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# PERMACOL™ COLLAGEN PASTE FOR ANAL FISTULA TREATMENT

EXPERT OPINION
PRACTICE-BASED
RECOMMENDATIONS

WHITEPAPER

Medtronic

*This whitepaper is the result of the expert consensus meeting on anal fistula treatment organized on April 24th at the Sheraton Amsterdam Airport Hotel, Schiphol, The Netherlands*

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# PERMACOL™ COLLAGEN PASTE FOR ANAL FISTULA TREATMENT

## Whitepaper

### WHY

Though Permacol™ collagen paste may offer an attractive treatment option for many anal fistula patients, in the absence of evidence-based guidelines a lack of first hand expertise may hamper its use in clinical practice.

This expert opinion report provides expert guidance on the use of Permacol™ Paste for treatment of anorectal fistula aimed at surgeons who may not be familiar with the technique. This advice is based on the personal experience of surgeons with hands-on expertise using Permacol™ collagen paste in their clinical practice who clearly stated existing level of evidence is low.

### HOW

Clinical experts in anal fistula treatment were invited to participate to a written survey discussing the use of Permacol™ Paste in the broader context of anal fistula treatment in their practice. Each participant's response was discussed in a one-on-one phone interview.

The generalized results from the survey and interviews were presented in conjunction with an overview of relevant literature at an expert meeting, held on April 24 at the Sheraton Amsterdam Airport Hotel in Schiphol, Amsterdam. The results of this discussion are captured in this expert opinion recommendation whitepaper.

### WHAT

This whitepaper summarizes the expert opinion meeting discussion topics and expert opinion recommendations for the use of Permacol™ Paste in clinical practice.

## Expert panel participants

The following experts participated to the expert panel and endorse this whitepaper:

- **Meeting chairs**
  - Dr. Pasquale Giordano, Whipps Cross University Hospital, Barts Health, London, UK
  - Dr. Ben Griffiths, NUTH Foundation Trust, Newcastle, UK
  - Dr. Charlotte Molenaar, Proctos Kliniek, Bilthoven, The Netherlands
  - Dr. Grietje Vander Mijnsbrugge, Proctos Kliniek, Bilthoven, The Netherlands
- **Meeting participants**
  - Dr. Leonardo Lenisa, Casa di Cura Humanitas San Pio X, Milan, Italy
  - Dr. Klaus Matzel, University Hospital Erlangen, Erlangen, Germany
  - Dr. Raj Rajaganeshan, Whiston Hospital, Prescot, Merseyside, UK
  - Dr. Adal Saeed, St. Josefs-Hospital, Wiesbaden, Germany
  - Dr. Andrew Williams, Guy's and St. Thomas' NHS Trust, London, UK
- **Survey participants**
  - Dr. Gabriele Naldini, Cisanello University Hospital, Pisa, Italy

## Expert consensus management

The expert consensus process was facilitated by **hict**, an independent advisory company with a proven track record in health economics and expert data collection. The expert meeting was chaired by Dr. Giordano, Dr. Griffiths, Dr. Molenaar and Dr. Vander Mijnsbrugge and moderated by **hict**.

Medtronic provided financial support for facilitation and organization of the expert consensus process to **hict** and all meeting participants.

## 1. Permacol™ Collagen Paste

"Permacol™ paste conforms to the shape of the anal fistula tract, reducing the risk of early extrusion and recurrence."

Permacol™ collagen paste is a sterile suspension of acellular cross-linked porcine dermal collagen matrix and saline. Permacol™ paste is designed to act as a scaffold to support cellular infiltration, promote tissue vascularization and enable fistula closure without damaging the anal sphincter. Its core technology is also the primary composition for Permacol™ surgical implant (intended for soft tissue repair) and Permacol™ collagen injection (intended for filling and bulking indications). As an injectable collagen paste, it conforms to the shape of the anal fistula tract, differentiating it from other more rigid or more liquid implant materials, thereby theoretically reducing the risk of early extrusion and recurrence.

"Recent studies found Permacol™ to be a safe, minimally invasive, sphincter-preserving treatment that promotes a good healing rate, is acceptable to patients and is associated with low rates of postoperative fecal incontinence."

Recent studies evaluating the use of Permacol™ paste for treatment of complex anal fistulas found Permacol™ to be a safe, minimally invasive, sphincter-preserving treatment that promotes a good healing rate, is well perceived by patients and minimizes the risk of postoperative fecal incontinence [1], [2]. The multi-center MASERATI study [1], including 100 patients, reported a 56.7% healing rate at 6 months (53.2% after 3 months, 53.5% after 12 months), fast closure rates (average time to healing of just over 2 months; majority who healed after 12 months had done so after one month) with satisfactory pain levels (87.7% of patients reported no or mild pain after 1 month) and no reported impact on fecal continence. 73% of patients were satisfied with the intervention upon their last follow-up visit. Similar results were reported by Fabiani et al. [2], with a reported success rate of 47.6% twelve months after surgery and no differences in fecal continence pre- and post-intervention.

## 2. Treating Complex Anal Fistula

### Balancing risk and outcome

"Treating anal fistula requires balancing the desire for an optimal outcome with the treatment's associated risk of impacting continence."

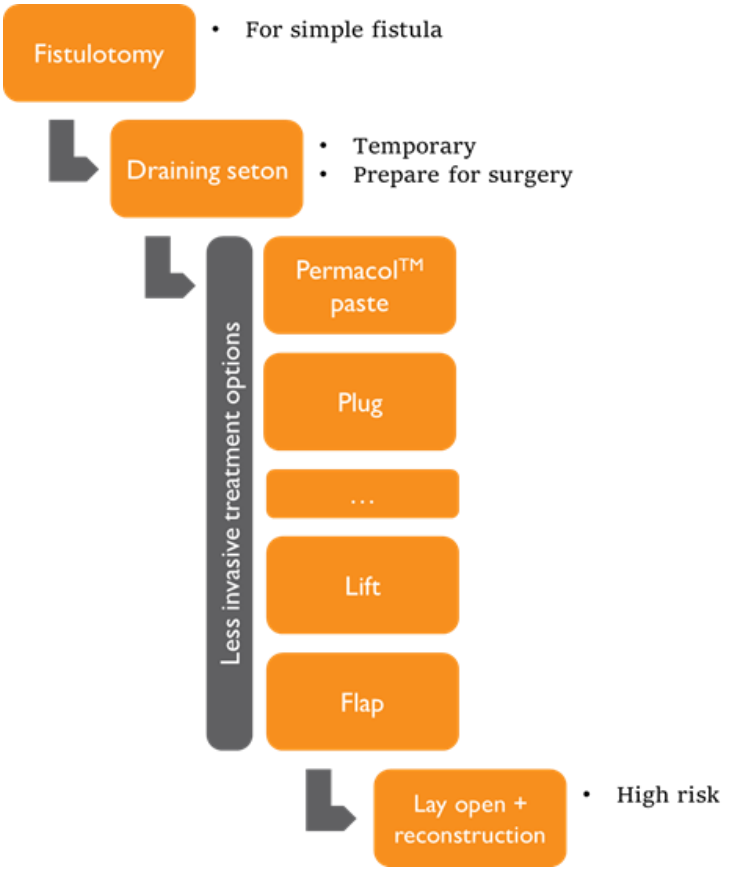
Selecting which treatment option to use for treating an anal fistula patient equates to balancing the desire for an optimal outcome (closure/healing of the fistula) with the treatment's associated risk on impacting fecal continence. A balancing act, in which the patient's preference plays an important role.

"For simple fistulas, fistulotomy is an effective treatment option."

For simple fistulas, fistulotomy is an effective treatment that results in healing in over 90% of patients [3]–[5]. However, in cases where the anal sphincter is impacted by the fistulotomy, continence may be impacted as well. For complex fistulas, while lay-open with primary reconstruction and flap may still yield good rates of fistula healing, the risk for damaging the sphincter which may lead to incurring incontinence is high. Between these options, different 'less-invasive' treatment options exist, with lower risk but also less evidence demonstrating favorable outcome.

"For complex fistula, the treatment landscape resembles a cascade, at each step trading off increased risk of incurring fecal incontinence for higher overall success rates. Often, the patient is the deciding factor in moving from one level to the next."

The treatment landscape for complex fistula thus resembles a cascade. Fistulotomy is the entry point for fistula that can be laid open without impacting sphincter function. For patients with increased risk of incurring fecal incontinence, 'less invasive' treatment options may be considered, trading off lower overall success rates for maximal preservation of continence. Finally, lay-open of the high fistula tract with primary reconstruction of the sphincter defect remains a treatment option suitable for resolving the fistula, but with a potentially important impact on sphincter function and continence. Often, the patient is the deciding factor in moving from one level to the next.



"Permacol™ collagen paste can be considered for all anal fistula patients where fistulotomy is not an option, except in the case of the presence of abscess or inflammation with active discharge."

Permacol™ collagen paste can be considered for all anal fistula patients, where fistulotomy is not an option, except in the presence of abscess or inflammation with active discharge. In the Maserati study, patients with anal abscess were more than four times more likely to experience treatment failure [1]. As for other interventions for particularly complex cases such as horse shoe fistula, very long fistula tracks or multiple branching tracks, reducing the complexity of the fistula by, for instance, using a staged approach or combining treatment techniques may improve success rates and reduce risk.

A recent systematic review and meta-analysis shows that none of the sphincter-preserving techniques proposed seem to be superior to the others [6]. Currently available clinical evidence on the use of Permacol™ in complex fistula [1], [2] does not yet suggest it delivers significantly superior results either. The choice of which 'less invasive' treatment option to use in the aforementioned treatment cascade, therefore, largely depends on shared decision making between surgeon and patient.

"Permacol™ paste is unlikely to cause harm, even in the case of failure. This, coupled to its relative ease of use and high patient satisfaction, makes it a good first choice 'less invasive' treatment option."

Due to its nature, Permacol™ paste is unlikely to cause harm, even in the case of failure. In essence, using Permacol™ does not impact upon future treatment options in the described treatment cascade. In fact, as for other techniques, clinical practice can indicate a more favorable starting position after failure, having reduced the extent or complexity of the fistula. These features, coupled to its relative ease of use and high patient satisfaction, make it a good 'first step' option for a 'less invasive' treatment option in the treatment cascade.

### Recurrent treatment

"The combination of the it being a 'no harm' intervention, high patient satisfaction and relative ease of use offer particular incentives for exploring recurrent Permacol™ paste treatment".

"There currently is no evidence on whether the failure of PermacolTM Paste is a predictor for the success rate of its reuse. There is a keen interest in evidence exploring this use case".

In general, for any of the 'less invasive' treatment approaches, there is little evidence how many times a technique should or could be done before moving on to a different technique. Much of the evidence is anecdotal and the choice of again performing the same intervention after previous failure is left to the individual physician's discretion. For Permacol™ paste as well, there is little to no evidence whether the failure of Permacol™ paste is a predictor for the success rate of its re-use. The combination of it being a 'no harm' intervention, high patient satisfaction and relative ease of use do, however, offer particular incentives for exploring recurrent Permacol™ paste treatment. Though currently lacking, there is therefore a keen interest in evidence exploring recurrent use of Permacol™ paste.

## 3. Practical Considerations for the Use of Permacol™ Collagen Paste

Patient preparation and practical application of Permacol™ paste can differ depending on individual patient context and surgeon preference. Nevertheless, a number of best-practice practical recommendations should be highlighted. These are based on the manufacturer's guidelines, clinical experience and are reflected in most recent clinical trials concerning Permacol™ paste.

- Patient preparation: antibiotics prophylaxis and bowel preparation at the surgeon's discretion;
- Identify internal and external openings;
- Debridement of the tract, de-epithelializing the fistula tract with a brush or equivalent to remove granulation tissue;
- Preparation of the internal opening edges at the physician's discretion;
- Inject Permacol™ paste under pressure (e.g. applying pressure to the internal opening), to make sure the entire tract is filled; tract filling can be evaluated by visualizing paste at both the internal and externa openings;
- Some physicians prefer closing the internal opening prior to Permacol™ paste injection;
- Loose/partial closure of the external opening, often with a single suture; the objective is to prevent extrusion but allow drainage of the fistula;
- Standard post-operative care may differ from other fistula interventions;
- Advise patients to refrain from physical activities for at least 4 weeks post-surgery;
- Advise patients to expect mild indolent discharge in the first weeks or months post-surgery; this does not mean the treatment failed; diagnosis of recurrence can, in most cases, only be done after 3 to 6 months.

While the use of Permacol™ paste is, from a physician's perspective, fairly straightforward, it does require building routine practice, developing the expertise required to apply the technique correctly, in order to obtain optimal results. Any technique may, in inexperienced hands, fail to deliver its full potential.

## 4. References


[1] Giordano, P. *et al.* Final results of a European, multicentre, prospective, observational Study of Permacol™ collagen paste injection for the treatment of anal fistula. *Colorectal Dis.* Accepted Author Manuscript. doi:10.1111/codi.13715

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[6] Göttgens, K.W.A. *et al.* Systematic review and meta-analysis of surgical interventions for high cryptoglandular perianal fistula. *Int J Colorectal Dis.* 2015 (30): 583–593. doi:10.1007/s00384-014-2091-8


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### A need for evidence

The treatment of anal fistula remains, in many ways, an art looking for a solid evidence base to guide its practice. For Permacol™, as for most other interventions, there remains a pressing need for evidence to establish its effectiveness outside controlled trials, develop an understanding of the optimal target (sub) population for its use, determine the appropriateness of repeated interventions and further demonstrate its added value in terms of outcomes and costs.

The expert panel strongly advocates for setting up observational patient registries capturing relevant patient, intervention and outcome data, preferentially on the international or minimally on the national level with provisions for exchange or linking of data. Specific thresholds, such as dealing with issues of ownership and financing and managing differing national regulatory guidelines should not stand in the way of its realization.

### A minimal data set for meaningful evidence generation

To be useful for evidence generation, a minimal data set should ideally include

- Patient information:
  - Anatomical fistula features;
  - Patient context (including comorbidities);
- Intervention information:
  - Number and type of previous interventions, including 'experience level' of the physician performing the intervention;
  - Diagnostic tools used (US, MRI, ...);
  - Current intervention;
- Outcome measures:
  - Closure rates at 3/6 months;
  - 12 month follow-up for detection of recurrence;
  - (Additional) Occurrence of adverse events;
  - (Additional) Patient-reported outcomes:
    - Patient satisfaction (SF-36 or EQ-5D);
    - Wexner or other fecal incontinence score.

### Contact information


This whitepaper was developed by **hict** (Sebastian Vermeersch, Ann Tanghe, Britt Callebaut and Lieve Staessens) for Medtronic.

**Contact:** sebastian.vermeersch@hict.be – www.hict.com