptoms within the first 5 years following TKA. These categories of outcomes are often termed "failed" TKA and many of these patients end up undergoing revision TKA.

Failed TKAs are often divided into early failures (<5 years) and late failures. Late failures may be due to a variety of clinical and biomechanical factors that influence wear and loosening of the implanted components, such as age, physical activity, obesity and/or other factors. Early failures are more problematic and may represent improper patient selection, improper surgical techniques, or infections. Approximately 2% of all patients undergoing first TKA will have "failed" TKA and need early revision surgery within the first 5 years (Kane et al. 2003).

As a result of these factors there has been large increase in the incidence of TKA revision surgery that parallels the increase in primary TKA. In 2007, the number of revision TKAs performed in the U.S. is slightly less than 50,000. This number is expected to grow rapidly, with an increase of 601% to a total of 270,000 by the year 2030.

Revision TKA is associated with a high burden of morbidity and costs. Revision TKA is associated with higher rates of perioperative and long-term complications, and also results in poorer functional outcomes compared with first TKA (Lavernia et al. 2006). The average costs for revision surgery, approximately $37,000, are higher than for first TKA. The cost projections associated with TKA revision surgery are of sufficient magnitude to put an increasing burden on the healthcare budget (Ong et al. 2006).

Because of the high burden of morbidity associated with revision surgery, considerable attention has been focused on factors contributing to the need for TKA revision, particularly those that might be preventable or modifiable. Multiple predictors of the need for revision surgery have been identified, many of which are patient-related or demographic factors that are not modifiable. For example, younger age has been associated with a higher likelihood of revision TKA (Rand et al. 2003), presumably resulting from greater activity levels in younger patients who receive knee replacement.

The underlying diagnosis also appears to be a predictor of the need for revision. Patients with osteoarthritis have a greater likelihood of needing revision compared to patients with rheumatoid arthritis (Rand et al. 2003). Other factors predicting need for revision include the type of implant used and specific procedural aspects, such as whether the posterior cruciate ligament is retained or whether cement is used for fixation (Rand et al. 2003).

Other preventable or modifiable reasons for revision surgery have also been identified. These types of factors generally consist of technical aspects of surgery, such as use of incorrectly sized prostheses, improper ligamentous balancing, and malalignment. However, the overall contribution of these types of technical errors to the total number of revision TKAs is not well understood.

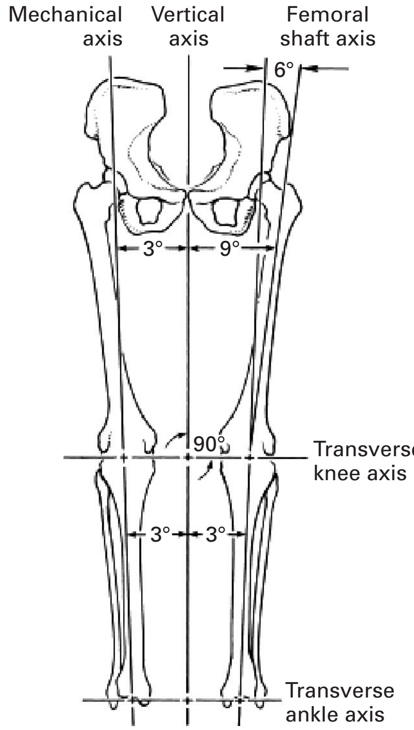
Component malalignment is the primary correctable technical factor that may be addressed by computer-assisted navigation. Component alignment is a complicated process that involves multiple types of alignment. Overall alignment refers to the angle made by the tibial shaft with the femoral shaft in the coronal plane (Figure) (Bargren et al. 1983). Tibial component alignment refers to the angle of the tibial prosthesis with the proximal half of the tibia in the anteroposterior plane (Bargren et al. 1983). Femoral component alignment refers to the angle of the femoral prosthesis with the femur in the anteroposterior plane (Bargren 1983). Rotational alignment refers to the angle made by the prosthetic condyles relative to the epicondylar line in the axial plane. As a cross-sectional measurement, rotational alignment cannot be assessed by plain X-rays. CT scanning can be used to determine rotational alignment, or it can be directly assessed at the time of surgery.

Malalignment of prosthetic components has long been considered to be a major reason for failed TKA, since it can lead to abnormal biomechanics of the legs. Abnormal biomechanics may in turn lead to excessive wear and tear on both the native elements and the prosthetic components, and may result in a higher likelihood for revision TKA. Early studies that examined implants removed which had been malaligned demonstrated abnormal patterns of wear associated with malalignment. Other studies simulated load-bearing at different degree of alignment, demonstrating abnormal patterns of weight-loading associated with excessive degrees of malalignment (Hsu et al. 1989; Wasielewski et al. 1994). In addition, rotational malalignment has been shown in cadaver studies to be associated with abnormal patellar tracking (Nagamine et al. 1996; Akagi et al. 1999). Abnormal patellar tracking may in turn lead to early failure of the patellar component of TKA.

Conventional Total Knee Arthroplasty Techniques

TKA was developed in the 1970s and has undergone significant evolution in technique in the ensuing time period (Campbell's Operative Orthopaedics 2003). The current technique of TKA generally refers to the implantation of tricompartmental prosthesis (Campbell's Operative Orthopaedics 2003).

Figure. Overall Limb Alignment (mechanical axis); Femoral Component Alignment; and Tibial Component Alignment in the Coronal Axis. (reproduced with permission from *Campbell's Operative Orthopaedics*, 2003).



Mechanical axis of lower limb extends from center of femoral head to center of ankle joint and passes near or through center of knee. It is in 3 degrees of valgus from vertical axis of body. Anatomical axis of femur is in 6 degrees of valgus from mechanical axis of lower limb and 9 degrees of valgus from true vertical axis of body. Anatomical axis of tibia lies in 2 to 3 degrees of varus from vertical axis of body. *(Redrawn from Moreland JR, Hanker GJ: Lower-extremity axial alignment in males. In Dorr LD, ed: The knee. Papers of the First Scientific Meeting of the Knee Society, 1985, Aspen.)*

The three components of the prosthesis are the femoral component, the tibial component, and the patellar component.

In the open technique, an incision is made over the anterior knee to enter the joint space. Once appropriately sized components have been selected, bone preparation, component alignment and tissue balancing are undertaken. Tissue balancing refers to evaluation of the patellar ligaments in order to avoid excess laxity or excess stress. Bone preparation readies the surface of the tibia and femoral shaft to accommodate implants.

Alignment of the implanted components is accomplished by a combination of manual examination and intramedullary guides. Intramedullary guides are implanted into the femur because landmarks for alignment with the proximal femur are not palpable. The femoral cutting guide is aligned by determining the angle of the guide with the femoral condyles. The use of intramedullary guides in the tibia is more controversial. They are sometimes used, but alignment can also be done through use of extramedullary guides with palpation of anatomical landmarks in the knee and ankle joints. The tibia may be aligned with or without an intramedullary guide by positioning the tibial cutting guide between the center of the knee and the ankle (Campbell's Operative Orthopaedics 2003).

Once alignment of the implants is complete, the surgeon manipulates the knee in order to test tracking of the prosthesis. This is to ensure that the implanted knee retains full range of motion without abnormal biomechanics. After the preparation is completed, ligamentous balancing is adequate, and extensor mechanism is tracking satisfactorily, the prostheses are implanted.

While mechanical guides have improved the ability to properly align prosthetic implants, conventional techniques for TKA still may not result in optimal component alignment. In a cadaver study, Novotny et al. (2001) evaluated the degree of error in alignment using an intramedullary guide. This report estimated by computer modeling that the degree of error in limb alignment may be as high as 6 degrees. Stulberg (2003) evaluated 7 measures of alignment in 20 TKA surgeries done by conventional techniques. In only 4 of the 20 cases were all measures of alignment within 3 degrees of target. In addition, the reproducibility of component alignment has been reported to be low, especially for rotational alignment (Jenny and Boeri 2004).

Computer-Assisted Navigation

Computer-assisted navigation devices were developed in order to assist surgeons in positioning prosthetic implants and to improve component alignment. These devices may be image-based or non-image based. Image-based devices use preoperative CT scans and operative fluoroscopy to direct implant positioning. Non-image based devices, which are more recent, use information obtained in the operating room, typically with infrared probes. For TKA, specific anatomic reference points are made by fixing signaling transducers with pins into the femur and tibia, which are detected by signal-emitting cameras.

During the surgical procedure, multiple surface points are taken from the distal femoral surfaces, the tibial plateaus, and the medial and lateral epicondyles. The femoral head center is typically calculated by kinematic methods that involve movement of the thigh through a series of circular arcs, and the computer produces a 3-dimensional model that includes the mechanical, transepicondylar, and tibial rotational axes (Laskin and Beksac 2006). Computer-assisted navigation directs the position of the cutting blocks and placement of the prosthetic implants based on the digitized surface points and model of the bones in space. The accuracy of each step of the operation (cutting block placement, saw cut accuracy, seating of the implants) can be verified with the computer, allowing adjustments to be made during surgery.

FDA Status. TKA is a surgical procedure that is not subject to U.S. Food and Drug Administration (FDA) regulations. Several systems for computer-assisted navigation have been cleared for marketing by the FDA via the 510(k) process (e.g., PiGalileo™ Computer-Assisted Orthopedic Surgery System, PLUS Orthopedics; OrthoPilot® Navigation System, Braun; Navitrack® Navigation System, ORTHOSoft).

Methods

Search Methods

A MEDLINE® search was conducted for the periods of January 1980 to August 2007. For randomized, controlled trials evaluating implant alignment, the following search was used: ((computer or navigation OR navigated) AND total AND knee) AND ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH® Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH® Terms] OR therapeutic use[MeSH® Subheading]). For studies of the relationship between alignment and clinical outcomes the keywords ("total knee arthroplasty" OR "TKA" OR "total knee replacement") were cross-referenced with the terms ("alignment" OR "malalignment" OR "revision").

Searches were limited to full-length publications in the English language. Initial electronic search was supplemented with use of the "related articles" function in PubMed and by the hand search of relevant bibliographies.

Study Selection

Selection criteria for clinical trials of computer-assisted navigation versus conventional TKA were as follows: 1) patients were randomized to treatment assignment, 2) study compared conventional open (not minimally invasive) TKA to TKA with computer-assisted navigation and used tricompartmental knee replacement, 3) enrolled at least 25 patients per treatment group, and 4) reported on at least one of the following relevant outcomes:

Surgical outcomes

- alignment (tibial component/femoral component/overall)(axial/coronal/rotational)
- blood loss
- thromboembolism

Functional outcomes
- standardized functional status measure
- pain
- other measures of function

Selection criteria for the relationship of malalignment to clinical outcomes were as follows:
- cohort studies that 1) used postoperative alignment as a predictor of future outcomes, 2) enrolled at least 100 patients, and 3) analyzed the relationship of postoperative prostheses alignment with at least one relevant clinical outcome, such as need for TKA revision, standardized functional status measure, or pain
- case-control studies that 1) compared patients who have poor outcomes (e.g., revision, persistent pain) with patients who have good outcomes, 2) enrolled at least 25 patients per group, and 3) compared relevant measures of alignment between the two groups
- case series that 1) reported a series of patients undergoing TKA revision surgery, 2) included a majority of patients (>80%) undergoing first revision surgery, 3) included at least 25 patients, 4) reported on the number of patients that have malalignment as a potential underlying cause of TKA failure

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on October 17, 2007. In order to maintain the timeliness of the scientific information in this Assessment, literature search updates were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no that would change the conclusions of this Assessment.[1]

Formulation of the Assessment

Patient Indications

Patient indications are those individuals undergoing first time TKA for osteoarthritis. This will primarily consist of patients with end-stage degenerative arthritis who have symptoms of pain and/or activity limitations that have not responded adequately to conservative treatment. A minority of patients undergoing TKA will have other indications, e.g., traumatic knee injury or other degenerative process.

Technologies to be Compared

The comparison of interest will be TKA performed by conventional methods, without computer-assistance. This will specifically refer to patients undergoing tricompartmental knee (i.e., total knee) replacement, done by the open surgery route. Unicompartmental TKA and TKA performed by the minimally invasive route will not be considered valid comparisons for the purposes of this Assessment.

Health Outcomes

The most important health outcomes are clinical outcomes associated with TKA. Relevant clinical outcomes associated with TKA include the following:
- pain
- other symptoms, such as stiffness, instability, etc.
- functional status
- need for TKA revision surgery

Physiologic outcomes from surgery will also be considered as intermediate outcomes. These outcomes will primarily relate to alignment of the implanted prostheses, and may be measured in several ways:
- percent of patients with malalignment. The definition of malalignment may vary by study, however the most common definition of an overall tibiofemoral alignment greater than 3 degrees varus or valgus will be used where possible
- average deviation from optimal alignment

[1] As this Assessment was in press, two additional relevant reports were published. An additional study on alignment outcomes following computer-assisted navigation with TKA (Mullaji et al. 2007) concluded, "…it remains to be proven by long-term studies whether this improved precision in restoring the limb alignment and optimizing component placement will translate into superior longevity of the prosthesis." A prospective study by Tingart et al. (2008) compared conventional alignment techniques to computer-assisted navigation in 1,000 patients undergoing TKA. This study concluded, "Computer-assisted TKA leads to a more accurate restoration of leg alignment and component orientation compared to the conventional technique," but that "Potential benefits in long-term outcome and functional improvement require further investigation." The results of these publications do not change the conclusions of this Assessment.

Surgical outcomes will also be considered as potentially important outcomes that may be addressed by computer-assisted navigation. The particular surgical outcomes considered for this Assessment include:

- operating room time
- surgical blood loss
- postoperative thromboembolic complications

Specific Assessment Questions:

1. For patients with indications for TKA, does computer-assisted navigation improve alignment of implanted prostheses during TKA, compared to conventional TKA?
   - Does computer-assisted navigation decrease the number of outliers (patients with clinically significant malalignment) compared with conventional surgery?

2. Does computer-assisted navigation lead to improvements in other surgical outcomes, compared with conventional surgery?
   - operating time
   - surgical blood loss
   - postoperative thromboembolic complications

3. Does the degree of improvement in alignment following TKA performed with computer-assisted navigation result in meaningful improvements in clinical outcomes associated with TKA?
   - decrease in need for revision surgery
   - reduction in pain and/or other symptoms
   - improvement in functional status

Review of Evidence

For patients with indications for TKA, does computer-assisted navigation improve alignment of implanted prostheses during TKA, compared to conventional TKA?

- **Does computer-assisted navigation decrease the number of outliers (patients with clinically significant malalignment) compared with conventional surgery?**

The evidence for this question consists of 9 publications from 7 RCTs that compare conventional TKA to TKA performed with computer-assisted navigation (Tables 1–3) and that enrolled more than 25 patients per treatment group. An additional 8 small RCTs were identified but excluded because they enrolled less than 25 patients per treatment group or did not otherwise meet the inclusion criteria.

All of the studies are RCTs, with 25–100 patients per treatment arm. All were done at a single center, with either a single surgeon or two surgeons performing all the procedures. None of the studies reported that patients were blinded to treatment assignment. All of the RCTs except for two (Matziolis et al. 2007; Decking et al. 2007) had assessment of post-operative alignment performed by a clinician blinded to treatment assignment.

Four of the 9 studies evaluated short-term, postoperative outcomes only. These studies primarily reported on alignment outcomes, and other surgical outcomes, such as blood loss and operating room time. Five of the studies followed patients for longer periods, ranging from 6–36 months. These studies generally reported postoperative outcomes, as well as longer-term functional outcomes.

Formal quality assessment for these RCTs was performed according to the methods of Harris et al. (2001; Table 4). Five studies from 4 trials met all of the quality criteria and were rated "good" quality (Chauhan et al. 2004; Chin et al. 2005; Decking et al. 2005; Kim et al. 2007; Spencer et al. 2007). The remaining studies did not meet all of the quality parameters, but did not contain any fatal flaws, and therefore were rated "fair" quality. Quality deficiencies that were noted in the studies included lack of reporting of methods for randomization, lack of blinded outcome assessment and failure to analyze outcomes by intention-to-treat.

The majority of these studies used a definition of malalignment as greater than 3-degree deviation from target. Two studies used a definition of 2-degree deviation from target. The most common types of alignment outcomes reported were overall alignment in the mechanical axis (7 studies), femoral component alignment (6 studies), and tibial component alignment (6 studies).

Alignment outcomes from these studies are summarized in Table 2. Seven studies reported the outcome of overall alignment (mechanical axis), with 4 studies reporting a statistically significant reduction in the percent outliers. In 3 of the studies, there was a reduction in the number of outliers in the computer-assisted navigation group that did not reach statistical significance. The weighted mean for this outcome is shown in Table 2. For all 7 studies, there were 32.8% outliers (110/335) in the

Table 1. RCTs of TKA Performed with Computer-Assisted Navigation vs. Conventional TKA: Study Characteristics

Study/Yr	Patients	n	Selection C riteria	Follow-up	Outcomes Reported	Comments
Post-op						
Chauhan et al. 2004	Consecutive patients; No patient refused to enter the study	71	TKA; Excluded patients with active infection or malalignment	Post-op	LLR, CT, rotation, BL, AEs	Industry funds; one surgeon with 12 prior CAN cases; see Spencer et al. 2007 for follow-up
Chin et al. 2005	No other information was reported	90	Primary TKA; no exclusion criteria were used	Post-op	LLR, AE, BL Collective outliers (on any of the 4 angles)	Single institution; two surgeons experienced in CAN; also compared tibial EM and IM guides
Decking et al. 2005	Primary or secondary OA; 6 subjects didn't meet the exclusion criteria)	52	Primary TKA; specific exclusion criteria were not reported	Post-op	LLR, WOMAC, KSS, BL	Single institution; two surgeons experienced in CAN; >2 degree cutoff; tibial EM guide; see Decking et al. 2007 for follow-up
Victor and Hoste 2004	Selected patients for condylar TKA (100% enrollment)	100	Primary TKA; there were no exclusion criteria	Post-op	LLR, knee score, function score, patients w/ROM deficit, patellar shift	Single surgeon with limited experience; >2 degree cutoff; used a tibial EM guide
6–36 Months						
Matziolis et al. 2007	Primary arthritis	60	Excluded prior surgery or inability to have an unconstrained short-stem implant	6 months	CT, KSS, ROM, planned slope, rotation	Single institution; blinding not specified
Decking et al. 2007	Follow-up on 52 (100%) patients from Decking et al. 2005	[52]	See Decking et al. 2005, above	1 year	LLR, KSS, WOMAC	
Ensini et al. 2006	Selected from surgeries between 2002-2003 (13 bi-lateral, 120 knees)	107	Primary TKA; Excluded infection, revision, severe knee instability	2-3 years	LLR, 3 questionnaires	Single institution; used a tibial EM guide
Kim et al. 2007	Consecutive patients out of 115 bilateral procedures (200 knees)	100	Bilateral primary TKA; 15 patients excluded for >20° varus or >30° flexion	2-3 years	LLR, CT, KSS, HSS	Single institution, limited experience in CAN
Spencer et al. 2007	Follow-up of 60 of 71 (85%) patients from Chauhan et al. 2004, above	[60]	Loss to FU of 6 patients who died, 3 who were lost to follow-up and 2 couldn't attend clinic	2 years	KSS, WOMAC, Oxford, Bartlett Patellar, SF-36 from 3 months to 2 years	No patients had revision surgery

Abbreviations
AE: adverse events; BL: blood loss; CAN: computer-assisted navigation; TKA: total knee arthroplasty; CT: computed tomography; EM: extramedullary; FU: follow-up;
HSS: Hospital for Special Surgery; IM: Intramedullary; KSS: Knee Society score; LLR: long-leg weight-bearing radiograph; NR: not reported; OA: osteoarthritis; ROM: Range of motion;
SF-36: Short form 36; WOMAC: Western Ontario and MacMaster Universities Osteoarthritis Index

Table 2. RCTs of TKA Performed with Computer-Assisted Navigation vs. Conventional TKA: Radiographic Alignment Outcomes

			Radiographic Outcomes					
Study/Yr	Treatment Groups	n	Overall Tibial/ Femoral Outliers (n) [range][1]	Femoral Comp Outliers [range][1]	Tibial Comp Outliers [range][1]	Femoral Slope Outliers [range][1]	Tibial Slope Outliers [range][1]	Other Outcomes[2]
Post-op								
Chauhan et al. 2004	Conv	36	28% (11/36) [-4 to 6]	8% [-4 to 4]	8% [-4 to 2]	17% [0 to 7]	81% [1 to 10]	25% [-11 to 10]
	CAN	35	14% (5/35) [-4 to 6]*	0% [-3 to 3]*	0% [-3 to 2]*	11% [0 to 5] ns	51% [0 to 7]***	20% [-4 to 7]***
Chin et al. 2005	Con EM	30	37% (11/30) [0-6]	33% [-2 to 7]	16% [-3 to 5]	87% [0 to -15]	63% [-12 to 7]	53%
	Con IM	30	37% (11/30) [0-13]	70% [-4 to 13]	47% [-6 to 4]	88% [0 to -12]	47% [-7 to 0]	73%
	CAN	30	20% (6/30) [0-6] ns[3]	7% [-4 to 4]*	7% [-2 to 3]***	60% [0 to -11]***	60% [-9 to 5] ns	17%*
Decking et al. 2005	Conv	25	64% (16/25)	20%	20%	40%	4%	
	CAN	27	48% (13/27) *	19% ns[3]	4% ns[3]	20% NR	20% NR	
Victor and Hoste 2004	Conv	49	27% (13/49) [-4 to 4]			[0 to 6]		[0 to 3]
	CAN	48	0% (0/48) [-2 to 2]*** [3]			[0 to 6]		[0 to 3]
6–36 Months								
Matziolis et al. 2007	Conv	28	25% (7/28) [-5 to 7]	11% [-2 to 5]	18% [-4 to 6]	[-3 to 5]	47% [-4 to 10]	11% [-3 IR-5ER]
	CAN	32	3% (1/32) [-3 to 3]**	0% [-2 to 3] ns[3]	0% [-2 to 3]* [3]	[-4 to 3] NR	28% [-4 to 4] NR	3% [-5IR-2ER]
Decking et al. 2007	Conv	[25]						No lysis in
	CAN	[27]						either group
Ensini et al. 2006	Conv	60	25% (15/60)	15%	3%	50%	42%	77%
	CAN	60	12% (7/60) ns	0% **	2% ns	27% *	37% ns	63% NR
Kim et al. 2007	Conv	107	35% (37/107)	9%	16%	33%	9%	29% IR/ER
	CAN	107	28% (30/107) ns	13% ns	7% ns	31% ns	25% ns	15% IR/ER
Spencer et al. 2007	Conv	[30]						
	CAN	[30]						
Combined	Conv	335	32.8% (110/335)					
	CAN	339	18.3% (62/339) ***[3]					

[1] Outliers are >3 degrees of target unless otherwise specified; [range] refers to the range of angles (in degrees) for the entire group.
[2] See outcome measures on Table 3 (*p<0.05, **p<0.01, ***p<0.001)
[3] Statistical testing not reported in article; calculated from raw data using Fisher's exact test, two-sided.
CAN: computer-assisted navigation; Conv: conventional; EM: extramedullary; ER: external rotation; IM: intramedullary; IR: Internal rotation; NR: Not reported; ns: not significant

Table 3. RCTs of TKA Performed with Computer-Assisted Navigation vs. Conventional TKA: Surgical and Functional Outcomes

			Surgical and Functional Outcomes							
Study/Yr	Treatment Groups	n	Surgical Time (min)	Blood Loss (mL)	Knee Society Score	WOMAC or HSS	WOMAC (Stiffness)	WOMAC (Function)	Oxford Knee Score	Patello-femoral Scores
Post-op										
Chauhan et al. 2004	Conv	36	67	446						
	CAN	35	80***	252***						
Chin et al. 2005	Con EM	30	90	401						
	Con IM	30	84	396						
	CAN	30	118***	290*						
Decking et al. 2005	Conv	25	79 ± 8	985 ± 470	161 ± 22	1.9 ± 1.7[1]	2.8 ± 1.9	2.3 ± 1.5		
	CAN	27	92 ± 9***	1,088 ± 426 ns	168 ± 25 ns	1.9 ± 2.0 ns	2.3 ± 1.8 ns	2.0 ± 1.6 ns		
Victor and Hoste 2004	Conv	49	74		154					
	CAN	48	93***		155 ns					
6–36 Months										
Matziolis et al. 2007	Conv	28	94 ± 18	520 ± 295	144 ± 29					
	CAN	32	101 ± 13 ns	469 ± 327 NR	149 ± 34 ns					
Decking et al. 2007	Conv	[25]			168 ± 25	1.2 ± 1.01	2.8 ± 1.9	1.9 ± 1.8		
	CAN	[27]	N/A	N/A	176 ± 17 ns	0.9 ± 0.9 ns	2.0 ± 2.1 ns	1.6 ± 1.5 ns		
Ensini et al. 2006	Conv	60	96 ± 8						19 ± 7[1]	22 ± 5
	CAN	60	98 ± 13 ns						20 ± 7 ns	23 ± 4 ns
Kim et al. 2007	Conv	100	82	265	94 [91-100]	89 [76–100] [3]				
	CAN	100	97***	277 ns	93 [89-100]	90 [75–100] ns				
Spencer et al. 2007	Conv	[30]			159 ± 29	14 ± 13[2]			20 ± 6[1]	24 ± 5
	CAN	[30]	N/A	N/A	156 ± 33 ns	23 ± 22 ns			27 ± 22 ns	23 ± 6 ns

[1] WOMAC pain component
[2] WOMAC Total score
[3] Hospital for Special Surgery (Total for functional and pain scores)
*p<0.05, **p<0.01, ***p<0.001

Table 4. Quality Assessment for Clinical Trials						
Study/yr	Initial Assembly of Comparable Groups	Maintenance of Comparable Groups	Comparable Intervention(s)	Comparable Measurements	Appropriate Analysis of Outcomes	OVERALL QUALITY LEVEL
Chauhan et al. 2004	YES	YES 100% follow-up	YES	YES	YES Blinded assessment	GOOD
Chin et al. 2005	YES	YES 100% follow-up	YES	YES	YES Blinded assessment	GOOD
Decking et al. 2005	YES	YES 100% follow-up	YES	YES	YES Blinded assessment	GOOD
Victor and Hoste 2004	Randomized blocks of 4 based on 4 surgeries per day (2 Conv, 2 CAN)	YES 98% and 96% follow-up, loss unrelated to procedure	YES	YES	Reviewers were different from the surgeon, but blinding was not specified	FAIR
Matziolis et al. 2007	YES Random number generator	YES 100% follow-up	YES	YES	Blinding not specified	FAIR
Decking et al. 2007	YES	YES 100% follow-up Trend for increased body mass index in controls	YES	YES	Blinding not specified	FAIR
Ensini et al. 2006	Randomization procedure not described	YES Follow-up not well described	YES	YES	Blinded, 13 were bilateral	FAIR
Kim et al. 2007	YES (Randomized left or right side)	YES 100% follow-up	YES	YES	YES Blinded assessment	GOOD
Spencer et al. 2007	YES	YES 83% Controls 86% CAN	YES	YES	Blinded Used final n at 2 years	GOOD

conventional surgery group and 18.3% outliers (62/339) in the computer-assisted navigation group. For this combined outcome, the difference was statistically significant at the p<0.001 level (Fisher's exact test, 2-sided). A fixed-effect, inverse-variance-weighted pooling of data from these 7 trials suggests that malalignment of greater than 3 degrees will be avoided in approximately 15.5% of patients (95% CI: 9.4–21.7% when computer-assisted navigation is used (number needed to treat [NNT] of 6.45 to avoid one instance of malalignment [95% CI: 4.61–10.69]).

Six studies reported on femoral component alignment in the coronal plane (Table 2), with 3 studies reporting a statistically significant reduction in the percent outliers. In 2 studies, there was a reduction in the number of outliers in the computer-assisted navigation group that did not reach statistical significance, and in the final study there was an increase in the number of outliers for the computer-assisted navigation group that did not reach statistical significance.

Six studies reported on tibial component alignment in the coronal plane (Table 2), with 3 studies reporting a statistically significant reduction in the percent outliers. In the remaining 3 studies, there was a reduction in the number of outliers in the computer-assisted navigation group that did not reach statistical significance. Similar patterns of reductions in comparison of outliers was seen for other alignment outcomes such as the femoral slope and tibial slope outcomes.

The range of alignment outcomes for each group is shown in Table 2 for 4 studies. In nearly all measures reported (e.g., overall and individual component alignment), the range for the computer-assisted navigation groups is more narrow than the range for the conventional TKA groups. This indicates that computer assistance results in a greater precision of implant alignment compared to conventional TKA.

A recent meta-analysis (Bauwens et al. 2007) also evaluated whether computer-assisted navigation resulted in improved alignment following TKA. This analysis included 29 clinical trials, both randomized and nonrandomized, that compared alignment outcomes between conventional TKA and TKA with computer-assisted navigation. The authors reported that these studies varied widely in methodologic quality, and that there was a high degree of statistical heterogeneity. Combined analysis of several outcomes was performed, including the relative risk for overall limb malalignment as defined by greater than 3 degrees' deviation from target. The combined relative risk for this outcome was 0.79 (95% CI: 0.71–0.87, p<0.001), indicating a relative risk reduction of approximately 20% for this outcome. Similar results were found when malalignment was defined by greater than 2 degrees' deviation from target.

Does TKA performed with computer-assisted navigation lead to improvements in other surgical outcomes, compared with conventional surgery?

- **operating time**
- **surgical blood loss**
- **postoperative thromboembolic complications**

All 7 RCTs compared operating time among the treatment groups (Table 3). In all 7 trials, operative time was longer for the computer-assisted navigation group. The difference was statistically significant in 5 of the 7 trials. The range of increased operative time in these was 2–34 minutes. This represented a relative increase in operating time of 2–40%. None of the trials examined whether the increased time was due to a training effect, i.e., whether the increase in operating time decreased as the surgeons accumulated greater experience with the computer-assisted navigation technique.

Five studies compared the total blood loss between the groups (Table 3). Two of these studies reported a significant decrease in blood loss for the computer-assisted navigation group. Chauhan et al. (2004) reported a significant mean decrease of 194 mL and Chin et al. (2005) reported a mean decrease of 106 mL for the computer-assisted navigation group. For the other 3 studies, there were small differences in blood loss that did not reach statistical significance. None of the studies reported whether transfusion requirements were different between groups as a result of this difference in blood loss.

None of the included studies addressed the impact of computer-assisted navigation on other surgical complications such as thromboembolism or fat embolism. While some experts hypothesize that computer-assisted navigation leads to a lower risk of these complications, these outcomes could not be evaluated from the RCTs included in the present review.

Relationship of Alignment with Clinical Outcomes

Does the degree of improvement in alignment following TKA performed with computer-assisted navigation result in meaningful improvements in clinical outcomes associated with TKA?

- **decrease in need for revision surgery**
- **reduction in pain and/or other symptoms**
- **improvement in functional status**

The strongest type of evidence to answer this question would be RCTs that established that alignment was superior in the computer-assisted navigation group and that followed patients over a long period of time to compare clinical outcomes. These outcomes would ideally include both functional status outcomes and comparison of the incidence of poor outcomes between groups (or the long-term survival rates for the implanted devices). Poor outcomes would consist of patients with persistent pain and/or limitations in function following TKA ("failed TKA"). A closely related outcome would be the need for TKA revision surgery, especially "early" TKA revisions that are performed within 5 years of the original procedure. To date, the longest follow-up reported is 2–3 years.

Seven of the RCTs included some measure of functional status (Table 3). The largest study that evaluated functional outcomes was Ensini et al. (2007), which included 60 patients per treatment arm. This study used two validated knee scores as well as a patient satisfaction measure. There were no differences between groups on either functional status measurement or on the patient satisfaction measure at 2- to 3-year follow-up (Table 3).

Kim et al. (2007) included the most number of knees, with 100 patients undergoing bilateral TKA, thereby including 200 knees and comparing computer-assisted navigation with conventional surgery within each patient. This study used two functional status measurements, the Knee-Society Score, and the Hospital for Special Surgery score, with a mean follow-up of 2.6 years. There were no differences between groups on either functional status score at any of the postoperative time periods.

An additional 4 studies used similar or identical validated functional status measurements designed for TKA. In addition, some of the studies used general functional status and/or quality of life measures such as the SF-36. In all cases, the differences between groups on the functional status measures were not statistically significant (Table 3). Decking et al. (2007) calculated that they would have to increase the number of subjects studied by a factor of 20 to achieve adequate power to detect functional differences.

There were no RCTs that directly evaluated whether the revision rate was reduced for patients undergoing computer-assisted navigation. The longest length of follow-up in the available RCTs is 2–3 years, and this is likely not an adequate length of follow-up to evaluate poor outcomes such as the need for revision surgery. In the absence of direct evidence on the effect of computer-assisted navigation on long-term clinical outcomes, evidence on the relationship of malalignment with poor outcomes was sought. The goal of this analysis is to consider whether a convincing argument based on established medical facts could be made that an improvement in alignment will result in a decreased revision rate.

Indirect evidence was found in 3 different categories: cohort studies, case-control studies, and case series. The strongest type of indirect evidence of this type would be prospective cohort studies that measure postoperative alignment in large numbers of patients undergoing TKA, and that analyze postoperative alignment as a predictor of future outcomes in a multivariate fashion. Of 5 cohort studies that met the inclusion criteria (Tables 5 and 6), only one (Berend et al. 2004) used this general approach.

Berend et al. (2004) was a retrospective analysis of prospectively collected data on patients undergoing TKA between the years of 1983–2000 that attempted to determine predictors of tibial component failure requiring revision surgery. This study evaluated 2,125 patients (3,152 knees) and reported patient follow-up over a mean of 5 years, with 41 patients requiring TKA revision as a result of tibial component failure. Postoperative malalignment was defined as overall tibial alignment of greater than 3 degrees' varus. The authors used a multi-step "data mining" approach to determine the best model predicting the need for

Table 5. Cohort Studies Evaluating the Association of Malalignment and Poor Outcomes: Study Characteristics

Study/Yr	Patients	n (pts) n (knees)	Follow-up	Study Design	Predictor Variables	Outcome Variable(s)	Comments
Berend et al. 2004	Consecutive pts receiving TKA for OA using AGCS[1] at one institution between 1983 and 2000, with minimum 2 years f/u	2125 3152	5.0 years (mean) 2-14.2 years (range)	Prospective cohort study, Measurements recorded preoperatively and at 2 mos, 6 mos, 1 year, 3 years and every 2 years thereafter.	Overall limb alignment Age BMI Knee Society Clinical Score Knee Society Pain Score	Tibial component failure requiring revision surgery (n=41/3152, 1.3%)	
					Groups		
Morgan et al. 2007	All TKAs performed by one surgeon between 1990-1993	153 197	9 ± 2.2 years (mean)	Retrospective cohort study F/u visits generally done yearly	Divided into three groups: 1) Varus (<4° valgus) 2) Neutral (4-9° valgus) 3) Valgus (>9°valgus)	TKA failures requiring revision	Compared revision rates among three different groups
Ritter et al. 1994	421 TKAs performed at one institution[2]	308 421	NR (351/421 knees had >1 year f/u)	Prospective (?) cohort study F/u visits at 2 mos, 6 mos, 1 year, every 2-3 years thereafter, standard AP radiographs obtained at each f/u visit.	Divided into three groups: 1) Varus (>0° varus) 2) Neutral (0-5° valgus) 3) Valgus (>5°valgus)	TKA failures requiring revision (n=8)	Compared revision rates among three different groups
Tew and Waugh 1985	428 TKAs done at one institution for which alignment measurements were available postoperatively and at latest f/u	NR 428	NR	Retrospective cohort study (?). F/u visits not specified	Divided into five groups: 1) Varus >2° 2) Varus 2° to valgus 2° 3) Valgus 3° to 7° 4) Valgus 7° to 12° 5) Valgus >12°	TKA failures requiring revision	Compared revision rates among five different groups
Bargren et al. 1983	32 patients with TKA done at one institution and with at least 5.5 years f/u.	32 32	5.5-9 years (range)	Retrospective cohort study. Radiographic alignment measured 6 weeks postoperatively. Patients evaluated for pain, ROM and function at each f/u visit, f/u schedule not specified.	Divided into three groups: 1) Varus ≥1° 2) Varus 1° to valgus 1° 3) Valgus >1°	Unsatisfactory result (defined as revision or consistent pain due to loosening or instability)	Compared revision rates among three different groups

[1] Anatomic Graduated Component System
[2] Population in this study overlapping with that of Berend et al. 2004
f/u: follow-up; ROM: range of motion

Table 6. Cohort Studies Evaluating the Association of Malalignment and Poor Outcomes: Results

Study/Yr	n (patients) n (knees)	Follow-up	Multivar Analysis	Outcome Variable	Predictor Variable(s)	RR	95% CI	p-value
Berend et al. 2004	2125 3152	5.0 years (mean)	Yes	Tibial component failures (n=41)	Overall limb alignment (>3° varus vs ≤3° varus) Age (<57 years vs ≥57 years) BMI Gender Knee Society Clinical Score Knee Society Pain Score	 17.2 8.3 NR NR		 0.007 0.002 NS NS
					Groups	Outcome Rates		Comments
Morgan et al. 2007	153 197	9 ± 2.2 years (mean)	No	TKA failure requiring revision (n=6)	1) Varus (<4° valgus) 2) Neutral (4-9° valgus) 3) Valgus (>9°valgus)	3.0% (2/66) 4.1% (3/73) 1.7% (1/58)		Differences between groups NS
Ritter et al. 1994	308 421	NR (351/421 knees had >1 year f/u)	No	TKA failure requiring revision (n=8)	1) Varus (>0° varus) (n=20) 2) Neutral (0-5° valgus) (n=234) 3) Valgus (>5°valgus) (n=82)	25% (5/20) 1.3% (3/234) 0% (0/82)		Kaplan-Meier survival analysis better for neutral group (p<0.02) and valgus group (p<0.04) compared to varus group
Tew and Waugh 1985	NR 428	NR	No	TKA failure requiring revision (n=122)	1) Varus >2° 2) Varus 2° to valgus 2° 3) Valgus 3° to 7° 4) Valgus 7° to 12° 5) Valgus >12°	41.9%* (13/31) 32.3% (31/96) 23.4% (45/192) 24.1% (11/77) 54.5%* (12/22)		*Significantly higher rates at p<0.001 (method of analysis NR).
Bargren et al. 1983	32	5.5-9 years	No	Unsatisfactory result (defined as revision or consistent pain due to loosening or instability) (n=14)	1) Varus ≥1° 2) Varus 1° to valgus 1° 3) Valgus >1°	91% (9/11)* 100% (3/3) 11% (2/16)		Statistical analysis NR Calculated chi-square: Group 1v3 p<0.001 Group 1v2 p<0.01

revision surgery. This included an initial step of recursive partitioning that examined "…all possible breaks of the data across every clinical and surgical variable…" in order to select the most statistically relevant variables associated with revision surgery. This was followed by Cox proportional hazards analysis that included iterative algorithms to further verify the range of variables that resulted in the greatest statistical significance.

The authors reported that tibial malalignment was a strong predictor of the need for revision, with an odds ratio of 17.2. Younger age was also a significant predictor of revision surgery, while overall tibial-femoral alignment was not identified as a predictor of tibial component failure. The combination of malalignment and obesity (body mass index >33.7) indicated an especially strong risk for revision, with a relative risk of approximately 168.

The other 4 cohort studies (Tables 5 and 6) used a comparative cohort design. In these studies, patients were divided into groups based on degree of postoperative malalignment. Different definitions for these groups were used, but generally they classified patients as varus alignment, neutral, or valgus alignment (Table 5). The rates of outcomes in these studies varied widely, with the older studies such as Tew and Waugh (1985) reporting TKA revisions in over 25% of patients undergoing TKA, while the newer studies such as Morgan et al. (2007) reported a revision rate of approximately 3% (Table 6).

In 2 of the 4 studies (Tew and Waugh 1985; Ritter et al. 1994), the authors reported a significantly higher rate of revision in the group with varus malalignment. In a third study (Bargren et al. 1983), statistical analysis was not reported. Calculated chi-square of the reported data (Fisher's exact test, two-sided) revealed a statistically significant difference in revision rates between the varus group and the valgus group. The fourth study of this type (Morgan et al. 2007) reported no difference in revision rates between groups. This study, however, had a very small number of outcomes (n=6), and therefore had limited power to detect a difference.

The second category of studies that addressed this question were case-control studies. These studies selected patients with poor outcomes, used a control group of patients with favorable outcomes, and compared postoperative alignment between groups. Two studies of this type were identified for this Assessment (Tables 7 and 8). These were small studies; one enrolled 11 patients with poor outcomes (Barrack et al. 2004), the second study enrolled 30 patients with poor outcomes. (Berger et al. 1998).

Barrack et al. (2004) compared both overall axial alignment and rotational alignment (femoral, tibial, and combined) in the poor-outcome group with that in the good-outcome group. There was no difference in overall axial alignment between the two groups. There was a significant difference in rotational alignment, with the poor outcome group demonstrating excessive amounts of internal rotation (4.7 degrees) relative to the good-outcome group (2.6 degrees of external rotation).

Berger et al. (1998) specifically attempted to evaluate rotational alignment, and therefore excluded patients with axial malalignment. This study also reported excessive greater internal rotation among the patients with poor outcomes. The difference between groups in the individual measures (tibial component rotation and femoral component rotation) were not significantly different, but the combined rotation (tibial component rotation plus femoral component rotation) in the poor-outcome group was significantly different from that in the good-outcome group.

Finally, case series of patients with poor outcomes, primarily patients needing TKA revision, that report on the underlying reasons for revision TKA, can also provide evidence on the proportion of patients needing revision who have malalignment as a contributing factor. Four studies of this type were included in the review of evidence (Table 9). These studies classified patients into categories of reasons for revisions. While there are many such studies in the literature, only a minority included malalignment as a reason for revision.

The definition of malalignment in these studies was not generally defined, except for one study (Windsor et al. 1989). It appeared that malalignment was determined by the surgeon at the time of revision, either based on plain X-rays and/or direct examination of the components at the time of surgery. In all 4 studies, there was a relatively consistent rate of malalignment reported, ranging from 9.4–12%.

Table 7. Case-Control Studies of the Association between Poor Outcomes from TKA and Malalignment: Study Characteristics

Study/yr	Patients - Cases	Patients - Controls	Follow-up Interval	Measurement(s) of Alignment	Other Measured Covariates	Comments
Barrack et al. 2001	11 pts (14 knees) with anterior knee pain at least 3/10 on visual analog scale	11 pts (14 knees) without knee pain matched for age, gender, length of f/u, and method of TKA	5.7 years (mean)	1) Tibiofemoral axial alignment measured by plain radiography 2) Femoral and tibial rotational alignment as measured by CT scanning		
Berger et al. 1998	30 patients with isolated patello-femoral problems scheduled for TKA revision. All patients with normal axial alignment.	20 patients with well-functioning TKAs and no patellofemoral problems, chosen from the authors' group practice		Femoral, tibial, and combined rotational alignment as measured by CT scanning		

Table 8. Case-Control studies of the Association between Poor Outcomes from TKA and Malalignment: Outcomes

					Rotational Alignment						
Study/yr	Groups	MV Analysis	Axial Alignment	p value	Femoral	p value	Tibial	p value	Combined	p value	Comments
Barrack et al. 2001	Knee pain	No	4.6° valgus	NS	1.5° ER	NS	6.2° IR	0.012	4.7° IR	0.004	
	No knee pain		5.3° valgus		2.2° ER		0.4° IR		2.6° ER		
Berger et al. 1998	Patellofemoral problems	No	NA[3]	NS	2.5° IR	NS	6.2° IR	NS	8.6° IR	0.0001	In case pts, combined rotational alignment correlated with severity of presenting patellofemoral problems
	No patellofemoral problems		NA[3]		NR		NR		NR (range 0-10° ER)		

[1] ER – external rotation
[2] IR - internal rotation
[3] patients with axial malalignment were excluded from study

Table 9. Case Series of TKA Revisions Reporting on Contribution of Malalignment to Revisions

Study/Yr	Patients	Study Design	Definition of Malalignment	Reasons for Revisions	Percent*	Comments
Sheng et al. 2006	2637 TKA revisions (first revisions) performed in Finland between 1990-2002.	Retrospective case series of prospectively collected registry data (Finnish Arthroplasty Registry)	NR	Implant loosening Infection Patellar subluxation **Malalignment** Bone fracture Prosthesis fracture Other patellar complications Other	32.5% 4.7% 3.8% **11.3%** 2.1% 8.3% 31.7% 5.4%	
Mulhall et al. 2006	318 consecutive patients with failed TKA undergoing revision.	Prospective , multicenter case series with predefined inclusion/exclusion criteria and standardized data collection	Radiologic evaluation (specific criteria NR)	Instability Polyethylene wear Failed polyethylene insert Infection Implant loosening/migration Bone lysis **Malalignment** Implant breakage Metal wear Other	28.9% 24.5% 18.1% 10.4% 41.3% 59.4% **9.4%** 3.4% 2.7% 2.9%	Malalignment associated with instability in 60% of cases
Sharkey et al. 2002	212 consecutive TKA revisions done between 1997 and 2000 from one institution	Retrospective case series of previously treated patients	Radiologic evaluation (specific criteria NR)	Polyethylene wear Infection Implant loosening Instability Arthrofibrosis **Malalignment** Extensor mechanism lag Avascular necrosis of patella Prosthetic fracture	25% 18% 24% 21% 15% **12%** 6.6% 4.2% 2.8%	
Windsor et al. 1989	25 TKA revisions done over a 15yr period by one surgeon.	Retrospective case series of previously treated patients	Varus tibiofemoral alignment >5°	Implant loosening Infection **Malalignment** Instability Tibial subluxation Femoral fracture	52% 36% **12%** 8% 8% 4%	

* Reasons for revisions not mutually exclusive; totals greater than 100%

Discussion

The ideal type of evidence, RCTs with adequate power to compare long-term health outcomes (such as pain, function, or the need for revision surgery), is not available. Such RCTs would require very large numbers of patients followed over long periods of time in order to determine whether differences in these types of outcomes exist. As discussed previously, the number of patients with poor outcomes is small, as are the absolute differences in alignment reported in the RCTs. Also, there are many other factors that also are related to the success or failure of TKA making it difficult to determine 1) whether the degree of improvement in alignment reported in these studies leads to meaningful differences in health outcomes and 2) the contribution other variables might have to outcomes.

The available RCTs allow conclusions on postoperative alignment outcomes. The RCTs are relatively consistent in demonstrating a reduction in alignment outliers for the computer-assisted navigation group across different studies and different measures of alignment. For overall alignment, the absolute reduction in patients who are outliers ranged from 7–27%. A fixed-effect, inverse-variance-weighted pooling of data from these 7 trials suggests that malalignment of greater than 3 degrees will be avoided in approximately 15.5% of patients (95% CI: 9.4–21.7% when computer-assisted navigation is used (NNT 6.45 to avoid one instance of malalignment [95% CI: 4.61–10.69]). A similar pattern of results was reported for other measures of alignment. The RCTs are also consistent in showing reductions in alignment outliers across a number of different alignment outcomes. A recent meta-analysis (Bauwens et al. 2007) that included a larger number of clinical trials, both randomized and non-randomized trials of any size, came to a similar conclusion, estimating a 20% reduction in this same outcome.

While approximately 15.5% of patients avoid malalignment by our analysis, it is not possible to conclude that all these patients benefit from computer-assisted navigation. The threshold definition for malalignment (greater than a 3-degree deviation from target) is derived from older, biomechanical studies. It is not certain that this threshold is the most clinically relevant definition of malalignment in the current era of TKA. There have been many advances in TKA that might mitigate the impact of malalignment seen in earlier studies. In addition, there is a lack of clinical studies that define the threshold for malalignment, and there may be an interaction between alignment and other risks for poor outcome, such as obesity.

In the RCTs that included comparisons of functional outcomes, there were no differences between groups. This establishes that there are not large differences in functional outcomes between conventional TKA and TKA performed with computer-assisted navigation when evaluated in the entire population of patients undergoing TKA. However, this conclusion is expected from the nature of computer-assisted navigation and its intended effect. While several of the RCTs followed patients for up to 2–3 years, none was adequately powered to detect expected differences on the functional outcome measures. This is because the vast majority of patients do well following TKA, and the percent of "failed" TKAs is relatively low. As a result, any differences in functional status for the small number of patients with poor outcomes is likely to be diluted by the patients with favorable outcomes.

These RCTs were relatively small, confined to single centers and one or two surgeons, and mostly represent the early experience of academic orthopedic surgeons. This does not allow examination of any training effects that might occur with increasing experience with the technique. Also, the RCT data do not address the issue of surgeon variability or variability among institutions. As a result, the generalizability of this RCT data is uncertain. It is possible that individual surgeons may derive more or less benefit from the use of computer-assisted navigation, depending on their prior expertise and skill in aligning prosthetic implants.

Other types of studies that address the relationship between alignment and clinical outcomes are not of high methodologic quality. There is only one cohort study that evaluated malalignment as a risk factor for revision in a multivariate analysis (Berend et al. 2004), and this study had a number of limitations that reduce confidence in the validity of the reported results. First, the authors restricted their analysis to tibial component failures, thereby only examining a minority of all TKA revisions. Second, the study encompassed a long time frame from 1983–2000 and thus is prone to maturation effects as a result of the many changes in TKA surgery occurring over this time. Second, there were only a relatively small number of revisions (n=41). As a result of this limited number of outcomes, the study may not have had adequate power to consider all of the many different factors that may be related to the need for TKA revision. Finally, the analysis used data mining techniques and iterative modeling to select the variables and the range of variables that provided maximum predictive ability. This approach likely resulted in an overestimate of the true predictive ability of malalignment.

The other cohort studies compared revision rates among groups with different degrees of alignment, but did not control for other factors related to the outcome of revision. Furthermore, these cohort studies were generally older studies completed in the 1980s and may not accurately represent the outcomes achieved with current conventional techniques for TKA.

The other types of evidence available for this question are case-control studies and case-series, both of which are relatively weak study designs to answer the specific question. These studies did not use postoperative malalignment to predict future outcomes, but rather measured alignment at the time of the poor outcome. In this type of analysis, it is not possible to determine whether the abnormal alignment was the cause of the prosthetic failure, or to determine the contribution of malalignment in the presence of many other potential factors. A further problem in interpreting these studies is the inability to determine whether overall axial malalignment was present immediately after surgery or whether it developed at a later time as a result of other factors. Alignment may change over longer periods of time if the prosthetic device is not adequately constrained, or if loosening of the components occurs for some other reason.

The case series of patients undergoing TKA revision are consistent in reporting malalignment in approximately 10% of cases. In addition to the limitation of not defining malalignment at the time of surgery, these studies are not rigorous in their definitions of malalignment and rely on the judgment of the individual surgeon in determining whether malalignment was present at the time of surgery. In many cases, multiple reasons for TKA failure were present, and it is not possible to determine the degree to which alignment was a causative factor apart from other potential causes of failure.

In summary, the positive associations reported across different types of observational studies suggests that there is a relationship between malalignment and poor outcomes. However, as a result of deficiencies in the available evidence, it is not possible to determine whether the degree of improvement in alignment reported in the RCTs leads to meaningful improvements in health outcomes, such as pain, function or revision surgery. Therefore, it is not possible to conclude that the use of computer-assisted navigation with TKA leads to improved health outcomes.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the use of computer-assisted navigation for total knee arthroplasty (TKA) meets the Blue Cross and Blue Shield Association's Technology Evaluation Center (TEC) criteria.

1. **The technology must have final approval from the appropriate governmental regulatory bodies.**

TKA is a surgical procedure that is not subject to U.S. Food and Drug Administration (FDA) regulations. Several systems for computer-assisted navigation have been cleared for marketing by the FDA via the 510(k) process (e.g., PiGalileo™ Computer-Assisted Orthopedic Surgery System, PLUS Orthopedics; OrthoPilot® Navigation System, Braun; Navitrack® Navigation System, ORTHOsoft).

2. **The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

The evidence is sufficient to conclude that the use of computer-assisted navigation with TKA results in more accurate implant alignment. This conclusion is derived from RCT evidence comparing TKA using computer-assisted navigation with conventional TKA and reporting on the number of patients in each group with malalignment. Approximately 15.5% of patients may avoid malalignment of greater than 3 degrees in overall limb alignment with the use of computer-assisted navigation.

The evidence is not sufficient to conclude that the improvement in alignment associated with computer-assisted navigation leads to meaningful differences in health outcomes, such as pain, function, and revision surgery. Long-term evidence from RCTs is not available to answer this question. Observational studies that evaluate the association between alignment and clinical outcomes consistently report an association between malalignment and poor outcomes. However, these studies have a variety of methodologic limitations and, by their nature, are hypothesis generating. Thus, the evidence is not sufficient to determine that the degree of improvement in alignment reported in the RCTs leads to a meaningful benefit in health outcome.

3. **The technology must improve the net health outcome; and**
4. **The technology must be as beneficial as any established alternatives.**

Evidence is not sufficient to permit conclusions as to whether computer-assisted navigation improves the net health outcome or is as beneficial as conventional alignment techniques.

5. **The improvement must be attainable outside the investigational settings.**

It cannot be determined whether any improvement is attainable outside the investigational setting since the evidence is not sufficient to permit conclusions on the effect of computer-assisted navigation on health outcomes.

For the above reasons, the use of computer-assisted navigation for total knee arthroplasty does not meet the TEC criteria.

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