Healthcare Improvement Scotland | SHTG Advice on health technologies

Evidence Synthesis
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In response to enquiry from Scottish Microbiology & Virology Network

Clinical and cost effectiveness of multiplex polymerase chain reaction gastrointestinal pathogen panels for people with suspected gastroenteritis.

What were we asked to look at?

The Scottish Microbiology and Virology Network (SMVN) asked us to examine evidence on testing with multiplex polymerase chain reaction (PCR) gastrointestinal pathogen panels (GPPs) compared with conventional testing methods in people with suspected gastroenteritis.

Why is this important?

Conventional testing comprises multiple tests, such as immunoassay and stool culture, which can take several days to return results. Multiplex PCR GPP tests return results within hours. A faster diagnosis has implications for improved cost effectiveness and patient management outcomes, such as reduction in empirical antibiotic prescribing, length of hospital stay and use of isolation bays. Rapid detection of infectious pathogens can also limit and prevent outbreaks.

What was our approach?

We produced an Evidence Synthesis to capture the published literature on the clinical effectiveness and cost effectiveness of multiplex PCR GPPs. The literature search was limited to studies published since the National Institute for Health and Care Excellence (NICE) diagnostic guidance on the use of PCRs published in 2017.

What next?

SMVN will use the findings of this Evidence Synthesis to inform the development of practice recommendations and a business case for use of GPPs in people with suspected gastroenteritis.

Key points

- The evidence base consisted of one good quality systematic review (23 observational studies of poor quality) and a further four non-UK observational studies published since the NICE diagnostic guidance in 2017.
- Due to observational study designs, the overall evidence is not robust and data on morbidity, mortality and quality of life outcomes is lacking Integrated GPPs demonstrate consistently faster turnaround time than conventional tests, which may be associated with improved antibiotic use and reduced requirement for additional diagnostic tests. Testing using GPPs did not affect length of hospital stay compared with conventional methods.
- There is substantial uncertainty around the probability of cost effectiveness due to lack of clarity on the diagnostic accuracy of GPPs and the absence of patient outcome data.
    - In hospitalised adults, children and people who are immunocompromised, the probability of cost effectiveness of GPPs (Luminex xTAG® and Biofire FilmArray™) is around 54-58% compared with conventional testing.
    - In the recently returned from travel population and for patients in community settings the probability of cost effectiveness varied widely between the Luminex xTAG® GPP (99-100% probability) and the Biofire FilmArray™ GPP (6% probability) compared with conventional testing. PCR tests could be useful as preliminary screening tests, particularly in the case of potential outbreaks of harmful infectious pathogens, such as Shiga-toxin producing *E.coli*. Positive PCR results should be confirmed by culture.
- More robust evidence on clinical effectiveness may become available following completion of ongoing randomised controlled trials (RCTs). One UK study is due to be completed in September 2020 (GastroPOC). A US study is due to be completed in November 2019 (NCT03809117).

Contents

Literature search

A systematic search of the secondary literature was carried out between 12 April 2019 and 16 April 2019 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline and Embase databases were also searched for systematic reviews and meta-analyses.

The primary literature was systematically searched on 12 April 2019 using the following databases: Medline, Embase. Results were limited to English and 2016-2019. The literature search was limited to studies published from 2016 onwards, as this Evidence Synthesis is an update of the evidence since the NICE diagnostic guidance in 2017[1].

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing clinical trials. Websites of relevant organisations, for example Health Protection Scotland, were also searched.

Concepts used in all searches included: gastroenteritis diagnosis, faecal PCR. A full list of resources searched and terms used is available on request.

Introduction

Acute diarrhoea caused by infectious gastroenteritis is a common, but usually minor, illness[2]. While infectious gastroenteritis is a self-limiting illness, outbreaks can be costly. For example, it has been estimated that foodborne illnesses cost the UK £1.5 billion per year[3]. The management of Norovirus outbreaks in NHS Lothian 2007-2009, was estimated to cost £1.2 million due to lost bed-days and staff absences[4].

The diagnosis of gastroenteritis is usually based on clinical presentation, primarily characterised by diarrhoea or vomiting[1]. Diarrhoea can also arise from non-infectious causes, such as inflammatory bowel disease (IBD), urinary tract infections and medications. Therefore, when patients present with diarrhoea, it is advised that possible infectious causes are ruled out in the first instance[1]. Rapid diagnosis of infectious pathogens can reduce unnecessary antibiotic treatment, the need for additional testing, and the need for infection control measures, such as patient isolation[1]. This, in turn, can reduce burden on healthcare services and improve antimicrobial stewardship[5].

Conventional testing comprises multiple tests, such as stool culture, microscopy and enzyme immunoassays, to determine whether infectious gastroenteritis is caused by bacterial, viral or parasitic pathogens. Current practice in the UK is determined by the Public Health England (PHE) syndromic algorithm, which recommends the pathogens that should be tested for depending on different clinical presentations[6-8]. The PHE Standards for Microbiology Investigations[8] (due to be updated in 2019) state that rapid diagnostic methods, such as PCR, can be used where available, but recommend that confirmation by conventional methods is conducted.

In 2017, NICE evaluated the evidence for clinical effectiveness and cost effectiveness of three commercial integrated multiplex polymerase chain reaction (PCR) gastrointestinal pathogen panels (GPPs): Biofire FilmArray™, Luminex xTAG® Gastrointestinal Pathogen Panel, and AusDiagnostics Faecal Pathogens B[1]. Integrated GPPs simultaneously detect and identify viral, bacterial and parasitic pathogens in suspected gastroenteritis from one stool sample. The 2017 NICE diagnostic guidance included evidence on the diagnostic accuracy of GPPs and some evidence for secondary outcomes, but no studies reported patient management outcomes[1]. The diagnostic accuracy of the GPPs reported by NICE is presented in appendix 1. There was uncertainty around the diagnostic accuracy of GPPs due to the lack of an adequate reference standard. Furthermore, the reasons for discordant results were unclear, and the true proportion of false negatives and false positives could not be ascertained. NICE concluded that the evidence was insufficient to recommend routine adoption of GPPs and that the reasons for discordant results would need to be identified before routine adoption in the NHS could be recommended. One possible reason for discordant results between GPPs and conventional methods is that PCR tests may not be able to distinguish between symptomatic and asymptomatic colonisation. Further, misdiagnosis may arise from difficulty interpreting results from PCR tests, potentially leading to unnecessary treatment[9].

NICE focused their review on evidence for integrated multiplex PCR tests only. Although the diagnostic accuracy for these tests was assessed, the evidence base was lacking in terms of impact on patient management outcomes. Additionally, the NICE report did not include evidence on organism-specific GPPs which target microorganism-specific groups, for example viral pathogen panels. Therefore, this Evidence Synthesis presents the recent evidence of clinical and cost effectiveness, particularly in relation to patient management outcomes, when testing with multiplex GPPs compared with conventional testing. The outcomes of interest included test turnaround time, changes to patient management plans, length of hospital stay, duration of isolation, duration of barrier nursing, resource utilisation, morbidity arising from either the presenting condition or side-effects of treatment, mortality, and patient reported outcomes such as health-related quality of life.

Epidemiology

Gastroenteritis is a commonly occurring, short-lived illness which presents as an acute onset of diarrhoea and can occur with or without vomiting, as well as abdominal pain and fever[2]. The estimated incidence of gastroenteritis each year in the UK is 20%[2]. Gastroenteritis can arise from bacterial, viral or parasitic pathogens[2]. In a large-scale prospective study in the UK, it was identified that the most common viral cause of infectious gastroenteritis was Norovirus and the most common bacterial cause were *Campylobacter* spp.[10].

The time taken for symptoms to develop depends on the cause of infection and can range from a few hours to a few days. Similarly, the time for symptoms to remit depends on the cause of the infection. The majority of cases resolve within several days without the need for treatment[2]. As such, most cases are self-managed in the community. If severe or persistent symptoms occur, patients may require admission to hospital for observation and symptom management.

In a minority of cases, infectious pathogens can cause complications which lead to chronic illness or mortality. Infectious gastroenteritis caused by toxin-producing pathogens, such as Verotoxigenic *E. coli* (VTEC) or Shiga-toxigenic *E. coli* (STEC) can lead to hemolytic uremic syndrome (HUS) and renal disease, which can result in death[11]. Approximately 9% of cases of symptomatic STEC in Scotland between 1999 and 2008 resulted in HUS[12]. Although rare, severe diarrhoea can cause dehydration which can result in mortality[2]. The effects of complications from infectious gastroenteritis can result in significant healthcare costs[13].

A higher prevalence of gastroenteritis-causing pathogens occur in children <5 years, recent travellers, those who are immunocompromised, people who have IBD, and people who have recently been hospitalised or taken antibiotics[13, 14].

Health technology description

Multiplex PCR tests are highly sensitive and return results within a shorter timeframe than conventional methods, as they detect nucleic acids (DNA or RNA) of viruses, bacteria and parasites directly from stool samples[1]. There are a range of commercial integrated multiplex GPPs available, as well as smaller molecular panels that target organism-specific groups, for example viral pathogen panels. A list of organism-specific and integrated commercial platforms is provided in table 1.

Table 1: organism-specific and integrated commercial multiplex PCR GPPs

Organism-specific GPPs	Integrated GPPs
■ BD MAX™ System (BD Diagnostics, USA) ■ Allplex™ Gastrointestinal Panel Assays (Seegene, Korea) ■ RIDA GENE-gastrointestinal kits (R-Biopharm, Germany) ■ LightMix Modular Gastro Panel Assays (Roche Diagnostics, Switzerland) ■ EasyScreen™ (Genetic Signature, Australia) ■ EntericBio real-time Gastro Panel I (Serosep, Ireland) ■ Seeplex® Diarrhea ACE detection (Seegene, Korea) ■ Amplidiag® Bacterial GE (Mobidiag Ltd., Finland)	■ Biofire FilmArray™ (BioFire Diagnostics, USA) ■ Luminex xTAG® Gastrointestinal Pathogen Panel (Luminex, Canada) ■ Faecal Pathogens A & B (AusDiagnostics, Australia) ■ BioCode Gastrointestinal Pathogen Panel (Applied BioCode Inc., USA) ■ QIAstat-Dx™ (previously DiagCORE®) Gastrointestinal Panel V2 (QIAGEN Group, Netherlands)

■ VIASURE RNADNA Extraction Kit (Certest Biotec, Spain) ■ GeneXpert system panels (Cepheid, USA)	

Some multiplex PCR GPPs are already in use across the UK. In 2015, NICE reported that the BD MAX™ System (BD Diagnostics, USA), which has separate bacterial, viral and parasite panels, was being used in 27 NHS Trusts[15]. The EntericBio real-time Gastro Panel I (Serosep, Ireland), which targets only bacterial pathogens, has been rolled out in NHS Wales and was reported to be used in 85% of microbiology labs in Ireland in 2014[16].

A number of evaluations and pilots of GPPs have been undertaken in NHSScotland. A comparison of the xTAG®, Cepheid Xpert® Norovirus Assay and BD MAX™ for the detection of Norovirus was conducted in NHS Lothian and published in 2018[17]. Detection of pathogens was satisfactory for all GPPs. There is an ongoing evaluation of the xTAG® in Ninewells Hospital, NHS Tayside, of diagnostic accuracy, clinical utility and costs compared to routine testing[18] (D Yirrell, Consultant in Virology, NHS Tayside. Personal Communication, 28 June 2019). NHS Dumfries and Galloway and NHS Fife are currently conducting an evaluation of the Quiagen QIAstat-Dx™, while NHS Greater Glasgow and Clyde previously evaluated the EntericBio real-time Gastro Panel, but it is not currently in use (F MacKenzie, SMVN Scientific Manager, NHS Grampian. Personal Communication, 16 July 2019).

The literature search only identified evidence relating to the Biofire FilmArray™ and Luminex xTAG®, and so the other GPPs, listed above, will not be described further. The Biofire FilmArray™ detects 22 pathogens and the Luminex xTAG® detects 15 pathogens which are listed in table 2, along with the pathogens that are recommended for screening in the PHE syndromic algorithm.

Table 2: bacteria, viruses and parasites within the PHE syndromic algorithm[6, 8] and detected by Biofire Filmarray™ and Luminex xTAG®

Biofire FilmArray™	Luminex xTAG®	PHE syndromic algorithm
Bacteria		
Campylobacter (*jejuni, coli and upsaliensis*)	*Campylobacter*	*Campylobacter* species
C. difficile (toxin A/B)	*C. difficile* (toxin A/B)	*C. difficile* (for antibiotic-associated diarrhoea)
E. coli O157	*E.coli* O157	Verocytotoxic *E.coli* (including O157)
Salmonella	*Salmonella*	*Salmonella*
Shigella/enteroinvasive E. coli	*Shigella*	*Shigella* species

Vibrio cholerae	*Vibrio cholerae*	*Vibrio* species (if indicated by clinical presentation)
Yersinia enterocolitica	*Yersinia enterocolitica*	*Yersinia* species (if indicated by clinical presentation)
Plesiomonas shigelloides	–	*Plesiomonas* species (if indicated by clinical presentation)
Enterotoxigenic *E. coli* LT/ST	Enterotoxigenic *E. coli* LT/ST	–
Shiga-like toxin-producing *E. coli stx1/stx2*	Shiga-like toxin-producing *E. coli* stx1/stx2	–
Vibrio (*parahaemolyticus, vulnificus and cholerae*)	–	–
Enteroaggregative *E.coli*	–	–
Enteropathogenic *E. coli*	–	–
Viruses		
Norovirus GI/GII	Norovirus GI/GII	Norovirus
Adenovirus F 40/41	Adenovirus 40/41	Adenovirus (if indicated by clinical presentation)
Rotavirus A	Rotavirus A	Rotavirus (if indicated by clinical presentation)
Astrovirus	–	Astrovirus (if indicated by clinical presentation)
Sapovirus (I, II IV and V)	–	Sapovirus (if indicated by clinical presentation)
Parasites		
Cryptosporidium	*Cryptosporidium*	*Cryptosporidium*
Entamoeba histolytica	*Entamoeba histolytica*	*Entamoeba*
Giardia lamblia	*Giardia*	*Giardia*
Cyclospora cayetanensis	–	–

FilmArray™ is a CE-marked highly multiplexed qualitative PCR. It is a closed, integrated system which detects pathogen nucleic acids from stool samples in Carey-Blair transport media[14, 19]. The FilmArray™ can process eight samples in one run, and results for one sample can be returned within one hour. The manufacturer reports an overall sensitivity of 98.5% and specificity of 99.2% for the FilmArray™[20].

The xTAG® is also a CE-marked highly multiplexed qualitative PCR that simultaneously detects and identifies nucleic acids of pathogens. The xTAG can directly analyse stool samples that are fresh, frozen or in a holding medium. Each run requires at least one positive control and it is recommended that three negative controls are included. To ensure that the assay is functioning as intended, an internal control is included in the assay. The preparation and run-time for processing 24 stool samples (plus controls) takes 5-6 hours[14].

Clinical effectiveness

One systematic review, which was the basis of the NICE diagnostic guidance and conducted as part of a health technology assessment (HTA), assessed diagnostic accuracy and secondary outcomes such as turnaround time, and patient management outcomes[14]. Additional studies, published since the NICE report, were also identified. Of the three observational studies considered relevant for inclusion, two assessed turnaround times, three assessed antibiotic prescribing, two assessed length of hospital stay, and two reported the impact on additional diagnostic tests undertaken.

Turnaround time

The systematic review included 23 low quality, observational studies[14]. The comparator was conventional testing as defined by the PHE algorithm. The PHE algorithm states that primary testing includes culture to test for *Salmonella* spp., *Campylobacter* spp., *Shigella* spp. and VTEC (O157); microscopy or enzyme immunoassay should be conducted for *Cryptosporidium*; and enzyme immunoassay or nucleic acid amplification tests (NAATs) should be conducted for *C. difficile*. Secondary testing includes NAATs for Norovirus and microscopy for ova, cysts, parasites and *Giardia*. For children under 5 years, additional enzyme immunoassay or NAATs should be used to test for Rotavirus, Adenovirus 40 and 41, as well as NAATs for Norovirus, Sapovirus and Astrovirus.

The systematic review[14] referenced a study which stated time to detection for xTAG® was 5 hours compared with 72 hours for conventional testing, and there was also a reduction in hands-on technician time by 7.5 hours when testing with xTAG®. Another study in the systematic review reported a median turnaround of one day for xTAG® compared with three days for conventional testing ($p<0.0005$). Expanding on this, an additional study in the systematic review specified turnaround times of 26.6 hours for laboratory turnaround and 41.8 hours for clinical turnaround (includes sample collection and transport time) when testing with xTAG®. This was compared with clinical turnaround times for conventional testing of 17.3 hours for *C. difficile*; 27 hours for Norovirus, Adenovirus and Rotavirus; and 66.5 hours for bacterial culture and parasites. Additionally,

two studies in the systematic review reported longer turnaround times for xTAG® compared with FilmArray™.

Two prospective studies published after the systematic review were included. The first of these, which included 241 patients either admitted or presenting to the emergency department, compared the FilmArray™ with conventional testing[21]. Conventional testing included stool culture and additional tests included *C. difficile* PCR (for both the FilmArray™ and conventional testing groups); enzyme immunoassay for ova, parasites, *Giardia*, *Cryptosporidium* and Rotavirus; culture for STEC and *Yersinia* and *Vibrio; Microsporidia* stain and modified acid-fast stain. This study reported a significantly shorter mean turnaround time for the FilmArray™ (8.94 hours) compared with a historical control group tested by stool culture (54.75 hours, $p<0.0001$)[21].

The second, a larger prospective study examined 1,887 specimens from newly-admitted (<3 days) inpatients and outpatients from 17 clinics. A historical control group of patients who had been tested by conventional stool culture were compared to patients tested using the FilmArray™. Additional conventional tests included enzyme immunoassay for STEC, ova and parasite examination, *Cryptosporidium /Cyclospora* testing by modified acid-fast smear, Giardia ProSpecT stool antigen testing (Remel Inc), and a laboratory-developed viral gastroenteritis multiplex PCR panel. There was a significantly faster median turnaround time for FilmArray™ than for stool culture (18 versus 47 hours, $p<0.0001$). Additionally, return of all results for FilmArray™ (18 hours) were significantly faster than return of STEC positive results by culture and immunoassay (60 hours, $p=0.0006$) and return of negative STEC results by culture and immunoassay (75 hours, $p<0.0001$)[22].

The evidence on turnaround times suggests variable durations for the return of test results by the xTAG®, FilmArray™ and conventional testing. However, the evidence illustrates that GPP tests consistently returned results faster than conventional testing. It should be noted that xTAG® can run 24 samples at once while FilmArray™ can test eight samples in one run. These differences in throughputs may lead to variation in turnaround times in practice. For example, it is reasonable to expect that laboratories may delay running samples to permit for batching, particularly with the xTAG®. One study identified by the systematic review stated that while the laboratory turnaround time for the xTAG® was 10.4 hours for a morning run, it was 26.6 hours for an afternoon run.

Patient management outcomes

Antibiotic prescribing

Three observational studies reported outcomes on antibiotic prescribing. It should be noted here that PHE guidance states that antibiotics are not recommended for infection of unknown pathology and that empirical antibiotic prescribing is not recommended unless *C. difficile* or *Campylobacter* spp. is suspected[23]. However, the studies have been described here to help ensure a comprehensive overview of the available evidence.

Both of the prospective studies, which were described above, reported data on antimicrobial prescribing when testing was conducted by FilmArray™ compared with conventional testing[21, 22]. The prospective study with smaller sample size indicated that patients tested with FilmArray™ received antibiotics for fewer days, but the difference was not statistically significant (1.73 versus 2.12, p=0.06)[21].

The larger prospective study demonstrated a significantly faster median time from sample collection to instigation of antibiotic treatment when using FilmArray™ (26 hours), compared with stool culture testing in the historical control (72 hours, p<0.0001)[22]. There was also a reduction in empirical antibiotic prescribing when using FilmArray™ compared with historical controls tested by stool culture (23.5% versus 40%, p=0.0148)[22]. In addition, 9/21 patients who were positive for STEC had been empirically prescribed antimicrobials. Faster turnaround times when using FilmArray™ allowed for the discontinuation, in 8/9 cases, of empirically prescribed antimicrobials when test results were returned as positive for STEC. Rapid removal of antimicrobials when tests are positive for STEC is of benefit to the patient as use of antimicrobials for a STEC infection increases risk of developing HUS[24, 25]. There was a median of 8 hours (range 0.5 hours to 25 hours) between test-result release and therapy discontinuation.

A cross-sectional study identified records of patients with suspected gastroenteritis over a 26 month period who were tested by FilmArray™ and compared them with patients, also identified by their records, who were tested by conventional testing in the previous 26 month period[26]. The study included 9,402 patients who underwent testing by FilmArray™ from March 2015 to May 2017 and 5,986 patients who underwent conventional testing from December 2012 to February 2015. Conventional testing included stool culture, antigen testing and modified acid-fast staining for ova and parasite examination (including *Giardia* and *Cryptosporidium* spp.), and enzyme immunoassay for Rotavirus and Adenovirus 40/41. This study found patients tested by FilmArray™ were significantly less likely to be prescribed antibiotics (n=3,408, 36.2%) than patients whose samples were tested by stool culture (n=2,449, 40.9%, p<0.001).

Length of hospital stay and patient isolation

A small prospective study recorded outcomes on length of hospital stay (LOS)[21]. The average LOS of patients who received testing by FilmArray™ was not significantly different to historical control patients tested by conventional methods (5.2 versus 5.6, p=0.14). The study[21] also reported additional indices of LOS, such as LOS after stool sample collection and LOS where results were known at discharge, and these outcomes favoured FilmArray™ in adult samples but not paediatric samples.

The systematic review[14] identified one study reporting outcomes on LOS. Frozen samples from patients, which were previously tested by conventional methods, were re-tested with FilmArray™. For patients who were negative for pathogens when tested by routine methods, testing by FilmArray™ would not have reduced the LOS for patients. However, a reduction in the number of patients required to be in isolation may have been possible, based on samples which originally

tested positive by routine testing. Twenty-four percent of samples re-tested by FilmArray™ did not test positive for any infectious pathogen. The median isolation time for those patients was 3.8 days (interquartile range 1.8 to 11 days).

A cross-sectional study recorded LOS between participants who were identified as having gastroenteritis from their records and tested by either FilmArray™ or conventional methods. The study reported that there were no differences in LOS or the number of emergency room visits at 30 days between those tested by conventional methods and those tested with FilmArray™[26].

Additional diagnostic tests

Two studies reported data on additional resource utilisation. Both studies reported that patients who underwent testing by FilmArray™ were significantly less likely to receive further testing. The prospective study described above[21] reported that patients tested by FilmArray™ required significantly fewer follow-up stool tests (0.58 vs 3.02, $p<0.0001$) and imaging studies (0.18 vs 0.39, $p=0.0002$). The cross-sectional study described previously[26] found that, compared with stool culture, patients tested by FilmArray™ were less likely to undergo upper endoscopy (8.4% versus 9.6%, $p=0.008$) or abdominal imaging (29.4% versus 31.7%, $p=0.002$)[26].

Organisational issues/context

Health Protection Scotland have produced guidance on the role of PCR tests in the public health management of STEC and VTEC[27, 28]. A positive PCR result should always be confirmed by culture and referral of the isolate, or faecal sample, to the Reference Laboratory. Owing to the potential severe consequences of an outbreak of VTEC/STEC, the threshold for action for introducing infection control measures is low. Rapid identification of VTEC/STEC could allow infection control measures to be put in place quickly, mitigating further exposure to the public. If a positive result is obtained for VTEC/STEC by a validated PCR in a local laboratory, the physician and local Health Protection Team should be notified. The significance of the positive PCR result should be assessed in relation to clinical and public health information. Clinical and public health management should be instigated when a positive result is found by PCR. Health Protection Scotland suggest that PCR tests could be used as preliminary screening tests and recommend that culture facilities are retained by diagnostic laboratories if PCR tests are introduced for routine use.

Microbiological clearance is ascertained by two consecutive negative samples taken at least 24 hours apart and the first sample should be taken no earlier than 48 hours after symptoms resolve. Therefore, given the implications and resources involved in isolating patients, PCR tests could be beneficial for decisions about infection control practices. Isolation can be a negative experience for patients and result in many missed work and school days. The rapid return of a negative result for VTEC/STEC could allow for faster de-isolation of patients.

Safety

Gastroenteritis occurs commonly in people with IBD and flare-ups of IBD have a similar symptom presentation to gastroenteritis[29, 30]. Accurate testing to determine appropriate treatment is essential in this group.

A time-interrupted retrospective cohort study compared the effect of testing by FilmArray™ with conventional testing (stool culture for bacterial pathogens and *C. difficile* toxin PCR testing) on outcomes in patients with IBD[31]. 268 IBD patients presented with symptoms over a 12 month period[31]. Patients who had been tested with FilmArray™ were three times more likely to require IBD-related hospitalisation, surgery or emergency department visit within 30 days of testing (Odds Ratio=3.03, 95% CI 1.27 to 7.14) than those tested by conventional methods. Similar results were observed within 90 days of testing. The increased risk may be accounted for as patients tested by FilmArray™ were significantly less likely to receive modification of IBD treatment (35% vs 64%, p<0.01) but they were equally as likely to receive antibiotics (26.1% vs 19.4%, p=0.24).

The negative impact of testing by FilmArray™ may be explained by the tendency of the non-gastroenterologists in this study to order GPP instead of conventional testing; the gastroenterologists in this study were more likely to order conventional testing than FilmArray™ (61% vs 39%). Conversely, non-gastroenterologists were more likely to order FilmArray™ than conventional testing (62% vs 38%). There were higher odds of IBD-related hospitalisation, surgery or emergency visit when a non-gastroenterologists ordered the tests (OR= 3.73, 95% CI 1.34 to 10.36, p=0.011).

The administration of GPP to patients with IBD by non-gastroenterologists may increase likelihood of adverse outcomes However, given the increased risk of bias due the observational design of this retrospective study, the evidence is not robust.

Cost effectiveness

An economic evaluation was conducted as part of the aforementioned HTA[14].

The economic model developed for the simulation of cost-effectiveness results was structured as a decision-tree based on several different potential patient pathways. The pathways were informed by the systematic review of clinical effectiveness, published literature and expert opinion. The pathways were determined by the initial decision to isolate patients or not based on symptoms, continue/start to isolate or de-isolate with/without treatment based on test results, and discharge or re-test based on symptoms resolving or persisting. The model structure is the same for both the multiplex GPP tests arm and the conventional testing arm. Hence, the relative cost-effectiveness between the two arms is driven by test results turnaround and whether or not patients move from isolated to non-isolated care earlier, are treated earlier or are discharged earlier. The model does not take into

account the possibility of multiple testing, adverse events of treatment, subsequent readmission, persistent complications or mortality.

Prevalence rates and probabilities were provided by the meta-analysis in the HTA and clinical expert opinion. The proportions of patients who follow each pathway according to each pathogen were derived from the prevalence rates and the treatment decision for each pathogen. The true prevalence rates were determined by the respective pathogen detection rate of conventional testing, which was assumed to be correct and used as the benchmark. Proportions of patients who would be treated and not treated were determined by clinical experts. The proportion of patients isolated or not isolated was determined on the basis of an economic analysis identified in the systematic review for the HTA[32].

Resource use and costs considered in the model included costs of each testing method, bed-days, cleaning, other required investigative tests, blood tests, medications and rehydration costs. The cost of each testing method accounted for test consumables, capital outlays, labour and overheads. The number of bed-days differed based on the results turnaround of each test (assumed to be faster for the multiplex GPP tests) and the subsequent treatment and re-testing decision following the initial result.

Mean quality-adjusted life-year (QALY) losses for each pathogen type were derived from a US study which collected EQ-5D data associated with food-borne illnesses caused by known viruses, bacteria and parasites, and applying the US tariff. As gastroenteritis is a self-limiting illness with no significant impact on quality of life for most patients beyond the symptomatic impact while the infection lasts, the model time frame was limited to the immediate index hospitalisation (approximately 2 weeks). The analysis is conducted from a NHS and Personal Social Services perspective. The relative cost-effectiveness results were reported as the incremental cost per QALY gained based on a direct comparison between the xTAG® or FilmArray™ and conventional testing. Probabilistic and one-way sensitivity analyses were conducted to quantify the model parameter uncertainty.

Five economic models were developed to account for different populations and settings. The base-case model was developed for acute hospitalisation of adults with suspected gastroenteritis. Additional models were developed for young children, people who are immunocompromised, people in the community and people who have recently travelled. The justification for conducting separate models was due to differing prevalence rates of gastroenteritis-causing pathogens in different samples and different cost assumptions in the case of hospital versus community care. A summary of the results of deterministic and probabilistic analysis for each model are reported in table 3.

Table 3: cost effectiveness of xTAG® and FilmArray™ compared to conventional testing in people with suspected gastroenteritis (GBP)

Test	Total mean costs	Incremental costs	Incremental QALYs gained	ICER (cost per QALY gained)	Net monetary benefit
Model 1: hospitalised adults patients					
Conventional	3157	-	-	-	-
xTAG	3089	-69	0.00018	Dominant	72
FilmArray	3096	-61	0.00013	Dominant	64
Model 2: hospitalised young children					
Conventional	3300	-	-	-	-
xTAG	3237	-63	0.00025	Dominant	68
FilmArray	3221	-79	0.00017	Dominant	82
Model 3: people in the community					
Conventional	72	-	-	-	-
xTAG	40	-32	0.00003	Dominant	32
FilmArray	97	25	0.00002	1,653,939	-25
Model 4: hospitalised people who are immunocompromised					
Conventional	3561	-	-	-	-
xTAG	3486	-76	0.00023	Dominant	80
FilmArray	3493	-68	0.00017	Dominant	72
Model 5: hospitalised people with a recent history of travel					
Conventional	73	-	-	-	-
xTAG	41	-32	0.00006	Dominant	33
FilmArray	98	25	0.00002	1,020,674	-25

These results indicate xTAG® dominates conventional testing (i.e. higher incremental QALY gain for lower cost) in all models. Meanwhile, FilmArray™ dominates conventional testing in adults, young children and people who are immunocompromised. In people in the community and people who have recently travelled, FilmArray™ was associated with very high ICERs and hence unlikely to provide good value for money, as also indicated by the negative net monetary benefit. Cost differences and QALY gains were very small and hence wide confidence intervals are to be expected around these results when considering the uncertainties in model inputs.

The results of the probabilistic sensitivity analysis indicate that for hospitalised adults, young children and people who are immunocompromised, the probability of xTAG® being cost-effective compared to conventional testing at a willingness-to-pay threshold of £20,000/QALY ranged

between 55-58% for xTAG® and between 54-57% for FilmArray™. In the models of recent travellers and people in the community, on the other hand, the xTAG® was estimated to have approximately 99-100% probability of being cost-effective. Meanwhile, the probability of being cost-effectiveness for FilmArray™ in these same populations was reported as only 6%. One-way sensitivity analysis indicated results are most sensitive to the number of bed-days and the costs of each testing method.

There are several limitations to the study. The costs reported are accurate for 2014/15 and so may not be accurate now. The GPP tests were directly compared to conventional testing and the model did not take into account the cost of transitioning to implementing the GPPs or using both GPP and conventional tests simultaneously. Also, the use of conventional testing as the benchmark is problematic as it is not 100% accurate in detection of pathogens. Although, there is no alternative reference standard. The data on test costs and probabilities of patients being isolated or not came from only one study[32]. Limitations of this study included the assumption that the GPP tests were 100% accurate in detection of pathogens, and number of isolation days for the GPP were not observed but were estimated. This study[32] also had poor quality reporting and only conducted a partial economic evaluation.

The smaller prospective study described above in the clinical effectiveness section included an economic analysis of costs associated with LOS, although it was unclear whether patients were isolated or not[21]. A cost-comparison was provided between the FilmArray™ and conventional testing in the US. Therefore, reported costs are unlikely to be generalisable to Scotland. There appeared to be some cost benefit of using the FilmArray® compared with conventional testing. The cost-savings were driven by the difference in cost of hospital stay and test costs. Although, given that there were negligible differences in the total LOS between FilmArray™ and conventional testing, and the FilmArray™ was more costly to implement, the reported savings are inconclusive[21].

Across both economic studies[14, 21], it appears that the FilmArray™ is cost saving compared with conventional testing only if LOS is reduced by using the GPP. However, discharge is usually based on symptoms resolving, as opposed to diagnosis. As yet, there is no convincing evidence that use of FilmArray™ would reduce time to discharge. While the economic analysis was tentatively in favour of the xTAG®, the findings are not robust Conducting a cost-effectiveness analysis based on better quality evidence and longer-term data may provide a more robust estimate of cost-effectiveness.

Identified research gaps

Studies which evaluate the diagnostic accuracy of GPPs need to establish the reasons for discordant results so that clinicians can have confidence in results from PCR tests. NICE reported that the resolution of discordance between GPPs and conventional tests are required before routine adoption could be recommended[1].

RCTs are required, to compare the effect of testing by GPPs with conventional methods on patient management outcomes or costs. The addition of RCTs will provide higher quality evidence and, therefore, will add more certainty to the evidence base.

There is also a lack of clinical effectiveness evidence in children, people returning from travel and immunocompromised patients. It would be beneficial to determine whether testing with GPPs in these groups improves patient management outcomes, as the prevalence is higher and adverse outcomes from diarrhoea are more common in these populations[13, 14].

Studies that assess the clinical and cost effectiveness of testing by PCR tests that target specific micro-organisms, such as the EntericBio and BD MAX™ assays.

Ongoing clinical trials

Three relevant ongoing clinical trials were identified[33-35] which may provide further evidence on the clinical effectiveness of GPPs. The Impact of the Introduction of a Gastro-intestinal Panel by Polymerase Chain Reaction (PCR) Trial[34] (NCT03551340) is evaluating the impact of using GPPs on antibiotic prescribing, number of pathogens identified and number of patients who underwent additional investigations by using a time-interrupted cohort study. The estimated completion date for this clinical trial is July 2019.

Another ongoing clinical trial[33] (NCT03809117) is conducting an RCT to evaluate the effectiveness of the FilmArray™ compared with usual care in patients with acute infectious diarrhoea in the emergency department. The outcomes of this trial are listed as: optimal use of antibiotics; time to resolution of symptoms/clinical improvement; rate of appropriate use of anti-motility medications; diagnostic yield at time of discharge; diagnostic yield at 72 hours post discharge; length of stay in emergency department; hospital admission rate; patient satisfaction; rate of additional imaging tests; rates of emergency department return visits and readmission; and turnaround time. This clinical trial is estimated to be completed in November 2019.

A pilot RCT[35] (GastroPOC Trial) within University Hospital Southampton NHS Trust (which was due to be completed in September 2020) is assessing the impact of routine use of FilmArray™ at point-of-care, compared with conventional testing. Outcomes being evaluated include use of isolation facilities, duration of hospital stay, use of antibiotics, rate of pathogen detection and time to diagnosis.

Conclusion

There is a lack of good quality evidence on the clinical and cost effectiveness of GPPs. No test-treat RCTs or meta-analyses were identified. The evidence on clinical effectiveness is limited to four observational studies, which compared testing by GPPs to a historical control group, and one

uncontrolled observational study. These five observational studies were conducted in non-UK settings, therefore they may not be generalisable to Scotland.

Based on the evidence identified, compared with conventional testing, GPPs had a faster turnaround time. There is also some evidence that faster turnaround times using the GPPs may reduce unnecessary and inappropriate antibiotics prescribing and additional testing. These findings are based on observational historical cohort studies.

There is some evidence that GPPs may be cost effective compared with conventional testing in people who have recently travelled and in community settings. In hospitalised adults, children and people who are immunocompromised, testing by xTAG® may be cost effective compared with conventional testing if it results in shorter hospital stays. There is substantial uncertainty around the probability of cost effectiveness when using GPPs and the current evidence suggests that length of stay is not reduced by use of GPPs. The economic evaluation[14] in the HTA was conducted from an NHS and Personal Social Services perspective and so may reflect cost-effectiveness in Scotland. However, owing to the limitations of the underlying evidence, the cost effectiveness of GPPs cannot be determined.

Using GPPs to test for infectious gastroenteritis in patients with IBD may not be suitable. One observational study suggested that misattribution of test results to gastroenteritis by non-gastroenterologists can potentially lead to adverse outcomes resulting from delayed adjustment of IBD treatment. The suitability of using GPPs for diagnosis should be considered on a case by case basis.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

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Appendix 1: Diagnostic accuracy of Luminex xTAG and BioFire FilmArray

The overall positive and negative agreement of the xTAG and FilmArray reported in the NICE diagnostic guidance report are demonstrated below[1]. For further details of how the positive and negative agreement were calculated and for the positive and negative agreement for each pathogen, please see the HTA.

Table 4: overall positive and negative agreement of Luminex xTAG GPP

Benchmark	Overall Positive Agreement (95% CIs)		Overall Negative Agreement (95% CIs)	
	I^2	Pooled result (95% CIs)	I^2	Pooled result (95% CIs)
GPPs	83%	0.929* (0.898 to 0.955)	95%	0.982* (0.976 to 0.988)
Conventional testing	97%	0.678* (0.580 to 0.770)	77%	0.998* (0.997 to 0.999)

*p<0.001

Table 5: overall positive and negative agreement of Biofire FilmArray GI Panel

Benchmark	Overall Positive Agreement (95% CIs)		Overall Negative Agreement (95% CIs)	
	I^2	Pooled result (95% CIs)	I^2	Pooled result (95% CIs)
GPPs	89%	0.954* (0.897 to 0.991)	88%	0.996* (0.993 to 0.998)
Conventional testing	81%	0.820* (0.761 to 0.872)	77%	1.000* (0.999 to 1.000)

*p<0.001

Appendix 2: Abbreviations

CI	confidence interval
GPP	gastrointestinal pathogen panel
HTA	health technology assessment
HUS	hemolytic uremic syndrome
IBD	inflammatory bowel disease
ICER	incremental cost effectiveness ratio
LOS	length of hospital stay
NAAT	nucleic acid amplification tests
NICE	National Institute for Health and Care Excellence
OR	odds ratio
PCR	polymerase chain reaction
PHE	Public Health England
QALY	quality adjusted life year
RCT	randomised controlled trial
SMVN	Scottish Microbiology and Virology Network
STEC	Shiga-toxigenic *E coli*
VTEC	Verotoxigenic *E coli*