Considered Judgement Form

This form is a checklist of issues that may be considered by the Purchasing Guidance Advisory Group when making purchasing recommendations

Meeting date:	**31 August 2016**
Topic:	**Use of allograft tissue for primary ACL reconstruction**

Purpose

The Clinical Advisory Panel at ACC requested a review of the evidence comparing outcomes following primary anterior cruciate ligament (ACL) reconstruction using autograft (patient's own tissue) or allograft (donor tissue obtained from cadaver) tissue, in order to form a purchasing decision on the use of allograft for primary ACL reconstruction. The CAP requested robust information regarding the clinical effectiveness, failure rates and safety of allograft tissue for ACL reconstruction, including information about which specific patient groups may or may not benefit from the use of allograft.

There is current debate both in the literature and in the orthopaedic surgical community regarding the costs, benefits and risks associated with using allograft tissue for primary and revision ACL reconstruction. The NZ Knee Society, as part of the NZ Orthopaedic Association, has released a position statement which does not support the use of allograft tissue for primary ACL reconstruction because of concerns regarding the failure rate, risks, costs and quality of allograft tissue (NZOA 2015). There are indications in the literature that the failure rate for allograft can be high, especially when the grafts are irradiated to reduce the risk of disease transmission. The NZ Knee Society believes that outcomes following primary ACL reconstruction with allograft do not justify its increased cost, and suggests that allograft is only appropriate for primary ACL reconstruction where the patient's own tissue is of poor quality. In contrast, some NZ orthopaedic surgeons are actively promoting the use of allograft tissue for primary ACL reconstruction, suggesting that improvements in the processing of allograft tissue and surgical technique have significantly reduced the risk of graft failure, and that it offers the opportunity for faster healing, less donor site morbidity and a quick return to sports.

ACC has no official guidance on the use of allografts for ACL reconstruction. ACC is currently paying for some primary and revision ACL surgeries using allograft tissue because there is no specific code for allograft surgeries and we have no official position on it's use. An analysis of a sample of ACL repairs in the ACC dataset, indicates an increased number of allograft ACL surgeries based on 2014/2015 data, mostly among a small subset of surgeons. Costs in this dataset range from $5000 to $9000 for ACL repairs using allograft tissue, which has to be sourced overseas, compared with approximately $2000-3000 for autograft surgeries, which is broadly in line with the estimates quoted by the NZ Knee Society. There are also anecdotal reports of increased complications where allografts have been used, with associated costs of revision surgery.

Background

Surgery to repair the ACL following a complete rupture involves the replacement of existing damaged tissue with a substitute. Several options for replacement are available. Autograft involves harvesting the patient's own tissue from another part of their body, usually the patellar tendon or the hamstring tendon, to replace the ruptured ACL. Autografts are associated with relatively good outcomes, including a low graft failure rate (approximately 5.5%), and are considered the gold standard option for primary ACL reconstruction (Lamblin et al 2013). The disadvantages of autograft are that the treatment involves healing of both the donor site and the repair of the ACL, and the ability to use the patient's own tissue relies on them having good quality tissue.

Allograft involves the use of tissue from a donor cadaver to repair the ruptured ACL. Its advantages are that there is no donor site, so it has shorter surgical times and no need to recover from harvesting the replacement tendon (Lamblin et al 2013). It has been proposed as a good option for people whose own donor material is not of good enough quality to replace their ruptured ACL. The

disadvantages are that outcomes rely on the quality of donor material and there is a risk of serious disease transmission, including bacterial infection, hepatitis and human immunodeficiency virus (HIV). Methods of sterilization and preservation include the use of radiation to kill bacteria and viruses in the tissue, and chemical preservation. Unfortunately, exposing the tissue to radiation affects its structure and tensile strength and it is thought that this has been a major source of the higher graft failure rate associated with allograft tissue (Park et al 2014). Lower levels of radiation have been proposed as an alternative method of sterilization but these are not sufficient to kill HIV and may not improve graft failure and other outcomes (Park et al 2014).

1. Effectiveness, Volume of Evidence, Applicability /Generalisability and Consistency / Clinical impact

Comment here on the extent to which the service/product/ procedure achieves the desired outcomes. Specific reference needs to be made to safety. Report number needed to treat and harm where possible, any issues concerning the quantity of evidence and its methodological quality and the extent to which the evidence is directly applicable or generalisable to the New Zealand Population, and the degree of consistency demonstrated by the available evidence. Where there are conflicting results, indicate how the group formed a judgement as to the overall direction of the evidence. Comment on the clinical impact e.g. size of population, magnitude of effect, relative benefit over other management options, resource implications, balance of risk and benefit.

Overall size and quality of the evidence base

Twelve systematic reviews, all with meta-analyses, met inclusion criteria. Four of the reviews compared autograft with nonirradiated allograft only. The remaining reviews compared autograft with allograft, irradiated or nonirradiated, with some reporting subanalyses for irradiated and nonirradiated tissue.

One review reported on autograft compared with allograft in young (<25 years) or highly active patients (military cadets, athletes).

The reviews varied in quality from low to moderate, based in part on the quality of included primary studies. Two reviews included large numbers of clinical series and were graded low quality as a result. The remaining reviews were graded moderate quality with some including prospective and retrospective comparative studies and some only randomised controlled trials. The randomised trials were published between 2009 and 2014 and all compared autograft with non-irradiated, fresh-frozen allograft.

Autograft v allograft (irradiated or nonirradiated)

<u>Graft Failure</u>

Three reviews reported significantly higher failure rates (defined as re-operation or re-rupture) with allograft tissue compared with autograft tissue, with odds ratios indicating the failure rate for allograft is approximately 3 to 5 times the failure rate of autograft. In all three reviews, the comparison was between BPTB autograft and BPTB allograft. Two reviews reported no significant difference in failure rates. One (Carey et al 2009) included studies of any type of autograft and any type of allograft and

reported a reduced risk of failure for autograft which did not reach significance (OR 0.61, 95% CI 0.21 – 1.79). The other review compared hamstring autograft with soft tissue allograft and found no significant difference in failure rate.

Instrumented and patient-reported laxity and stability

Overall there were few significant differences between autograft and allograft for both patient-reported (IKDC, Lysholm, Tegner scores) and instrumented (KT1000/2000, Lachman, Pivot-shift tests) laxity and stability measures. One low quality study reported significant differences in several outcomes but was in noticeable contrast to the three moderate quality studies which reported no significant differences. One moderate quality study reported a significant difference in hop test index scores in favour of autograft (OR 5.66, 95% CI 3.09 – 10.36). There were no significant differences for any other laxity or stability outcomes.

Very few reviews included an analysis of other complications such as anterior knee pain and patellofemoral crepitus. Where they were included, there were no significant differences reported except in one low quality meta-analysis which reported a significant difference in the odds of anterior knee pain favouring allograft (OR 0.29, 95% CI 0.20 – 0.42).

Autograft v nonirradiated allograft

Graft Failure

Four reviews reported no significant differences in graft failure rates for autograft and nonirradiated allograft. This was despite some differences in the way graft failure was defined, with some studies basing it solely on reoperation, revision and re-rupture rates, and some using laxity measures as well.

Instrumented and patient-reported laxity and stability

Overall there were few significant differences between autograft and allograft for both patient-reported (IKDC, Lysholm, Tegner scores) and instrumented (KT1000/2000, Lachman, Pivot-shift tests) laxity and stability measures. Some differences in Tegner scores in favour of autograft were reported by two moderate quality studies. There were no significant differences between autograft and allograft for any instrumented measure of laxity or stability.

Autograft compared with allograft in young (<25 years) or highly active people

Graft Failure

Wasserstein et al (2015) conducted a meta-analysis of the graft failure rate following ACL reconstruction with autograft or allograft tissue in young people (</= 25 years) or those with a high activity level (military/Marx activity level >12/collegiate or semiprofessional athlete). The data from one randomized trial and six cohort studies were included in the analyses. In this study, the authors reported a clear difference in relative risk of failure in favour of autograft for both BPTB and hamstring tendon autografts (overall RR = 0.36, 95% CI 0.24 – 0.53). Overall graft failure rates were 9.6% for

autograft and 25% for allograft.

When subgroups were analysed, a similar pattern of results was reported for BPTB autografts versus allograft and hamstring autografts versus soft tissue allografts. When autografts were compared with nonirradiated allografts, the results were in the same direction as for other subgroups, but were no longer significant (Failure rate autograft = 9%; failure rate nonirradiated allograft = 19.5%). The single randomized trial (Bottoni et al 2014) included in these analyses indicated that the failure rate for allograft was three times that of autograft (failure rate autograft = 8.3%, failure rate nonirradiated allograft = 26.5%; RR = 0.31, 95% CI 0.11 – 0.90).

Instrumented and patient-reported laxity and stability

There were no significant differences in the overall Lysholm score based on three primary studies. The authors were unable to calculate summary risk ratios for any other measures.

Low-dose (<Mrad) allograft compared with nonirradiated allograft

Park et al (2014) conducted a systematic review comparing the performance of low dose and nonirradiated allograft for primary ACL reconstruction. The findings indicated that low dose irradiation of allograft tissue was associated with similar outcomes to fully irradiated tissue. Two studies directly compared low dose irradiated allograft with autograft. The findings indicated that low-dose irradiated allograft tissue performed significantly worse than autograft tissue in terms of revision surgery, Lysholm scores, KT-1000 arthrometer scores and Lachman scores.

Safety

There is a small but serious risk of disease transmission from donor allograft tissue. Tissue is only available from sources outside New Zealand. In the United States accredited tissue banks have to meet the standards of screening, sterilisation and preservation recommended by the Food and Drug Administration and the American Association of Tissue Banks. Irradiation of the tissue is used to kill bacteria and viruses, such as HIV and hepatitis, but this affects the structural integrity of the tissue and is associated with higher failure rates. Some studies have investigated the effect of low-dose irradiation on the strength of the tissue, but the outcomes seem to be very similar to fully irradiated tissue, and some viruses, for example HIV, are not eliminated by low dose irradiation. The American Academy of Orthopaedic Surgeons recommends site inspection of tissue banks, which is clearly not an option in New Zealand. Disease transmission is said to be rare, but is higher in “minimally processed” musculoskeletal tissues (AAOS 2011).

Guidelines and other insurance jurisdictions

Both Cigna and AETNA do not consider the use of allograft tissue for primary ACL reconstruction medically necessary unless at least one of the following criteria is met:

- Previous reconstruction has failed and requires revision

- Surgical reconstruction requires the use of multiple ligament transfers
- Individual has a medical condition (e.g. collagen disease, anatomic anomaly, prior knee injury or prior knee surgery) that precludes the use of autograft tissue

There is a paucity of information in clinical guidelines about the use of allograft tissue for ACL reconstruction. The American Academy of Orthopedic Surgeons (AAOS 2012) recommends the use of autograft ***or*** appropriately processed (nonirradiated) allograft tissue for most patients, but allograft is not recommended for young people or athletes.

The New Zealand Knee and Sports Society does not support the use of allograft tissue as a first option for primary ACL reconstruction because it has been associated with higher graft failure rates, especially in younger populations; heals at a slower rate; is associated with a small but serious risk of disease transmission; and is costly to obtain in New Zealand (NZOA 2015).

2. Cost

Where possible and reported in the published research literature any economic analysis of the new treatment is considered. Where possible the following will be considered; total costs of the new intervention and number of claimants likely to be affected are considered, along with comparison with the cost of current treatments or interventions, actuarial assessment of the impact of the intervention on scheme liability (including direct and indirect impact e.g. other services and access), expected "accrued benefit" in terms of quality of life, longer life or speedier return to the workforce, implications of cost to the wider health sector.

Allograft tissue for ACL reconstruction has to be sourced outside of New Zealand and is associated with costs of $5000-7000 per allograft (according to ACC data and the NZ Knee Society), in addition to the costs of surgery. The length of surgery is shorter for procedures using allograft v autograft, which requires an additional procedure to harvest the tendon replacement, and some surgeons have suggested that this makes up for the higher cost of allograft. Several analyses of the cost-effectiveness of allograft and autograft have been completed internationally but these have used allograft costs in the region of USD$1100, so are not consistent with the New Zealand setting.

Surgeons in New Zealand who advocate the use of allograft would like to see funding approved in part so they can negotiate the bulk-purchase of allograft tissue from overseas and thereby reduce costs per surgery. There have also been suggestions that the additional costs of the donor tissue will be absorbed by a faster return to activity, including work and sports activities. The studies included in the current review suggest however, that there is no evidence of faster return to sporting activities. All of the randomised trials comparing autograft and nonirradiated allograft employed a standardised rehabilitation plan, with return to sports over a 6-12 month period, and warned against more rapid rehabilitation plans. In addition, there is current debate around the timing of return to sports following ACL reconstruction, with some evidence of higher rates of second injury in the first 12 – 24 months, especially in highly active and younger patients.

3. Equity

The extent to which the intervention reduces disparities in health status; in particular equity of access and health outcome. The

extent to which the intervention supports the objectives of the Maori access strategy and will encourage access to assessment, treatment and rehabilitation services for those groups where there is evidence of that access is problematic.

No access issues were identified, however some patients may find the idea of using donor allograft tissue unacceptable for cultural or other reasons.

4. Consistency with the intent of the Accident Compensation Act 2001

Purchasing decisions made by ACC must be consistent with and reflect consideration of factors described in the ACC Act, Schedule 1, clause 2(1 and 2) and these decisions must be defensible against this statutory requirement in respect of individual claimants.

No issues were identified.

5. Possible purchasing options

The options are:

1. Purchase,
2. Don't purchase, or
3. Purchase on a case by case basis on the decision of the Corporate Medical Advisor (or equivalent).

6. Evidence statements

Summarise the advisory group's synthesis of evidence relating to this service, product or procedure, taking the above factors into account, and indicate the evidence level that applies.

There is moderate quality evidence of a significantly higher graft failure rate for primary ACL reconstruction completed with irradiated allograft tissue compared with autograft tissue. The evidence suggests that there are no significant differences in measures of laxity and stability between irradiated allograft and autograft for primary ACL reconstructions.

There is moderate quality evidence that there is no significant difference in graft failure rate, laxity or stability outcomes between primary ACL reconstruction completed with autograft tissue or nonirradiated allograft tissue.

There is low to moderate quality evidence that low-dose irradiated allograft tissue has about the same failure rate as fully irradiated tissue. Irradiation is used to sterilize the allograft tissue and reduce the risk of disease transmission, however, some viruses e.g. HIV, are not eliminated by low-dose irradiation. While stringent donor screening processes are recommended by the FDA and AATB, the risk of disease transmission is still a pertinent issue.

There is moderate quality evidence of a significantly higher graft failure rate for primary ACL reconstruction completed using allograft tissue compared with autograft tissue in young patients under

the age of 25 and patients who are highly active.

There were no direct comparisons of rehabilitation protocols in the studies included in this review, but the authors of many of the studies noted that all the randomized trials have utilized standard rehabilitation protocols with return to sports 6-12 months after surgery. The authors cautioned against extrapolating their findings to situations where accelerated rehabilitation protocols were employed.

Conclusions:

- Given the lack of evidence of any improvement in outcomes relative to autograft, and also considering the higher cost and the potential risk of disease transmission, allograft is not recommended for primary ACL reconstruction as a first option.
- In particular, allograft is not recommended for young or highly active people, where there is evidence of worse outcomes, including a higher rate of graft failure, in young people under the age of 25 years who undergo an ACL reconstruction using allograft tissue.
- In some cases, where a patient's own tissue is not of high enough quality, allograft may be a suitable option. However, patients would need to be fully informed of the source of the donor tissue, and the potential risks, including the risks of graft failure and disease transmission.
- In addition, patients would need to understand and commit to the recommended standardized rehabilitation protocol, as the included reviews were unable to extrapolate their findings to situations where a standard rehabilitation protocol (2-3 months return to running, 6-12 months return to sports activities) was not followed.

7. Purchasing recommendations

What recommendation(s) does the advisory group draw from this evidence?

Suggested purchasing recommendations[i]:

- Do not purchase allograft as a first option for primary ACL reconstruction
- If at least one of the following conditions are met, allograft may be considered for some patients:
  - Previous autograft reconstruction has failed and requires revision
  - Surgical reconstruction requires the use of multiple ligament transfers
  - Individual has a medical condition (e.g. collagen disease, anatomic anomaly) that precludes the use of autograft tissue

i. This *do not purchase* recommendation was ratified by the Clinical Governance Committee and adopted as official ACC purchasing policy in September 2016.

PGAG discussions

The group emphasized that patient counseling and the informed consent process was especially important in considering the use of allograft tissue. Patients must be fully informed of the source of the tissue, including what precautions had been taken in sourcing safe tissue and the potential risks of disease transmission and graft failure.

The PGAG therefore recommended the inclusion of the following two good practice points:

- If allograft tissue is used, people must be fully informed of the:
    - Source of the donor tissue - including that the tissue is obtained from cadavers and is sourced from overseas tissue banks
    - Potential risk of disease transmission
    - Potential risk of graft failure.

- If allograft tissue is used, providers must ensure that the allograft tissue is obtained from a reputable source which uses appropriate donor screening and tissue processing.

References

Aetna Policy Statement. Allograft transplants of the extremities. Policy statement 0364. w*ww.**aetna**.com/cpb/medical/data/300_399/0364.html*

American Academy of Orthopaedic Surgeons (2011). Use of Musculoskeletal Tissue Allografts. Information Statement 1011.

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Bottoni CR, Smith EL, Raybin SG et al. (2014). Autograft vs allograft ACL reconstructions: A prospective, randomized clinical study with minimum 10 year follow-up. Orthop J Sports Med, 2 (suppl 2):

Cigna (2016). Musculoskeletal knee surgery: Arthroscopic and open procedures. Medical Coverage Policy. *https://www.evicore.com/**cigna**clinicalguidelines/*

New Zealand Orthopaedic Association (2015). Position statement of the NZ Knee Society on allograft use in primary ACL reconstruction. http://nzoa.org.nz/position-statements

Park SS, Dwyer T, Congiusta F, Whelan DB, Theodoropoulos J (2015). Analysis of irradiation on the clinical effectiveness of allogenic tissue when used for primary anterior cruciate ligament reconstruction. Am J Sports Med. 2015;43:226-235.

Wasserstein D, Sheth U, Cabrera A, Spindler KP (2015). A Systematic Review of Failed Anterior Cruciate Ligament Reconstruction With Autograft Compared With Allograft in Young Patients. Sports Health. 2015 May;7(3):207-16.

Appendix A: Peer review reports

Peer review completed by a Senior Lecturer, Musculoskeletal/Sports Physiotherapy, with a specialized area of research and publication in ACL injuries.

Overall, I suggest that the conclusions of the review are valid, namely that current evidence suggests that allografts are no better than autografts in terms of failure rate (re-rupture) and other outcomes. The conclusions make sense given the evidence that is provided. I've made specific comments where I suggest that the Methods and Results could be strengthened in terms of the documentation, as follows. Tracked changes are also added in the draft Report, and you are welcome to consider these.

Peer review completed by an Orthopaedic Surgeon, Fellow of the NZ Orthopaedic Association and member of the NZ Knee Society.

This review provides some help in answering the primary question with respect to autograft versus allograft tissue in ACL reconstruction. The conclusions are limited by the quality of the utilised systematic reviews and meta-analyses. Many of these studies do not include randomised controlled trials and randomised controlled trials make up a minority of those papers. However when a difference is found between autograft and allograft tissue almost always the outcome is better in patients having had surgery with autograft tissue. The recommendations that have been made are reasonable but I would be cautious in making any recommendations for older less active patients as this has not been clearly investigated in this study. Finally it would be worth a separate smaller review of the randomised controlled trials on their own and in particular assessing the size and power of those particular studies.