

# Integrated multiplex PCR tests for identifying gastrointestinal pathogens in people with suspected gastroenteritis (xTAG Gastrointestinal Pathogen Panel, FilmArray GI Panel and Faecal Pathogens B assay)

Diagnostics guidance

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[nice.org.uk/guidance/dg26](https://www.nice.org.uk/guidance/dg26)

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## 1 Recommendations

- 1.1 There is currently insufficient evidence to recommend the routine adoption in the NHS of the integrated multiplex polymerase chain reaction tests, xTAG Gastrointestinal Pathogen Panel, FilmArray GI Panel and Faecal Pathogens B assay, for identifying gastrointestinal pathogens in people with suspected gastroenteritis.
- 1.2 The tests show promise but further research is recommended on their effect on health outcomes and resource use in clinical practice (see [section 6](#)).

## 2 Clinical need and practice

### *The problem addressed*

- 2.1 The integrated multiplex polymerase chain reaction (PCR) tests, xTAG Gastrointestinal Pathogen Panel, FilmArray GI Panel and the Faecal Pathogens B assay, are intended to simultaneously detect and identify pathogens that cause gastroenteritis. The tests are designed to analyse multiple viral, parasitic and bacterial nucleic acids (DNA or RNA) directly from stool samples and produce results within a shorter timeframe than traditional microbiology techniques, which can involve multiple tests and culture of organisms.
- 2.2 Using the tests may allow earlier targeted treatment for people with suspected gastroenteritis, and reduce the length of antibiotic treatment when non-bacterial causes are identified. In addition, the shorter turnaround times of the tests may result in more efficient use of isolation facilities and allow people to have treatment in open bays when infectious pathogens are not present.
- 2.3 Other standard tests may be used in conjunction with the integrated multiplex PCR tests to confirm *Clostridium difficile* as the cause of infection, because it is the toxin produced by the pathogen that results in gastrointestinal disease rather than the presence of the pathogen itself; PCR can detect the presence of the toxin gene but cannot confirm that the gene is expressed and consequently, that toxin has been produced. Supplementary testing may also be needed for bacterial targets to meet Public Health England's mandatory reporting requirements or to provide information on antimicrobial susceptibility.
- 2.4 The purpose of this assessment is to evaluate the clinical and cost effectiveness of using the xTAG Gastrointestinal Pathogen Panel, the FilmArray GI Panel and the Faecal Pathogens B assay for identifying gastrointestinal pathogens in stool samples from patients in the NHS.

### *The condition*

- 2.5 Gastroenteritis is a common, transient disorder that is usually caused by infection with viruses, bacteria or parasites. The second study of infectious intestinal disease in the community (IID2; 2011) estimated that around 25% of

people in the UK have a gastrointestinal infection each year. Gastroenteritis is characterised by acute onset of diarrhoea with or without vomiting. Depending on the cause of the infection, the symptoms can take a few hours to a few days to develop. The IID2 study found that the most commonly identified pathogens in stool samples in the UK were norovirus, sapovirus, *Campylobacter* and rotavirus. People taking, or who have recently taken, antibiotics can get antibiotic-associated diarrhoea, a condition often caused by *Clostridium difficile* or less often by *Clostridium perfringens*, *Staphylococcus aureus*, *Klebsiella oxytoca* or *Salmonella* species.

- 2.6 If bacterial gastroenteritis is identified, gastrointestinal symptoms can be caused by toxins produced by the bacteria rather than by the bacteria themselves. When symptoms are caused by toxins, the onset is usually rapid (less than 12 hours) and is typically caused by *Staphylococcus aureus*, *Bacillus cereus* or *Clostridium perfringens*. Some bacteria are able to cause serious illness, for example, infections with *Escherichia coli* O157 can result in haemolytic uraemic syndrome and renal failure.
- 2.7 Diarrhoea may have non-infectious causes such as inflammatory bowel disease, and so it is important to be able to identify or exclude infectious causes of gastroenteritis in people presenting to health services with diarrhoea or vomiting. Differential diagnoses for gastroenteritis include non-gastrointestinal infections (for example, pneumonia, urinary tract infection or HIV), irritable bowel syndrome, inflammatory bowel disease, coeliac disease, side effects of medicines, endocrinopathy (for example, diabetes or hyperthyroidism) and secretory tumours.

## *The diagnostics and care pathways*

### **Diagnosis**

- 2.8 Gastroenteritis is usually diagnosed based on clinical features alone. Although diarrhoea is common in people who are in hospital, it is estimated that less than 2% of people in the UK consult their GP for an episode of infectious intestinal disease ([IID2 2011](#)). The main symptom of gastrointestinal infection is diarrhoea, but other symptoms can include nausea, sudden onset of vomiting, blood or mucus in the stool, or systemic features such as fever or malaise. Occasionally, diagnostic investigations are needed to confirm that an infection is

present or to determine the causative pathogen. The NICE clinical knowledge summary on [gastroenteritis](#) recommends that stool samples for microbiological diagnosis are taken when there is:

- persistent diarrhoea
- blood or pus in the stool
- a history of diarrhoea or vomiting, and the patient is systemically unwell
- a history of recent hospitalisation or
- a history of antibiotic therapy.

2.9 If parasitic infections are suspected, the NICE clinical knowledge summary on gastroenteritis recommends that 3 samples are sent for testing, 2 to 3 days apart because ova, cysts and parasites are shed intermittently. Hospitals may follow the 3-day rules when deciding whether to send stool samples from inpatients to the microbiology laboratory, but testing for *Clostridium difficile* should be done as soon as infective diarrhoea is suspected.

## Treatment

2.10 Infectious gastroenteritis is usually self-limiting and treatment is not needed. However, if symptoms are severe, medicines may be needed. Symptoms are often most severe in older people or younger children, or in people who are immunocompromised. Treatment for gastroenteritis may include anti-diarrhoeal medicines such as loperamide and anti-emetic medications such as metoclopramide to control symptoms, depending on the causative pathogen. Anti-diarrhoeal medicine is not recommended if a person has blood or mucus in the stools or a high fever, and confirmed or suspected *Escherichia coli* O157, *Shigella* or *Clostridium difficile* infection. Antibiotics are not appropriate if the diarrhoea is of unknown pathology. If the causative pathogen has been microbiologically confirmed, antibiotics may be recommended for amoebiasis (*Entamoeba histolytica*), Campylobacteriosis (*Campylobacter*), giardiasis (*Giardia intestinalis*), Shigellosis (*Shigella*) and *Clostridium difficile* infection.

2.11 Admission to hospital may be needed if a person is vomiting and cannot retain fluids, or if shock or severe dehydration are suspected. Other factors influencing a clinical decision to recommend hospital admission include the age of the

person or any comorbidities that may place them at a greater risk of complications, fever, bloody diarrhoea or abdominal pain and tenderness, or if diarrhoea has lasted more than 10 days.

## Infection control

- 2.12 Isolation and barrier nursing, essential aspects of infection prevention and control, are used to stop infections spreading to other patients or staff, and to protect people who are immunocompromised from getting an infection while in hospital (reverse barrier nursing). Isolation involves caring for a person in a single room or side room of a ward. People with suspected infectious diarrhoea and vomiting are usually nursed in isolation or barrier nursed until negative microbiology results are available or they have been symptom-free for 48 hours. People in isolation will be asked to remain in the room and not enter other areas of the ward or hospital until they have been advised otherwise by members of a hospital infection control team. If side rooms are not available, barrier nursing may be done on the main ward, with extra precautions, for example, staff wearing protective clothing (such as gloves, apron and mask), to prevent the spread of an infection. Cohort nursing (nursing in the same bay) may also be used for several patients who have the same infection, for example, infection with *Clostridium difficile*. When infection control measures are advised for a person, some non-urgent procedures (for example, endoscopy), may be postponed until the infection has resolved.
- 2.13 Communicable infections for which isolation or barrier nursing is needed are not restricted to gastrointestinal infections such as *Clostridium difficile* and norovirus, and include colonisation or infection with methicillin resistant *Staphylococcus aureus* and multidrug-resistant gram-negative bacteria, such as extended spectrum beta-lactamases and carbapenamase producers. It seems that these bacteria are becoming more common and are increasing pressure on existing isolation facilities. Also, these bacteria are currently detected using culture-based screening because PCR technologies do not give information on a pathogen's likely resistance to antimicrobial therapies.
- 2.14 When infectious gastroenteritis is suspected in the community, people are often advised to stay away from work or, in the case of children, from schools and nursery. Advice is also given on reducing the risk of transmission, particularly if infection with highly transmissible pathogens such as norovirus or *Shigella* is



suspected. Infectious gastroenteritis can have implications for people in certain professions, such as food handlers and healthcare workers. Food handlers are typically advised to stay at home until 48 hours after symptoms have resolved; however, people with infections due to certain pathogens, including *Salmonellatyphi* or *paratyphi*, and *Escherichia coli* O157, may need negative microbiology results before they can return to work. Sometimes, the detection of suspected food-borne pathogens may result in public health teams investigating the outbreak.

### 3 The diagnostic tests

The assessment compared 3 intervention tests with 1 comparator.

#### *The interventions*

#### xTAG Gastrointestinal Pathogen Panel

3.1 The xTAG Gastrointestinal Pathogen Panel (Luminex) is a CE-marked qualitative, highly multiplexed polymerase chain reaction (PCR) test that can simultaneously detect and identify nucleic acids from up to 15 gastroenteritis-causing viruses, parasites and bacteria (see table 1). It can analyse human stool samples that are fresh, frozen or in a holding medium, and the results should be used in conjunction with other clinical and laboratory findings. It is intended to be used in a laboratory setting.

**Table 1** Pathogens detected and identified by the xTAG Gastrointestinal Pathogen Panel

Bacteria and bacterial toxins	Viruses	Parasites
<i>Campylobacter</i>	Adenovirus 40/41	<i>Cryptosporidium</i>
<i>Clostridium difficile</i> , toxin A/B	Norovirus GI/GII (genogroup)	<i>Entamoeba histolytica</i>
<i>Escherichia coli</i> O157	Rotavirus A	<i>Giardia</i>
Enterotoxigenic <i>Escherichia coli</i> LT/ST		
Shiga-like toxin-producing <i>Escherichia coli</i> stx1/stx2		
<i>Salmonella</i>		
<i>Shigella</i>		
<i>Vibrio cholerae</i>		
<i>Yersinia enterocolitica</i>		

3.2 The assay uses reverse transcription PCR and the procedure includes 5 distinct phases:

- pre-treatment of the sample
- nucleic acid extraction and purification using an automated nucleic acid extraction system
- broad-range PCR reaction using a thermal cycler
- bead hybridisation and detection using a thermal cycler
- data acquisition and analysis (using Luminex 100/200 or MAGPIX analyser).

3.3 Ten microlitres of purified sample are needed for the first broad-range PCR reaction, which amplifies nucleic acids present in the sample. Five microlitres of the broad-range PCR products are then added to a hybridisation and detection reaction, in which target nucleic acids bind to species-specific tagged beads. If pathogen nucleic acid is present, fluorescence is emitted by a streptavidin and R-Phycoerythrin conjugate, which is included in the reaction. Fluorescence intensity is measured by either the Luminex 100/200 or MAGPIX analyser to determine which bacterial, viral or parasitic DNA is present in the sample. Positive and negative controls should be included in each test run. The company recommends that each run includes 3 negative controls (RNase-free water) and at least 1 positive control (known positive samples). The assay also contains an internal control that is added to each sample before extraction and shows whether the assay is functioning as intended.

3.4 The estimated turnaround time for the xTAG Gastrointestinal Pathogen Panel is 5 to 6 hours, including sample preparation time. Up to 96 samples (including controls) can be processed in 1 run, depending on the capacity of a laboratory's PCR thermal cyclers. The test does not give any information on antimicrobial resistance genes or antimicrobial susceptibility.

## FilmArray GI Panel

3.5 The FilmArray Gastrointestinal Panel (BioFire Diagnostics) is a CE-marked qualitative, highly multiplexed PCR test that can simultaneously detect and identify up to 22 pathogens (see table 2) from stool samples in Cary Blair transport media. It is intended for use in a clinical laboratory and the results should be used in conjunction with other clinical and laboratory findings.

### Table 2 Pathogens detected and identified by the FilmArray GI Panel

Bacteria	Viruses	Parasites
<i>Campylobacter (jejuni, coli and upsaliensis)</i>	Adenovirus F 40/41	<i>Cryptosporidium</i>
<i>Clostridium difficile (toxin A/B)</i>	Astrovirus	<i>Cyclospora cayetanensis</i>
<i>Plesiomonas shigelloides</i>	Norovirus GI/GII	<i>Entamoeba histolytica</i>
<i>Salmonella</i>	Rotavirus A	<i>Giardia lamblia</i>
<i>Yersinia enterocolitica</i>	Sapovirus (I, II, IV and V)	
<i>Vibrio (parahaemolyticus, vulnificus and cholerae)</i>		
<i>Vibrio cholerae</i>		
Enteraggregative <i>Escherichia coli</i>		
Enteropathogenic <i>Escherichia coli</i>		
Enterotoxigenic <i>Escherichia coli</i> lt/st		
Shiga-like toxin-producing <i>Escherichia coli</i> stx1/stx2		
<i>Escherichia coli</i> O157		
<i>Shigella/Enteroinvasive Escherichia coli</i>		

3.6 The FilmArray GI Panel is intended for use with the FilmArray and the FilmArray 2.0 system. The FilmArray systems are integrated and include automated sample preparation. The FilmArray system can process 1 sample per hour, whereas the FilmArray 2.0 system allows several FilmArray systems to be linked to process up to 8 samples per hour depending on how many modules are available in a laboratory (1 sample per hour per module). All reagents needed for sample preparation, reverse transcription, PCR and detection are provided freeze-dried in a single-use pouch. Before inserting the reagent pouch into the analyser, the sample is combined with sample buffer and is injected into the pouch along with a hydration solution. After the pouch has been inserted, the system automatically processes a sample through the following stages:

- nucleic acid purification

- broad-range reverse transcription PCR
- second-stage 'nested' PCR with species-specific primers
- detection with melting curve analysis.

3.7 The system extracts and purifies nucleic acids, which then undergo reverse transcription and are amplified in the first broad-range PCR reaction. A second nested PCR reaction containing species-specific primers is run to detect and identify any pathogens in the sample by fluorescence. Each single-use pouch also contains 2 internal controls: 1 RNA process control assay and 1 control assay for the second-stage PCR. Both controls must be positive for the sample to be reported. Results are reported automatically using the FilmArray software. The test does not give any information on antimicrobial resistance genes or antimicrobial susceptibility.

## Faecal Pathogens B assay

3.8 The Faecal Pathogens B assay (AusDiagnostics) is a CE-marked highly multiplexed PCR test that can detect and identify up to 15 pathogens from nucleic acid extracted from fresh faecal samples. The assay is intended to be used in conjunction with other clinical and laboratory findings. The pathogens that can be identified by the assay are shown in table 3.

**Table 3 Pathogens detected and identified by the Faecal Pathogens B assay**

Bacteria	Viruses	Parasites
<i>Salmonella</i> species	Rotavirus A	<i>Giardia lamblia</i> (18s)
<i>Shigella</i> species and <i>Shigella</i> /Enteroinvasive <i>Escherichia coli</i>	Norovirus genogroup I	<i>Cryptosporidium</i> ( <i>parvus</i> and <i>hominis</i> )
<i>Campylobacter</i> species	Norovirus genogroup II	<i>Entamoeba histolytica</i> (not <i>dispar</i> )
<i>Clostridium difficile</i>	Adenovirus group F and group G	
Shiga toxin 1 and 2	Sapovirus	
<i>Escherichia coli</i> O157	Astrovirus	

- 3.9 The assay is intended to be used in conjunction with the High-Plex Multiplex Tandem PCR system and the Easy-Plex results software. The assay procedure includes the following processes:
- nucleic acid extraction and purification
  - broad-range PCR (using the High-Plex MultiPlex Tandem PCR system)
  - real-time PCR with species-specific primers (using the High-Plex Multiplex Tandem PCR system)
  - detection with melting curve analysis.
- 3.10 In the first PCR step, broad-range primers are used and the product of this reaction is diluted and divided into several real-time PCR reactions, which use nested species-specific primers to detect and identify any pathogens in the sample by fluorescence. Results are reported using the Easy-Plex results software. When multiple pathogens are present in a sample, the software indicates the relative quantitation between the targets, which may allow the relative importance of each detected pathogen to be determined. Each tube used for the broad-range PCR reaction includes an internal positive control (SPIKE), and the company recommends that each run includes both positive and negative (water) controls. Up to 24 samples, including positive controls, can be processed in 1 run. The estimated test turnaround time is 3 to 4 hours. The test does not give any information on antimicrobial resistance genes or antimicrobial susceptibility.

### *The comparator*

- 3.11 The comparator used in this assessment is the syndromic algorithm for routine testing in sporadic cases from Public Health England's [UK standards for microbiology investigations for gastroenteritis and diarrhoea](#). The standard recommends that, except for requests for a single-organism screen, all samples should be screened for the following pathogens that are commonly associated with gastrointestinal infection:
- *Campylobacter* species
  - *Salmonella* species

- *Shigella* species
- *Verocytotoxic Escherichia coli* including O157
- *Clostridium difficile* (for antibiotic-associated diarrhoea)
- *Cryptosporidium*
- rotavirus (children younger than 5)
- adenovirus (children younger than 5)
- norovirus (children younger than 5 and people in hospital).

3.12 The testing pathway incorporates a range of tests including:

- microbiological culture
- nucleic acid amplification tests
- immunoassays
- microscopy.

3.13 People who have a history of recent travel (to areas other than western Europe, North America, Australia or New Zealand) have additional primary testing for *Vibrio* and *Plesiomonas* species by bacterial culture. A 2-staged testing approach is currently recommended for *Clostridium difficile*, which involves first testing for glutamate hydrogenase using either a nucleic acid amplification test or enzyme immunoassay. If the test is positive, a sensitive toxin enzyme immunoassay should be done to detect the toxins that cause illness. The syndromic algorithm also notes that laboratories may decide to only test for rotavirus during cooler months when the incidence peaks (November to April). Blood cultures may also be done if a patient is systemically unwell.

3.14 In clinical practice, it is likely that the integrated multiplex PCR tests would be used in conjunction with a toxin assay when *Clostridium difficile* is detected and with culture when *Escherichia coli*, *Salmonella*, *Shigella* or *Yersinia* are detected to confirm toxin production or give additional identification or antimicrobial sensitivity information.

## 4 Evidence

The diagnostics advisory committee ([section 8](#)) considered evidence on the integrated multiplex polymerase chain reaction (PCR) tests for identifying gastrointestinal pathogens in people with suspected gastroenteritis from several sources ([section 9](#)). Full details of all the evidence are in the [committee papers](#).

### *Clinical effectiveness*

- 4.1 In total, 23 studies reported data for the xTAG Gastrointestinal Pathogen Panel and the FilmArray GI Panel, all of which were observational studies. One study was retrospective and used stored samples, and the remaining 22 were prospective. No data were available for the Faecal Pathogens B assay. All studies reported diagnostic accuracy and other intermediate outcome data; no studies reported clinical end outcomes.
- 4.2 Most studies did not differentiate between people in hospital and people in the community, and it was assumed that they were a mixed population. Eleven studies included people from European countries, with 3 of these studies done in the UK. The studies were often poorly reported and used an inadequate reference standard. In most studies, it was unclear how participants were selected. In 10 of the studies, there was concern about the applicability of the population included in the studies to the decision question, and all 15 studies that included a reference standard were rated as high risk for applicability concerns relating to the reference standard.

### **Diagnostic accuracy**

- 4.3 Diagnostic accuracy data were presented as positive and negative agreement and were included in exploratory random-effects meta-analyses. Positive and negative agreement data were meta-analysed and reported for both the intervention compared with the comparator and the comparator compared with the intervention.

### ***xTAG Gastrointestinal Pathogen Panel***

- 4.4 The accuracy of the xTAG Gastrointestinal Pathogen Panel was reported in 19 studies, 2 of which also included the FilmArray GI Panel. The number of pathogens on the xTAG test panels varied: 15 pathogens in 16 studies;



11 pathogens in 2 studies; and 14 pathogens in 1 study. The test is currently marketed as containing 15 pathogens.

- 4.5 Only 8 studies included enough information for inclusion in the meta-analyses. Two of these studies, both of which used the 15-pathogen version of the xTAG Gastrointestinal Pathogen Panel, were based in the UK; Halligan et al. (2014) was the largest study with 2,187 samples and Pankhurst et al. (2014) included 839 samples.
- 4.6 The results of the exploratory meta-analyses for the xTAG Gastrointestinal Pathogen Panel are summarised in table 4. There was substantial heterogeneity in the pooled summary estimates. The overall positive and negative agreement between xTAG compared with conventional testing is high but positive agreement falls when conventional testing is compared with the xTAG Gastrointestinal Pathogen Panel. This is because a large proportion of samples that are positive with the xTAG Gastrointestinal Pathogen Panel are confirmed by positive testing, but when the xTAG Gastrointestinal Pathogen Panel is used as the benchmark, conventional testing appears to report fewer positive results. This suggests that the xTAG Gastrointestinal Pathogen Panel detects more pathogens than conventional testing, but the clinical significance of the increased diagnostic yield is unknown.

**Table 4 Accuracy estimates for xTAG Gastrointestinal Pathogen Panel**

Comparison	Positive agreement			Negative agreement		
	I <sup>2</sup>	Pooled result (95% CI)	p value	I <sup>2</sup>	Pooled result (95% CI)	p value
xTAG GPP versus conventional testing	83%	0.929 (0.898 to 0.955)	<0.001	95%	0.982 (0.976 to 0.988)	<0.001
Conventional testing versus xTAG GPP	97%	0.678 (0.580 to 0.770)	<0.001	77%	0.998 (0.997 to 0.999)	<0.001

Abbreviations: CI, confidence interval; I<sup>2</sup>, Cochran Q statistic; xTAG GPP, xTAG Gastrointestinal Pathogen Panel.

## FilmArray GI Panel

- 4.7 The accuracy of the FilmArray GI Panel was reported in 6 studies, 2 of which also included the xTAG Gastrointestinal Pathogen Panel. Five studies reported a version of the FilmArray GI Panel that contained 23 pathogens and 1 study reported a version with 22 pathogens. The test is currently marketed as containing 22 pathogens.
- 4.8 Two US-based studies were included in the meta-analyses. The results of the exploratory meta-analyses for the FilmArray GI Panel are summarised in table 5. There was substantial heterogeneity in the pooled summary estimates. As with the xTAG Gastrointestinal Pathogen Panel meta-analyses, the results suggest that the FilmArray GI Panel detects more pathogens than conventional testing, but the clinical significance of the increased diagnostic yield is unknown. The increased diagnostic yield of the FilmArray GI Panel is slightly less than that for the xTAG Gastrointestinal Pathogen Panel (1.5 compared with 1.2 times more pathology); but only 2 studies contributed data to the meta-analyses for this test.

Table 5 Accuracy estimates for the FilmArray GI Panel

Comparison	Positive agreement			Negative agreement		
	I <sup>2</sup>	Pooled result (95% CI)	p value	I <sup>2</sup>	Pooled result (95% CI)	p value
FilmArray versus conventional testing	89%	0.954 (0.897 to 0.991)	<0.001	88%	0.996 (0.993 to 0.998)	<0.001
Conventional testing versus FilmArray	81%	0.820 (0.761 to 0.872)	<0.001	80%	1.000 (0.999 to 1.000)	<0.001

Abbreviations: CI, confidence interval; I<sup>2</sup>, Cochran Q statistic.

## xTAG Gastrointestinal Pathogen Panel compared with the FilmArray GI Panel

- 4.9 Two studies compared the xTAG Gastrointestinal Pathogen Panel with the FilmArray GI Panel. Khare et al. (2014) reported that both tests detect more pathogens than conventional testing, whereas Gu et al. (2015) reported that both assays detected a similar number of pathogens.

## Causes of additional positive results

- 4.10 Nine studies commented on the possible causes of additional positive results from either the new technologies or conventional testing; that is, they reported whether additional positives associated with the new technologies arose because of these technologies having a broader coverage of pathogens than the comparator, or because the new tests are more sensitive. All 9 studies reported data for the xTAG Gastrointestinal Pathogen Panel and the FilmArray GI Panel. In 8 of the 9 studies, additional positive results were reported to have arisen because of both improved sensitivity and greater coverage. A further 3 studies reported that additional positive results with conventional testing occurred because pathogens or serotypes of pathogens not included in the new technologies were detected. Although the new technologies seem to have an increased detection rate, the absence of an accurate reference standard results in uncertainty about the clinical significance of the additional positive results.

## Analysis of discordant results

- 4.11 Five studies reported the verification of discordant results, 1 of which reported results for the FilmArray GI Panel and the remaining 4 for the xTAG Gastrointestinal Pathogen Panel. In general, the results of the discordant analyses reported in favour of the new tests. However, PCR methods were often used as the verification test, which are likely to verify in favour of the new tests because they use the same analytical approach, particularly for bacterial pathogens. An important area of uncertainty is the clinical significance of detecting bacterial DNA compared with detecting viable bacteria with culture.

## Test-failure rates

- 4.12 Eight studies reported test-failure rates; 2 for the FilmArray GI Panel, 5 for the xTAG Gastrointestinal Pathogen Panel, and 1 for both tests. Gu et al. (2015) reported results for both the xTAG Gastrointestinal Pathogen Panel, which had a failure rate of 5%, and the FilmArray GI Panel, which had no failures. In the 2 other studies reporting results for the FilmArray GI Panel, the test-failure rate ranged from 0.8% to 5.1%. Of the 5 studies reporting results for the xTAG Gastrointestinal Pathogen Panel, 2 reported test-failure rates per pathogen, which ranged from 7.8% to 17.12%, and 3 reported aggregated test-failure rates, that is, for all targets in the panel, which ranged from 2.1% to 19%.

## Test-turnaround times

- 4.13 Laboratory turnaround times for the integrated multiplex PCR tests were reported in 8 studies, 1 of which (Spina et al. 2015) reported the time between sampling and testing with the FilmArray GI Panel only. Two studies, Gu et al. (2015) and Khare et al. (2014), reported results for both the xTAG Gastrointestinal Pathogen Panel and the FilmArray GI Panel. Both studies reported the turnaround time for the FilmArray GI Panel as about 1 hour (1 sample per run) and about 6.5 hours per run (multiple samples) for the xTAG Gastrointestinal Panel. A 1-hour turnaround time for the FilmArray GI panel was also reported by Buss et al. (2015).
- 4.14 Two further studies compared the turnaround time of the xTAG Gastrointestinal Pathogen Panel with conventional methods. A UK-based study, Halligan et al. (2014), reported a laboratory turnaround time with the xTAG Gastrointestinal Pathogen Panel of 26.6 hours for an afternoon run compared with 10.4 hours for a morning run. When sample collection and transport time was included, the median turnaround time was 41.8 hours for an afternoon run with the xTAG Gastrointestinal Pathogen Panel compared with conventional methods, which ranged from 17.3 hours (*Clostridium difficile* testing) to 66.5 hours (bacterial culture). A study based in Germany, Kahlau et al. (2013), reported a median turnaround time of 1 day for the xTAG Gastrointestinal Pathogen Panel compared with 3 days for conventional methods ( $p=0.0000021$ ). A study based in China, Deng et al. (2015), reported a turnaround time of 5 hours for the xTAG Gastrointestinal Pathogen Panel. A further study, based in the US, by Patel et al. (2014) reported the duration of laboratory technician hands-on time to be 2.5 hours for the xTAG Gastrointestinal Pathogen Panel compared with 10 hours for conventional testing and a time to detection of 5 hours for the xTAG Gastrointestinal Pathogen Panel compared with 72 hours for conventional testing.

## Frequency of detecting multiple pathogens in a sample

- 4.15 All 23 studies reported data on the frequency of the tests detecting multiple pathogens in a sample, which ranged from 4% to 58%. The proportion of samples with multiple pathogens detected in the 3 UK-based studies ranged from 4% to 8%, and most samples contained 2 pathogens; the most common pathogens detected in combination were norovirus, *Clostridium difficile*, rotavirus, *Campylobacter*, *Salmonella* and *Shigella*.

## Use of isolation facilities

- 4.16 Use of isolation facilities was reported in 2 studies. The UK-based Halligan et al. (2014) study on using the xTAG Gastrointestinal Pathogen Panel, reported that in a hospital inpatient population a greater proportion of people with community-acquired infections were isolated compared with people with hospital-acquired infections (69% compared with 52.1%), but more people with community-acquired infections were subsequently removed from isolation (60.1% compared with 41.6%;  $p < 0.01$ ). The reasons for this difference are not clear. The median time that people with a community-acquired infection spent in isolation ranged from 1 day with either adenovirus or *Entamoeba histolytica* to 4 days with *Clostridium difficile* or *Escherichia coli* O157. For people with hospital-acquired infection, the median time spent in isolation ranged from 0 days with *Salmonella* to 13.5 days with *Cryptosporidium*. The most common reasons for not removing people from isolation included the person being colonised or infected with multi-drug-resistant organisms, being immunocompromised, or having a respiratory viral infection.
- 4.17 A US-based study, Rand et al. (2015), concluded that 24.6% (25/102) of people who had negative test results with the xTAG Gastrointestinal Pathogen Panel could have been removed from isolation.

## Change in clinical management

- 4.18 One study, Coste et al. (2013), which was done in France and included retrospective testing with the xTAG gastrointestinal Pathogen Panel and other molecular panel tests, reported that 18% (9/49) of patients had an intestinal endoscopy, and that changes to immunosuppressive therapy (including dose reduction) were seen in 24% (13/54) of episodes of diarrhoea. The authors did not change management recommendations on the basis of molecular panel test results because the study was retrospective, but reported that if the study had been prospective, they could potentially have been changed, with 5 of 9 colonoscopies and 6 of 13 therapy changes in immunosuppressed patients possibly being avoided.

## Cost effectiveness

### Systematic review of cost effectiveness

- 4.19 One study met the inclusion criteria (Goldenberg et al. 2015) for the systematic review of existing economic evaluations. The study had limited generalisability because the outcomes reported for the xTAG Gastrointestinal Pathogen Panel were simulated and were not reported as quality-adjusted life years (QALYs).
- 4.20 The study reported a cost-benefit analysis of the xTAG Gastrointestinal Pathogen Panel compared with conventional laboratory testing and took the perspective of the NHS. The time horizon for the model was the duration of the index episode of suspected infectious gastroenteritis. The economic model was based on a non-randomised, parallel testing study of samples from 800 patients, and assumed that the xTAG Gastrointestinal Pathogen Panel was 100% accurate. The clinical outcomes, which included treatment for the infection, admission to an isolation room, and discharge from hospital, were simulated for the xTAG Gastrointestinal Pathogen Panel arm of the model. This resulted in a higher pathogen-detection rate for patients in isolation using the xTAG Gastrointestinal Pathogen Panel (37.2%) compared with current practice (19.8%) and a reduced time in isolation from 2,202 to 1,447 days. The test costs associated with the xTAG Gastrointestinal Pathogen Panel were £22,283 greater than with conventional testing, but these were offset by savings associated with reduced use of isolation facilities, which led to cost savings of £44,482 compared with current practice. Sensitivity analyses showed that an overall reduction in isolation time of 252 days (based on a simulated population of 800 people) would be needed to make implementing the xTAG Gastrointestinal Pathogen Panel cost neutral.

### Modelling approach

- 4.21 Five de novo economic models designed to explore the cost effectiveness of the xTAG Gastrointestinal Pathogen Panel and the FilmArray GI Panel were developed. Each model had a similar structure but the core inputs were varied to take account of the population included in the model. The analysis took the perspective of the NHS and personal social services. Clinical effectiveness was modelled from diagnostic accuracy data using a linked-evidence approach because no data on clinical end outcomes were identified. A model was developed for each of the following populations:

- adults in hospital (base-case model)
- younger children in hospital (Model 2)
- people in the community (Model 3)
- people who are immunocompromised and in hospital (Model 4)
- people with a recent history of foreign travel (Model 5).

### ***Base-case model structure***

- 4.22 A decision tree model was developed, which included testing, isolation and treatment. A decision tree with a time horizon of 2 weeks was chosen because gastroenteritis usually resolves within this time, and so the model did not take into account any adverse events from treatment, persistent complications, readmissions, or mortality.
- 4.23 The model starts with patients having testing with either conventional methods or 1 of the new technologies (the xTAG Gastrointestinal Pathogen Panel or the FilmArray GI Panel). They are then either isolated or not isolated based on clinical judgement, and their subsequent care is determined by whether or not a pathogen is detected. The model structure was the same for patients having testing with conventional methods or the new technologies, but there were differences in the time to get test results and then whether patients were moved from isolation, treated or discharged earlier.

### ***Model inputs***

- 4.24 For all models, data on the prevalence of pathogens and agreement between the new technologies and conventional testing were taken from the clinical-effectiveness review. The proportions of people who were treated, isolated or discharged were estimated using expert opinion or were taken from Goldenberg et al. (2015). No discounting was applied to costs and effects because of the short time horizon of the model.

### ***Costs***

- 4.25 Resource use and costs included in the hospital-based models were:
- cost of testing



- bed days
  - cleaning
  - blood tests and other investigations, including flexible sigmoidoscopy and abdominal X-ray.
- 4.26 Medicine and rehydration costs were included in both hospital and community-based models.
- 4.27 The test costs used in all models, which included consumables, staff costs and overheads, were:
- conventional test: £66.18 per sample
  - xTAG Gastrointestinal Pathogen Panel: £37.10 per sample
  - Film Array GI Panel: £93.53 per sample.
- 4.28 Additional costs for confirmatory testing were applied to the integrated multiplex PCR tests when *Clostridium difficile*, *Escherichia coli* O157, *Salmonella* or *Shigella* were detected. Resource use and medicine costs were taken from published NHS reference costs and the British national formulary, although antimicrobial therapy is not recommended for most gastrointestinal infections. The length of hospital stay was determined by whether a pathogen was identified, whether symptoms persisted, and the identity of the detected pathogen. Length of stay ranged from 2 days for viruses to 19 days for *Clostridium difficile*. If a second test was needed, discharge was delayed.

### ***Health-related quality of life and quality-adjusted life year decrements***

- 4.29 For all models, utility values were taken from the literature. One study, Minor et al. 2015, estimated healthcare costs associated with gastrointestinal infections in the US and estimated utilities for different pathogens as quality-adjusted life days lost. These utility values were converted to QALYs so they could be used in the model. The mean QALY losses from Minor et al. (2015) ranged from 0.0007 for adenovirus to 0.0126 for *Escherichia coli* O157. Expert opinion was used to estimate a QALY loss of 0.0137 for *Clostridium difficile*. There was no disutility included in the model for being hospitalised.



## **Main assumptions**

4.30 The assumptions applied in the base-case analysis were:

- Conventional testing was the comparator, and was 100% accurate.
- The pathogen detection rate for conventional testing was 24.1%, 22.2% for the xTAG Gastrointestinal Pathogen Panel, and 22.9% for FilmArray GI Panel.
- False negatives were identified using a second confirmatory test, which was taken because of persisting symptoms.
- The daily throughput of the new technologies was 24 samples.
- Test results were returned in 3 days for conventional testing, 1 day for the xTAG Gastrointestinal Pathogen Panel, and half a day for the FilmArray GI Panel, but this did not affect the length of stay.
- The minimum total number of bed days for both conventional testing and integrated multiplex PCR tests was 3 days.
- On admission, every patient had a full blood count and 30% of patients had further biochemistry tests.
- A flexible sigmoidoscopy was done for 1% of patients if a pathogen was detected, and 10% of patients if a pathogen was not detected.
- An abdominal X-ray was done for 10% of patients if *Clostridium difficile* was detected, and for 10% of patients if no pathogen was detected. For all other pathogens detected, 5% of patients in the conventional testing arm and 3% of patients in the integrated multiplex PCR testing arm had abdominal X-ray.
- For each day in hospital, 60% of patients had oral rehydration (200 ml of dioralyte every 4 hours) and 30% had intravenous (IV) fluids (2 litres of sodium chloride 0.9%).

## **Base-case model results – adults in hospital**

4.31 In the base-case model, no difference in length of stay between the interventions and the comparator was assumed. Both deterministic and probabilistic results were presented for the base-case model. In both the deterministic and probabilistic base case, the xTAG Gastrointestinal Pathogen

Panel and the FilmArray GI Panel dominated current practice (that is, they were more effective and cost less).

- 4.32 The cost-effectiveness planes showed that the bootstrap estimates were spread across all 4 quadrants of the plane. The cost-effectiveness acceptability curves show that at a maximum acceptable incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, the xTAG Gastrointestinal Pathogen Panel has a 57% probability of being cost effective and the FilmArray GI Panel has a 54% probability of being cost effective.
- 4.33 A scenario analysis was also done, in which the length of stay for the integrated multiplex PCR tests was decreased because of their shorter test turnaround time. If people are discharged a day earlier, the incremental cost saving increases to £679 per person for the xTAG Gastrointestinal Pathogen Panel (from £63 per person in the base case) and £677 for the FilmArray GI Panel (from £52 per person in the base case). The net monetary benefit also increases, but the 95% credible intervals for this calculation cross zero at a maximum acceptable ICER of £20,000 per QALY gained, showing that there is substantial uncertainty about the cost savings.
- 4.34 One-way deterministic sensitivity analyses showed that the base-case model results were most sensitive to changes in the number of bed days. The proportion of false-positive results also had an effect because this parameter drives additional testing and care, but the effect was relatively small compared with bed days.
- 4.35 The effect of changing the assumptions on daily throughput of tests was also explored in a sensitivity analysis. The daily throughput was reduced to 12 samples and increased to 48 samples; under both assumptions, the base-case conclusions were unchanged and the new technologies still dominated conventional testing (that is, they were more effective and cost less).
- 4.36 The cost of the comparator was changed from £66.18 to £20 in an additional analysis. Under this assumption, the new technologies remained dominant but the cost savings reduced to £26 for the xTAG Gastrointestinal Pathogen Panel and £24 for the FilmArray GI Panel.

## **Model 2 results – young children in hospital**

- 4.37 The structure used for Model 2 was the same as the base-case model, but some parameters were changed:
- The pathogen detection rate was assumed to be 24.2% for conventional testing, 21.4% for the xTAG Gastrointestinal Pathogen Panel, and 22.3% for the FilmArray GI Panel. The pathogen prevalence data were also updated using expert opinion.
  - The probability of being isolated and treated after a positive result was lower in Model 2 and there was a greater probability of having no treatment and being discharged.
  - Fewer patients had a flexible sigmoidoscopy and an abdominal X-ray.
  - QALY loss for rotavirus was changed to 0.0022 to reflect the values applied in UK studies on rotavirus vaccination in children.
  - The condition was treated with oral rehydration in 75% of patients and IV fluids in 20% of patients.
- 4.38 Both deterministic and probabilistic results were presented for Model 2. In both the deterministic and probabilistic analyses, the xTAG Gastrointestinal Pathogen Panel and the FilmArray GI Panel dominated current practice.
- 4.39 The cost-effectiveness planes showed that the bootstrap estimates are located in all 4 quadrants. The cost-effectiveness acceptability curves show that at a maximum acceptable ICER of £20,000 per QALY gained, the probability of being cost effective is 58% for the xTAG Gastrointestinal Pathogen Panel and 57% for the FilmArray GI Panel.
- 4.40 A scenario analysis was done, in which the length of stay for the integrated multiplex PCR tests was decreased because of their shorter test turnaround time. If people are discharged a day earlier, the incremental cost saving increases to £959 per person for the xTAG Gastrointestinal Pathogen Panel (from £73 per person when there is no difference in length of stay) and £969 per person for the FilmArray GI Panel (from £83 per person when there is no difference in length of stay). The net monetary benefit of the interventions also increases compared with current practice as bed days drop, and the 95% credible interval does not cross zero when the length of stay reduces by 1 day,

suggesting that the net monetary benefit of the tests is likely to be positive under this assumption.

- 4.41 The cost of the comparator was changed from £66.18 to £20 in an additional analysis. As with the base-case model, under this assumption the new technologies stayed dominant but the cost savings reduced to £16 for the xTAG Gastrointestinal Pathogen Panel and £43 for the FilmArray GI Panel.

### ***Model 3 results – people in the community***

- 4.42 In this model, the structure of the base-case model was changed to remove the hospital-based decision nodes for admission, isolation and discharge. Changes were also made to some of the parameters:
- Pathogen prevalence was taken from the Food Standard Agency's [second study of infectious intestinal disease in the community](#).
  - The pathogen detection rate was 34.9% for conventional testing, 31.6% for the xTAG Gastrointestinal Pathogen Panel, and 32.5% for the FilmArray GI Panel.
  - The probability that a patient's symptoms resolved naturally was 0.75 and that the symptoms persisted was 0.25.
  - All patients were assumed to visit their GP before a test was taken.
  - In 10% of patients, oral rehydration was used to treat the condition.
- 4.43 The deterministic and probabilistic results were presented for Model 3. In both these analyses, the xTAG Gastrointestinal Pathogen Panel dominated current practice. In the deterministic analysis, the FilmArray GI Panel had an ICER of £1,653,939 per QALY gained and in the probabilistic analysis an ICER of £1,309,346 per QALY gained.
- 4.44 The cost-effectiveness planes showed that the xTAG Gastrointestinal Pathogen Panel is cost saving, whereas the FilmArray GI Panel is cost incurring. For both interventions, it is uncertain whether they are more or less effective than the comparator. The cost-effectiveness acceptability curves show that at a maximum acceptable ICER of £20,000 per QALY gained, the xTAG Gastrointestinal Pathogen Panel has almost a 100% probability of being cost

effective, whereas the FilmArray GI Panel has a 6% probability of being cost effective.

- 4.45 One-way deterministic sensitivity analyses were also done, which showed that the model results were most sensitive to changes in the costs of both the interventions and the comparator.
- 4.46 The cost of the comparator was changed from £66.18 to £20 in an additional analysis. Under this assumption, the ICER for the xTAG Gastrointestinal Pathogen Panel is £518,112 per QALY gained and the FilmArray GI Panel's ICER increases to £3,264,373 per QALY gained. A threshold analysis showed that when the cost of the comparator was reduced to £36.60, the xTAG Gastrointestinal Pathogen Panel was no longer dominant.

#### ***Model 4 results – people who are immunocompromised and in hospital***

- 4.47 The structure used for Model 4 was the same as the base-case model, but changes were made to some of the parameters:
- The pathogen detection rate, estimated using expert opinion, was 31.1% for conventional testing, 28.7% for the xTAG Gastrointestinal Pathogen Panel, and 29.4% for the FilmArray GI Panel. The pathogen prevalence data were also updated using expert opinion.
  - The proportion of patients having treatment for each pathogen was also updated using expert opinion.
  - The probability of being isolated after a pathogen was detected was greater than in the base-case model.
  - In patients with negative test results, 20% would have a flexible sigmoidoscopy.
  - An abdominal X-ray would be done in 10% of patients with *Clostridium difficile*, 20% of people with no pathogen detected, 5% of people with other pathogens detected with conventional tests, and 2% of people with other pathogens detected with the new technologies.
  - Every patient had 2 full blood count tests.

- 4.48 Deterministic and probabilistic results were presented for Model 4. In both the deterministic and probabilistic analyses the xTAG Gastrointestinal Pathogen Panel and the FilmArray GI Panel dominated current practice.
- 4.49 The cost-effectiveness planes showed that the bootstrap estimates are located in all 4 quadrants, highlighting the uncertainty in the results. The cost-effectiveness acceptability curves show that at a maximum acceptable ICER of £20,000 per QALY gained, the probability of being cost effective was 55% for the xTAG Gastrointestinal Pathogen Panel and 57% for the FilmArray GI Panel.
- 4.50 The cost of the comparator was changed from £66.18 to £20 in an additional analysis. As with the base-case model, under this assumption the new technologies stayed dominant but the incremental cost savings reduced to £25 for the xTAG Gastrointestinal Pathogen Panel (from £81 when the comparator costs £66.18) and £30 for the FilmArray GI Panel (from £77 when the comparator costs £66.18).

### ***Model 5 results – people with a recent history of foreign travel***

- 4.51 The structure used for Model 5 was the same as Model 3 (people in the community with suspected gastroenteritis), but changes were made to some of the parameters:
- Pathogen prevalence was estimated by clinical experts using Model 3 and data from the Food Standard Agency's [second study of infectious intestinal disease in the community](#) as a base case, and resulted in higher rates of bacteria and parasites in this model (Model 5).
  - The overall pathogen detection rate was 31.1% for conventional testing, 28.0% for the xTAG Gastrointestinal Pathogen Panel, and 29.2% for the FilmArray GI Panel.
  - There was a greater probability of people having treatment compared with Model 3.
  - In 10% of people, the condition would be treated with oral rehydration.
- 4.52 The deterministic and probabilistic results were presented for Model 5. In both analyses, the xTAG Gastrointestinal Pathogen Panel dominated current practice. In the deterministic analysis, the FilmArray GI Panel had an ICER of £1,020,674 per QALY gained and in the probabilistic analysis an ICER of £560,220 per QALY gained.

- 4.53 The cost-effectiveness planes show that the xTAG Gastrointestinal Pathogen Panel is cost saving, whereas the FilmArray GI Panel is cost incurring. For both new technologies, it is uncertain whether they are more or less effective than current practice. The cost-effectiveness acceptability curves show that at a maximum acceptable ICER of £20,000 per QALY gained, the probability of being cost effective is almost 100% for the xTAG Gastrointestinal Pathogen Panel whereas it is 6% for the FilmArray GI Panel.
- 4.54 The cost of the comparator was changed from £66.18 to £20 in an additional analysis. Under this assumption, the xTAG Gastrointestinal Pathogen Panel had an ICER of £356,931 per QALY gained and the FilmArray GI Panel's ICER increased to £4,203,556 per QALY gained. A threshold analysis showed that when the cost of the comparator was reduced to £36.80, the xTAG Gastrointestinal Pathogen Panel was no longer dominant.

## 5 Committee discussion

- 5.1 The committee discussed the current management of suspected gastroenteritis in the NHS. It heard from clinical experts that the condition is usually self-limiting and does not need further investigation or treatment. The committee noted that there may be specific groups of people in whom gastroenteritis could have a greater clinical impact, for example, people who are younger, older, are immunocompromised or who have pre-existing health problems. It heard that these groups of people may benefit from treatment and hospitalisation, and also that there are specific pathogens that may need treatment, such as *Salmonella*, *Campylobacter* and *Shigella*. The committee concluded that although gastroenteritis is generally a self-limiting condition, for certain groups of people or clinical scenarios, the identification of gastrointestinal pathogens is of substantial clinical benefit.
- 5.2 The committee considered the effect of gastroenteritis on infection control practice. It heard from the clinical experts that people in hospital who have diarrhoea are often nursed in isolation until their symptoms resolve or the presence of infectious organisms has been excluded. It also noted that infection control teams often have a low threshold for isolating people because of the risks associated with infectious pathogens causing hospital outbreaks; that is, people who have symptoms that may be associated with an infection are isolated before the cause of the symptoms has been investigated. The committee also heard from a patient expert that being nursed in isolation may not be a positive experience for the patient, especially because they are prevented from having contact with other people on the ward. This can be particularly damaging for children who also miss school attendance during isolation. It also heard that patients and carers can feel anxious while waiting for test results to confirm whether or not an infection is present, particularly when they are not fully informed of the possible effect of the results on their treatment plan. The committee concluded that because the integrated multiplex polymerase chain reaction (PCR) tests are intended to give results quicker than current methods, they could potentially benefit infection control practices by allowing earlier decisions to stop isolation and so improve the experience for patients, who are being cared for by the infection control team.



## Clinical effectiveness

- 5.3 The committee reviewed the evidence available on the xTAG Gastrointestinal Pathogen Panel, the FilmArray GI Panel and the Faecal Pathogens B assay. The committee noted that most of the included studies reported data on diagnostic accuracy only and further, that no subgroup analyses had been possible because of a lack of data. It also noted that no data were available for the Faecal Pathogens B assay and concluded that it could not consider this test further in its discussions.
- 5.4 The committee discussed the accuracy of the xTAG Gastrointestinal Pathogen Panel and the FilmArray GI Panel. It noted that because of the absence of a reference standard, the external assessment group (EAG) had not been able to calculate traditional measures of test accuracy such as sensitivity and specificity. Instead, it had presented the data as measures of both positive and negative agreement. The committee heard from the clinical experts that this was an acceptable approach because the tests used in current practice (culture, single PCR tests, enzyme immunoassays and microscopy) are unlikely to be 100% accurate. It noted that the results of the meta-analyses suggested that there was good agreement between the new tests and current methods, but that there were exceptions to this. One study (Pankhurst et al. 2014) reported low (0.455) positive agreement for *Salmonella* with the xTAG Gastrointestinal Pathogen Panel when compared with culture. The committee considered that the reasons for this were not clear, but heard from the clinical experts that detecting *Salmonella* with current methods is known to be highly accurate because enrichment broth is routinely used in the culture process, reducing the likelihood of false-negative results. It also noted that a further study (Gu et al. 2015) showed low positive agreement for adenovirus with both the xTAG Gastrointestinal Pathogen Panel (0.130) and the FilmArray GI Panel (0.130) when compared with PCR for adenovirus. The committee heard from the clinical experts that this is probably because the PCR test used as the comparator was designed to detect multiple serotypes of adenovirus, some of which are not common causes of gastroenteritis. The committee concluded that the tests showed reasonably good agreement with the tests used in clinical practice, but that there was substantial uncertainty around their diagnostic accuracy because of the absence of a reference standard.

- 5.5 The committee discussed the clinical significance of discordant results for the new tests compared with current methods of detecting gastrointestinal pathogens. It noted that only limited data on verifying discordant results were available from the systematic review because studies that tried to resolve discordant results often used a PCR test that would show bias in favour of the new tests. The reason for the bias, particularly for bacteria and parasites, was because they use the same analytical approach. The committee concluded that this introduced substantial uncertainty into an assessment of diagnostic accuracy, particularly regarding the proportion of true- and false-positive results and the new tests' accuracy for clinically significant disease.
- 5.6 The committee discussed the complexity of verifying discordant results in clinical practice. It heard from the clinical experts that verifying discordant results could be problematic because of the lack of an accurate reference standard, but that clinical follow-up may be used to establish the clinical significance of positive results. The committee also heard that the reasons for additional positive results with the new tests could include the new tests detecting a broader spectrum of pathogens than current methods (for example, non-O157-shiga toxin producing *Escherichia coli*), the new tests having greater sensitivity for pathogens, or the new tests detecting non-viable pathogens that are unlikely to be of clinical significance. The committee concluded that the clinical significance of additional positive results arising from the new tests, and the reasons for discordance need to be established before the new tests can be recommended for routine use in the NHS (see [section 6.1](#)).
- 5.7 The committee discussed the likely effect of the new tests on clinical practice. It noted that the systematic review had not found any evidence of clinical management being changed because of the results from the xTAG Gastrointestinal Pathogen Panel and the FilmArray GI Panel. The committee heard from the clinical experts that early detection and treatment may have substantial benefits for certain groups of patients, for example, people who are immunocompromised, or for certain pathogens, for example, *Escherichia coli* O157. Early identification of pathogens could also result in early discharge when a more benign pathogen that is less likely to lead to complications is identified. It also noted that negative test results that are received more quickly could benefit hospitals, because they would allow people to return to the main ward rather than being nursed in isolation, or in some instances allow discharge from hospital. However, the committee heard from the clinical experts that in

practice, the reasons for de-escalating infection control measures or discharging a person from hospital are complex and also take into account the resolution of clinical symptoms or whether a person is known to be colonised with drug-resistant pathogens. Furthermore, any de-escalation decision taken using the information from the new tests would highly depend on the clinician's confidence in the tests' negative-predictive values and the breadth of pathogens included in the panel. It also heard that the effect of the new tests on resource use could vary between NHS trusts, hospitals and departments depending on the case mix of patients that they see and the isolation facilities that are available. The committee concluded that using the new tests could affect treatment and infection control decisions, but that the lack of evidence on these outcomes means that it is not possible to determine whether this would be realised in clinical practice at present.

## *Cost effectiveness*

- 5.8 The committee considered the cost-effectiveness analyses for the xTAG Gastrointestinal Pathogen Panel and the FilmArray GI Panel. It noted that 5 economic models were available, but heard from the EAG that they should be considered as exploratory models only because of the lack of clinical outcome data for the new tests, and the assumption that the comparator is 100% accurate. The committee noted that the models suggested that the new tests could be cost effective, but that the confidence intervals around the incremental costs were very wide, reflecting the substantial uncertainty in the models' conclusions. The committee concluded that the models were useful for investigating which parameters have the greatest effect on the model outputs, but that conclusions on the cost effectiveness of the new tests could not be made with the evidence available at present.
- 5.9 The committee discussed the hospital-based models and noted that the one-way sensitivity analysis for the base-case hospital-model suggested that it is highly sensitive to the assumptions made about length of stay and treatment, partly because the incremental cost and quality-adjusted life year (QALY) differences are small. Also, the hospital base-case model was sensitive to the assumption made about the proportions of false-positive results because this parameter drives unnecessary treatment and hospital stays. The committee heard from the clinical experts that it was uncertain whether the new tests would reduce length of stay in practice because it was likely that the test results

would not affect the duration of symptoms. It also heard that a decision to discharge a patient from hospital or stop infection control measures may only be considered if a clinician had confidence in the negative test results. The committee therefore concluded that data on clinical outcomes and resource use in the hospital setting, particularly the effect on management after a negative test result, are needed to reduce the substantial uncertainty around these key parameters.

- 5.10 The committee discussed the influence of negative test results in the hospital-based models. It heard from the EAG that around 70% of results obtained with the xTAG Gastrointestinal Pathogen Panel and the FilmArray GI Panel were negative in the studies included in the systematic review. The committee noted that the sensitivity analyses suggested that negative results were a possible driver of cost savings because they could influence resource use and length of stay. It heard from the clinical experts that false-negative results or insufficient pathogen coverage by the new test could lead to infections being missed, which may then cause outbreaks in a hospital. This may also be a significant problem for residential homes. The committee noted that these possible adverse outcomes from false-negative results had not been included in the economic models and concluded that these potential effects would need to be considered in future cost-effectiveness analyses.
- 5.11 The committee considered the test costs used in the economic models. It heard from the clinical specialists that the cost of the comparator could have been overestimated in the model. It noted that the cost of the comparator was from a published study (Goldenberg et al. 2015), which the clinical experts suggested may have used additional PCR tests that are not mandated by Public Health England's [UK standards for microbiology investigations for gastroenteritis and diarrhoea](#), for example, for *Clostridium difficile*, and consequently are not widely used in current practice. The committee considered that the costs used may not represent standard practice. It also noted that the additional scenario analyses on test costs provided by the EAG suggested that test costs only influence the community-based models because the new tests remain cost saving in the hospital-based models under all test cost assumptions. This is because there are no hospital-stay costs and only limited treatment costs in the community models. The committee also noted the threshold analyses provided by the EAG, which suggested that when conventional testing costs drop below £37, the xTAG Gastrointestinal Pathogen Panel is no longer cost saving in the

community-based models. Under all assumptions, the FilmArray GI Panel test cost was always greater than the cost of current practice. The committee concluded that the cost of conventional testing was subject to uncertainty in each of the models, and is also likely to vary between trusts in practice.

- 5.12 The committee considered the level of uncertainty in both the clinical- and cost-effectiveness analyses. It noted that there was substantial uncertainty around the accuracy of the new tests and also a lack of evidence on their effect on clinical management and resource use. In combination, these uncertainties mean that there is insufficient evidence to determine the cost effectiveness of the new tests at present. However, it noted that the exploratory cost-effectiveness analyses done for the xTAG Gastrointestinal Pathogen panel and the FilmArray GI Panel suggested that the new technologies could be cost saving. The committee therefore decided that there was too much uncertainty at present to recommend the new tests for routine use, but wished to encourage further research (see [section 6](#)).

## *Research considerations*

- 5.13 The committee heard from the clinical experts that there are several modular multiplex assays that can detect bacteria, viruses or parasites, available to the NHS. It noted that these technologies fall outside of the scope for this assessment, which focused on integrated multiplex assays that are able to detect bacteria, parasites and viruses simultaneously. However, it considered that the uncertainties highlighted in this assessment, particularly regarding the clinical significance of PCR positive results, might reasonably apply to the modular multiplex assays.
- 5.14 The committee noted that assessing the integrated multiplex PCR tests is further complicated by the lack of a reference standard against which the new tests can be compared. It heard from the clinical experts that culture and microscopy are unlikely to be 100% accurate and that the comparison of viral PCR tests may be confounded by the serotypes detected by each assay. Nevertheless, the committee concluded that verifying discordant results was an important area of further research for the new tests and it therefore wished to encourage further methodological research on ways of assessing diagnostic accuracy in the absence of a reference standard.

5.15 The committee noted that the clinical outcomes and resource use associated with the new tests were likely to differ between population subgroups and hospital- and community-based settings. It discussed the importance of outcomes such as length of time excluded from work and school in community settings but noted that these fall outside the reference case, which takes the perspective of the NHS and personal social services. Subgroups that could be considered in further research include children younger than 5, people with a recent history of foreign travel to areas other than western Europe, North America, Australia or New Zealand, and people who are immunocompromised. The committee noted that the ongoing [Integrate study](#), funded by the Department of Health and Wellcome Trust, aims to assess the clinical utility of molecular panel tests in managing gastroenteritis in the community. The committee concluded that future research should take into account differences that may arise between these subgroups and different healthcare settings.

## 6 Recommendations for further research

- 6.1 The committee was aware that the ongoing [Integrate study](#) may address some of the uncertainties in this assessment relating to diagnosing and managing gastroenteritis in the community. It recommended further research to determine the clinical significance of discordant results between the new tests (the xTAG Gastrointestinal Pathogen Panel, the FilmArray GI Panel and the Faecal Pathogens B assay) and conventional tests. Studies should aim to collect clinical follow-up data that may show which method correctly identifies clinically significant disease. The committee was particularly interested in further research to resolve the discordance between results that are positive with the new technologies and negative by conventional methods.
- 6.2 The committee recommended further research on resource use and clinical effects associated with using the xTAG Gastrointestinal Pathogen Panel, the FilmArray GI Panel and the Faecal Pathogens B assay. The committee was advised that outcomes and resource use may vary according to healthcare setting and case mix, and so research should take place in multicentre studies that take account of these factors. Outcome data that should be collected include but are not limited to:
- length of stay in hospital
  - length of time in isolation
  - change of treatment plan as a result of testing.

## 7 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 6](#) into its guidance research recommendations database (available on the [NICE website](#)) and highlight these recommendations to public research bodies.



## 8 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 and Professor of Haematology, Barts Health NHS Trust

##### **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

##### **Dr Simon Fleming**

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

**Dr James Gray**

Consultant Microbiologist, Birmingham Children's Hospital

**Mr John Hitchman**

Lay member

**Professor Chris Hyde**

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

**Mr Patrick McGinley**

Head of Costing and Service Line Reporting, Maidstone and Tunbridge Wells NHS Trust

**Dr Michael Messenger**

Deputy Director and Scientific Manager NIHR Diagnostic Evidence Co-operative, Leeds

**Mrs Alexandria Moseley**

Lay member

**Dr Peter Naylor**

GP, Chair Wirral Health Commissioning Consortia

**Dr Dermot Neely**

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

**Dr Simon Richards**

VP Regulatory Affairs, Europe and Middle East (EME), 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**

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**Specialist committee members**

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**Mary Foss**

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**Dr Robert Logan**

Consultant Gastroenterologist, Kings College Hospital NHS Trust

**Dr David Partridge**

Consultant Microbiologist, Sheffield Teaching Hospitals NHS Trust

**Dr Giovanni Satta**

Consultant in Medical Microbiology and Infectious Diseases, Imperial College Healthcare NHS Trust

***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.

**Rebecca Albrow**

Topic Lead (until September 2016)

**Jessica Maloney**

Topic Lead (from October 2016)

**Frances Nixon**

Technical Adviser (until September 2016)

**Rebecca Albrow**

Technical Adviser (from October 2016)

**Rob Fernley**

Project Manager

## 9 Sources of evidence considered by the committee

The diagnostics assessment report was prepared by Warwick Evidence.

- Freeman K, Mistry H, Tsertsvadze A et al. Multiplex tests to identify gastrointestinal bacteria, viruses and parasites in people with suspected infectious gastroenteritis: systematic review and economic analysis. June 2016.

### *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 and the diagnostics consultation document.

### **Manufacturers of technologies included in the final scope:**

- AusDiagnostics UK Ltd
- BioMerieux
- Luminex BV

### **Other commercial organisations:**

- BD Diagnostics

### **Professional groups and patient/carer groups:**

- British Infection Association
- British Society for Gastroenterology
- Primary Care Society for Gastroenterology
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Short Bowel Survivors and Friends

## Research groups:

None

## Associated guideline groups:

None

## Others:

- Department of Health
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- NHS England
- Public Health England
- Welsh Government

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## Accreditation

