National Institute for Health and Care Excellence

Diagnostics consultation document

Therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease (LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits)

The National Institute for Health and Care Excellence (NICE) is producing guidance on using LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits in the NHS in England. The Diagnostics Advisory Committee has considered the evidence submitted and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report and the diagnostics assessment report addendum), which is available from http://www.nice.org.uk/guidance/indevelopment/gid-dt24.

The Advisory Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

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. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology

- could have any adverse impact on people with a particular disability or disabilities.

Note that this document is not NICE's final guidance on LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits. The recommendations in section 1 may change after consultation.

After consultation, the Committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the Committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the 'Diagnostics assessment programme manual' (available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-diagnostics-guidance).

Key dates:

Closing date for comments: 23rd September 2015

Second Diagnostics Advisory Committee meeting: 4 November 2015

1 Provisional recommendations

1.1 The LISA-TRACKER, IDKmonitor and Promonitor enzyme-linked immunosorbent assay (ELISA) kits show promise for therapeutic monitoring of tumour necrosis factor (TNF)-alpha inhibitors in people with Crohn's disease but there is insufficient evidence to recommend their routine adoption across the NHS.

1.2 Laboratories currently using LISA-TRACKER, IDKmonitor and Promonitor ELISA kits for therapeutic monitoring of TNF-alpha inhibitors in people with Crohn's disease whose disease loses response to TNF-alpha inhibitors should:

- participate in data collection through a registry, audit or prospective study (see section 7.2)
- have specialist expertise in immunoassay analysis, including an understanding of the technical factors that may affect the results of the ELISA kits

- work closely with the treating or referring clinician, in a network, to ensure appropriate use of the tests and interpretation of the results.

1.3 Further research is recommended on the clinical and cost effectiveness of using LISA-TRACKER, IDKmonitor and Promonitor ELISA kits in people with Crohn's disease to monitor levels of TNF-alpha inhibitors and antibodies to TNF-alpha inhibitors if the disease responds to treatment with TNF-alpha inhibitors (see section 7.3).

2 The technologies

2.1 The LISA-TRACKER, IDKmonitor, and Promonitor enzyme-linked immunosorbent assay (ELISA) kits are intended to be used for measuring the levels of tumour necrosis factor (TNF)-alpha inhibitors and antibodies against TNF-alpha inhibitors in the blood of people having TNF-alpha-inhibitor treatment for Crohn's disease. TNF-alpha is a cell signalling protein that promotes inflammatory responses. Dysregulation of TNF-alpha production can contribute to inflammatory diseases, such as Crohn's disease. TNF-alpha inhibitors, such as infliximab and adalimumab, are given to people with Crohn's disease to inhibit TNF-alpha production and suppress the inflammatory response.

3 Clinical need and practice

The problem addressed

3.1 Although tumour necrosis factor (TNF)-alpha inhibitors can help many people with Crohn's disease, there are some people whose disease does not respond to treatment. Furthermore, many people whose disease first responds to treatment find that their disease stops responding over time (loss of response). This loss of response may be caused by:

- changes in disease characteristics over time
- inflammation unrelated to TNF-alpha concentrations
- antibodies to TNF-alpha inhibitors
- fluctuations in circulating drug levels.

3.2 The concentration of TNF-alpha inhibitor in the blood immediately before the next dose of TNF-alpha inhibitor is due (referred to as the 'trough level') can vary widely between people who have had the same previous dose. These variations can be caused by:

- differences in drug pharmacokinetics between individuals
- antibodies that bind to the TNF-alpha inhibitor, neutralising its activity and leading to increased clearance
- concomitant treatment with some immunosuppressive drugs, such as methotrexate.

3.3 Currently, treatment decisions for people with Crohn's disease are based on clinical judgement and 'trial and error', so tailoring treatment to the person may be difficult. People whose disease responds well to a TNF-alpha inhibitor may continue having the same level of treatment even when it may be possible to reduce the dose or withdraw the treatment without having any detrimental effect on clinical outcomes. This continued treatment may lead to people having side-effects of the treatment unnecessarily. People whose disease loses response are typically treated with a higher dose of TNF-alpha inhibitor to try to recover a clinical response. This approach can be successful for some people, but for others, the intensified treatment regimen is not effective, which results in people continuing to have an expensive drug that gives them no benefit and they may have treatment side-effects unnecessarily.

3.4 The symptoms of Crohn's disease can vary widely between people. Furthermore, the personal preferences of clinicians and patients make it difficult to establish a standardised pathway for people with

Crohn's disease. Measuring levels of TNF-alpha inhibitors and antibodies against TNF-alpha inhibitors in a person's blood could help clinicians to identify the best treatment strategy for a person with Crohn's disease.

3.5 The purpose of this assessment is to evaluate the clinical and cost effectiveness of using ELISA kits (LISA-TRACKER, IDKmonitor and Promonitor) to test levels of TNF-alpha inhibitors and antibodies to TNF-alpha inhibitors in people with Crohn's disease:

- whose disease responds to treatment with a TNF-alpha inhibitor
- whose disease loses response to maintenance treatment with a TNF-alpha inhibitor.

The condition

3.6 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. The prevalence of Crohn's disease in the UK is estimated to be 157/100,000 (Steed et al. 2010). The condition can affect people of all ages, but most develop it between the ages of 16 and 30 years. Many also develop it between the ages of 60 and 80 years. Although the cause of Crohn's disease is unknown, it is likely that a genetic predisposition, smoking and intercurrent infection increase the risk of it developing.

3.7 The clinical course of Crohn's disease is marked by relapses (when the disease flares up) and remission (when there are few or no signs or symptoms). During relapses, people can have diarrhoea, abdominal pain, fatigue and weight loss.

3.8 There is no cure for Crohn's disease, therefore treatment is directed at symptom relief. The 2 main aims of treatment are inducing remission (active treatment of acute disease) and

maintaining remission (preventing relapse). Complications of Crohn's disease include:

- Intestinal stricture: inflammation may cause scar tissue to form, resulting in a narrowing of the affected area of the intestine. This can cause an obstruction leading to pain and vomiting.
- Perforation: stricture can cause rupture of the bowel resulting in infection.
- Fistula: inflammation may cause an ulcer to develop in the lining of the gastrointestinal tract, which over time can deepen and become a channel to another hollow organ or the skin, known as a fistula.
- 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 because of poor absorption of nutrients from food and the use of steroid medication.
- Problems with growth and development in children with Crohn's disease, because their bodies are not absorbing enough nutrients.

The diagnostic and care pathways

3.9 Treatments for Crohn's disease aim to reduce symptoms and maintain or improve quality of life, while minimising toxicity related to drugs over both the short- and long-term. 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 (2012) NICE guideline CG152
- Infliximab (review) and adalimumab for the treatment of Crohn's disease (2010) NICE technology appraisal guidance 187

3.10 The World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization produced the London Position Statement (published in the American Journal of Gastroenterology); a paper that provides support to clinicians on when to start and stop therapy, 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:
  - shortening the interval between dosing
  - 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-alpha inhibitor.
- When TNF-alpha inhibitors fail, switching treatment to an agent with a different mechanism of action is logical.

3.11 Tests for the therapeutic monitoring of TNF-alpha inhibitors and antibodies to TNF-alpha inhibitors may be done in 2 ways:

- Concurrent testing: tests for TNF-alpha-inhibitor drug levels and antibodies to TNF-alpha inhibitors are done at the same time.
- Reflex testing: the test for TNF-alpha-inhibitor drug levels is done first and the result used to guide follow-up testing by the laboratory without a further request from the treating clinician. If the drug is undetectable, testing for antibodies to the TNF-alpha inhibitor would be done. If TNF-alpha inhibitor is present in the sample, then testing for antibodies would not be done.

4 The diagnostic tests

The interventions

LISA-TRACKER ELISA kits

4.1 LISA-TRACKER enzyme-linked immunosorbent assay (ELISA) kits are manufactured by Theradiag and distributed in the UK by Alpha Laboratories. There are 6 LISA-TRACKER ELISA kits relevant to this assessment. Two kits measure the levels of free antibodies to tumour necrosis factor (TNF)-alpha inhibitor, 2 kits measure the levels of free TNF-alpha inhibitor and 2 kits measure the levels of both free TNF-alpha inhibitor and antibodies to TNF-alpha inhibitor.

4.2 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.

IDKmonitor ELISA kits

4.3 IDKmonitor ELISA kits (previously called Immundiagnostik TNFα-blocker ELISA kits) are manufactured by Immundiagnostik AG and distributed in the UK by Biohit Healthcare. There are 6 IDKmonitor ELISA kits relevant to this assessment. Two kits measure the levels of free anti-drug antibodies, 2 kits measure the levels of total anti-drug antibodies (free antibodies and antibodies bound to the drug), and 2 kits measure the levels of free TNF-alpha inhibitor.

4.4 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 done manually or run on an automated ELISA processor.

Promonitor ELISA kits

4.5 Promonitor ELISA kits are manufactured by Proteomika and distributed in the UK by Grifols UK. There are 4 Promonitor ELISA kits relevant to this assessment. Two of these kits measure the levels of free anti-drug antibodies and 2 kits measure the levels of free TNF-alpha inhibitor.

4.6 The kits consist of strips of pre-coated microtitre plate (96 wells), reagents, buffers, standards, controls and ELISA cover films. The ELISAs can be done manually or run on an automated ELISA processor.

The comparator: No testing

4.7 The comparator for this assessment is treatment decisions based on clinical judgement without measuring levels of TNF-alpha inhibitor or antibodies to TNF-alpha inhibitor.

5 Outcomes

The Diagnostics Advisory Committee (section 11) considered evidence from a number of sources (section 12).

How outcomes were assessed

5.1 The External Assessment Group (EAG) conducted a systematic review of the evidence on tests to monitor levels of tumour necrosis factor (TNF)-alpha) inhibitors and antibodies to TNF-alpha inhibitors in people with Crohn's disease treated with infliximab or adalimumab. The review had 4 key objectives:

- compare the performance of the different tests available
- compare optimal cut-offs identified in different studies
- analyse the correlation between test results and clinical state

- describe and compare test-informed algorithms used in studies, and review the clinical effectiveness of these test-informed algorithms compared with standard care (no testing done).

5.2 For the purpose of this assessment and to aid understanding, tests have been split into 3 groups: index tests, alternative tests, and other tests. The 6 different tests are summarised in table 1. Because there were no direct clinical outcome data for the index tests (LISA-TRACKER enzyme-linked immunosorbent assay [ELISA] kits, IDKmonitor ELISA kits and Promonitor ELISA kits), the clinical effectiveness review considered alternative tests for which clinical outcome data were available. Evidence on the comparative performance of the index tests and the alternative tests was then sought in order to make a link between the index tests and the clinical outcomes. Other tests are also mentioned in the review because they form an indirect link between the index tests and clinical outcomes through the alternative tests.

Table 1. Summary of the different tests

Test group	Name of test	Use in the assessment
Index tests	• LISA-TRACKER ELISA kits • Promonitor ELISA kits • IDKmonitor ELISA kits	Named in the scope and are subject to recommendations by the Diagnostics Advisory Committee
Alternative tests	• Prometheus ELISA and HMSA • Leuven in-house ELISA	Form a link between the index tests and clinical outcomes.
Other tests	• Amsterdam Sanquin in-house ELISA and radioimmunoassay	Form a link between the index tests and the alternative tests
Abbreviation: ELISA, enzyme-linked immunosorbent assay.		

Evidence on clinical outcomes

5.3 Three studies were identified that implemented a test-informed algorithm in managing Crohn's disease treated with infliximab or adalimumab and reported clinical outcomes.

Steenholdt et al. 2014 and 2015

5.4 This was a single-blind randomised controlled trial of 69 adults with Crohn's disease on maintenance infliximab treatment whose disease had lost response to treatment. Patients were randomised to either an infliximab intensified arm (n=36) or to an algorithm arm (n=33). In the infliximab intensified arm, the dose frequency of 5 mg/kg infliximab was increased from every 8 weeks to every 4 weeks. In the algorithm arm patients had treatment according to a defined algorithm based on serum concentrations of infliximab and of antibodies to infliximab. Samples were taken immediately before infliximab infusion and were analysed by radioimmunoassay. The algorithm categorised patients into 1 of 4 groups and guided treatment as described in table 2.

Table 2. Treatment algorithm used in the Steenholdt et al. (2014 and 2015) study

Group	Drug levels	Antibody levels	Treatment	Intention to treat population
Group 1	Sub-therapeutic infliximab	Detectable anti-infliximab antibodies	Change to a different TNF–alpha inhibitor (adalimumab)	14 (20%)
Group 2	Sub-therapeutic infliximab	Undetectable anti-infliximab antibodies	Intensify infliximab treatment	3 (4%)
Group 3	Therapeutic infliximab	Undetectable anti-infliximab antibodies	Discontinue treatment with TNF–alpha inhibitors. Review of condition.	48 (70%)
Group 4	Therapeutic infliximab	Detectable anti-infliximab antibodies	Repeat testing. If results are unchanged act as for group 3.	4 (6%)
Abbreviation: TNF, tumour necrosis factor				

5.5 In the dose-intensification arm, all patients had treatment according to the protocol. In the algorithm arm, 14 of 33 patients did not have treatment according to the algorithm (13 in group 3; 1 in group 4). Most of these 14 patients continued to have infliximab. There were

2 withdrawals from the algorithm arm and 8 withdrawals from the dose intensification arm.

5.6 In the intention to treat population (n=69), clinical response at week 12 was seen in 53% of patients in the dose intensification arm and in 58% of patients in the algorithm arm (relative risk [RR] 1.09; 95% confidence interval [CI] 0.713 to 1.673; p=0.810). At week 20, clinical response was seen in 56% of the dose intensification arm and in 76% of the algorithm arm (RR 1.4; 95% CI 1.0 to 1.9; p=0.128). Remission was achieved at week 20 in 39% of patients in the dose intensification arm and in 55% of patients in the algorithm arm (RR 1.4; 95% CI 0.8 to 2.4; p=0.232).

Vaughn et al. 2014

5.7 This was a retrospective observational pilot study of patients with inflammatory bowel disease in clinical remission who were having infliximab. Patients were identified from records and classified into those who had proactive drug monitoring and those who did not (control group). Samples were analysed first by ELISA (Prometheus) and later with a HMSA (Prometheus). In the proactive monitoring group, serum trough levels of infliximab guided dose changes to achieve target drug levels according to the algorithm presented in table 3. Reactive testing was done in both groups if the disease lost response or there was a concern for side effects because of antibody formation.

Table 3. Treatment algorithm used in the Vaughn et al. (2014) study

Test result	Treatment
Undetectable trough levels of infliximab	Infliximab dose increased to 7.5 mg/kg and next infusion given after 6 weeks, then future infusions given every 8 weeks.
Detectable trough level of infliximab, but less than 5 micrograms/ml	Infliximab dose increased by 50 mg or 100 mg.
Trough levels of infliximab of greater than 10 micrograms/ml on at least 2 occasions	Infliximab dose reduced.
Trough drug level between 5 micrograms/ml and 10 micrograms/ml	No changes made.

5.8 There were 48 patients in the proactive drug monitoring group and 78 patients the control group. In the proactive drug monitoring group, infliximab dose was adjusted in 35% of patients after initial testing (71% dose escalation, 18% dose decrease, and 12% stopped infliximab). After subsequent proactive tests, the dose was adjusted in 25% of patients (80% dose escalation and 20% dose decrease).

5.9 After 5 years, the probability of remaining on treatment was 86% in the proactive drug monitoring group and 52% in the control group (hazard ratio 0.3; CI 0.1 to 0.6; p=0.0006). In the control group, the main reasons for stopping infliximab treatment were recurrence of symptoms and acute infusion reactions. In the proactive drug monitoring group, the main reasons for stopping infliximab treatment were adverse events and high antibody levels.

Vande Casteele et al. 2015 – the TAXIT trial

5.10 This was a randomised controlled trial of 251 patients with inflammatory bowel disease (173 with Crohn's disease and 78 with ulcerative colitis). Patients were randomised to clinically-based dosing or to infliximab trough-level-based dosing. Before randomisation, patients were screened and had an optimisation treatment phase, to identify patients whose trough levels of infliximab could be brought to the target range. Therefore, all

randomised patients entered the maintenance phase of the study with trough infliximab levels in the target range of 3–7 micrograms/ml. In the clinically-based dosing arm, all subsequent infliximab dosing was according to clinical symptoms and C-reactive protein levels. In the trough level-based dosing arm, all subsequent infliximab dosing was according to the algorithm presented in table 4. Samples were analysed using Leuven in-house ELISAs.

Table 4. Treatment algorithm used in the TAXIT trial

Test result	Treatment
Trough level infliximab greater than 7 micrograms/ml	Dose decrease (by 5 mg/kg) to 5 mg/kg or increase dosing interval by 2 weeks.
Trough level infliximab less than 7 micrograms/ml but greater than 0.3 micrograms/ml	No dose adaption.
Trough level infliximab less than 0.3 micrograms/ml	Decrease dosing interval by 2 weeks (to minimum of 4 weeks) or increase dose (by 5 mg/kg) to a maximum of 10 mg/kg.
Trough level infliximab less than 0.3 micrograms/ml with antibodies to infliximab less than 8 micrograms/ml	Decrease dosing interval by 2 weeks (to minimum of 4 weeks) or increase dose (by 5 mg/kg) to a maximum of 10 mg/kg.
Trough level infliximab less than 0.3 micrograms/ml with antibodies to infliximab greater than 8 micrograms/ml	Stop treatment with infliximab.

5.11 In the optimisation phase, 74% of patients with Crohn's disease were in remission before dose optimisation, and 80% were in remission after optimisation. Dose escalation was done in 43 of 178 patients and the percentage of patients in remission in this group increased from 65% to 88%. Dose reduction was done in 51 of 178 patients and the percentage of patients in remission in this group decreased from 80% to 69%. For the dose escalation group an average of 2.1 optimisations were needed to reach target trough infliximab levels, and at the end of optimisation the median infusion interval was 6 weeks (range 4–8 weeks). For the dose reduction

group an average of 1.4 optimisations were needed and the median infusion interval was 8 weeks (range 6–12 weeks).

5.12 In the maintenance phase, similar rates of clinical remission were seen in both groups: 69% in the concentration-based dosing group, and 66% in the clinically-based dosing group. When restricted to patients with Crohn's disease, rates of clinical remission were 63% in the concentration-based dosing group, and 55% in the clinically-based dosing group.

5.13 There was little difference between groups in the probability of maintaining durable remission (26% in the concentration-based dosing group and 27% in the clinically-based dosing group). More patients in the concentration-based dosing group than in the clinically-based dosing group (74% compared with 57%) had an infliximab trough concentration between 3 micrograms/ml and 7 micrograms/ml. The risk of patients in the clinically-based dosing group having undetectable trough levels of infliximab was statistically significantly greater than in the concentration-based dosing group (RR 3.7; 95% CI 1.7 to 8.0; $p<0.001$). None of the patients in the concentration-based dosing group were positive for anti-drug antibodies but 3 patients in the clinically-based dosing group had anti-drug antibodies.

5.14 No deaths occurred in either group. However, 2 patients in the clinically-based dosing group needed hospital admission: one for acute appendicitis and the other for ileostomy complications. There were 12 discontinuations in the clinically-based dosing group and 13 discontinuations in the concentration-based dosing group. More patients in the clinically-based dosing group (17%) relapsed and needed rescue therapy than in the concentration-based dosing group (7%) (RR 2.4; 95% CI 1.2 to 5.1; $p=0.018$).

Summary

5.15 Key conclusions from the 3 studies are summarised in table 5.

Table 5. Summary of studies

Study	Methods	Tests used	Author conclusions
Steenholdt et al. (2014 and 2015)	Patients whose disease lost response to infliximab were randomised to either an algorithm group (patients had treatment according to a defined algorithm based on serum concentrations of infliximab and antibodies to infliximab) or a dose-intensification group (patients had 5 mg/kg infliximab every 4 weeks).	Samples were first analysed by radioimmunoassay and retrospectively analysed by ELISA and homogenous mobility shift assay (HMSA; Prometheus).	The clinical response in the test-algorithm group was similar to the clinical response in the dose-intensification group.
Vande Casteele et al. (2015)	Patients with inflammatory bowel disease and stable response to infliximab were randomised to a test-algorithm group or a control group. In the test-algorithm group, the infliximab dose was adjusted based on trough levels of infliximab to target an infliximab trough level of 3–7 micrograms/ml. In the control group, the infliximab dose was guided by clinical symptoms and C-reactive protein levels.	Samples were analysed using the Leuven in-house ELISA.	Clinical response was similar in the test-algorithm group and in the control group.
Vaughn et al. (2014)	Patients with inflammatory bowel disease in clinical remission, who were having infliximab, were retrospectively identified. Patients were classified into those who had dose changes guided by trough levels of infliximab (proactive drug monitoring group) and those who did not (control group).	Samples were first analysed using ELISA (Prometheus Laboratories) and later with HMSA (Prometheus).	Proactive monitoring of trough levels of infliximab resulted in a greater probability of staying on infliximab compared with no monitoring.

Evidence on the comparative performance of different tests

5.16 The comparative performance of the index tests (LISA-TRACKER ELISA kits, IDKmonitor ELISA kits or Promonitor ELISA kits) with alternative tests that did have data on clinical outcomes was reviewed. Data comparing the performance of the 3 index tests were also assessed. There were 14 studies that had relevant test comparisons, of which 5 reported concordance as numerical data or Cohen's kappa. In addition, an unpublished analysis of data was provided by a company.

Comparisons between the index tests

5.17 Based on limited evidence on the correlation between the 3 index tests, it appears that the LISA-TRACKER ELISAs have the most variation in test results compared with the IDKmonitor ELISAs and Promonitor ELISAs. However, it is not clear how this would affect test results at clinically meaningful cut-offs.

Adalimumab levels:

- One analysis provided by a company compared the correlation of the 3 different ELISAs. The results of this analysis are commercial in confidence.
- In an analysis using both patient samples and spiked samples, test results differed between the Promonitor ELISA and the LISA-TRACKER ELISA, and Pearson R^2 was 0.83. The authors concluded that the LISA-TRACKER ELISA underestimated adalimumab levels (Nagore et al. 2015).

Antibodies to adalimumab:

- One analysis provided by a company compared the correlation of the 3 different ELISAs. The results of this analysis are commercial in confidence.

- The analysis by Nagore et al. (2015) reports a Cohen's Kappa of 0.8 between the Promonitor ELISA and the LISA-TRACKER ELISA.

Infliximab levels:

- One analysis provided by a company compared the correlation of the 3 different ELISAs. The results of this analysis are commercial in confidence.
- In an analysis using both patient samples and spiked samples, test results differed between the Promonitor ELISA and the LISA-TRACKER ELISA, and Pearson R^2 was 0.98. The authors concluded that the LISA-TRACKER ELISA overestimated infliximab levels (Nagore et al. 2015).
- A study of 66 patient samples showed that results from the IDKmonitor ELISA were on average 1.8 micrograms/ml lower than results from the Promonitor ELISA (Daperno et al. 2013).

Antibodies to infliximab:

- One analysis provided by a company compared the correlation of the 3 different ELISAs. The results of this analysis are commercial in confidence.
- The analysis by Nagore et al. (2015) reports a Cohen's Kappa of 1.0 between the Promonitor ELISA and the LISA-TRACKER ELISA, indicating complete agreement.
- The study by Daperno et al. (2013) found that test results from the IDKmonitor ELISA and the Promonitor ELISA were 'identical' in only 6 out of 63 cases.

Comparisons between the index tests and the alternative tests

5.18 There was insufficient evidence for linking any of the index tests (LISA-TRACKER ELISA kits, IDKmonitor ELISA kits or Promonitor ELISA kits) to any of the alternative tests with links to clinical

outcomes (Prometheus HMSA, radioimmunoassay, Prometheus ELISA, or Leuven in-house ELISA).

LISA-TRACKER ELISAs:

- One study was identified that has data on the LISA-TRACKER ELISAs and the Leuven in-house ELISAs for infliximab and antibodies to infliximab (Vande Casteele et al. 2012). This study also included the Amsterdam Sanquin ELISA and radioimmunoassay. A mix of clinical and spiked samples was used. Results suggest that the LISA-TRACKER ELISA may give some false positive results for infliximab levels in the presence of antibodies to infliximab or adalimumab. For detecting antibodies to infliximab, the LISA-TRACKER ELISA gave fewer positive results than the radioimmunoassay, but a greater number of positive results than the Leuven in-house ELISA. However, it is not clear if these results are true positives.
- There were no data linking the LISA-TRACKER ELISAs to any of the alternative tests for detecting adalimumab or antibodies to adalimumab.

Promonitor ELISAs:

- One study compared the Promonitor ELISAs with the Amsterdam Sanquin ELISA and radioimmunoassay (Ruiz-Arguello et al. 2013), and a further study compared the Amsterdam Sanquin ELISA and radioimmunoassay with the Leuven in-house ELISA (Vande Casteele et al. 2012), giving an indirect link between the index test and the alternative test.
- Ruiz-Arguello et al. (2013) used spiked samples and results suggested that for drug levels, although the analytical sensitivity of the Amsterdam Sanquin ELISA was higher than that of the Promonitor ELISA, the Amsterdam Sanquin ELISA may overestimate drug levels at higher drug concentrations. For anti-drug antibodies, the analytical sensitivity of the Promonitor

ELISA was higher than that of the Amsterdam Sanquin radioimmunoassay.

- Vande Casteele et al. (2012) reported that the Amsterdam Sanquin ELISA and the Leuven in-house ELISA for drug levels performed similarly across all cut-offs used. However, the Amsterdam Sanquin radioimmunoassay gave a greater number of positive results for anti-drug antibodies than the Leuven in-house ELISA.

IDKmonitor ELISAs:

- Two studies compared the IDKmonitor ELISAs with the Prometheus HMSA (Eser et al. 2013a and 2013b). The Immundiagnostik ELISAs were compared with the Amsterdam Sanquin ELISA and radioimmunoassay in 1 study (Schatz et al. 2013), and Vande Casteele et al. (2012) compared the Amsterdam Sanquin ELISA and radioimmunoassay with the Leuven in-house ELISAs.
- Eser et al. (2013a and 2013b) used patient samples and reported that the Prometheus HMSA could detect anti-infliximab antibodies in the presence of infliximab, whereas the IDKmonitor ELISA returned inconclusive results because of interference from infliximab.
- Schatz et al. (2013) used patient samples and reported agreement between the IDKmonitor ELISA and the Amsterdam Sanquin ELISA for infliximab levels with a Cohen's Kappa of 0.792. A greater number of positive results were returned by the Amsterdam Sanquin tests than the Immundiagnostik ELISAs for both infliximab levels and antibodies to infliximab.
- There were no data linking the IDKmonitor ELISAs to any of the alternative tests for detecting adalimumab or antibodies to adalimumab.

Evidence on optimal cut-off points

5.19 Receiver operating characteristic threshold analyses to determine optimal cut-offs predictive of clinical response for infliximab, adalimumab or both were reported in 24 studies. Different studies used different markers to assess clinical response. When identifying optimal cut-offs, some studies aimed for high sensitivity (0.90) at the expense of specificity (0.37), whereas others favoured high specificity (1.00) at the expense of sensitivity (0.33). Reported cut-offs for infliximab ranged from 0.6 to 7 micrograms/ml. Reported cut-offs for adalimumab ranged from 3 micrograms/ml to 6.85 micrograms/ml.

5.20 The range of cut-off points reported across the included studies shows that no validated threshold has been established. Cut-off points strongly depend on the assay used, the drug measured, the clinical marker investigated and the time of testing.

Evidence on the correlation between test results and clinical state

5.21 The review identified 34 studies that reported on the relationship between test results and the clinical status of patients with Crohn's disease or inflammatory bowel disease. Of these, 3 were systematic reviews that included a meta-analysis, and 31 were primary studies.

5.22 The test accuracy of drug-level tests and anti-drug antibodies tests as predictors of clinical status was moderate. Positive and negative predictive values across clinical prevalence ranges indicated that 20% to 30% of test results were incorrect.

5.23 Nanda et al. (2013) included 11 studies in a meta-analysis and reported a 3-fold greater risk of the disease losing response in patients with a positive anti-drug antibodies test result compared

with patients who had a negative anti-drug antibodies test result (RR 3.16; 95% CI 2.00 to 4.98). Hierarchical meta-analysis gave a sensitivity of 0.70 (95% CI 0.55 to 0.82) and specificity of 0.81 (95% CI 0.67 to 0.89) for the anti-drug antibody test in predicting loss of response. At a loss of response prevalence of 34.7%, the positive predictive value was 65% and the negative predictive value was 84%.

5.24 Lee et al. (2012) included 10 studies in a meta-analysis and reported no statistically significant decrease in rates of remission in patients with a positive test result for anti-drug antibodies compared with patients with a negative test result for anti-drug antibodies (RR 0.96; 95% CI 0.77 to 1.19). Hierarchical meta-analysis gave a sensitivity of 0.42 and specificity of 0.69 for the anti-drug antibody test in predicting remission.

5.25 Lee et al. (2012) also examined the association between the development of anti-drug antibodies and the use of immunosuppressant therapies. Meta-analysis of 11 studies indicated a 50% reduction in risk of developing anti-drug antibodies when immunosuppressants were administered (0.50; 95% CI 0.42 to 0.59).

5.26 Paul et al. (2014) included 3 studies in adults and 2 studies in children and reported statistically significantly greater odds of experiencing a lack of clinical response in patients with sub-therapeutic adalimumab levels compared with patients with therapeutic levels of adalimumab (odds ratio 2.60; 95% CI 1.79 to 3.77). They also reported statistically significantly greater odds of experiencing a lack of clinical response in patients with antibodies to adalimumab compared with patients who had no antibodies to adalimumab (odds ratio 10.15; 95% CI 3.90 to 26.40).

Systematic review of cost-effectiveness evidence

5.27 The EAG conducted a search to identify studies investigating the cost effectiveness of LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits for measuring levels of TNF-alpha inhibitors and of anti-drug antibodies.

5.28 Four relevant studies were identified. All studies indicated that a testing strategy might be cheaper than a no-testing strategy. However, studies reported variable small effects on effectiveness, with some indicating small reduced benefits and some indicating small increased benefits.

5.29 Vande Casteele et al. (2015) conducted a randomised controlled trial to determine whether concentration-based infliximab dosing is more cost effective than clinically-based infliximab dosing in people with moderate to severe Crohn's disease or ulcerative colitis (TAXIT trial). The time horizon of the model was 1 year and the perspective was that of the third-party payer. The base-case results showed that concentration-based dosing was slightly less effective (0.8227 quality-adjusted life years [QALYs] compared with 0.8421 QALYs) and less costly (€20,700 compared with €21,000) than clinically based dosing, but overall differences were small.

5.30 Steenholdt et al. (2014) assessed the cost-effectiveness of having treatment based on serum concentrations of infliximab and antibodies to infliximab compared with having infliximab at an increased dose frequency of 5 mg/kg every 4 weeks. In all patients, the disease lost response to infliximab while the patient was having maintenance treatment. The authors reported that costs at 12 weeks were statistically significantly lower in the algorithm group than in the infliximab intensification group. Mean costs in the intention to treat population at 12 weeks were €6038 in the

algorithm group compared with €9178 in the infliximab intensification group ($p<0.001$).

5.31 Steenholdt et al. (2015) conducted a follow-up to the original study (Steenholdt et al. 2014) which extended the time horizon to 1 year to assess the long-term costs of treating Crohn's disease that lost response to infliximab maintenance therapy. Costs were assessed at 20 weeks and at 1 year. The authors reported that the algorithm group had significantly lower costs than the infliximab intensification group at 20 weeks and this was maintained throughout the year. At 20 weeks, the average costs in the algorithm group were US$11,900 compared with US$17,200 in the infliximab intensification group. At 1 year, the average costs in the algorithm group were US$22,100 compared with US$29,100 in the infliximab intensification group.

5.32 Velayos et al. (2013) used a decision analytical model to assess the cost-effectiveness of a testing-based strategy compared with an empiric dose-escalation strategy for patients with moderate to severe Crohn's disease whose disease lost response to infliximab. The study had a third party payer perspective and a 1-year time horizon. The base-case results showed that that the testing strategy was cheaper and marginally more effective than the empiric dose-escalation strategy.

Economic analysis

Model structure

5.33 The EAG constructed 2 de novo economic models designed to assess the cost-effectiveness of monitoring levels of TNF-alpha inhibitor and anti-drug antibody compared with standard care in patients with Crohn's disease. The first model focuses on patients whose disease responds to infliximab maintenance therapy and the

second model focuses on patients whose disease loses response to infliximab maintenance therapy.

5.34 Both models have a 10-year time horizon, a 4-week cycle length and assume a cohort of people aged 30 years with moderate-to-severe Crohn's disease. In each model, patients can have either standard care, treatment according to an algorithm based on concurrent testing, or treatment according to an algorithm based on reflex testing.

5.35 Patients in the responder model enter in the responder health state, that is, their disease responds to treatment with maintenance infliximab. Patients may stay in this state or their disease may lose response to infliximab, that is, a recurrence of active symptoms while on maintenance infliximab treatment. After a dose change or switch in the TNF-alpha inhibitor, the disease may regain response or may continue to lose response and the TNF-alpha-inhibitor treatment is stopped. Disease that regains response may continue to respond or may lose response again. Patients who stop TNF-alpha-inhibitor treatment will have best supportive care and some may need surgery. After surgery, patients move to a post-surgery health state and may have a TNF-alpha inhibitor, immunosuppressant, a combination of TNF-alpha inhibitor and immunosuppressant or no treatment. Patients who have a TNF-alpha inhibitor alone or in combination will re-enter the model in the re-gain response state or the loss of response state. Patients who have an immunosuppressant or no treatment will stay in the post-surgery state until they need further surgery or they die.

5.36 Patients in the loss of response model enter the model in the loss of response to TNF-alpha-inhibitor state, that is, patients are experiencing a recurrence of active symptoms while on

maintenance infliximab treatment. The model then follows the same structure as the responder model.

5.37 In the standard care pathway:

- people whose disease is categorised as a responder continue having infliximab maintenance therapy every 8 weeks until they lose response
- people whose disease loses response will have an increased dose; as a result, the disease may regain response or continue with loss of response
- people whose disease continues to lose response will have another drug in addition to their current treatment; as a result, the disease may regain response or continue with loss of response
- people whose disease continues to lose response will switch TNF-alpha-inhibitor treatment
- people whose disease does not respond to a different TNF-alpha inhibitor will be considered for surgery.

5.38 In the concurrent-testing scenario, tests for infliximab levels and antibodies to infliximab would be done at the same time. Patients would fall into 1 of 4 categories:

- drug absent and antibodies present
- drug and antibodies absent
- drug and antibodies present
- drug present and antibodies absent.

5.39 In the reflex-testing scenario, a test for infliximab levels is done first. If the drug is absent, a test for antibodies to infliximab would be done. If the drug is present, no further testing would be done. Patients would fall into 1 of 3 categories:

- drug absent and antibodies present
- drug and antibodies absent
- drug present.

5.40 For patients whose disease is in the responder state, treatment options for each of the categories are based on the algorithm used in the TAXIT trial by Vande Casteele et al. (2015); table 6.

Table 6. Treatment algorithm for responders

Category	Treatment
Drug absent, antibodies present (greater than 8 mg/ml)	Switch TNF-alpha inhibitor.
Drug absent, antibodies absent (less than 8 mg/ml)	Increase dose of current TNF-alpha inhibitor.
Drug present, antibodies present	If the trough level is below the target range – decrease the dosing interval. If the trough level is within the target range – no dose change. If the trough level is above the target range – increase the dosing interval.
Drug present, antibodies absent	
Abbreviation: TNF, tumour necrosis factor.	

5.41 For patients whose disease loses response, treatment options for each of the categories are based on the algorithm used in the study by Steenholdt et al. (2014); table 7.

Table 7. Treatment algorithm for loss of response

Category	Treatment
Drug absent and antibodies present	Switch TNF-alpha inhibitor.
Drug and antibodies absent	Increased dose of current TNF-alpha inhibitor.
Drug and antibodies present	TNF-alpha inhibitor stopped and best supportive care provided.
Drug present, antibodies absent	
Abbreviation: TNF, tumour necrosis factor alpha.	

Model inputs

5.42 The model was populated with data from the clinical-effectiveness review and supplemented with information from secondary sources and values obtained from clinical experts.

5.43 For patients whose disease is in the responder state, the proportions that fall into each of the test categories were sourced from Imaeda et al. (2012). For patients whose disease is in the loss of response state, the proportions in each test category were taken from Steenholdt et al. (2014). For patients with detectable trough drug levels, the proportions with below target range, within target range and above target range were based on the study by Vande Casteele et al. (2015). The proportions of patients having different post-surgery treatment options were based on a study by Van der Have et al. (2014).

5.44 Costs were obtained from standard sources such as the British National Formulary (BNF) and NHS Reference cost database. The test costs used in the model were based on the LISA-TRACKER ELISA kit costs provided by the company; however costs of the other index tests were similar (table 8).

Table 8. Index test costs

Test	Price	Patient samples tested	Cost per patient
LISA-TRACKER drug level ELISA	£850	42	£20.24
LISA-TRACKER anti-drug antibodies ELISA	£850	42	£20.24
LISA-TRACKER Duo	£1568	2×42	£37.33
IDKmonitor drug level ELISA	£855	40	£21.38
IDKmonitor anti-drug antibodies ELISA	£775	45	£17.22
IDKmonitor total anti-drug antibodies ELISA	£775	45	£17.22
Promonitor drug level ELISA	£800	40	£20.00
Promonitor anti-drug antibodies ELISA	£800	40	£20.00

5.45 Utility values were taken from published literature (table 9). The utility values reported in Velayos et al. (2013) were obtained from the study done by Gregor et al. (1997).

Table 9. Utility values and sources

Health state	Utility	Source
Responder	0.77	Velayos et al. (2013)
Loss of response	0.62	Gregor et al. (1997)
Regain response	0.77	Assumption
Surgery	0.60	Marchetti et al. (2014)
Post-surgery	0.86	Velayos et al. (2013)

Model assumptions

5.46 The following assumptions were applied in the base-case analysis:

- Patients have had intravenous infusions of infliximab of 5 mg/kg at weeks 0, 2 and 6.
- Patients weigh more than 70 kg.
- Patients whose disease regained response have the same utility as those who whose disease is categorised as a responder.
- People with Crohn's disease are not at increased risk of dying from the disease over the lifetime of the model, and there is no difference in mortality between the test-algorithm group and the standard-care group.
- For people who have had surgery, there is an increased risk of 0.0015 of dying from the procedure.
- The treatment effects for people having a dose increase (from 5 mg/kg to 10 mg/kg of infliximab) and a decreased interval (from 8-week to 6-week intervals) are the same.
- People whose disease is categorised as a responder and who have trough concentrations within the range that the treatment algorithm suggests receive no dose change.

- Transition probabilities in the test-algorithm group are the same as the transition probabilities in the standard-care group for the following transitions:
  - loss of response to infliximab maintenance therapy (Juillerat et al. 2015)
  - loss of response with dose escalation (Ma et al. 2014)
  - loss of response to adalimumab maintenance therapy (Karmaris et al. 2009).
- People whose disease stays in the loss of response health state (TNF-alpha inhibitor stopped) have symptoms of Crohn's disease that in time may need surgery. People will have best supportive care until active symptoms develop that need surgery.

5.47 The testing schedules in the base-case models were:

- In the responder model, testing was done every 3 months whilst patients' disease was responding to a TNF-alpha inhibitor. If patients' disease lost response to a TNF-alpha inhibitor they would also be tested every 3 months until the TNF-alpha inhibitor was stopped.
- In the loss of response model, patients whose disease lost response were tested on entry into the model. If their disease regained response they would then enter onto the 3-monthly testing regimen. If their disease continued to lose response to a TNF-alpha inhibitor they would also be tested every 3 months until the TNF-alpha inhibitor was stopped.

5.48 Two sets of base-case results were provided. The first base-case results use non-constant hazard time-to-event transition probabilities. The second base-case results use exponential transition probabilities (which assume constant hazard of time-to-event transition probabilities). These different sets of transition

probabilities reflect different assumptions on the time taken for people with Crohn's disease to leave one health state and pass to another in the model. The EAG states that the constant hazard transition probabilities appear to be more appropriate for the model.

Results – responder model

5.49 The second base-case results for the responder model show that the testing strategies are cheaper but less effective than the standard care strategy. Incremental costs (savings) compared with no testing are £11,800 for reflex testing and £10,700 for concurrent testing. Incremental QALYs (lost) compared with no testing are 0.2323 for reflex testing and 0.2447 for concurrent testing. Incremental cost-effectiveness ratios (ICERs) show that if testing strategies were adopted, savings of between £43,700 and £50,800 would be made for each QALY lost.

5.50 Scenario analyses of the responder model included:

- testing done annually in patients whose disease responds to treatment with a TNF-alpha inhibitor
- testing done initially at 3 months and then annually in patients whose disease responds to treatment with a TNF-alpha inhibitor
- testing done only at 3 months in patients whose disease responds to treatment with a TNF-alpha inhibitor, and in patients whose disease regains response after loss of response to TNF-alpha-inhibitor treatment
- testing done only at 3 months in patients whose disease responds to treatment with a TNF-alpha inhibitor (no testing of patients whose disease regains response after losing response to TNF-alpha-inhibitor treatment).

5.51 Results of scenario analyses show that the testing strategies are cheaper and less effective than the standard-care strategy. Incremental costs (savings) compared with no testing range from

£36,400 (annual testing) to £48,500 (testing at 3 months only in people whose disease responds). Incremental QALYs (lost) compared with no testing range from 0.2694 (testing at 3 months in people whose disease responds or regains response) to 0.2823 (annual testing). ICERs show that if testing strategies were adopted, savings of between £126,600 and £176,300 would be made for each QALY lost.

Results – loss of response model

5.52 The second base-case results for the loss of response model show that the testing strategies are cheaper but less effective than the standard-care strategy. Incremental costs (savings) compared with no testing are £84,800 for reflex testing and £86,100 for concurrent testing. Incremental QALYs (lost) compared with no testing are 0.2985 for reflex testing and 0.3154 for concurrent testing. ICERs show that if testing strategies were adopted, savings of between £273,000 and £284,100 would be made for each QALY lost.

5.53 A scenario analysis of the loss of response model examined a test schedule in which patients whose disease lost response to a TNF-alpha inhibitor are tested, but patients whose disease regains response to treatment with a TNF-alpha inhibitor are not tested. Testing is done every 3 months until the patient's disease regains response to the TNF-alpha inhibitor, or the patient stops treatment with the TNF-alpha inhibitor. Results show that the testing strategies are cheaper but less effective than the no-testing strategy. Incremental costs (savings) compared with no testing are £118,100 for reflex testing and £119,600 for concurrent testing. Incremental QALYs (lost) compared with no testing are 0.3331 for reflex testing and 0.3508 for concurrent testing. ICERs show that if testing strategies were adopted, savings of between £340,900 and £354,500 could be made per QALY lost.

Sensitivity analyses

5.54 In addition to the scenario analyses, a range of univariate sensitivity analyses were done. These included:

- Changing the time horizon from 10 years to 1 year.
- In the no-testing strategy arm, transition probabilities derived from Juillerat et al. (2015) were used for people whose disease lost response after dose escalation.
- In the responder model, transition probabilities derived from Vande Casteele et al. (2015) were used.
- Reducing the proportion of people with infliximab and antibodies to infliximab from 0.7878 to 0.200.
- Changing the transition probabilities from exponential transition probabilities (which assume a constant hazard rate over time) to time-to-event transition probabilities.
- Patients whose disease did not regain response after best supportive care.

5.55 Most of these changes had no impact on the direction of the results. However, changing the transition probabilities from exponential transition probabilities to time-to-event transition probabilities resulted in the testing strategies becoming more costly and less effective than the no-testing strategy. Also, in the responder model, if patients' disease was assumed not to regain response after best supportive care, this resulted in the no-testing strategy becoming cheaper than the testing strategies. Incremental QALYs also reduced, but the no-testing strategy remained slightly more effective than the testing strategies.

5.56 In further sensitivity analyses, key model input parameters were varied to determine which inputs influence the ICER. Results showed that the models are stable to most changes, but sensitive

to a 10% increase in the utility value for people whose disease regains response.

5.57 Probabilistic sensitivity analyses were done on the revised base-case models. In the responder model, the scatterplot shows considerable uncertainty around both the incremental costs and incremental QALYs. The cost-effectiveness acceptability curve suggests that there is a 50% probability of the no-testing strategy being cost effective if the maximum acceptable ICER is £20,000 per QALY gained. It should be noted however, that this analysis is of the base-case model in which testing was done every 3 months.

5.58 In the loss of response model the scatterplot shows less uncertainty in the incremental costs, but considerable uncertainty in the incremental QALYs. The cost-effectiveness acceptability curve suggests that there is no preference between a no-testing strategy and a testing strategy if the maximum acceptable ICER is £20,000 per QALY gained. However, if the maximum acceptable ICER is greater than £30,000 per QALY gained, a no-testing strategy is likely to be the most cost-effective strategy. Again, it should be noted that this analysis is using the base-case model in which patients whose disease regained response to a TNF-alpha inhibitor were tested every 3 months, in addition to testing of patients whose disease lost response.

6 Considerations

6.1 The Diagnostics Advisory Committee considered the impact of Crohn's disease on a person's life. It heard from a clinical expert on the Committee that the disease most often presents in early adulthood, but can occur at any age. It heard further that severe Crohn's disease can have devastating effects on a person's life, such as extreme weight loss, fistulas and abscesses, the need for surgery and enteral or parenteral nutrition. The Committee heard

from a patient expert that even mild or moderate Crohn's disease can have a substantial impact on a person's day-to-day quality of life in the form of fatigue, fever, anaemia, diarrhoea and joint pain. It also heard that having Crohn's disease can result in a person needing substantial time off work and can restrict their participation in activities with their family. The Committee concluded that Crohn's disease substantially impacts the quality of life of the person with Crohn's disease and their family.

6.2 The Committee considered the complexity of managing Crohn's disease. It heard from a clinical expert that many different factors influence the development and progression of Crohn's disease, including genes and the environment. It heard further that because of these different influences, tailoring treatment to individual patients can be difficult and that there are limited options for treatment, particularly in those with severe disease. The Committee concluded that managing Crohn's disease is extremely complex and that new tests that can aid clinical decision-making could improve management of the condition and improve outcomes for the patient.

6.3 The Committee reviewed the evidence available on the clinical and cost effectiveness of using enzyme-linked immunosorbent assay (ELISA) kits (LISA-TRACKER, IDKmonitor, and Promonitor) to test levels of tumour necrosis factor (TNF)-alpha inhibitors and antibodies to TNF-alpha inhibitors in the following 2 populations:

- people with Crohn's disease whose disease responds to treatment with a TNF-alpha inhibitor
- people with Crohn's disease whose disease loses response during maintenance treatment with a TNF-alpha inhibitor.

The Committee noted that no clinical outcome data were available on the 3 index tests (LISA-TRACKER, IDKmonitor and Promonitor

ELISA kits) and therefore the results of the economic model were based on the results from studies of alternative tests (Prometheus ELISA, Prometheus homogeneous mobility shift assay [HMSA]), radioimmunoassay and Leuven in-house ELISA).

6.4 The Committee considered the test performance of the ELISA kits (LISA-TRACKER, IDKmonitor and Promonitor) compared with the alternative tests that have direct clinical outcome data (Prometheus ELISA, Prometheus HMSA, radioimmunoassay and Leuven in-house ELISA). It noted that the evidence base on comparative test performance was very small, which led to great uncertainty in the comparability of the different tests. The Committee heard from clinical experts that most testing in the UK is done in a few centres with each using different test kits or laboratory-developed methods. The Committee concluded that because of the absence of clinical data, it was uncertain which of the tests would be most clinically useful in both scenarios. It concluded further, that in the absence of robust positive or negative evidence linking the index tests to the alternative tests, the outcomes of the economic model can be applied to the index tests (LISA-TRACKER, IDKmonitor and Promonitor ELISA kits), and the Committee noted the uncertainty in making this assumption.

6.5 The Committee considered the analytical validity of the ELISA kits (LISA-TRACKER, IDKmonitor and Promonitor). It heard from experts on the Committee that measuring TNF-alpha inhibitor levels can be problematic if antibodies to TNF-alpha inhibitors are also present in the sample. It heard further that tests measuring antibodies to TNF-alpha inhibitors do not distinguish between transient antibodies (antibodies that disappear and reappear over time) and stable antibodies (antibodies that stay at high levels), but that the type of antibodies is clinically important and could impact treatment decisions. The Committee noted that some ELISAs for

antibodies to TNF-alpha inhibitors are quantitative and others are semi-quantitative, and concluded that it was uncertain which would be most clinically useful. The Committee also heard from a clinical expert that there is no formal external quality assurance scheme for measuring levels of TNF-alpha inhibitors and antibodies to TNF-alpha inhibitors, but that some laboratories take part in sample-exchange schemes as a form of quality assurance. The Committee concluded that further research into the analytical performance of the ELISAs is needed.

6.6 The Committee considered the evidence on the optimal thresholds for use with the ELISA kits (LISA-TRACKER, IDKmonitor and Promonitor). It noted that the information-for-use documents for each of the kits do not specify thresholds to guide interpretation of test results. Therefore each laboratory is expected to identify and validate a threshold for use with the tests. The Committee heard from clinical experts that the same thresholds should not be used between different kits, making it difficult to compare the results from different kits. It heard further that thresholds for infliximab levels were better established than thresholds for adalimumab levels, and that thresholds for TNF-alpha-inhibitor levels were better established than thresholds for antibodies to TNF-alpha inhibitors. The Committee noted that a precise threshold was less critical for people whose disease loses response, because the objective of testing was to identify the presence or absence of the TNF-alpha inhibitor. It noted further that a precise threshold was more important in people whose disease was responding to treatment with a TNF-alpha inhibitor in whom the objective of testing was to titrate the dose of the TNF-alpha inhibitor to achieve a trough level in a target range. The Committee concluded that further research is needed to establish clinically meaningful thresholds for each of the ELISAs, and laboratories currently doing these tests should have

specialist expertise in immunoassay analysis and should be interpreting the results with caution.

6.7 The Committee considered the accuracy of the ELISA kits (LISA-TRACKER, IDKmonitor and Promonitor) for predicting the clinical state of Crohn's disease. The Committee noted that evidence suggested that the ability of these tests to classify clinical state is poor, which could result in misclassification of people with Crohn's disease. The Committee concluded that the uncertainty in the accuracy of these tests would lead to uncertainty in the model, and that further research is needed on the clinical validity of the ELISA kits.

6.8 The Committee considered the outcomes used to assess the response of Crohn's disease to treatment with TNF-alpha inhibitors. It heard from an expert on the Committee that the outcomes often used to assess response include blood serum biomarkers and mucosal healing (through endoscopy). It heard further that the outcome most important to people with Crohn's disease is that they feel better. The Committee noted that the levels of TNF-alpha inhibitor needed to achieve mucosal healing are higher than the levels of TNF-alpha inhibitor needed for the person to feel better. It concluded that future studies should include patient-reported outcomes measures.

6.9 The Committee considered the assumptions used in the economic models. It noted that 2 different sets of transition probabilities were used to generate 2 sets of base-case results. The first base case used time-to-event transition probabilities, whereas the second base case used exponential transition probabilities. The Committee heard from the External Assessment Group (EAG) that the time-to-event transition probabilities best reflect the data from the key studies used to provide inputs for the model. However, the

exponential transition probabilities assume that people progress through the model at a constant rate over time, and this better reflects clinical practice. The Committee concluded that the results of the second base case were the most plausible.

6.10 The Committee considered the test schedules assessed in the models. It noted that in the base case, people whose disease responded to TNF-alpha-inhibitor treatment were tested for TNF-alpha-inhibitor levels and antibodies to TNF-alpha inhibitors every 3 months. The Committee heard from a clinical expert that in UK practice the most likely testing strategy is to test for TNF-alpha-inhibitor levels and antibodies to TNF-alpha inhibitors yearly and on loss of response. The Committee concluded that the most plausible ICER for the responder model was from the 'annual testing' scenario (£126,600 saved per QALY lost for concurrent testing compared with no testing), and the most plausible ICER for the loss of response model was from the 'testing only on loss of response' scenario (£340,900 saved per QALY lost for concurrent testing compared with no testing).

6.11 The Committee considered the QALY losses resulting from the economic model that were spread over 10 years. It noted that in the responder model with annual testing the QALY losses compared with a no-testing strategy were 0.280 for a reflex-test strategy and 0.288 for a concurrent-test strategy. It also noted that in the loss of response model when testing was done only in people whose disease lost response to a TNF-alpha inhibitor the QALY losses compared with a no-testing strategy were 0.333 for a reflex-test strategy and 0.351 for a concurrent-test strategy. The Committee concluded that these QALY losses are quite large and unexpected, especially given the low quality of life experienced by people with Crohn's disease that loses response to a TNF-alpha inhibitor.

6.12 The Committee considered the drivers behind the QALY losses. It heard from the EAG that 1 of the drivers was the high proportion (79%) of people in the model in the loss of response health state with TNF-alpha inhibitor present and antibodies to TNF-alpha inhibitors absent. This proportion was taken from the study by Steenholdt et al. (2014). An expert on the Committee noted that the proportion of patients in the UK with loss of response, TNF-alpha inhibitor present and antibodies to TNF-alpha inhibitors absent is much lower than 79%. The Committee also heard from the EAG that these people in the model, with a testing strategy, would stop TNF-alpha-inhibitor treatment and have best supportive care, which would eventually include surgery. A no-testing strategy would result in these patients staying on TNF-alpha-inhibitor treatment longer before stopping the TNF-alpha inhibitor and having best supportive care. The Committee noted that in the model, people whose disease loses response but still have TNF-alpha inhibitors have a greater utility than people with disease that loses response but who have best supportive care (0.62 compared with 0.60). Therefore, people having testing for TNF-alpha-inhibitor levels and antibodies to TNF-alpha inhibitors would stop TNF-alpha-inhibitor treatment faster, and be assigned a lower utility sooner, than people who don't have testing. The Committee also noted its conclusion that the uncertainty in the accuracy of the ELISA kits for predicting clinical state could lead to misclassification of some people with Crohn's disease (section 6.7). It noted further that if people with Crohn's disease are being misclassified by the test results this may explain some of the QALY losses seen in the economic model. The Committee concluded that the QALY losses in the models were uncertain and may not reflect clinical practice in the NHS.

6.13 The Committee considered the cost savings resulting from the economic model. It noted that the cost savings in the testing strategies compared with the no-testing strategy were driven by

reduced use of TNF-alpha inhibitor in the testing strategies, particularly by:

- not increasing the dose of TNF-alpha inhibitor in people whose disease loses response and who have high levels of antibodies to TNF-alpha inhibitor
- stopping treatment with, or reducing the dose of TNF-alpha inhibitor in people whose disease is in remission and have undetectable or low trough level of TNF-alpha inhibitor.

The Committee heard from an expert on the Committee that biosimilars for infliximab and adalimumab are likely to be introduced soon. The Committee noted that biosimilar drugs are cheaper than the original drugs, which would be likely to reduce the cost savings in the model. The Committee concluded that the small evidence base led to uncertainties in the modelling, which resulted in uncertainty in the cost savings.

6.14 The Committee considered the probabilistic sensitivity analyses done by the EAG. It noted that the scatterplots for both the loss of response model and the responder model showed considerable uncertainty in the QALY losses, and that there was overlap between the results of the testing strategies and the no-testing strategy in terms of QALY losses. The Committee noted further that the scatter plot for the responder model showed considerable uncertainty in the cost savings, and there was overlap between the results of the testing strategies and the no-testing strategy in terms of cost savings. However, the scatterplot for the loss of response model showed slightly less uncertainty in the cost savings, and there was no overlap between the results of the testing strategies and the no-test strategy in terms of cost savings. The Committee concluded that there was greater uncertainty in the cost savings in people whose disease was responding to TNF-alpha-inhibitor

treatment compared with people whose disease loses response to TNF-alpha-inhibitor treatment.

6.15 The Committee considered the current UK use of testing for TNF-alpha inhibitors and antibodies to TNF-alpha inhibitors in Crohn's disease. It heard from clinical experts on the Committee that approximately a third to a half of all centres are referring samples for testing to help manage the treatment of Crohn's disease, especially in people whose disease loses response to a TNF-alpha inhibitor. The Committee noted that there is a lot of interest in using these tests to support decision making in people with Crohn's disease, and that clinicians find them useful. It was concerned however, that the complexities in interpreting the results in the absence of a defined threshold (section 6.6) and the potential for misclassification (section 6.7) meant that there was the potential for tests to be incorrectly used by clinicians without specialist knowledge of the tests. The Committee therefore concluded that at this time, the number of laboratories using these tests should not expand beyond current numbers, unless the tests are used in the context of data collection or a research study.

6.16 The Committee considered the different scenarios for using the ELISA kits, that is, in people whose disease loses response to TNF-alpha-inhibitor treatment, and in people whose disease is responding to TNF-alpha-inhibitor treatment. The Committee noted the differences in the ICERs between the 2 scenarios, and that use of the ELISA kits in people whose disease loses response to TNF-alpha-inhibitor treatment was associated with greater savings per QALY lost compared with use of the ELISA kits in people whose disease is responding to TNF-alpha-inhibitor treatment (section 6.10). It also noted that there was less uncertainty in the cost savings in people whose disease loses response to TNF-alpha-inhibitor treatment compared with people whose

disease was responding to TNF-alpha-inhibitor treatment (section 6.14). The Committee further noted that people with Crohn's disease with loss of response to TNF-alpha inhibitors have a low quality of life (section 6.11) and limited treatment options (section 6.2). The Committee concluded that in people whose disease loses response to TNF-alpha-inhibitor treatment, the ELISA kits should be used in laboratories alongside data collection through a relevant registry or audit. The Committee also concluded that only laboratories that are currently using these tests and have expertise in immunoassay analysis and a thorough understanding of the technical factors that may affect the results should continue to use them. These laboratories should work closely in a network with the treating or referring clinician to ensure the appropriate use of the tests and interpretation of the results. The Committee concluded further that in people whose disease responds to TNF-alpha-inhibitor treatment, the ELISA kits should be used only in research.

6.17 The Committee considered the use of ELISA kits (LISA-TRACKER, IDKmonitor, and Promonitor) in children with Crohn's disease and noted that no evidence on children was identified in the assessment. It heard from a clinical expert on the Committee that the effect of Crohn's disease on children can be slightly different to in adults, for example, resulting in growth delay and psychiatric problems. It heard further that there is growing interest from paediatric clinicians in using these tests to help guide treatment in children with Crohn's disease. The Committee concluded that data collection and further research into the use of ELISA kits (LISA-TRACKER, IDKmonitor and Promonitor) to support decision-making in children with Crohn's disease is encouraged.

6.18 The Committee considered the advantages and disadvantages of concurrent testing and reflex testing. It heard from a clinical expert

on the Committee that most centres in the UK use a concurrent-test strategy. The Committee noted that when a concurrent-testing strategy is used, some tests may be wasted because samples with TNF-alpha inhibitor present are unlikely to have free antibodies to TNF-alpha inhibitor present (which is what most of the anti-drug antibody ELISAs measure). However, a reflex-test strategy may cause an unacceptable delay in giving results because fewer samples would be tested for antibodies to TNF-alpha inhibitor and a laboratory would often wait for a full batch of samples before doing the test. The Committee noted that the ICER for the concurrent-test strategies and the reflex-test strategies were similar. It concluded that either test strategy could be used in research.

6.19 The Committee considered the research being conducted on tests to measure levels of TNF-alpha inhibitors and antibodies to TNF-alpha inhibitors in Crohn's disease. The Committee heard from a clinical expert that this is a fast-moving area and a lot of research is being done. It also noted that the UK-based PANTS – Personalised Anti-TNF Therapy in Crohn's Disease study should provide relevant data; however, results are not expected until the end of 2016. The Committee concluded that data from this ongoing research is likely to be important when the guidance is considered for updating in the future.

7 Proposed recommendations for further research

7.1 Further research into the analytical and clinical validity of the enzyme-linked immunosorbent assay (ELISA) kits (LISA-TRACKER, IDKmonitor and Promonitor) is recommended, specifically on:

- the best methods to measure tumour necrosis factor (TNF)-alpha-inhibitor levels in the presence of antibodies to TNF-alpha inhibitors
- the accuracy for predicting clinical state
- clinically meaningful thresholds.

7.2 Further research is recommended on clinical outcomes associated with using the ELISA kits (LISA-TRACKER, IDKmonitor and Promonitor) in people whose Crohn's disease is losing response to a TNF-alpha inhibitor. This could be through a registry, audit or prospective study.

7.3 Further research is recommended on clinical outcomes associated with using the ELISA kits (LISA-TRACKER, IDKmonitor and Promonitor) to monitor TNF-alpha-inhibitor levels and antibodies to a TNF-alpha inhibitor in people with Crohn's disease whose disease responds to treatment with TNF-alpha inhibitors. This should be evaluated using prospective studies.

8 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 7 into its guidance research recommendations database (available on the NICE website) and highlight these recommendations to public research bodies.

9 Related NICE guidance

Published

- Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel. NICE diagnostics guidance 11 (2013)
- SeHCAT (tauroselcholic [75 selenium] acid) for the investigation of diarrhoea due to bile acid malabsorption in people with diarrhoea-predominant irritable bowel syndrome (IBS-D) or Crohn's disease without ileal resection. NICE diagnostics guidance 7 (2012)
- Crohn's disease: management in adults, children and young people. NICE guideline CG152 (2012)
- Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. NICE guideline CG118 (2011)
- Infliximab (review) and adalimumab for the treatment of Crohn's disease. NICE technology appraisal guidance 187 (2010)
- Extracorporeal photopheresis for Crohn's disease. NICE interventional procedure guidance 288 (2009)

Under development

NICE is developing the following guidance (details available from the NICE website):

- 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. Anticipated publication date August 2015.
- Crohn's disease (standing committee update). NICE guideline. Anticipated publication date May 2016.

10 Review

NICE updates the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and

other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Adrian Newland
Chair, Diagnostics Advisory Committee
August 2015

11 Diagnostics Advisory Committee members and NICE project team

Diagnostics Advisory Committee

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

Standing Committee members

Professor Adrian Newland

Chair, Diagnostics Advisory Committee

Dr Mark Kroese

Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Professor Ron Akehurst

Professor in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Dr Phil Chambers

Research Fellow, Leeds Institute of Cancer and Pathology, University of Leeds

Dr Sue Crawford

GP Principal, Chillington Health Centre

Professor Erika Denton

National Clinical Director for Diagnostics, NHS England, Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

Dr Steve Edwards

Head of Health Technology Assessment, BMJ Evidence Centre

Mr David Evans

Lay member

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Mr John Hitchman

Lay member

Professor Chris Hyde

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Mr Matthew Lowry

Director of Finance and Infrastructure, Doncaster and Bassetlaw Hospitals NHS Foundation Trust

Dr Michael Messenger

Deputy Director and Scientific Manager National Institute for Health Research Diagnostic Evidence Co-operative, Leeds

Dr Peter Naylor

GP**,** Chair Wirral Health Commissioning Consortia

Dr Dermot Neely

Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

Gail Norbury

Consultant Clinical Scientist, Guy's Hospital

Dr Simon Richards

Vice President Regulatory Affairs, EME (Europe and Middle East), Alere Inc

Dr Deirdre Ryan

Consultant Cellular Pathologist, Royal London Hospital

Professor Mark Sculpher

Professor of Health Economics, Centre for Health Economics, University of York

Dr Steve Thomas

Consultant Vascular and Cardiac Radiologist, Sheffield Teaching Hospitals Foundation Trust

Mr Paul Weinberger

Chief Executive Officer, DiaSolve Ltd, London

Professor Anthony Wierzbicki

Consultant in Metabolic Medicine and Chemical Pathology, St Thomas' Hospital

Specialist Committee members

Dr Peter Irving

Consultant Gastroenterologist, Guy's and St Thomas' NHS Foundation Trust

Dr Anjan Dhar

Senior Lecturer in Gastroenterology, Consultant Gastroenterologist, County Durham & Darlington NHS Foundation Trust

Dr Joanna Sheldon

Consultant Clinical Scientist in Immunology, St George's Healthcare NHS Trust

Dr Anja St.Clair-Jones

Lead Pharmacist Digestive Diseases, Brighton and Sussex University Hospitals NHS Trust

Miss Lisa Younge

Lead Inflammatory Bowel Disease Nurse Specialist, Barts and the London NHS Trust

Dr Rebecca Harmston

Lay member

NICE project team

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

Frances Nixon

Topic Lead

Sarah Byron

Technical Adviser

Robert Fernley

Project Manager

12 Sources of evidence considered by the Committee

The diagnostics assessment report was prepared by Warwick Evidence.

- Freeman K, Connock M, Auguste P, et al. Clinical and cost-effectiveness of use of therapeutic monitoring of TNFα inhibitors (LISA-TRACKER ELISA kits, Immundiagnostik TNFα-Blocker ELISA kits, and Promonitor ELISA kits) versus standard care in people with Crohn's disease: systematic reviews and economic modelling. April 2015.

Registered stakeholders

The following organisations accepted the invitation to participate in this assessment as registered stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturers/sponsors:

- Alpha Laboratories
- Biohit Healthcare
- Immundiagnostik AG
- Proteomika S.L.U.

Professional/specialist and patient/carer groups:

- British Society of Gastroenterology
- British Society of Paediatric Gastroenterology, Hepatology and Nutrition
- Crohn's and Colitis UK
- Pelvic Pain Support Network
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- UK Clinical Pharmacy Association (UKCPA)

Others:

- AbbVie Ltd
- Euro Diagnostica AB
- Matriks Biotek
- Merck Sharp and Dohme
- Viapath
- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Royal Devon and Exeter Foundation NHS Trust
- Sandwell and West Birmingham Hospitals NHS Trust
- Welsh Government