Horizon Scanning in Surgery: Application to Surgical Education and Practice

Surgisis AFP Anal Fistula Plug

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Disclaimer

This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

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Objective

This horizon scanning assessment provides short, rapidly completed, 'state of play' documents. These provide current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

Acronyms

AAF	Anorectal advancement flap
AFP	Anal fistula plug
BioLIFT	Bioprosthetic graft-reinforced ligation of the intersphinctertic tract
CCF-FI	Cleveland Clinic Florida – fecal incontinence
CI	Confidence interval
EAAF	Endoanal advancement flap
ERAF	Endorectal advancement flap
FDA	Federal Drug Administration
FG	Fibrin glue
GIQLI	Gastrointestinal quality of life index
HIV	Human Immunodeficiency Virus
HS	Horseshoe
LIFT	Ligation of the intersphincteric tract
LOS	Length of stay
MAF	Mucosal advancement flap
NIHR HTA (UK)	National Institute for Health Research, Health Technology Assessment
NR	Not reported
RCT	Randomized controlled trial
RV	Rectovaginal
SD	Standard deviation
SL	Supralevator
TS	Transsphincteric

Introduction

Background

A fistula is defined as an abnormal channel between any two epithelium-lined surfaces. There are many types of fistula, such as arteriovenous (between an artery and a vein), craniosinus (between the space inside the skull and a nasal sinus) and gastric (from the stomach to the surface of the skin) (MedlinePlus 2011).

Anal fistula, a channel that develops between the anus and the skin, often develops as the result of a previous abscess, the majority being caused by nonspecific cryptoglandular infections (Vasilevsky et al 2009). Obstruction of anal ducts results in stasis of glandular secretions, with these trapped secretions becoming prone to infection by a variety of opportunistic bacteria. As the purulent material is unable to drain back through the obstructed gland, it can track through a number of anatomical pathways, and this often leads to the development of a fistula (Hyman 1999).

The probability of fistula development is heightened if the abscess is allowed to burst spontaneously or was inadequately opened during surgery (Michalopoulos et al 2010). Other causes of anal fistula include trauma, fissures, surgical trauma (previous rectal, obstetrical or gynecological operations), diverticular disease, tuberculosis, Chlamydia infection, Crohn's disease, anal canal carcinoma, ulcerative colitis and human immunodeficiency virus (HIV) (Michalopoulos et al 2010; Legall 2007).

Several classification systems for anal fistulas have been developed. The most basic system divides fistulas into either high or low, based on their position in relation to the dentate line i.e. low fistulas originate below, and high fistulas originate above the dentate line (Michalopoulos et al 2010). The most widely accepted classification system is that of Parks et al (1976). This system separates anal fistulas into one of four categories, although it has since been amended to include a fifth category, superficial fistula (Michalopoulos et al 2010):

1. Superficial (~16% of all fistulas): Is not related to the sphincter or the perianal glands.

2. Intersphincteric (~56%): The tract forms between the internal and external sphincter muscles and travels through the intersphincteric plane, opening adjacent to the anus.

3. Transsphincteric (~21%): The tract forms between the internal and external sphincter muscles, passing from the intersphincteric plane through the external sphincter into the ischioanal fossa.

4. Suprasphincteric (~3%): The tract forms between the internal and external sphincter muscles. The fistula travels upwards, passing over the puborectal muscle, and then downwards again between the puborectal and levator ani muscles, opening adjacent to the anus.

5. Extrasphincteric (~3%): The tract forms outside the external sphincter complex, passing from the perianal skin, through the ischiorectal fat and levator muscles, into the rectum.

Diagnosis of anal fistula usually occurs through physical examination of the area surrounding the anus. In such cases when external signs are missing (such as an opening of the skin), the use of an anoscope facilitates an internal examination to identify indications of an abscess and/or inflammation (Cook Medical 'A Patients Guide' 2011).

Treatment options for fistulas vary according to their etiology, location and complexity. Fistulas classified as low (simple) can be effectively treated by fistulotomy. High (complex) fistulas often require more complex treatments, and a variety of procedures have been developed to treat these fistula, each with its own advantages and disadvantages, i.e. mucosal flap advancement, seton placement, collagen plugs, fibrin glue and ligation intersphincteric fistula tract (LIFT). Irrespective of the method employed to repair fistula, the aim is always to heal the fistula without compromising continence whilst achieving a low recurrence rate (Thekkinkattil et al 2008).

Burden of disease

The reported incidence of anal fistula varies according to different studies. Zanotti et al (2007) performed an analysis on the incidence of fistula in four European countries (England, Germany, Italy and Spain) and reported an incidence of 12-28 fistulas per 100,000 individuals. Thekkinkattil et al (2008) reported a slightly lower incidence figure of 8.6 per 100,000 individuals. More than twice as many men suffer from anal fistula than women, with ratios ranging from 2:1 to 5:1, and the disease most commonly affects individuals between 20 and 40 years of age (Adamina et al 2010).

Seneviratne et al (2009) used the gastrointestinal quality of life index (GIQLI) questionnaire to assess the quality of life of 21 patients both before and after surgery for recurrent anal fistula. Results demonstrated that a patient's quality of life was not greatly affected by the severity of symptoms; however, patients with fistulas experienced significant pre-operative psychological and social integration problems (Seneviratne et al 2009).

Technology

Surgisis AFP anal fistula plugs are composed of porcine small intestinal submucosa. Cells and cell debris are removed from the submucosa, leaving a biocompatible collagen matrix (Cook Medical, '*What Is ECM"*? 2011). The matrix is rolled into a cylindrical shape, presenting a highly efficient scaffold which effectively closes the fistula tract upon insertion. The material is inherently resistant to infection, does not cause foreign body or giant cell reactions, and is readily populated by the host's own cells, with full repopulation taking approximately three to six months (Johnson et al 2006).

Prior to operation, the plug is submerged in sterile water to facilitate rehydration. Once the desired characteristics are achieved, a resorbable suture is attached to facilitate insertion into the fistula track. The internal (primary) fistula opening is identified through the use of either a probe or injection of saline or hydrogen peroxide into the external fistula opening by analyzing the location of fluid emergence. Following debridement or curettage, the plug is drawn into the fistula through the internal (primary) opening until the plug securely blocks the internal opening. The internal end of the plug is sutured in place, while the external end remains unfixed to prevent the potential accumulation of fluid, infection, or abscess. Plug material that is not implanted is trimmed away and discarded. The application of a sterile dressing completes the procedure (Cook Medical '*Instructions for Use'* 2011).

Following surgery, patients are required to refrain from any physical activity that may result in the dislocation of the plug, such as heavy lifting and rapid movement. It is also requested that patients take a sitz bath three to four times daily for comfort and after bowel movements (Ellis 2007).

The first published results using the anal fistula plug (AFP) resulted in success rates of 83% at 12 months median follow-up (Champagne et al 2006); however, subsequent studies have produced lower success rates ranging from 24% to 78% (Adamina et al 2010). Failure is usually due to sepsis or plug extrusion before the fistula could heal.

AFP repair of cryptoglandular fistulas is more successful for long-tract fistulas, with fistulas longer than 4 cm being nearly three times more likely to heal compared with shorter fistulas (McGee et al 2010). Several studies have also demonstrated high levels of success when treating patients with Crohn's disease-based anal fistulas, i.e. 16/20 patients (80%) in O'Connor et al 2006, and 6/7 patients (86%) in Schwandner et al 2008.

Stage of development

Regulatory approval

The Surgisis AFP was first approved as a Class II device by the United States Food and Drug Administration (FDA) under the name of SIS fistula plug, on 03/09/2005 (510(k) no: K050337) (FDA 2005). In the following year, a modified version of the device was cleared for use on patients with rectovaginal fistulae (10/10/2006; 510(k) no: K062729)(FDA 2006), and in 2009 a further modified version, the Surgisis Biodesign Enterocutaneous Fistula Plug, was approved (02/27/2009; 510(k) no: K082682) (FDA 2009a). Recently, a direct competitor, the Gore Bio-A Fistula Plug, was granted FDA approval (03/27/2009; 5109(k) no: K083266) (FDA 2009b). One study comparing these two fistula plugs has been published, the results of which are included in this report (Buchberg et al 2010).

Current clinical trials

A search uncovered four clinical trials currently underway (Table 1).

Table 1: Clinical trials underway for the Surgisis AFP *(retrieved January 2011)*

Source	ID	Title	Study Design	Estimated Completion Date
Clinicaltrials.gov	NCT00545441	A Randomized Clinical Trial Comparing Surgisis AFP to Advancement Flap for the Repair of Anal Fistulas (SurgiSIS AFP).	Randomized	December 2011
	NCT00703131	Surgisis Anal Fistula Plug Study: An Experience in Saudi Arabia (SurgiSIS AFP).	Case series	December 2011
	NCT00450617	Treatment of Perirectal Fistula With Cutting Seton vs. Collagen Plug.	Randomized	February 2012
NIHR HTA (UK)	ISRCTN78352529	The Fistula-In-Ano Trial comparing Surgisis anal fistula plug versus surgeon's preference (advancement flap, fistulotomy, cutting seton) for transsphincteric fistula-in-ano.	Multicenter phase-III randomized controlled trial	January 2015

AFP: anal fistula plug

Current treatment and alternatives

Fistulotomy, or the lay-open technique is considered the gold standard treatment for patients with simple (low) transsphincteric fistulae who demonstrate good preoperative anal sphincter function (Ellis 2007). It is not indicated in patients with inflammatory bowel disease, high transsphincteric fistulas, suprasphincteric fistulas, multiple and complex fistulas, previous multiple sphincter operations, and in women with anterior fistulas (Beck et al 2009). As such, fistulotomy does not present a direct comparator to AFPs.

The mucosal flap advancement method is considered to be the gold standard for treating high (complex) fistulas (van Koperen et al 2008), and as such presents the most meaningful technique with which to compare AFPs. A horizontal incision is made in the rectal mucosa below the internal opening, facilitating the dissection of a rectal flap 2 to 5 cm in length. Following curettage of the fistulous tract and internal opening, the distal portion of the flap is excised and used to cover the internal opening. The flap is secured by means of tension free sutures to the lateral and distal mucosal margins of the wound (de Parades et al 2010). Mucosal flap advancement can be technically challenging and can be complicated by bleeding and the development of ectropion (eversion, or outward rolling of the flap; Amin et al 2003). Studies demonstrate a high variability in success rates, although there is a significant improvement in success rate using full-thickness advancement flaps compared with partial-thickness mucosal rectum flaps (Dubsky et al 2008).

Fibrin glue has gained widespread attention due to the observation that it is easy to apply, preserves sphincter integrity, results in minimal patient discomfort, and can be reapplied for treatment failures (Ellis 2007). Debris and granulated tissue are removed from the fistula, the channel is washed, and fibrin glue is injected directly into the external opening until it appears at the internal opening (de Parades et al 2010). Both primary and secondary fistula openings are then secured using sutures. Although the use of fibrin glue has many benefits, success rates are only in the range of 40% to 60%. The glue itself is an issue as its liquid consistency predisposes the glue to extrusion from the fistula tract before healing has occurred, particularly after events such as coughing or straining (Johnson et al 2006).

Setons made of silk, penrose drains, rubber bands, vessel loops or silastic catheters may be inserted into the fistula tract to encircle the sphincter muscles. The ends are tied with multiple knots to create a handle for manipulation. This handle facilitates tightening of the seton at regular intervals to slowly cut through the sphincter, allowing the tract to become more superficial (Beck et al 2009). Studies demonstrate a low recurrence rate using this technique; however, the incidence of incontinence is reportedly high, and they are also associated with significant discomfort (Ellis 2007).

Ligation of the intersphincteric fistula tract is a novel method of treating complex anal fistulas. An incision is made at the intersphincteric groove and the intersphincteric tract is identified and ligated close to the internal opening. The fistula tract is curetted and the external sphincter opening is sutured (Rojanasakul 2009). Although this technique appears promising, there is little published data available comparing this technique with other methods of fistula treatment, although there is a randomized controlled trial (RCT) underway comparing the LIFT procedure with AFPs (Clinicaltrials ref: NCT00830661).

Recently, treatment combinations have been used in an attempt to improve fistula healing efficacy. The LIFT procedure has been used in conjunction with AFPs to treat complex anal fistulas in a process termed BioLIFT. Ellis (2010) achieved complete healing of fistulas in 29/31

(94%) patients. A novel porcine dermal matrix injection (Permacol™, Covidien, Dublin, Ireland) has also been used as an infill material to treat fistulas, and has recently been used in conjunction with non-cutting setons and mucosal advancement flap repair to treat complex fistulas (Sileri et al 2010). Both treatment options appear promising; however, insufficient data are available to allow definitive conclusions regarding efficiency.

Literature review

Search criteria

Keyword/MeSH terms utilized:
Anal fistula plug, fistula plug, anal fistula, Surgisis

Databases utilized:
PubMed, OVID

Inclusion criteria

Table 2: Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Randomized controlled trials; non-randomized comparative studies NOTE: In particular, case series were not eligible for inclusion (see Appendix A)
Patient	Patients with high (complex) anal fistulas
Intervention	Surgisis AFP
Comparator	Fistulotomy, mucosal flap advancement, fibrin glue, seton placement, Gore Bio-A fistula plug, ligation of the intersphincteric fistula tract.
Outcome	Success rate, recurrence, complications, median time to failure/success, operation time, length of postoperative hospital stay, pain scores, risk factor analysis, early versus late cohort outcomes, cost analysis
Language	English only

AFP: anal fistula plug,

Included studies

Table 3: Characteristics of included studies

Study/location	Level of evidence (Appendix B)	Intervention and number of patients
Johnson et al 2006 *United States*	Level III-2 Comparative	AFP fistula plug (n=15) Fibrin glue (n=10)
Ellis 2007 *United States*	Level III-2 Comparative	AFP fistula plug (n=18) Advancement flap repair (n=95)*
Christoforidis et al 2009 *United States*	Level III-3 Comparative	AFP fistula plug (n=37) Endorectal advancement flap (n=43)
Chung et al 2009 *Canada*	Level III-3 Comparative	AFP fistula plug (n=27) Fibrin glue (n=23) Seton drain (n=86) Mucosal advancement flap (n=96)
Ortiz et al 2009 *Spain*	Level II Randomized Comparative	AFP fistula plug (n=16) Endorectal advancement flap (n=16)
Wang et al 2009 *United States*	Level III-3 Comparative	AFP fistula plug (n=29) Mucosal advancement flap (n=26)
Adamina et al 2010 *Canada*	Level III-3 Comparative	AFP fistula plug (n=12) Endoanal advancement flap (n=12)
Buchberg et al 2010 *United States*	Level III-3 Comparative	AFP fistula plug (n=12) Gore fistula plug (n=10)**

AFP: anal fistula plug
*Flap repairs varied; mucosal advancement flap: n=68, anodermal advancement flap: n=27.
**Patients in whom AFP failed received Gore plugs (n=6).

Critical appraisal

Patient demographics varied but were generally matched between treatment groups within each study (in studies that separated treatment group data). Mean patient age was similar among studies, with most patients in their mid to late forties, the exceptions being the AFP cohort in Ellis 2007 (mean age 32) and the AFP and advancement flap cohorts in Wang et al 2009 (39 and 40 years, respectively; Table 4). The male to female ratio of patients included in each study reflects the higher incidence of anal fistula in males, although such ratios differed significantly within several studies between treatment options (Ellis 2007; Chung et al 2009; Adamina et al 2009).

Table 4: Patient demographics for included studies

Study	Age	Gender (Male/Female)	Fistula anatomy	Previous fistula
Johnson et al (2006)				
AFP (n=15)	45.4 ± [SD] 2.4	11/4	HS = 9; Radial = 6	n=12
fibrin glue (n=10)	46.5 ± [SD] 3.3	8/2	HS = 7; Radial = 3	n=8
P value	*> 0.5*	*> 0.05*	*> 0.05*	*> 0.05*
Ellis (2007)				
AFP (n=18)	32 (21-56)	12/6	TS = 13; RV = 5	NR
MAF/AAF (n=95)	42 (21-69)	43/52	TS = 51; RV = 44	NR
Christoforidis et al (2009)				
AFP (n=37)	48.3 ± [SD]12.0	24/13	Anterior:Posterior ratio: 20:17	12 (32%)
ERAF (n=43)	47 ± [SD]11.5	20/23	Anterior:Posterior ratio: 25:18	18 (42%)
P value	*0.58*	*0.12*	*0.82*	*0.49*
Chung et al (2009)				
AFP (n=27)	46 (23-68)	18/9	TS: 13; HS: 14; SL: 0	NR
fibrin glue (n=23)	49 (22-68)	22/1	TS: 6; HS: 15; SL: 2	NR
seton drain (n=86)	46 (21-82)	70/16	TS: 14; HS: 67; SL: 5	NR
MAF (n=96)	46 (28-75)	71/25	TS: 33; HS: 58; SL: 5	NR
Ortiz et al (2009)				
AFP (n=16)	46.5 (30-76)	20/12	NR	n=16 ERAF
ERAF (n=16)				
Wang et al (2009)				
AFP (n=29)	40 (19-67)	17/12	NR	27 (93%)
MAF (n=26)	39 (29-58)	17/9	NR	22 (85%)
P value	*0.6*	*0.6*	-	*0.9*
Adamina et al (2010)				
AFP (n=12)	47.2	3/9	NR	NR
EAAF (n=12)	47.3	8/4	NR	NR
P value	*0.967*	*0.099*	-	-
Buchberg et al (2010)				
AFP (n=12)	48.4 (31-72)	12/4	Anterior: 6; Posterior: 8; HS: 1; anoperineal: 1	n=12
Gore (n=10)*				

AFP: anal fistula plug; SD: standard deviation; HS: horseshoe; MAF: mucosal advancement flap; AAF: anorectal advancement flap; TS: transphincteric; RV: rectovaginal; NR: not reported; ERAF: endorectal advancement flap; SL: supralevator; EAAF: endoanal advancement flap.
*Patients in whom AFP treatment failed received Gore plugs (n=6).

Descriptions of fistula anatomy varied among studies. Where reported, the majority of studies described transsphincteric, horseshoe, rectovaginal and supralevator fistulas (Johnson et al

2006; Ellis 2007; Chung et al 2009; Buchberg et al 2010). Several studies based fistula descriptions on anatomical orientation, i.e. anterior and posterior (Christoforidis et al 2009; Buchberg et al 2010) and radial (Johnson et al 2006). Christoforidis et al (2009) did not apply a fistula classification system. Data were provided for the median degree of external sphincter involvement (flap: 60%, range 15% to 100%; plug: 50%, range 20% to 100%, *P*=0.16) and fistulas involving less than one third of the external sphincter (flap: n=4 (9%); plug: n=9 (24%), *P*=0.13).

Few studies reported the incidence of previous fistula repair, although those that reported tended to present a high rate (80% of patients in Johnson et al 2006; 50% in Ortiz et al 2009; 75% in Buchberg et al 2010 and approximately 90% in Wang et al 2009). One exception was Christoforidis et al (2009), with 32% and 42% of patients with AFP and mucosal advancement flap repairs having undergone previous fistula surgery, respectively. Previous fistula surgery treatments varied considerably in the study by Wang et al (2009). Patients in the advancement flap group had previously undergone extrasphincteric fistulotomy, seton placement and fibrin glue injection. Patients receiving AFP had received all of the above treatments with the addition of advancement flap and fistula plug placement. Specific patient numbers for each group were not reported (Wang et al 2009).

Detailed inclusion and exclusion criteria were presented in each study (Table 5). Although criteria varied, all studies excluded patients with low (simple) fistulas or Crohn's disease, and included patients with high (complex) transsphincteric fistulas. The majority of studies excluded patients with rectovaginal fistulas, with the exception of Ellis (2007). In contrast, only one study mentioned the exclusion of horseshoe fistulas (Ortiz et al 2009).

Table 5: Fistula etiology and surgery inclusion/exclusion criteria

Study	Inclusion Criteria	Exclusion Criteria
Johnson et al (2006)	Patients with high anorectal fistulas (high transphincteric or deeper).	Patients with Crohn's disease or superficial fistulas (low transphincteric or more superficial).
Ellis (2007)	NR	**AFP**: Patients whose anal fistulas were managed by fistulotomy; patients whose fistulas were related to acute obstetrical trauma or radiation. **Flap**: Patients whose anal fistulas were managed by fistulotomy; patients whose fistulas were related to acute obstetrical trauma or radiation, or patients with a history of Crohn's disease.
Christoforidis et al (2009)	Patients with cryptoglandular fistulas with sufficient follow-up.	Patients with rectovaginal fistulas, fistulas that did not involve the external sphincter, fistulas related to Crohn's disease, fistulas related to surgery (sphoincteroplasty, ileal pouch-anal anastomosis, or ileoanal anastomosis); patients who had anodermal and not endorectal mucosa advancement flaps; patients for whom follow-up was insufficient.
Chung et al (2009)	Patients > 18 years of age with high transsphincteric fistulas of cryptoglandular origin.	Patients with simple fistulas, rectovaginal fistulas, and fistulas of Crohn's disease etiology.
Ortiz et al (2009)	Patients with high fistulas in ano of cryptoglandular etiology (fistulas that included the upper two-thirds of the external sphincter complex).	Patients with secondary tracts, horseshoe fistulas, anovaginal fistulas or rectourethral fistulas; patients with Crohn's disease; fistulas with any signs of infection, e.g. fistulas with associated anorectal abscess formation, a persistent cavity or induration or purulent drainage.
Wang et al (2009)	Patients with transsphincteric fistulas; patients with prior transsphincteric fistula repair.	Patients with rectovaginal fistulas or Crohn's disease.
Adamina et al (2010)	Patients with complex anal fistulas not amenable to simple fistulotomy (high transsphincteric involving >30% of the external anal sphincter); women with anterior transsphincteric fistulas; patients with previous fistulotomies; patients with fistulas presenting with multiple fistula openings (including horseshoe); patients with fecal incontinence.	Patients with uncomplicated fistulas curable by simple fistulotomy, rectovaginal fistulas, local sepsis, pregnancy, Crohn's disease or ulcerative colitis.
Buchberg et al (2010)	NR	NR

AFP: anal fistula plug; Flap: advancement flap repair; NR: not reported.

Definitions of success were similar among studies, with the predominant criteria being the absence of drainage and abscess formation, and closure of external fistula openings (Table 6). All studies applied the same criteria to their different treatment groups with the exception of Chung et al (2009), who varied definitions between seton placement and other treatment options (due to the nature of setons, which do not allow full closure). Follow-up periods varied, ranging from 12 weeks to over 1 year.

Table 6: Definition of success and follow-up period

Study	Success Definition	Follow up
Johnson et al (2006)	Closure of all secondary openings, an absence of fistular drainage, and an absence of abscess formation.	AFP: 13.8 ± 3.1 weeks FG: 13.6 ± 0.9 weeks *P>0.05*
Ellis (2007)	No clinical criteria reported regarding recurrence.	Flap:10 months (6-22) AFP: 6 months (3-11)
Christoforidis et al (2009)	Closure of all external openings and no reported drainage.	AFP: 14 months (6-22) ERAF: 56 months (6-136)
Chung et al (2009)	**AFP, fibrin glue, MAF**: Full healing defined as closure of the external fistular opening with no drainage or infection. **Seton**: Full healing defined as a persistent fistular opening at the seton site but with absence of drainage or infection.	12 weeks postoperatively
Ortiz et al (2009)	Based on follow up examinations.	1 year postoperatively*
Wang et al (2009)	Absence of drainage, swelling or pain at fistula site.	Determined by telephone interview in 51% of cases and last available follow-up information in 49% of cases
Adamina et al (2010)	Absence of drainage and fistular openings on physical examination and absence of abscess formation at any time during follow-up.	6 months (physical examination)
Buchberg et al (2010)	Closure of all external openings and absence of drainage and perineal abscess formation at the last follow-up.	NR

AFP: anal fistula plugs; FG: fibrin glue; Flap: advancement flap; ERAF: endorectal advancement flap; MAF: mucosal advancement flap; NR: not reported.
*Excluding one AFP patient (n=15).

Study profiles

Twenty-five patients with high anorectal fistulas were prospectively enrolled in the study by Johnson et al (2006) during a 12-month period (specific dates not provided). Treatments varied chronologically, with fibrin glue being used in the first six months (n=10), and AFP being used in the second six months (n=15). The ratio of horseshoe to radial fistulas was matched between the groups. Six patients in each treatment group had multiple fistula tracts with subsequent multiple secondary openings. Three patients, two in the fibrin glue group and one in the AFP group, had multiple primary openings (*P*>0.05).

Ellis (2007) retrospectively analyzed prospectively collected data on patients treated with anal fistula between June 2000 and May 2003 for the control group, and between May 2005 and January 2006 for the AFP group. Patients with rectovaginal fistulas in the AFP group had Crohn's disease (n=5), one of whom had both rectovaginal and transsphincteric fistulas. Of the 95

patients included in the control arm, 68 underwent mucosal advancement flap procedures and 27 underwent anorectal advancement flap procedures. Postoperative pain scores were measured using an analog pain scale ranging from 0 (no pain) to 10 (intolerable pain).

Christoforidis et al (2009) retrospectively reviewed the records of all patients treated for anal fistulas using endorectal advancement flap (ERAF) or AFP from their institution. The authors identified 125 consecutive patients who were treated with ERAF from April 1996 to April 2007, and 47 consecutive patients who were treated with AFP from January 2006 to April 2007. Following the application of exclusion criteria, 43 ERAF and 37 AFP patients were included in the study. Nine patients (21% and 24%) in each group were smokers. The authors surveyed patients in December 2007 to see whether they recalled having gas, liquid stool, or solid stool incontinence prior to their last procedure, and whether symptoms and signs of fistula recurrence were present. Patients were also asked to complete a Cleveland Clinic Florida-Fecal Incontinence (CCF-FI) score based on their symptoms. In total, 23/27 (85%) patients in the ERAF group and 7/12 (58%) patients in the AFP group responded.

Chung et al (2009) performed a retrospective analysis of all patients who were treated for anal fistulas from January 1997 to December 2008. Two hundred and thirty two patients were included in the analysis and were separated based on the treatment used, which consisted of AFPs (n=27), fibrin glue (n=23), seton drain (n=86) and mucosal advancement flap (n=96). The authors performed a risk factor analysis to determine possible associations between plug failure and age, fistula classification, and comorbidities (including diabetes, HIV, ulcerative colitis and immunosuppression using the drugs azathioprine, 6-mercaptopurine, methotrexate and prednisone).

Ortiz et al (2009) presented data from a prospective RCT comparing AFP with ERAF repair between May 2007 and October 2007. Patients were assigned randomly using a computer-generated table of random numbers. Of an initial 43 patients, five patients in the AFP group and six patients in the ERAF group did not receive the allocated intervention, resulting in 16 patients in each group. Reasons for such exclusions in the AFP group consisted of abscess at surgery (n=2), internal opening not identified (n=2) and arrhythmia at surgery (n=1). For the ERAF group, reasons for exclusion consisted of abscess at surgery (n=3), internal opening not identified (n=2) and Crohn's disease suspected at surgery (n=1). All patients included in the study had single internal and single external fistula openings, and all patients were followed up for one year, with the exclusion of one AFP patient, who did not attend follow-up examinations after surgery.

The case logs of six surgeons at two different institutions between 2001 and 2006 were retrospectively reviewed by Wang et al (2009). Fifty-five patients met the inclusion criteria including those who had undergone a mucosal advancement flap procedure (n=26) or AFP placement (n=29) for the treatment of transsphincteric cryptoglandular fistula. Based on recommendations from the manufacturer, a slight modification of the AFP technique occurred mid-way through the study period, facilitating a comparison between early (first 9 months) and late (second 9 months) outcomes.

Adamina et al (2010) compared clinical and cost data between a prospective cohort of patients receiving fistula plug from October 2006 to October 2007 (n=12) and a retrospective cohort of patients receiving endoanal advancement flap (EAAF) surgery from July 1999 to October 2005 (n=12). All patients were treated by the same surgeon.

Buchberg et al (2010) performed a chart review of prospective patients who had undergone surgery to treat complex fistula using either the Surgisis AFP or the Gore Bio-A fistula plug between August 2007 and December 2009. During the course of the study, 16 patients received

27 fistula plug insertions. A portion of the Gore plug cohort consisted of patients who had failed AFP treatment. Fistula etiology included cryptoglandular infection (n=10), surgical trauma (n=5), and HIV (n=1). Twelve patients underwent 20 previous procedures before fistula plug placement (mean number of previous procedures: 2; range 1-3).

Safety and efficacy

Safety

Three of the included studies (Christoforidis et al 2009; Adamina et al 2009; Buchberg et al 2010) reported safety data. In the study by Christoforidis et al, two patients in the ERAF group required reoperation due to bleeding at 5 and 7 days postoperative, and five patients in the AFP group required antibiotic administration postoperatively for pain and increased drainage (Christoforidis et al 2009). Adamina et al (2009) and Buchberg et al (2010) reported that no complications occurred in their patient populations. The remaining five studies did not report on complications.

Efficacy

Recurrence/success rate

In the study by Johnson et al (2006), recurrence rates were significantly lower in the AFP group (2/15; 13%) compared with the fibrin glue group (6/10; 60%; *P<0.05*). Recurrences in both groups were indicated by persistent drainage and/or a patent secondary opening. The median time to recurrence/failure was four weeks in both groups.

In the AFP group in the study by Ellis (2007), the recurrence rate was lower than that observed for a historical control group (2/18 [12%] versus 31/95 [33%], respectively); however, this difference was not statistically significant. Follow-up was a median of 6 months for the AFP group (range 3-11 months) and a median of 10 months for the control group (range 6-22 months). In the AFP group, one patient with poorly controlled diabetes and a horseshoe fistula experienced fistula recurrence after 28 days, and a second patient with a rectovaginal fistula related to Crohn's disease experienced fistula recurrence after 11 months. The mean time to recurrence in the control group was 14 days.

In the study by Christoforidis et al (2009), recurrence rates were lower in the AFP group (68%) compared with the ERAF group (37%, *P*=0.008) after mean follow-up periods of 14 months (range 6-22 months) and 56 months (range 6-136 months), respectively. Several patients in the AFP (n=5) and ERAF (n=3) groups experienced temporary healing, only to have the fistulas recur later than 6 months after surgery. Four patients underwent ERAF repair following failure of AFP treatment; two healed and the remaining two procedures were unsuccessful.

Healing rates differed significantly among the four treatment groups in the study published by Chung et al (2009) at 12-weeks follow-up, ranging from 33% for seton drain to 60% for mucosal advancement flap; the rate for AFP was 59% (*P<0.05*, see Table 7). Further follow up of the AFP group at 24 weeks demonstrated an increase in the numbers of fistulas healed, bringing the success rate to 19/27 (70%) patients; however, the other groups were not assessed at 24 weeks and thus this figure is not useful for comparison. Of the 11 unsuccessful AFP patients at 12 weeks, three had persistent infection, five experienced plug extrusion (four of which had occurred within the first week), and three others had persistent fistula openings (two of which had healed at 24 weeks postoperatively)

Table 7: Success rates of fistula treatment groups

Study	Treatment	Success Rate
Johnson et al (2006)	AFP Fibrin glue	13/15 (87%) 4/10 (40%)
Ellis (2007)	AFP MAF/AAF	16/18 (88%) 64/95 (67%)
Christoforidis et al (2009)	AFP ERAF	12/37 (32%) 27/43 (63%) *P=0.008*
Chung et al (2009)	AFP Fibrin glue MAF Seton drain	16/27 (59%) 9/23 (39%) 58/96 (60%) 28/86 (33%)
Ortiz et al (2009)	AFP ERAF	3/15 (20%) 14/16 (87.5)
Wang et al (2009)	AFP MAF	10/29 (34%) 16/26 (62%) *P=0.045*
Adamina et al (2010)	AFP EAAF	6/12 (50%) 4/12 (34%)
Buchberg et al (2010)	AFP Gore Bio-A	2/16 (13%) 6/11 (55%)

AFP: anal fistula plug; MAF: mucosal advancement flap; AAF: anodermal advancement flap; ERAF: endorectal anal flap; EAAF: endoanal advancement flap.

In the study by Ortiz et al (2009), recurrence rates were extremely high in the AFP group compared to the ERAF group (80% versus 12%, respectively). Failure of fistula closure in the AFP group was identified by the presence of an abscess arising in the same area as the original fistula two weeks post-surgery (n=1), extrusion of the fistula plug (n=3), and persistent leakage around the plug, such that the fistula could not close (n=8). In the ERAF group, failure to close was identified by the presence of an abscess arising in the same area as the original fistula. All such recurrences were identified within 3 months post-surgery. Of the 16 patients who had previously undergone fistula surgery, 9 (56%) experienced fistula recurrence, 8 of whom were in the AFP group. The recurrent fistula healed in 7/8 patients, one treated with AFP and six treated with ERAF repair (Ortiz et al 2009).

In the study published by Wang et al (2009), patients in the AFP group experienced lower rates of complete fistula closure than did those in the mucosal advancement flap group (Table 7). Following failed initial procedures, several additional treatments were performed, resulting in a total of 34 AFP procedures and 30 mucosal advancement flap procedures. Final fistula closure rates were 32% and 60% for AFP and mucosal advancement flap, respectively (*P*=0.027). There was no statistical difference in fistula healing rates observed for those receiving AFP in the first 9 months versus the subsequent 9 months.

Adamina et al (2010) reported a success rate of 67% in the AFP group after 6 months follow-up; however, two additional failures occurred at 37 and 44 weeks follow-up, resulting in a success rate of 50%. Although higher than the success rate in the EAAF group (33%), this was not statistically significant (*P*=0.680).

In the study by Buchberg et al (2010), overall success rates were extremely low for the AFP group (2/16 patients, 13%) compared to the Gore group (6/11 patients, 55%). Of the 19 patients with unresolved fistulas, two were the result of plug dislodgement (11%) and the remaining 17 experienced persistent drainage (90%). Subgroup analysis revealed a potential correlation between success rate and fistula etiology and seton placement, although patient numbers were too low to make any accurate conclusions. Patients with cryptoglandular fistulas experienced the

highest levels of success, with 7/10 (70%) fistulas healed compared with 2/5 (40%) in patients with non-cryptoglandular fistulas. Of interest, patients in whom fistula were pre-treated with setons experienced higher levels of success compared with those who had not (5/9 (55%) compared with 2/7 (29%), respectively).

Hospital Length of stay

Wang et al (2009) reported median hospital length of stay (LOS) as 0 days (range: 0-2 days) for the AFP group and 1 day (range: 0-3 days) for the mucosal advancement flap group. For the mucosal advancement flap group, this figure is slightly skewed toward the upper limit due to an included institution enforcing mandatory overnight admission due to treatment protocols (Wang et al 2009). In the study by Adamina et al (2010) median hospital LOS was also lower for patients receiving AFP (1 day, range: 1-1 days) than patients receiving EAAF (2.5 days, range: 2-4 days, *P = 0.0002*).

Pain scores

Ellis (2007) measured pain scores by means of an analog pain scale (0 = no pain; 10 = intolerable pain). Prior to fistula surgery, AFP patients presented average pain scores of 3.0 ± standard deviation (SD) 1.0. At the time of the initial postoperative phone interview, this score increased to 3.8 ± SD 1.3, which then decreased to 3.3 ± SD 1.1 at the initial clinic visit. In contrast, patients receiving mucosal advancement flap or anorectal advancement flap had lower average pain scores preoperatively (2.6 ± SD 0.8), which rose at the time of the telephone interview (4.4 ± SD 2.7) and further still at the initial clinic visit (5.8 ± SD 3.1).

CCF-FI scores

In the study by Christoforidis et al (2009), of the seven questionnaire respondents in the AFP group, six reported normal or near normal continence (CCF-FI score 0-2). The remaining patient reported daily gas and liquid incontinence (CCF-FI score 8); however, such symptoms were already present prior to surgery. With regards to the ERAF group, 11/23 (48%) patients had “no continence disturbance or gas/liquid incontinence less than once a month” (CCF-FI score 0-2), 8/23 (35%) had occasional gas incontinence and rare liquid incontinence (CCF-FI score 3-4), and 4/23 (17%) had frequent liquid stool incontinence and/or occasional solid stool incontinence (CCF-FI score 7-12).

Risk factor analysis

Chung et al (2009) performed a risk factor analysis to determine which variables contributed to a higher incidence of fistula plug failure. Following a multivariate analysis, it was established that age, fistula classification and comorbidities were not associated with fistula healing at 12 weeks; however, the cohort was too small to draw any definitive conclusions (Chung et al 2009).

Conflict of interest among authors

In the study by Johnson et al (2006), it was declared that the senior author (David N. Armstrong) received royalties on the sales of Surgisis AFP anal fistula plugs. No other conflicts of interest were declared in the remaining studies.

Cost impact

British authors Thekkinkattil et al (2008) suggested a cost price of $1000 for each Surgisis AFP device (currency not reported), and suggested that this was considerable compared to other fistula surgery techniques. Adamina et al (2010) supported this figure, stating that, based solely on commercial costs, one AFP represented an additional $1021 in costs per fistula treated.

Adamina et al (2010) performed a cost analysis which compared AFP surgery to advancement flap surgery with figures adjusted for inflation and reported in US dollars. All costs related to the surgical procedures and hospital stays were included but preoperative and follow-up costs were excluded. The total cost for fistula plug surgery was calculated at $2,096 (95% confidence interval [CI]: $1,978 - $2,214). This figure was substantially lower than that attributed to the advancement flap repair procedure of $3,690 (95% CI; $3,307 - $4,074) (*P < 0.0001*). The greatest contributing factor to total cost was hospital LOS, which was higher in the advancement flap group than the AFP group (median 2.5 days LOS compared to median 1 day, respectively). Other factors that contributed to the higher cost of advancement flap repair included higher operative room costs (surgical time) and anesthesiologist fees. When adjusting for LOS, age and sex, performing AFP surgery instead of advancement flap surgery resulted in an average savings of $825 per patient (95% CI; range: $133- $1,517), with an additional $444 added for every additional hospital day (Adamina et al 2010).

Clinical practice guidelines and consensus statements

In May 2007, a consensus conference was held in Chicago where 15 surgeons established a uniformity of opinion regarding the indications and techniques for use of the Surgisis AFP (Consensus Conference 2007). All recommendations presented below were unanimously agreed by those present.

- Indications for use of the plug include transsphincteric, anovaginal, intersphincteric and extrasphincteric fistulas, whereas exclusion criteria include conventional, uncomplicated intersphincteric fistulas (where success using standard fistulotomy approaches 100% with minimal morbidity). There are no specific guidelines regarding pre- and peri-operative management (including bowel preparation, use of anesthetic and patient positioning). These factors should be based on surgeon and patient preference.
- Debridement, curettage or brushing of the tract should not be performed as such intrusion would enlarge the fistula tract. Setons should be used temporarily after surgery until there is no evidence of acute inflammation, purulence, or excessive drainage; however, seton use prior to implantation is unnecessary in the absence of an acute inflammatory process.
- Excess plug should be trimmed at the level of the internal opening and sutured with 2-0 long-term, braided, absorbable material. Monofilament material should not be used.
- The majority of fistulas that heal do so within 3 months and a 50% to 60% success rate should be considered acceptable. Patient selection, avoidance of local infection, and meticulous technique are required to achieve the highest possibility of success.

Of interest, all conference participants received reimbursement and an honorarium from Cook Medical Incorporated (the device manufacturer) for dedicating their weekend to the task (Consensus Conference 2007).

Training and education impact

The participants at the Surgisis AFP Anal Fistula Plug Consensus Conference in Chicago (2007) unanimously agreed that the procedure should be performed only by trained surgeons familiar with anorectal anatomy and experienced in conventional anal fistula surgery and the management of its complications.

Summary

Anal fistulas often develop as a result of previous cryptoglandular infection. For the treatment of simple (low) fistulas, the fistulotomy technique has achieved a nearly 100% success rate and low levels of complications. Unfortunately, this procedure is ineffective at treating high (complex) fistulas. Several procedures have been developed with which to treat complex anal fistulas although none have yet to produce consistently high levels of success. The Surgisis AFP anal fistula plug presents a new alternative and was the first of its kind to be FDA-approved. The device consists of a cylindrical segment of porcine small intestinal submucosa. Insertion of the plug into the fistula ideally seals the tract and facilitates host cell repopulation of the matrix, resulting in a healed fistula.

Eight studies detailed in this report present comparative evidence between AFPs and alternative procedures for the treatment of complex anal fistulas.

- Six studies compare AFP with mucosal advancement flap repair. Results are mixed with two studies demonstrating higher levels of success using AFPs, and four studies demonstrating higher levels of success using mucosal advancement flap repair. However, patients undergoing AFP surgery presented with lower pain and CCF-FI scores and shorter hospital LOS.
- Both studies that compared treatment with AFPs versus fibrin glue demonstrated higher levels of success in the AFP group. It must be noted that fibrin glue has recently fallen out of favor as a means to treat complex anal fistulas due to such disappointing success rates, and as such these comparisons have assumed less clinical relevance.

The high variability in success rates makes it difficult to assess the true efficacy of AFPs and reflects a need to more clearly define indications for its use. Comparisons between AFP and mucosal advancement flap repair and fibrin glue attest to the efficacy of AFPs; however, further studies comparing AFPs to new and emerging techniques, such as the Gore Bio-A fistula plug, LIFT, BioLIFT, and collagen matrix injection technologies, will ultimately determine whether AFP has a lasting place in the surgeon's arsenal.

Recommendation

Comparative evidence suggests that mucosal advancement flap repair, the current gold standard treatment, generally achieves a higher level of success than AFP in the treatment of complex anal fistula. Based on this evidence, it is unlikely that AFP will replace mucosal advancement flap repair as the treatment of choice in these patients. However, initial results using the BioLIFT procedure are very promising, suggesting that AFP may contribute to increased levels of success when used in conjunction with the LIFT procedure. Further studies comparing BioLIFT to mucosal advancement flap and other alternatives are required before any definitive conclusions can be made. Other novel techniques, (e.g. LIFT and Permacol injection) must be monitored for safety and efficacy, as reproducibly high levels of success using such techniques may result in obsolescence of AFP.

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Appendix A

Additional papers not included in this assessment

Article reference	N=	Conclusions	Reason for exclusion
Lupinacci RM, Vallet C, Parc Y, Chafai N, Tiret E. Treatment of fistula-in-ano with the Surgisis® AFP™ anal fistula plug. *Gastroenterologie Clinique et Biologique* 2010;34(10):549-53	15	Provides moderate success rates.	Case series
McGee MF, Champagne BJ, Stulberg JJ, Reynolds H, Marderstein E, Delaney CP. Tract length predicts successful closure with anal fistula plug in cryptoglandular fistulas. *Diseases of the Colon and Rectum* 2010;53(8):1105-6	41	AFP repair of cryptoglandular anal fistulas is more successful for long-tract fistulas.	Case series
Owen G, Keshava A, Steward P, Patterson J, Chapuis P, Bokey E, Rickard M. Plugs unplugged. Anal fistula plug: the Concord experience. *ANZ Journal of Surgery* 2010;80(5):1105-6	32	Surgisis AFP is a useful option in the management of complex fistulae.	Case series
Lenisa L, Espin-Basany E, Rusconi A, Mascheroni L, Escoll-Rufino J, Lozoya-Trujillo R, Vallribera-Vallis F, Megevand J. Anal fistula plug is a valid alternative option for the treatment of complex anal fistula in the long term. International *Journal of Colorectal Diseases* 2010;25(12):1487-93	60	AFP treatment is a safe and viable surgical option that should be offered to complex fistula patients.	Case series
Ellis CN, Rostas JW, Greiner FG. Long-term outcomes with the use of bioprosthetic plugs for the management of complex anal fistulas. *Disease of the Colon and Rectum* 2010;53(5):798-802	63	Bioprosthetic plugs are effective for the long-term closure of complex fistulas.	Case series
Zubaidi A, Al-Obeed O. Anal fistula plug in high fistula-in-ano: an early Saudi experience. *Disease of the Colon and Rectum* 2010;147(1):72-8	22	Use of Surgisis AFP is safe and successful.	Case series
Schwandner T, Roblick MH, Kierer W, Brom A, Padberg W, Hirschburger M. Surgical treatment of complex anal fistulas with the anal fistula plug: a prospective, multicenter study. *Diseases of the Colon and Rectum* 2009;52(9):1578-83	60	New techniques for the treatment of complex anal fistula are required, AFPs are promising	Case series
Safar B, Jobanputra S, Sands D, Weiss EG, Nogueras JJ, Wexner SD. Anal fistula plug: initial experience and outcomes. *Diseases of the Colon and Rectum* 2009;52(2):248-52	35	AFP presents similar healing rates to mucosal flap advancement, both are superior to seton placement and fibrin glue.	Case series
El-Gazzaz G, Zutshi M, Hull T. A retrospective review of chronic anal fistulae treated by anal fistulae plug. *Colorectal Disease* 2010;12(5):442-7	33	AFPs were associated with lower success rates than previously reported, mainly due to sepsis.	Case series
Echenique I, Mella JR, Rosado F, Echenique IA, Mella MT, Quevedo G. Puerto Rico experience with plugs in the treatment of anal fistulas. *Boletin de la*	23	High incidence of recurrence, authors need to search for an operation which is more effective.	Case series

Asociacion Medica de Puerto Rico 2008;100(1):8-12			
Garg P. To determine the efficacy of anal fistula plug in the treatment of high fistula-in-ano: an initial experience. *Colorectal disease* 2009;11(6):588-91	23	High level of success, plug extrusion does not necessarily imply failure.	Case series
Thekkinkattil DK, Botterill I, Ambrose NS, Lundby L, Sagar PM, Buntzen S, Finan PJ. Efficacy of the anal fistula plug in complex anorectal fistulae. *Colorectal Disease* 2009;11(6):584-7	43	Only a moderate success was achieved, which may be due to the selection of highly complex fistula included the study.	Case series
Christoforidis D, Etzioni DA, Goldberg SM, Madoff RD, Mellgren A. Treatment of complex anal fistulas with the collagen fistula plug. *Diseases of the Colon and Rectum* 2008;51(10):1482-7	47	Moderate level of success, patients with less external sphincter involvement had a higher chance of success.	Case series
Lawes DA, Efron JE, Abbas M, Heppell J, Young-Fadok TM. Early experience with the bioabsorbable anal fistula plug. *World Journal of Surgery* 2008;32(6):1157-9	20	Low level of success, high incidence of perianal sepsis. Adjunctive treatment with advancement flap may improve success rates.	Case series
Ky AJ, Sylia P, Steinhagen R, Steinhagen E, Khaitov S, Ly EK. Collagen fistula plug for the treatment of anal fistulas. *Diseases of the Colon and Rectum* 2008;51(6):838-43	45	AFP should be considered first-line treatment in patients with simple fistulas, and an alternative in complex fistulas	Case series
Schwadner O, Stadler F, Dietl O, Wirsching RP, Fuerst A. Initial experience on efficacy in closure of cryptoglandular and Crohn's transsphincteric fistulas by the use of the anal fistula plug. *International Journal of Colorectal Disease* 2008;23(3):319-24	19	Medium level of success in high complex fistulas, high level of success in Crohn's associated fistulas. Needs comparison to traditional surgical techniques.	Case series
van Koperen PJ, D'Hoore A, Wolthuis AM, Bemelman WA, Slors JF. Anal fistula plug for closure of difficult anorectal fistula: a prospective study. *Diseases of the Colon and Rectum* 2007;50(12):2168-72	17	Medium levels of success. A large scale trial is required to establish AFP efficacy.	Case series
Champange BJ, O'Connor LM, Ferguson M, Orangio GR, Schertzer ME, Armstrong DN. Efficacy of anal fistula plug in closure of cryptoglandular fistulas: long-term follow-up. *Diseases of the Colon and Rectum* 2006;49(12):1817-21	46	High success, long-term closure is safe in patients with cryptoglandular anorectal fistula.	Case series
O'Connor L, Champagne BJ, Ferguson MA, Orangio GR, Schertzer ME, Armstrong DN. Efficacy of anal fistula plug in closure of Crohn's anorectal fistulas. *Diseases of the Colon and Rectum* 2006;49(10):1569-73	20	High success, closure rates were higher with single tracts than complex fistulas with multiple primary openings.	Case series

Appendix B

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,5 among consecutive persons with a defined clinical presentation6	A prospective cohort study[7]	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation6	All or none[8]	All or none[8]	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilized.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6 Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

8 All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C with statistical adjustment for B).

10 Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).

11 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.