NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Crohn's disease: Tests for therapeutic monitoring of TNF inhibitors (LISA-TRACKER ELISA kits, TNFα-Blocker ELISA kits, and Promonitor ELISA kits)

Final scope

October 2014

1 Introduction

The LISA-TRACKER ELISA kits are manufactured by Theradiag and distributed in the UK by Alpha Laboratories UK Ltd. The Medical Technologies Advisory Committee identified the LISA-TRACKER ELISA kits as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note. The final scope was informed by discussions at the scoping workshop held on 29 September 2014 and at the assessment subgroup meeting held on the 13 October. The following alternative technologies which were identified as similar to the LISA-TRACKER ELISA kits have been included in the final scope: TNFα-Blocker ELISA kits (Immundiagnostik), and Promonitor ELISA kits (Proteomika).

A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE from the manufacturers and on information available in the public domain. NICE has not carried out an independent evaluation of these descriptions.

2.1 Purpose of the medical technologies

The assays are intended for measuring the levels of anti-tumour necrosis factor-alpha drugs (TNF inhibitors) and the levels of antibodies against TNF inhibitors in patient blood sera. TNF inhibitors are often used to inhibit the activity of the cell signalling protein, TNF-α, which promotes inflammatory responses. When the production of TNF-α is dysregulated it can lead to

various inflammatory diseases, such as Crohn's disease. TNF inhibitors, such as infliximab and adalimumab, are therefore given to patients to inhibit TNF-α production and suppress the inflammatory response. Although TNF inhibitors can bring benefits to many patients with Crohn's disease, there are some patients whose disease does not respond to treatment with TNF inhibitors (primary non-responders). Furthermore, a large proportion of patients whose disease initially responds to treatment find their disease stops responding over time (secondary loss of response). This loss of response can be caused by:

- changes in disease characteristics over time,
- inflammation unrelated to Crohn's disease,
- the presence of antibodies to TNF inhibitors,
- fluctuations in circulating drug levels.

It is reported that the concentration of TNF inhibitor in the blood of patients immediately before their next dose of TNF inhibitor (trough level) can vary widely between patients even though they have received the same initial dose. These variations can be caused by:

- Individual differences in drug pharmacokinetics
- Presence of anti-drug antibodies which bind to the TNF inhibitor, leading to neutralisation of its activity and increased clearance
- Concomitant administration of some immunosuppressive treatments, such as methotrexate.

The clinical scenarios in which these assays may be used include (Table 1):

Table 1: Clinical scenarios for the use of assays for therapeutic monitoring of TNF inhibitors

Scenario	Description	Treatment options
Secondary loss of response	Patients whose disease initially responded to treatment with TNF inhibitor, but lost response over time	• Intensify treatment with the current TNF inhibitor (increased dose or decreased dosing interval); • Switch to an alternative TNF inhibitor; • Switch to a drug with a different mechanism of action (possibly one that has been used before).
Good response	Patients whose disease responds well to an induction phase of treatment with TNF inhibitor	• Optimize dosing in order to achieve therapeutic drug levels by increasing or decreasing the dose of current TNF inhibitor; • Predict future loss of response and risk of adverse events.

Scenario	Description	Treatment options
After 12 months of treatment with a TNF inhibitor	NICE technology appraisal infliximab and adalimumab for the treatment of Crohn's disease (TA187, 2010) recommends that treatment with infliximab or adalimumab should only be continued after 12 months if there is clear evidence of ongoing active disease	• Withdraw current TNF inhibitor; • Decrease dose of current TNF inhibitor; • Maintain treatment with current TNF inhibitor.

Currently, treatment decisions for patients with Crohn's disease are commonly based on clinical judgement and 'trial and error', so tailoring treatment to the individual patient can be difficult. Patients whose disease responds well to treatment with TNF inhibitor may continue to receive the same level of treatment even though a decrease in dose or withdrawal from the TNF inhibitor may be possible without any detrimental impact on clinical outcomes. This continued treatment may lead to patients experiencing side-effects of the treatment unnecessarily. Also, patients who experience a secondary loss of response are typically treated with an escalated dose of TNF inhibitor in an attempt to bring back the decreasing clinical response. This approach can lead to successful treatment for some patients, but for others, the intensified treatment regimen is not effective, which results in patients continuing to receive an expensive drug from which they do not benefit and they may experience treatment side-effects unnecessarily.

2.2 LISA-TRACKER ELISA kits (*Theradiag / Alpha Laboratories*)

LISA-TRACKER assay kits are enzyme linked immunosorbent assays (ELISAs) for the quantitative determination of TNF inhibitor levels and antibodies against TNF inhibitor. There are 6 LISA-TRACKER ELISA kits relevant to this assessment (table 2). Two of these kits measure the levels of free anti-drug antibodies, 2 kits measure the levels of free TNF inhibitor and 2 kits measure the levels of both free anti-drug antibodies and TNF inhibitor.

Table 2: LISA-TRACKER ELISA kits

Name (code)	Detects	Microplate pre-coat	Secondary reagent	Incubation times
LISA-TRACKER Adalimumab (LTA002)	Free adalimumab	TNF-α	Biotinylated anti-human IgG antibody	1 hour; 1 hour; 30 mins; 15 mins
LISA-TRACKER Infliximab (LTI002)	Free infliximab	TNF-α		

Name (code)	Detects	Microplate pre-coat	Secondary reagent	Incubation times
LISA-TRACKER anti-Adalimumab (LTA003)	Free anti-adalimumab antibodies	Adalimumab	Biotinylated adalimumab	1 hour; 1 hour; 30 mins; 15 mins
LISA-TRACKER anti-Infliximab (LTI003)	Free anti-infliximab antibodies	Infliximab	Biotinylated infliximab	
LISA-TRACKER Duo Adalimumab (LTA005)	As above; the Duo Adalimumab kit consists of a LISA-TRACKER Adalimumab kit and a LISA-TRACKER anti-Adalimumab kit			
LISA-TRACKER Duo Infliximab (LTI005)	As above – the Duo Infliximab kit consists of a LISA-TRACKER Infliximab kit and a LISA-TRACKER anti-Infliximab kit			

Note: There are 2 additional LISA-TRACKER ELISA kits which are available in some European countries, but not the UK. The LISA-TRACKER Premium Adalimumab and the LISA-TRACKER Premium Infliximab both measure 3 parameters: TNF inhibitor, TNF-α levels and anti-drug antibody levels.

The LISA-TRACKER ELISA kits consist of pre-coated strips of microtitre plate (96 wells), reagents, wash buffer, standards and controls. The assays can be run simultaneously or individually on any manual or automated standard ELISA based processor platform. The assay procedure is similar for all the assays but the reagents used are dependent on whether the ELISA is detecting levels of TNF inhibitor or levels of anti-drug antibody in the patient's sera.

Detecting levels of TNF inhibitor

Patient samples, the standards and controls are added to the pre-coated microtitre plate. The TNF inhibitor (adalimumab or infliximab) present in the patient samples, standards and controls, binds to the coated wells during the first incubation step and any unbound substances are removed in a subsequent washing step. The secondary reagent is then added which binds to the TNF inhibitor attached to the coated plate. Any unbound reagent is removed by a second wash step before peroxidase labelled streptavidin is added to the plate. Streptavidin binds to the biotin-labelled antibody complex and any unbound streptavidin is removed by a final wash step. Finally, a chromogenic substrate solution is added and colour develops in proportion to the amount of TNF inhibitor present in the patient sample. The colour change reaction is stopped by the addition of an acid solution and the optical density is read by a spectrophotometer. A range of calibration is determined based on the optical density of the standards and this is used to define the quantity of

drug in each patient sample. The limits of detection and assay ranges are presented in table 3.

Detecting levels of antibodies to TNF inhibitor

Patient samples, the standards and controls are added to the pre-coated microtitre plate. The free anti-infliximab antibodies or free anti-adalimumab antibodies present in the patient samples, standards and controls, bind to the coated wells during the first incubation step and any unbound substances are removed in a subsequent washing step. The secondary reagent is then added which binds to the anti-drug antibodies attached to the coated plate. Any unbound reagent is removed by a second wash step before peroxidase labelled streptavidin is added to the plate. Streptavidin binds to the biotin-labelled complex and any unbound streptavidin is removed by a final wash step. Finally, a chromogenic substrate solution is added and colour develops in proportion to the amount of anti-drug antibodies present in the patient sample. The colour change reaction is stopped by the addition of an acid solution and the optical density is read by a spectrophotometer. A range of calibration is determined based on the optical density of the standards and this is used to define the quantity of antibodies to TNF inhibitor in each patient sample. The limits of detection and assay ranges are presented in table 3.

Table 3: Interpretation of results, limits of detection and assay ranges for LISA-TRACKER assays

Name (code)	Results interpretation	Limit of detection	Assay range
LISA-TRACKER Adalimumab (LTA002)	Quantitative. Generation of standard curve and determination of drug level in µg/mL	0.1 µg/mL	0.1 to 8 µg/mL
LISA-TRACKER Infliximab (LTI002)		0.1 µg/mL	0.1 to 8 µg/mL
LISA-TRACKER anti-Adalimumab (LTA003)	Quantitative. Generation of standard curve and determination of ADAb level in ng/mL	10 ng/mL	10 to 160 ng/mL
LISA-TRACKER anti-Infliximab (LTI003)		10 ng/mL	10 to 200 ng/mL

2.3 TNFα-Blocker ELISA Kits (*Immundiagnostik AG*)

There are 6 Immundiagnostik ELISA kits relevant to this assessment, which are distributed in the UK by BioHit Healthcare Ltd (table 4). Two of these kits measure the levels of free anti-drug antibodies, 2 kits measure the levels of total anti-drug antibodies (free antibodies and antibodies already bound to the drug) and 2 kits measure the levels of free TNF inhibitor.

Table 4: Immundiagnostik ELISA kits

Name (code)	Detects	Microplate pre-coat	Secondary reagent	Incubation times
Immundiagnostik TNFα-Blocker monitoring, infliximab drug level (e.g. Remicade®) ELISA (K9655)	Free infliximab	Monoclonal anti-infliximab antibody	Peroxidase labelled antibody	1 hour; 1 hour; 10 to 20 mins
Immundiagnostik TNFα-Blocker monitoring, adalimumab drug level (e.g. Humira®) ELISA (K9657)	Free adalimumab	Monoclonal anti-adalimumab antibody	Peroxidase labelled antibody	
Immundiagnostik TNFα-Blocker ADA, antibodies against infliximab (e.g. Remicade®) ELISA (K9650)	Free anti-infliximab antibodies	Infliximab $F(ab)_2$ fragments	Peroxidase labelled infliximab	2 x 15 mins; 16 to 20 hours; 1 hour; 10 to 20 mins
Immundiagnostik TNFα-Blocker ADA, antibodies against adalimumab (e.g. Humira®) ELISA (K9652)	Free anti-adalimumab antibodies	Adalimumab $F(ab)_2$ fragments	Peroxidase labelled adalimumab	16 to 20 hours; 1 hour; 10 to 20 mins
Immundiagnostik TNFα-Blocker ADA, TOTAL antibodies against infliximab (e.g. Remicade®) ELISA (K9654)	Total anti-infliximab antibodies	Streptavidin	N/A	20 mins; 1 hour; 1.5 hours; 10 to 20 mins
Immundiagnostik TNFα-Blocker ADA, TOTAL antibodies against adalimumab (e.g. Humira®) ELISA (K9651)	Total anti-adalimumab antibodies	Streptavidin	N/A	

The kits consist of strips of pre-coated microtitre plate (96 wells), reagents, buffers, standards (drug level ELISAs only) and controls. The ELISAs can be performed manually or run on an automated ELISA processor. The two ELISAs that measure free infliximab or adalimumab (K9655 and K9657) follow a standard ELISA procedure for detecting levels of TNF inhibitor as described in section 2.2, except that the secondary reagent is directly labelled with peroxidase and therefore there is no biotin-streptavidin binding step. The two ELISAs that measure free anti-adalimumab antibodies or free anti-infliximab antibodies (K9650 and K9652) follow a standard ELISA procedure for detecting levels of antibodies to TNF inhibitor as described in section 2.2, except that the secondary reagent is directly labelled with peroxidase and

therefore there is no biotin-streptavidin binding step. Further, standards are not used in the anti-drug antibody ELISAs, therefore the results are interpreted semi-quantitatively using a cut-off control. Details on the interpretation of results, limits of detection and assay measurement ranges are presented in table 5.

The TOTAL anti-drug antibody ELISA kits (K9654 and K9651) enable the measurement of anti-drug antibodies in the presence of TNF inhibitor. During sample preparation immune complexes between anti-drug antibodies and adalimumab or infliximab are dissociated using an acidic buffer. Biotinylated and peroxidase-labelled adalimumab or infliximab are added to the sample and form complexes with the anti-drug antibodies. The complexes bind via biotin to the streptavidin coated plate. Following a wash step a chromogenic substrate is added, the colour change reaction is stopped by the addition of an acid solution and the optical density is read by a spectrophotometer.

Table 5: Interpretation of results, limits of detection and assay ranges for the Immundiagnostik ELISAs

Name (code)	Results interpretation	Limit of blank	Assay range
Immundiagnostik TNFα-Blocker monitoring, infliximab drug level (e.g. Remicade®) ELISA (K9655)	Quantitative. Generation of standard curve and determination of drug level in µg/mL	2.0 ng/mL	0.4 to 45 µg/mL
Immundiagnostik TNFα-Blocker monitoring, adalimumab drug level (e.g. Humira®) ELISA (K9657)		2.3 ng/mL	0.4 to 45 µg/mL
Immundiagnostik TNFα-Blocker ADA, antibodies against infliximab (e.g. Remicade®) ELISA (K9650)	Semi-quantitative. Evaluated by a cut-off control (10 AU/mL) to give a positive or negative result	5.787 AU/mL	N/A
Immundiagnostik TNFα-Blocker ADA, antibodies against adalimumab (e.g. Humira®) ELISA (K9652)		N/A	N/A
Immundiagnostik TNFα-Blocker ADA, TOTAL antibodies against infliximab (e.g. Remicade®) ELISA (K9654)	Semi quantitative. Evaluated by a cut-off control (10 AU/mL) to give a positive or negative result	2.653 AU/mL	N/A
Immundiagnostik TNFα-Blocker ADA, TOTAL antibodies against adalimumab (e.g. Humira®) ELISA (K9651)		2.765 AU/mL	N/A

2.4 Promonitor ELISA Kits (*Proteomika*)

There are 4 Promonitor ELISA kits relevant to this assessment (table 6). Two of these kits measure the levels of free anti-drug antibodies and 2 kits measure the levels of free TNF inhibitor.

Table 6: Promonitor ELISA kits

Name (code)	Detects	Microplate pre-coat	Secondary reagent	Incubation times
Promonitor-ADL ELISA (5080230000)	Free adalimumab	Anti-adalimumab human monoclonal antibody	Peroxidase labelled anti-adalimumab monoclonal antibody	1 hour; 1 hour; 25 to 35 mins
Promonitor-IFX ELISA (5060230000)	Free infliximab	Anti-TNF-α human monoclonal antibody bound to human recombinant TNF-α	Peroxidase labelled anti-infliximab monoclonal antibody	1 hour; 1 hour; 10 to 20 mins
Promonitor-ANTI-ADL ELISA (5090230000)	Free anti-adalimumab antibodies	Adalimumab	Peroxidase labelled adalimumab	1 hour; 1 hour; 25 to 35 mins
Promonitor-ANTI-IFX ELISA (5070230000)	Free anti-infliximab antibodies	Infliximab	Peroxidase labelled infliximab	1 hour; 1 hour; 25 to 35 mins

The kits consist of strips of pre-coated microtitre plate (96 wells), reagents, buffers, standards, controls and ELISA cover films. The IFX ELISA and ADL ELISA follow a standard ELISA procedure for detecting levels of TNF inhibitor as described in section 2.2, except that the secondary reagent is directly labelled with peroxidase and therefore there is no biotin-streptavidin binding step. The ANTI-IFX ELISA and the ANTI-ADL ELISA follow a standard ELISA procedure for detecting levels of antibodies to TNF inhibitor as described in section 2.2, except that the secondary reagent is directly labelled with peroxidase and therefore there is no biotin-streptavidin binding step. The ELISAs can be performed manually or run on an automated ELISA processor. Details on the interpretation of results, the assay ranges and limits of quantification are presented in table 7.

Table 7: Limits of quantification and assay ranges for Promonitor ELISAs

Name	Results interpretation	Limit of quantification	Assay range
Promonitor-ADL ELISA	Semi-quantitative. Evaluated using a cut-off value (0.024 µg/mL for adalimumab, 0.035 µg/mL for infliximab) to give a positive or negative result Quantitative. Generation of standard curve and determination of drug level in µg/mL	2.9 ng/mL	0.024 to 12 µg/mL
Promonitor-IFX ELISA		1.7 ng/mL	0.035 to 14.4 µg/mL
Promonitor-ANTI-ADL ELISA	Semi-quantitative. Evaluated using a cut-off value (10 AU/mL for anti-adalimumab antibodies, 5 AU/mL for anti-infliximab antibodies) to give a positive or negative result Quantitative. Generation of standard curve and determination of anti-drug antibody level in AU/mL	3.7 AU/mL	3.5 to 2000 AU/mL
Promonitor-ANTI-IFX ELISA		2 AU/mL	2 to 1440 AU/mL

3 Target condition: Crohn's disease

3.1 Background

Crohn's disease is a chronic inflammatory disease that affects the gastrointestinal tract, most commonly the large intestine or the last section of the small intestine. There are currently at least 115,000 people in the UK with Crohn's disease. The condition can affect people of all ages, but most cases develop between the ages of 16 and 30. A large number of cases also develop between the ages of 60 and 80. The cause of Crohn's disease is unknown, however it is likely that a genetic predisposition, smoking and intercurrent infection increase the risk of developing the condition.

The clinical course of Crohn's disease is characterised by relapses (when the disease flares up) and remission (when there are few or no symptoms). During relapses symptoms include:

- diarrhoea, which may be bloody and present for more than 6 weeks,
- abdominal pain,
- fatigue,
- weight loss.

There is no cure for Crohn's disease, therefore treatment is directed at symptom relief. The two main aims of treatment are inducing remission (active treatment of acute disease) and maintaining remission (preventing relapse). Complications of Crohn's disease may occur, including:

- Intestinal stricture: inflammation may cause scar tissue to form, leading to a narrowing of the area of the intestine affected. This can cause an obstruction leading to pain and vomiting.
- Perforation: stricture can cause rupture of the bowel resulting in infection.
- Fistulas: inflammation may cause ulcers to develop, which can over time develop into channels between two parts of the body, known as fistulas.
- Cancer: Crohn's disease is associated with a small increase in the risk of developing colorectal cancer in later life.
- Osteoporosis: weakening of the bones due to poor absorption of nutrients from food and use of steroid medication.

Children with Crohn's disease may also experience problems with their growth and development because their bodies are not absorbing enough nutrients.

3.2 Care pathway

The management of Crohn's disease in adults, young people and children is covered in the NICE pathway on Crohn's disease. The following NICE guidance was used to create the pathway:

- Crohn's disease. NICE clinical guideline 152 (2012)
- Infliximab (review) and adalimumab for the treatment of Crohn's disease. NICE technology appraisal guidance 187 (2010)

The aims of treatments for Crohn's disease are to reduce symptoms and maintain or improve quality of life, while minimising toxicity related to drugs over both the short- and long-term.

3.2.1 Inducing remission

For people with active Crohn's disease, with a first presentation or a single inflammatory exacerbation in a 12-month period, monotherapy should be offered with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission. For people who decline or cannot tolerate a conventional glucocorticosteroid, or in whom it is contraindicated, treatment with budesonide or 5-ASA should be considered.

For people with Crohn's disease who experience two or more inflammatory exacerbations in a 12-month period, or in whom the glucocorticosteroid dose cannot be tapered, the addition of an immunosuppressant (azathioprine, mercaptopurine or methotrexate) to a conventional glucocorticosteroid or budesonide to induce remission should be considered.

For adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy, infliximab and adalimumab (within their licensed indications), are recommended as treatment options. Infliximab, within its licensed indication, is also recommended as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy.

Infliximab induction treatment is given as a 5-mg/kg intravenous infusion over a 2 hour period followed by another 5-mg/kg infusion 2 weeks after the first. If a person's disease does not respond after two doses, no additional treatment with infliximab should be given. In people whose disease responds, infliximab is given as maintenance treatment (another 5-mg/kg infusion at 6 weeks after the initial dose, followed by infusions every 8 weeks). Dose escalation is an option for people whose disease has stopped responding.

Adalimumab induction treatment is 80 mg via subcutaneous injection (administered by a doctor or nurse or self-injected by the patient or a family member), followed by 40 mg 2 weeks later. If there is a need for a more rapid response to therapy, a dose of 160 mg followed by 80 mg 2 weeks later can be used. Maintenance treatment is 40 mg every other week. This can be increased to 40 mg every week in people whose disease shows a decrease in response to treatment. Continued therapy should be carefully reconsidered in patients whose disease does not respond within 12 weeks of initiating treatment.

Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate. Treatment with infliximab or adalimumab should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. In addition, the STORI criteria are a combination of clinical and biological markers to identify patients with a low risk of relapse

following withdrawal from TNF inhibitor (Louis et al., 2012). These criteria may be used to help guide decisions on which patients should remain on a TNF inhibitor and which patients should be withdrawn from TNF inhibitor. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.

Infliximab, within its licensed indication, is recommended for the treatment of people aged 6 to 17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.

A NICE technology appraisal of vedolizumab for treating moderate to severe active Crohn's disease in people who are intolerant of, not responsive to or resistant to either conventional therapy or a tumour necrosis factor antagonist is currently in development (expected publication June 2015).

Enteral nutrition should be considered as an alternative to a conventional glucocorticosteroid to induce remission for children in whom there is concern about growth or side effects, and young people in whom there is concern about growth.

Surgery should be considered as an alternative to medical treatment early in the course of the disease for:

- people whose disease is limited to the distal ileum
- children and young people whose disease is limited to the distal ileum and who have growth impairment despite optimal medical treatment and/or refractory disease.

3.2.2 Maintaining remission

For a person with Crohn's disease in remission, disease may be managed with or without treatment. For people who choose not to receive maintenance treatment, follow-up plans should be agreed and consultations should be arranged if they experience a relapse. Alternatively, azathioprine or mercaptopurine monotherapy can be used to maintain remission. Methotrexate may be used to maintain remission only in people who:

- needed methotrexate to induce remission, or
- have tried but did not tolerate azathioprine or mercaptopurine for maintenance or
- have contraindications to azathioprine or mercaptopurine.

Treatment with 5-ASA can be considered to maintain remission after surgery.

3.2.3 Management of loss of response

The World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization produced the London Position Statement; a paper which provides support to clinicians on when to start, when to stop, which drug to choose, and how to predict response to biological therapy. The paper states:

- A diminished or suboptimal response to infliximab can be managed by:
  - i. shortening the interval between dosing
  - ii. increasing the dose to 10 mg/kg
- A diminished or suboptimal response to adalimumab can be managed by weekly dosing (shortened from every other week).
- Patients who continue to have a diminished or loss of response after increasing the dose may benefit from switching to a different TNF inhibitor.
- When TNF inhibitors fail, switching treatment to an agent with a different mechanism of action is logical.

3.3 Potential care pathway with introduction of therapeutic monitoring of TNF inhibitor

Tests for the therapeutic monitoring of TNF inhibitors may be performed in one of 2 ways. Firstly, testing for TNF inhibitor drug levels and testing for antibodies to TNF inhibitor could be performed concurrently. Alternatively, reflex testing could be implemented. In this model, testing for TNF inhibitor drug levels is performed first and the result from this initial test is used to guide follow-up testing by the laboratory without a further request from the treating clinician. If the drug trough level is undetectable, testing for antibodies to TNF inhibitor would be performed. If TNF inhibitor is present in the sample, testing for antibodies would not be performed.

The report of the European Crohn's and Colitis Organisation pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases (Allez et al. 2010) states that 'In case of loss of response, drug trough levels and antibody measurements could aid in decision making':

1. In patients with undetectable drug levels, antibody measurement may be useful. Most will likely have high anti-drug antibody titres and switching the drug is probably the best option in this case.
2. In patients with low to intermediate drug readouts, and absence of high titre antibodies, an attempt to restore trough levels by dose escalation or shortening infusion/injection intervals should be considered.
3. In patients with symptoms suggestive of active disease despite high trough levels, disease reassessment including the use of CRP, fecal calprotectin, and/or imaging should be performed.
4. If these patients have active inflammation and no infection, use of a compound with another mechanism of action should be considered.

However, the report also cautions on the limitations of measuring anti-drug antibodies, stating that 'not only are the techniques for measurement of anti-drug antibodies different but the results obtained by the different methods are not reported in a uniform or standardized manner that would enable reproducibility across studies'.

The consensus guidelines of the European Crohn's and Colitis Organisation and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition on the medical management of pediatric Crohn's disease recommend:

- In case of partial response or loss of response, measurement of serum trough level and antibodies of both infliximab and adalimumab may facilitate decision-making whether to optimise or stop therapy.
- Higher doses of infliximab and/or shorter intervals may be required in those losing response to the drug or when the drug level is low.
- Weekly injections of adalimumab should be considered in patients losing response or with low trough levels.
- Physicians should consider reducing infliximab dose when trough levels are above 8 to 10 µg/mL and remission is achieved.

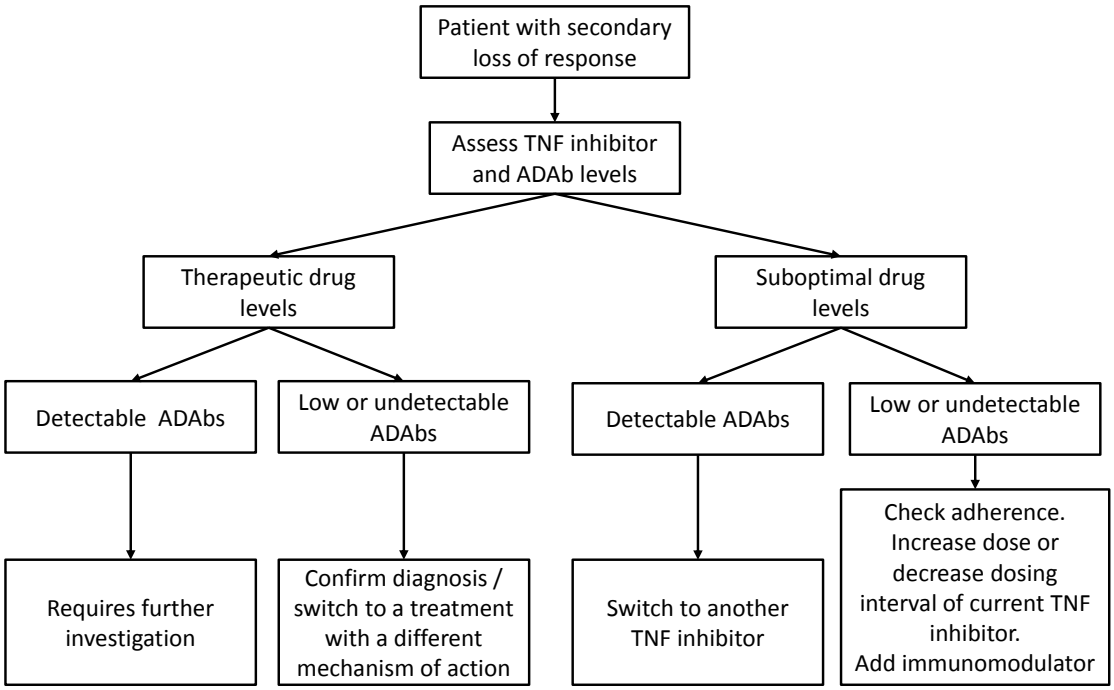
A suggested algorithm (figure 1; adapted from Scott and Lichtenstein, 2014) for the interpretation of results gained from these assays in people with secondary loss of response recommends the following:

- If anti-drug antibodies are present and there are suboptimal levels of TNF inhibitor, consider switching to an alternative TNF inhibitor
- If anti-drug antibodies are present and there are adequate levels of TNF inhibitor, the recommendations are currently unclear (tests

would likely be repeated using different methods to check for discrepant results)

- If anti-drug antibodies are low or undetectable and there are suboptimal levels of TNF inhibitor, adherence to treatment should be discussed with patients.
- If patients are compliant to the treatment regimen, the current TNF inhibitor dose should be increased or the dosing frequency decreased
- If anti-drug antibodies are low or undetectable and there are adequate levels of TNF inhibitor, consider switching to a drug with an alternative mechanism of action

Figure 1: Suggested treatment algorithm for utilising levels of TNF inhibitor and antibodies against TNF inhibitors in patients with secondary loss of response

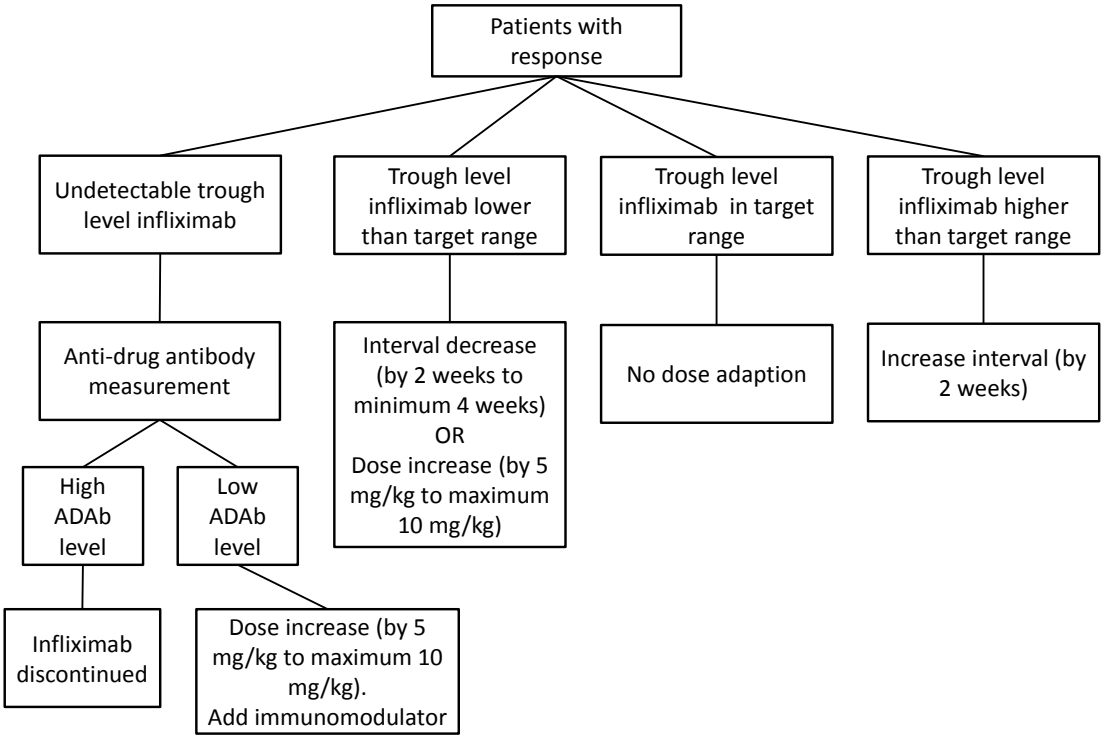


ADAbs: Anti-drug antibodies

Drug level thresholds used to help make a clinical decision are continuing to be defined and may differ depending on the assay used; therefore any result should be interpreted in combination with clinical judgement. Anti-drug antibody results are often reported as a positive or negative result; however the exact level, or a result categorised as undetectable, low, or high, may be more useful as this may impact treatment decisions. The TAXIT study used a specific algorithm to guide TNF inhibitor dose in patients whose disease responds well to treatment with TNF inhibitors (figure 2). In this algorithm:

- Patients with high levels of drug in their blood immediately prior to the next dose (trough level) have TNF inhibitor dose interval increased by 2 weeks until the trough level is within the target range.
- Patients with a drug trough level in the target range have no dose adaption.
- Patients with low drug trough level have their TNF inhibitor dose interval decreased, or the TNF inhibitor dose increased until the trough level is within the target range.
- Patients with undetectable drug trough level have antibodies to TNF inhibitor measured. If the anti-drug antibody level is high patients are removed from treatment with infliximab (withdrawn from TAXIT study). If the anti-drug antibody level is low patients have the TNF inhibitor dose increased.

Figure 2: Treatment algorithm for utilising levels of TNF inhibitor and antibodies against TNF inhibitors in patient's whose disease responds to TNF inhibitor



ADAb: Anti-drug antibodies

3.4 Patient issues and preferences

The ongoing and unpredictable nature of Crohn's disease can be difficult for patients to live with. Symptoms can have a substantial impact on quality of life. For example, diarrhoea and abdominal pain may make people fearful of

being in public places, which may affect their ability to enjoy leisure activities. In addition, malnutrition and fatigue may affect a person's ability to perform at work.

Infliximab is administered by infusion and adalimumab by subcutaneous injection. For some patients, especially those with a phobia of needles, treatment compliance may be a problem, particularly with adalimumab which can be self-administered.

Therapeutic monitoring of TNF inhibitors may help alleviate worries of patients who respond well to treatment and are considering reducing the dose of, or withdrawing from, TNF inhibitor. In patients who experience a secondary loss of response, therapeutic monitoring of TNF inhibitors may prevent patients from receiving a treatment from which they are gaining no clinical benefit but they may experience treatment related side-effects.

Additionally, therapeutic monitoring of TNF inhibitors may lead to a reduction in the number of other tests performed, which would be of benefit to the patients, especially if the number of colonoscopies is reduced.

4 Scope of the evaluation

Decision questions	1. Does concurrent testing of TNF inhibitor levels and antibodies to TNF inhibitors represent a clinically and cost-effective use of NHS resources in people with Crohn's disease whose disease responds to treatment with TNF inhibitor? Testing will be carried out: a. 3 to 4 months after start of treatment b. 3 to 4 months and every 12 months from start of treatment 2. Does concurrent testing of TNF inhibitor levels and antibodies to TNF inhibitors represent a clinically and cost-effective use of NHS resources in people with Crohn's disease who experience secondary loss of response during maintenance treatment with TNF inhibitor? 3. Does testing of TNF inhibitor levels followed by reflex testing of antibodies to TNF inhibitors if drug level is undetectable represent a clinically and cost-effective use of NHS resources in people with Crohn's disease whose disease responds to treatment with TNF inhibitor? Testing will be carried out: a. 3 to 4 months after start of treatment

	b. 3 to 4 months and every 12 months from start of treatment 4. Does testing of TNF inhibitor levels followed by reflex testing of antibodies to TNF inhibitors if drug level is undetectable represent a clinically and cost-effective use of NHS resources in people with Crohn's disease who experience secondary loss of response during maintenance treatment with TNF inhibitor?
Populations	People with Crohn's disease who are being treated with infliximab or adalimumab.
Interventions	LISA-TRACKER ELISA kits *(Theradiag/Alpha Labs):* • LISA-TRACKER Adalimumab (LTA002) • LISA-TRACKER Infliximab (LTI002) • LISA-TRACKER anti-Adalimumab (LTA003) • LISA-TRACKER anti-Infliximab (LTI003) • LISA-TRACKER Duo Adalimumab (LTA005) • LISA-TRACKER Duo Infliximab (LTI005) TNFα-Blocker ELISA kits *(Immundiagnosik/BioHit Healthcare):* • Immundiagnostik TNFα-Blocker ADA, antibodies against infliximab (e.g. Remicade®) ELISA (K9650) • Immundiagnostik TNFα-Blocker ADA, antibodies against adalimumab (e.g. Humira®) ELISA (K9652) • Immundiagnostik TNFα-Blocker ADA, TOTAL antibodies against infliximab (e.g. Remicade®) ELISA (K9654) • Immundiagnostik TNFα-Blocker ADA, TOTAL antibodies against adalimumab (e.g. Humira®) ELISA (K9651) • Immundiagnostik TNFα-Blocker monitoring, infliximab drug level (e.g. Remicade®) ELISA (K9655) • Immundiagnostik TNFα-Blocker monitoring, adalimumab drug level (e.g. Humira®) ELISA (K9657) Promonitor ELISA kits *(Proteomika):* • Promonitor-ADL ELISA (5080230000) • Promonitor-IFX ELISA (5060230000) • Promonitor-ANTI-ADL ELISA (5090230000) • Promonitor-ANTI-IFX ELISA (5070230000)
Linked-evidence approach	Test methods that are not included as an intervention but have evidence comparing it to an intervention test and evidence reporting clinical outcomes, should be included for

	the purpose of performing linked evidence modelling only.
Comparator	Treatment decisions made on clinical judgement without measuring levels of TNF inhibitor and antibodies to TNF inhibitors.
Healthcare setting	Secondary and tertiary care
Outcomes	Intermediate measures for consideration may include: • Time to result • Number of inconclusive results • Frequency of dose adjustment • Frequency of treatment switch
	Clinical outcomes for consideration may include: • Measures of disease activity • Rates of response, relapse and remission • Duration of response, relapse and remission • Rates of hospitalisation • Rates of surgical intervention • Time to surgical intervention • Adverse effects of treatment • Health related quality of life
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Costs of testing • Costs of treatment • Costs of other resource use – outpatient appointments – hospitalisation – additional tests – surgery
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

5 Modelling approach

5.1 Available evidence

During scoping two randomised controlled trials were identified: The TAXIT trial (Vande Casteele, 2013) and a study by Steenholdt et al. (2014). A cost-effectiveness model was also identified (Velayos et al., 2013).

The TAXIT trial

The TAXIT (Trough level Adapted infliXImab Treatment) trial reported that dosage adjustment based on drug levels during initiation of infliximab in patients with inflammatory bowel disease is beneficial. 270 consecutive patients on infliximab maintenance therapy were included in the trial. Before randomisation, trough levels were first optimised to have a baseline between 3 and 7µg/ml. Infliximab trough levels and antibodies to infliximab were measured with in-house developed ELISAs.

Only 43% of patients who started treatment on the standard induction dose of infliximab 5 mg/kg had drug levels in the target range of 3 to 7µg/ml. Among the remaining patients, 26% had levels above this range, and 31% had levels below the range, including 9% with undetectable levels. Dose intensification in patients with low levels of infliximab provided improved disease control, whereas dose reductions in patients with levels of infliximab above 7µg/ml lowered treatment costs, without sacrificing disease control.

Following this optimization phase patients were randomised to dosing based on infliximab trough levels or dosing and optimisation based on clinical symptoms. In this maintenance phase, the authors reported that continued level based drug adjustment did not show superiority over clinically based adjustment. Treatment guided by levels resulted in less anti-infliximab antibody formation, but the proportion of patients in clinical and biological remission was similar for both groups.

Steenholdt study

The Steenholdt study was a randomised controlled trial of 69 patients with Crohn's disease whose disease showed loss of response to treatment with infliximab. Two treatment strategies were compared: (1) routine infliximab dose intensification; and (2) use of a treatment algorithm based on serum concentrations of infliximab and antibodies to infliximab. Samples were analysed using radioimmunoassay (Biomonitor) and study intervention was based on these test results. After the study had been stopped, samples were also analysed by ELISA and homogeneous mobility shift assay (both at

Prometheus Laboratories). Clinical response rates and costs relating to the treatment of Crohn's disease were analysed.

The authors report that costs for intention-to-treat patients were substantially lower (34%) for those treated in accordance with the algorithm than for those treated with routine infliximab dose intensification: €6038 versus €9178, p<0.001. However, disease control, as judged by response rates, was similar: 58% and 53%, respectively, p=0.81. For per-protocol patients, treatment costs were even lower (56%) in the algorithm treated group (€4062 versus €9178, p<0.001) with similar response rates (47% vs 53%, p=0.78).

The authors conclude that use of an algorithm, based on the measurement of serum infliximab and antibodies to infliximab, to inform the treatment of patients with Crohn's disease who experience a loss of response to infliximab, significantly reduces average treatment costs per patient compared with routine infliximab dose intensification, without any negative effect on disease control.

Velayos model

Velayos et al. built a decision analytic model to investigate whether a testing-based strategy is more cost-effective than an empiric dose escalation strategy for patients with Crohn's disease who experience secondary loss of response to infliximab. An algorithm proposed by Afif et al. formed the basis for the testing-based strategy, whereas the London position statement issued by the World Congress of Gastroenterology formed the basis for the empiric dose escalation strategy.

The authors report that the testing-based strategy and the empiric dose escalation strategy were similar in terms of clinically effectivness (0.801 QALYs vs 0.800 QALYs, respectively) but the testing-based strategy was less expensive ($31,870 vs $37,266, respectively). In addition, patients in the testing-based strategy underwent more surgery and had lower use of TNF inhibitors compared to patients in the empiric dose escalation strategy. The authors conclude that a testing-based strategy is cost-effective compared to a strategy based on empiric dose escalation for managing patients with Crohn's disease who have lost responsiveness to infliximab.

5.2 Modelling possibilities

The assumptions used in the model for the appraisal of Infliximab (review) and adalimumab for the treatment of Crohn's disease (technology appraisal 187) should be used to inform the development of a de novo model. This will ensure consistency between the modelling approaches used in the appraisal

of ‘Crohn's disease - infliximab and adalimumab’ (technology appraisal 187) and the diagnostics assessment of assay to measure TNF inhibitor levels and anti-drug antibody levels. This assessment will not update technology appraisal 187.

6 Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Pregnant women with Crohn’s disease may want to limit use of TNF inhibitor in the third trimester if they are in remission in order to reduce the levels of TNF inhibitor in the newborn baby. Assays to measure TNF inhibitor levels and anti-drug antibody levels may help to inform treatment decisions.

7 Implementation issues

Key considerations for the implementation of assays to measure TNF inhibitor levels and anti-drug antibody levels include:

- Assays should only be performed in CPA accredited laboratories.
- If laboratories are testing large numbers of samples they might want to consider using an automated platform, which may be an additional cost.
- If laboratories are only testing a few samples this may impact on the turnaround time of results if samples are collected to run in batches.
- Alternatively, testing could be centralised in a few laboratories. Any laboratory offering a testing service should be able to demonstrate the stability of the sample.
- The ELISA technique does not require additional training to be provided. However, laboratory staff may need to develop skills in interpreting the results.
- The results should be reported alongside the test method used to produce the results as different tests require interpretation at different thresholds.
- If a significant number of laboratories offer testing, an external quality assurance scheme may be required.
- The provision of TNF inhibitors and the tests to measure levels of TNF inhibitors and anti-drug antibodies may be funded by separate departments. Therefore, if use of the tests is cost-effective because of improvements in patient outcomes and better allocation of

treatment, the department funding the test may incur costs while the department funding the treatment may have cost savings. Communication and collaboration will be required between departments to resolve this potential issue.

Appendix A Glossary of terms

Adalimumab: A recombinant human anti-TNF-α IgG1 monoclonal antibody

Anti-drug antibodies: Antibodies produced by the body in an immune response against a therapeutic antigen, for example a monoclonal antibody, which may inactivate the drug and modify the pharmacokinetic characteristics of the drug

Immunosuppressants: A class of drugs used to supress of prevent an immune response

Inflammatory bowel disease: A group of inflammatory conditions of the colon and small intestine, the two most common being Crohn's disease and ulcerative colitis

Infliximab: A chimeric (human-murine) anti-TNF-α IgG1 monoclonal antibody

Pharmacokinetics: The process by which a drug is absorbed, distributed, metabolized, and eliminated by the body

Primary non-response: A lack of improvement of clinical signs and symptoms during induction therapy

Secondary loss of response: Loss of clinical response to therapy in patients whose disease had initially demonstrated clinical response

Severe active Crohn's disease: Very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3 to 4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above.

TNF-α: An inflammatory cytokine which helps to regulate the immune system, but when present in high concentrations it is responsible for the destructive inflammatory processes that occur in inflammatory bowel disease

TNF inhibitors (Anti-TNF-α drugs): Biological therapies which target the TNF-α protein with the aim of modifying the inflammatory disease process

Trough level: The lowest concentration reached by a drug before the next dose is administered

Appendix B Abbreviations

ADAbs	Anti-drug antibodies
AU	Absorbance units
CPA	Clinical pathology accreditation
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
TNF	Tumour Necrosis Factor

Appendix C Related guidance and pathways

Related NICE guidance: published guidance

Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel. NICE diagnostics guidance, DG11, October 2013. Available from: guidance.nice.org.uk/DG11

SeHCAT (Tauroselcholic [75Selenium] acid) for the investigation of bile acid malabsorption (BAM) and measurement of bile acid pool loss. NICE diagnostics guidance, DG7, November 2012. Available from: guidance.nice.org.uk/DG7

Crohn's disease: management in adults, children and young people. NICE clinical guideline, CG152, October 2012. Available from: guidance.nice.org.uk/CG152

Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. NICE clinical guideline, CG118, March 2011. Available from: www.nice.org.uk/guidance/CG118

Use of tumour necrosis factor alpha (TNF a) inhibitors (adalimumab, and infliximab [review]) for Crohn's disease (review of TA40). NICE technology appraisal, TA187, May 2010. Available from: www.nice.org.uk/guidance/TA187

Extracorporeal photopheresis for Crohn's disease. NICE interventional procedures, IPG228. February 2009. Available from: www.nice.org.uk/guidance/IPG288

Related NICE guidance: under development

Inflammatory bowel disease (to cover Ulcerative colitis and Crohn´s disease). NICE quality standard. Publication expected: September 2014. guidance.nice.org.uk/QSD/70

Vedolizumab for treating moderate to severe active Crohn's disease in people who are intolerant of, not responsive to or resistant to either conventional therapy or a tumour necrosis factor antagonist. NICE technology appraisal. Publication expected: June 2015. http://www.nice.org.uk/guidance/indevelopment/GID-TAG461

Related pathways

The therapeutic drug monitoring of TNF inhibitors in Crohn’s disease guidance will be included in the NICE pathway on Crohn’s disease (October

2012). It may be appropriate to include the full recommendations of the guidance, or it may only be necessary to give a link to the guidance.

Relevant guidance from other organisations

Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. Ruemmele FM, Veres G, Kolho KL, et al. J Crohns Colitis. 2014 Jun 5. S1873-9946(14)00148-2.

British Society of Gastroenterology (September 2013) Inflammatory bowel disease biopsies

Clinical Knowledge Summaries (December 2012) Crohn's disease

British Society of Gastroenterology (September 2011) Guidelines for the management of inflammatory bowel disease in adults

The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD With the European Crohn's and Colitis Organization: When to Start, When to Stop, Which Drug to Choose, and How to Predict Response? D'Haens GR, Panaccione R, Higgins PD, et al. Am J Gastroenterol. 2011 Feb;106(2):199-212.

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Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. Allez M, Karmiris K, Louis E, et al. J Crohns Colitis. 2010 Oct;4(4):355-66.

British Society of Paediatric Gastroenterology Hepatology and Nutrition (October 2008) Guidelines for the Management of Inflammatory Bowel Disease (IBD) in Children in the United Kingdom

Royal College of Nursing (2007) Roles descriptives for inflammatory bowel disease nurse specialists

Appendix D References

OP001 Randomised controlled trial of drug level versus clinically based dosing of infliximab maintenance therapy in IBD: final results of the TAXIT study. N. Vande Casteele, A. Gils, V. Ballet, et al. UEG Week 2013 Oral Presentations

Crohn's Disease Condition Leaflet. Patient.co.uk. Available from: www.patient.co.uk/health/crohns-disease-leaflet

Crohn's Disease PatientPlus (Professional) Article. Patient.co.uk. Available from: www.patient.co.uk/doctor/crohns-disease-pro

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Therapeutic Drug Monitoring of Anti-TNF Therapy in Inflammatory Bowel Disease. Scott FI, Lichtenstein GR. Curr Treat Options Gastroenterol. 2014 Mar;12(1):59-75.

Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Steenholdt C, Brynskov J, Thomsen OØ, et al. Gut. 2014 Jun;63(6):919-27.

Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Louis E, Mary JY, Vernier-Massouille G, et al. Gastroenterology. 2012 Jan;142(1):63-70.

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