

Accuracy and comparison of two rapid multiplex PCR tests for gastroenteritis pathogens: a systematic review and meta-analysis

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ABSTRACT

Objectives The primary aim is to provide a summary of evidence for the diagnostic accuracies of multiplex PCR gastrointestinal (GI) panels—BioFire FilmArray and Luminex xTAG on the detection of gastroenteritis pathogens. The secondary aim is to compare the performance of these GI panels head to head.

Methods A comprehensive search up to 1 December 2019 was conducted on PubMed, Embase, Ovid Medline and Web of Science for studies that used FilmArray or Luminex xTAG Gastrointestinal Pathogen Panel (GPP) for diagnosis of acute gastroenteritis. A summary of diagnostic accuracies for the 16 pathogens were calculated by comparing the GI panels to the current gold standards (conventional standard microbiology techniques such as culture or PCR for bacteria, PCR or enzyme immunoassay (EIA) for viruses, microscopy or EIA for parasite). Hierarchical summary receiver operating characteristic (HSROC) curve analysis, pretest and post-test probabilities were used for estimating the pathogen detection performance.

Results A total of 11 studies with 7085 stool samples were eligible for analysis. Multiplex PCRs demonstrated high diagnostic accuracy, with specificity ≥ 0.98 and area under the ROC curve (AUROC) ≥ 0.97 for all the pathogens except for *Yersinia enterocolitica* (AUROC 0.91). The FilmArray panel demonstrated a higher sensitivity than xTAG GPP for most of the pathogens with the exception of Rotavirus A (xTAG GPP and FilmArray were both 0.93).

Conclusions This is the first meta-analysis that is a head-to-head comparison examining the performance of the novel multiplex PCR-based tests Luminex xTAG GPP and FilmArray GI panel in detecting each pathogen. Point estimates calculated from eligible studies showed that both GI panels are highly accurate and may provide important diagnostic information for early identification of gastroenteritis. In addition, although FilmArray has higher sensitivity and post-test probability than xTAG GPP for most of the pathogens, how this will translate to a clinical setting remains unclear.

INTRODUCTION

Every year, there are about 2 billion cases of diarrhoeal disease worldwide.¹ Most cases of

Summary box

What is already known about this subject?

► Recently, there has been tremendous interest in the development of multiplex molecular assays for the rapid detection and identification of pathogens responsible for causing diarrhoeal illness. Our review focuses on the first two Food and Drug Association-approved multiplex assays: FilmArray Gastrointestinal (GI) Panel and Luminex xTAG Gastrointestinal Pathogen Panel (GPP).

What are the new findings?

► Our study found that both FilmArray and GPP have high diagnostic accuracy. However, in comparison to GPP, the FilmArray GI panel demonstrated superior performance with higher sensitivity and summary area under the receiver operating characteristic curve than xTAG GPP. While there is significant statistical difference in their performances, how this will translate to a clinical setting remains unclear.

How might it impact on clinical practice in the foreseeable future?

► These results are essential to guide the advancement of multiplex technology and its implementation in the clinical world as our study suggests that multiplex assays can significantly enhance diagnostic output in the evaluation of acute diarrhoeal illness.

gastroenteritis are due to infections which include viral, bacterial and, less frequently, parasitic. Norovirus is the most common cause of acute gastroenteritis in young children and infants in the USA,² while severe diarrhoea is typically associated with bacterial causes.³ Furthermore, infectious diarrhoea is a frequent and serious complication in immunocompromised patients.⁴ As diarrhoeal diseases remain a leading cause of morbidity and mortality worldwide, the rapid accurate diagnosis of the underlying pathogen is



crucial for identifying any potential complications and to optimise treatment, particularly in patients with severe illness, significant comorbidities or high-risk features.^{5,6}

Conventional diagnostic methods, such as stool cultures, enzyme immunoassays (EIA) and one-target PCR assays, are time-consuming, laborious and operator dependent.⁷ In light of these limitations, the development of multiplex molecular assays has generated considerable interest. Multiplex molecular assays rapidly detect a wide range of bacterial, viral and parasitic pathogens simultaneously, reducing turnaround time and allowing for detection of coinfections. There are a number of US Food and Drug Association (FDA)-cleared multiplex panels available today for detecting gastrointestinal (GI) pathogens, each with pros and cons. Particularly, the FilmArrayGI Panel and the Luminex xTAG Gastrointestinal Pathogen Panel (GPP), which are the first two FDA-approved multiplex assays. The FilmArray GI panel is a qualitative, highly multiplexed PCR test that targets 22 pathogens (13 bacterial, 5 viral and 4 parasitic) from stool samples.⁸ On the other hand, the Luminex xTAG GPP is a multiplexed molecular test for 15 GI pathogens (9 bacterial, 3 viral and 3 parasitic) with overall sensitivity and specificity greater than 90% compared with conventional methods.⁹

In addition, FilmArray is a Clinical Laboratory Improvement Amendments (CLIA) -waived end-to-end system that requires minimal hands-on processing time (2 min per run) and offers a rapid turnaround time (~1 hour per run), making it suitable for use in the points of care outside the central laboratory, such as clinic, emergency room and military. In contrast, xTAG GPP, although a longer turnaround time of 3.5 hours, can analyse 96 samples at a time and accommodate 192 samples in a shift of 7–8 hours, making it optimal for high-volume reference laboratories.

Studies have shown, however, that the diagnostic accuracy for each pathogen varies among the different multiplex platforms.¹⁰ Therefore, the primary aim of this systematic review and meta-analysis is to evaluate the diagnostic value and reliability of xTAG GPP and FilmArray in detecting GI infections, and the secondary aim is to compare the diagnostic accuracies of xTAG GPP and FilmArray GI panel for each pathogen.

METHODS

The protocol of our study was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement^{11,12} and the standard guideline for systematic reviews of diagnostic tests by the Cochrane Collaboration.

Search strategy

A comprehensive search of literature was conducted using three databases: PubMed (from January 2016 to Dec 2019), Embase (from January 2016 to Dec 2019), Ovid Medline (from January 2016 to Dec 2019) and

Web of Science (from January 2016 to Dec 2019). The detailed search strategy is provided in online supplemental material S1. The search was then supplemented by manual searching of bibliographies of retrieved full-text articles and the latest narrative reviews. The articles before 2016 were supplemented by a previous systematic review.⁸

Study selection

Studies were included if they (1) included patients with acute diarrhoea, suspected secondary to infectious gastroenteritis, with tests (stool samples) from hospitals or clinics; (2) assessed the accuracy of xTAG GI panel or FilmArray GI panel; (3) used conventional standard microbiology techniques as comparators, such as culture or PCR for bacteria, PCR or EIA for viruses and microscopy or EIA for parasites and (4) provided sufficient information to calculate sensitivity and specificity. Studies were excluded if they (1) only analysed confirmed positive specimens without negative controls, (2) included spiked samples or swab testing, or (3) used other partial multiplex tests. We excluded reviews, case reports, editorials and opinions, letters, poster presentations without supporting abstracts or meeting abstracts without sufficient details on test performance. Two reviewers independently screened the titles and abstracts. Disagreements or uncertainties were resolved by consensus meeting after discussion with the senior author (C-CL).

Data extraction

We extracted the following characteristics for analysis: author, publish year, article title, country, data collecting time, clinical setting, mean age, case number, male proportion, GI panel used, pathogens, sensitivity, specificity, patient inclusion criteria, gold standard or reference. The 2×2 tables were further used to calculate sensitivities and specificities of the target assays. For the reference methods, conventional standard microbiology techniques, such as culture or PCR for bacteria, PCR or EIA for viruses, microscopy or EIA for parasites were grouped together because they are universally recognised as the reference standard.⁸ Composite reference standard was defined as a standard that used more than one comparator assays. Children were defined as patients younger than 18 years. Studies that included both children and adult population were categorised as mixed population. There are five studies that included discordant analysis. Discordant analysis means further analysing discordant results between routine reference tests and GI panels using an additional method, such as singleplex PCR, sequencing or other multiplex panels, to confirm the final results. Samples were considered true positives if they tested positive by both routine reference tests and GI panels and did not require additional testing. Samples were considered true negative if they tested negative by both routine reference tests and GI panels.

Quality assessment

The quality of the eligible studies was independently assessed by two reviewers using the Quality Assessment of Diagnostic Accuracy Studies 2 tool (QUADAS-2).¹³ Any disagreements were resolved by consensus or arbitration. Assessment was done across 4 domains of bias (patient selection, index test, reference standard and flow and timing). For each diagnostic study, we determined the risk for bias and general applicability in all four domains of QUADAS-2 and reported them separately. Those with low risk of bias or low concern regarding applicability were judged as low. A study would be judged as unclear if there were insufficient data for interpretation. We added several questions to evaluate the quality of included studies. The tailored QUADAS-2 form and guidance notes are provided in online supplemental material S2.

Data synthesis and statistical analysis

A bivariate random effect model was applied to estimate summary sensitivity and specificity with 95% CIs.¹⁴ The positive likelihood ratios (LR+) and negative LR (LR-) were then calculated from summary sensitivity and specificity. The bivariate model approach modelled the sensitivity and specificity simultaneously to account for the inherent negative correlation between sensitivity

and specificity that may arise due to different thresholds in different studies. In addition, the bivariate model could also account for between-study heterogeneity. We constructed a hierarchical summary receiver operating characteristic (HSROC) curve and calculated the area under the ROC curve (AUROC).¹⁵ Fagan plot analyses were conducted to infer positive and negative post-test probabilities. A pretest probability of the pathogen was estimated by the number of symptomatic cases in selected studies. The degree of between-study heterogeneity was calculated using the I² test.¹⁶ A two-sided p<0.05 indicates statistical significance for all tests. All analyses except for the summary ROC were performed by the 'mada' package in R software (R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org/>). The summary ROC and AUROC was calculated by the 'midas' package in STATA cer V.11 (STATA).

RESULTS

Identification of studies

After two rounds of inclusion and exclusion (figure 1), 11 studies with 21 data sets and 7085 stool samples were included in this analysis. Different studies were consolidated as one data set if they compared the same multiplex

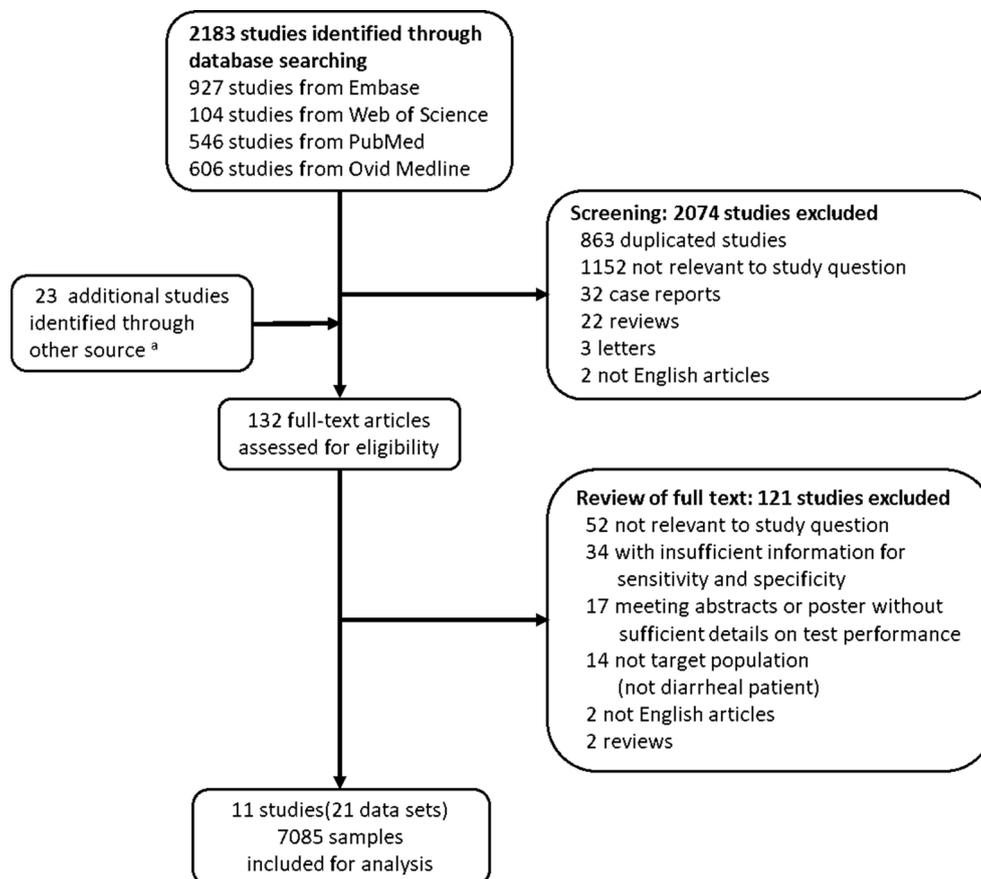


Figure 1 PRISMA flow diagram for selection of articles for meta-analysis. ^aThese 23 additional studies were identified from the inclusion studies of a systematic review: multiplex tests to identify gastrointestinal bacteria, viruses and parasites in people with suspected infectious gastroenteritis: a systematic review and economic analysis. The systematic review had the same inclusion and exclusion criteria as our study, and included the articles published before 2015. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.



platforms using the same patient group and reference methods. The number of data sets is regarded as two if a study compared two different multiplex platforms to conventional techniques or applied one multiplex platform to two different patient groups.

Characteristics of included studies

The characteristics of eligible studies are summarised in [table 1](#), and the summary was provided in online supplemental material S3. One data set included exclusively adult patients,⁴ two data sets (from one study) recruited children only¹⁷ and the majority of studies studied on mixed adult and children populations. Luminex xTAG GPP was used in 15 data sets (71%), while FilmArray GI panel was used in six data sets (29%). Both conventional microbiology techniques and molecular methods such as sequencing or real-time PCR were commonly employed reference standards. Nine studies with 15 data sets used the GI panel on prospectively collected samples from patients with suspected gastroenteritis^{4,7,9,10,18–22} while two studies (four data sets) evaluated the GI panel retrospectively.^{2,5} One study (two data sets) included both retrospective and prospectively collected samples.¹⁷ The comparison of FDA-approved GI panels included in our study are listed in online supplemental material S4.¹⁰ In general, the Luminex xTAG GPP has to be operated in a central laboratory with higher throughput (96 samples per round) but a longer turnaround time of 3.5 hours. The FilmArray system is a point-of-care machine that can complete the analysis within 1 hour but can only test 1 sample per round. Details of the characteristics and key results of each individual study are provided in online supplemental material S3 and S5).

Quality assessment

Quality assessment by the QUADAS-2 tool is demonstrated in [figure 2](#). For the ‘Patient Selection’ domain, some studies used samples with known etiologies from microbiological culture; others did not avoid a case-control design. For the ‘Index Test’ domain, the index test used in all the studies was performed independently and the threshold was prespecified within the GPP test. For the ‘Reference Standard’ domain, all patients received the reference standard tests, with minimal risk of verification bias. The reference standard was independent of the index test, and the interpretation threshold was prespecified, therefore, the risk of incorporation bias is low. Overall, all the studies had low concern regarding applicability for index tests. Regarding applicability of the reference standard, studies using singleplex PCR or sequencing as the standard raise concern because it may detect pathogens at levels that are unlikely to cause symptoms. Some studies included immunocompromised patients or travellers and could raise concerns on the applicability to the general population.

Diagnostic accuracy of GI panel

[Table 2](#) lists the point estimates of sensitivity, specificity, AUROC the HSROC, LR+, LR–, publication bias and I²

for each pathogen. All pathogens had a high discrimination (AUROC ≥ 0.96) by the two GI panel tests except for *Yersinia enterocolitica* by xTAG GPP (AUROC: 0.91). The specificity of the two GI panel tests were high, ranging from 0.98 to 1.00, except for Salmonella by xTAG GPP (Spe: 0.97) and *Clostridium difficile* by FilmArray (Spe: 0.97). The sensitivities were all greater than 0.81 with majority >0.90 , except for *Y. enterocolitica* (Sen:0.48), Adenovirus 40/41 (Sen: 0.70) and *Entamoeba histolytica* (Sen: 0.70) by xTAG GPP. FilmArray panel demonstrated a higher sensitivity than xTAG GPP for most of the pathogens with the exception of Rotavirus A (xTAG GPP and FilmArray are both 0.93). The overall LR+ was well beyond 10, indicating a high rule-in value of the positive test results. The LR– for FilmArray were all ≤ 0.1 , lower than xTAG GPP for all pathogens except for Rotavirus, suggesting a higher rule-out value for FilmArray panel than xTAG GPP. (Online supplemental materials S6 and S7 illustrate the HSROC curves for each pathogen by xTAG GPP (online supplemental material S6) and FilmArray (online supplemental material S7). Online supplemental material S8 shows the forest plot of sensitivity and specificity of the GI panel for each pathogen.

[Table 3](#) showed the pretest and post-test probability for each pathogen tested by GI panels. The post-test probability for positive test across all the pathogens tested by xTAG GPP varied between 11% and 86%; for FilmArray, the post-test probability for positive test varied between 68% and 96% ([table 3](#)). xTAG GPP demonstrated a poor positive post-test probability on *E. histolytica*, *Giardia lamblia*, *Cryptosporidium* and ETEC (11%, 25%, 40% and 42%, respectively). FilmArray has better post-test probability than xTAG GPP except for Rotavirus A (the post-test probability for positive test is 69% for FilmArray, 86% for xTAG) ([table 3](#)). I² was $>50\%$ in most of the analyses. Lastly, we pooled 10 studies of xTAG GPP and 6 studies of FilmArray GI panel and plotted the HSROC of two GI panel tests (online supplemental material S9). The FilmArray GI panel showed a higher AUROC than xTAG GI panel (AUROC 0.99 vs 0.98, $p=0.03$). Online supplemental material S10 shows subgroup analysis for GI panel sensitivity and specificity when tested with different gold standards on *Campylobacter*, *Shigella* and rotavirus A. The result showed that the p values were all >0.1 , which indicated that there were no significant differences between the overall results and the subgroups.

DISCUSSION

Our study found that both FilmArray and xTAG GPP have high diagnostic accuracies. To our knowledge, this is the first meta-analysis of a head-to-head comparison between the two currently available commercial multiplex PCR tests for GI pathogens. In this meta-analysis consisting of 7085 stool samples, we show that both systems have a nearly perfect specificity with high LR+, indicating a high rule-in value. The sensitivities and LR–, however, vary between the two systems. The FilmArray GI

Table 1 Summary of the characteristics of the included studies.

Author, year, country	Sample number	Patient age and characteristics	Study design	Inclusion criteria	Index test (multiplex PCR)	Routine testing methods	Adjudication methods for discordant results
Deng J <i>et al</i> ¹⁹ 2015, China	290 stool samples	Mixed (median age of 25 months and ranging from 11 days to 83 years.)	Prospective	Diarrheal patients	Luminex xTAG	Bacterial culture, serotyping for Salmonella and Shigella, real-time reverse transcription-polymerase chain reaction (RT-PCR) assays for viral detection, microscopic examination for parasite detection.	Singleplex PCR and sequencing
Chhabra P <i>et al</i> ² 2017, USA	300 stool samples	Mixed (from children and adults)	Retrospective	Patient with acute gastroenteritis	Luminex xTAG and FilmArray	TAC system, real-time PCR and sequencing	No
Alejo-Cancho I <i>et al</i> ⁴ 2017, Spain	95 stool samples	95 immunocompromised adult patients, with a median age of 52 years (46–64).	Prospective	Acute diarrheal patient	FilmArray	Routine microbiological techniques, including bacterial culture, <i>C. difficile</i> toxin study, microscopy for parasite, virus antigen.	Second multiplex assay (Allplex, Seegene, Korea)
Duong VT <i>et al</i> ⁵ 2016, Vietnam	479 stool samples were collected from 92 adults and 387 children	The median age of the adult patients was 50 years (interquartile range [IQR], 33 to 64 years). In children, the median age was 16.5 months (IQR, 6.7 to 20 months).	Retrospective	Diarrheal patients	Luminex xTAG	Microbiological culture and real-time PCR	No
Khare R <i>et al</i> ¹⁰ 2014, USA	230 prospectively collected samples and 270 additional previously characterized samples	Unclear	Prospective and retrospective	Stool samples submitted to laboratory for routine GI testing.	Luminex xTAG and FilmArray	Routine testing (e.g., culture, microscopy, antigen testing, and/or individual real-time PCR)	Real-time PCR
Buss SN <i>et al</i> ¹⁸ 2015, USA	1556 stool samples	Mixed (adult and children)	Prospective	Stool samples submitted with orders by the provider for stool culture	FilmArray	Stool culture, PCR	PCR and sequencing assays
Claas EC <i>et al</i> ⁹ 2013, The Netherlands	901 stool specimens	Mixed (adult and children)	Prospective	Stool collected in four hospitals	Luminex xTAG	Routine testing (e.g., culture, microscopy, EIA/DFA, or real-time PCR)	No

Continued

Table 1 Continued

Author, year, country	Sample number	Patient age and characteristics	Study design	Inclusion criteria	Index test (multiplex PCR)	Routine testing methods	Adjudication methods for discordant results
Halligan E et al ²⁰ 2014, UK	2187 diarrhoeal stool samples.	Unclear	Prospective	Diarrheal patients	Luminex xTAG	Conventional tests including microbiological culture, microscopy, microwell enzyme immunoassay, immunochromatographic test	No
Mengelle C et al ²¹ 2013, France	440 stool samples	4 groups included: 102 adult organ transplant recipients (mean age, 50.6; median, 56; range, 17–75), 50 immunosuppressed children (mean age, 5; median, 7; range, 0–14), 56 children attending the neonatal unit (aged under 1 year) and 121 children attending the emergency unit (mean age, 2.80; median, 9; range, 0–16).	Prospective	Diarrheal patients	Luminex xTAG	Routine diagnostic methods (e.g., culture, microscopy, immunochromatographic assay, and multiplex PCR)	No
Zboromyrska Y et al ²² 2014, Spain	185 stool samples	Traveller's diarrheal patients with unclear age	Prospective	Patients with traveller's diarrhea	Luminex xTAG	Routine diagnostic methods (e.g., culture, microscopy, mass spectrometry, and multiplex PCR)	Conventional PCR and bidirectional sequencing
Huang RS et al ¹⁷ 2016, USA	98 retrospective and 54 prospective stool samples	Pediatric patients	Retrospective and prospective	Patient with acute gastroenteritis	Luminex xTAG and FilmArray	Conventional testing including stool cultures, immunochromatographic rapid tests, and singleplex RT-PCR	No



Figure 2 QUADAS-2 for included studies. (A) QUADAS-2 risk of bias and concerns regarding applicability graph: review authors' judgements about each domain presented as percentages across included studies. (B) QUADAS-2 risk of bias and concerns regarding applicability summary: review authors' judgements about each domain for each included study. QUADAS-2, quality assessment of diagnostic accuracy studies 2.

panel has a sensitivity of greater than 0.90 for all pathogens, while xTAG GPP has a sensitivity between 0.81 and 0.95 for most pathogens. Of note, three pathogens *Y. enterocolitica*, Adenovirus 40/41 and *E. histolytica*, have exceptionally low sensitivities (0.48–0.70), insufficient for rule out use. Furthermore, xTAG GPP demonstrates a low positive post-test probability for *E. histolytica*, *G. lamblia* and *Cryptosporidium* (11%, 25%, and 40%, respectively) which suggests that xTAG GPP is not accurate in detecting GI parasites. In addition, FilmArray has higher sensitivity and post-test probability than xTAG GPP for most of the pathogens except for Rotavirus A (the post-test probability for positive test is 69% for FilmArray, 86% for xTAG). However, there is insufficient data for analysing the accuracy of detecting relatively rare pathogens such as *Y. enterocolitica* and *E. histolytica* by FilmArray. In contrast, xTAG GPP provides comparable diagnostic accuracy when those pathogens are suspected in clinical conditions and tested. The heterogeneities were high ($I^2 > 50\%$) which may reflect the different study population and gold standards used by the studies. For instance, one study solely included immunocompromised patients while Chhabra *et al* included virus positive stool samples⁴ and the other study focused on traveller's diarrhoea.²² These studies also used different microbiology techniques as their gold standards such as culture or PCR for bacteria, PCR or EIA for viruses, microscopy or EIA for parasites.

Unlike the conventional PCR test focusing on a single target, both xTAG GPP and FilmArray GI panel employ a syndromic approach to detect multiple pathogens simultaneously. This syndromic approach maximises the use of PCR starting material, uses fewer reagents, and allows increase in time and cost efficiency.²³

Compared with a previous systematic review,⁸ which includes only two studies for FilmArray and does not provide head-to-head comparisons between FilmArray and xTAG GPP, our updated review includes three additional studies^{2 4 17} and provides comprehensive quantitative analysis on the comparative accuracy of the two multiplex platforms. The analysis in the previous systematic review⁸ focuses on the comparison of each panel to the standard microbiology technique, and while it introduces prior studies examining agreement between FilmArray and xTAG GPP, does not provide any additional head-to-head quantitative analysis of the two. Our comparative analysis shows FilmArray may perform better than xTAG GPP in detecting certain pathogens which can be explained by the primer design or the open system and technician dependent nature of the xTAG GPP system. The open system increases the risk of amplicon contamination. In particular, xTAG GPP demonstrates relatively lower sensitivity for adenovirus type 40/41 (Sen: 0.70). The low sensitivity may be related to mismatches between the viral templates and the oligonucleotide primers and probes in the system. Furthermore, the reference

Table 2 Accuracy estimates of 11 included studies

Test	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	LR+ (95% CI)	LR- (95% CI)	Publication bias	I ² (%)
Campylobacter							
Luminex xTAG	0.92 (0.86 to 0.96)	0.98 (0.96 to 0.99)	0.99 (0.98 to 1.00)	55 (21 to 140)	0.08 (0.04 to 0.14)	0.94	95.73
FilmArray	0.95 (0.87 to 0.98)	0.99 (0.98 to 1.00)	0.99 (0.94 to 1.00)	120 (47 to 330)	0.05 (0.02 to 0.13)	0.93	63.26
Clostridium difficile							
Luminex xTAG	0.95 (0.91 to 0.97)	0.98 (0.96 to 0.99)	0.99 (0.97 to 1.00)	49 (24 to 100)	0.06 (0.04 to 0.09)	0.07	88.33
FilmArray	0.97 (0.90 to 0.99)	0.97 (0.96 to 0.98)	1.00 (0.98 to 1.00)	35 (26 to 47)	0.03 (0.01 to 0.11)	0.54	10.43
E. coli O157							
Luminex xTAG	0.87 (0.72 to 0.95)	0.99 (0.99 to 1.00)	0.96 (0.93 to 0.98)	150 (72 to 330)	0.13 (0.05 to 0.28)	0.72	71.10
ETEC							
Luminex xTAG	0.88 (0.63 to 0.97)	0.99 (0.94 to 1.00)	0.99 (0.91 to 1.00)	60 (13 to 290)	0.13 (0.03 to 0.38)	0.42	64.46
FilmArray	0.92 (0.67 to 0.98)	0.99 (0.99 to 1.00)	1.00 (0.90 to 1.00)	150 (80 to 280)	0.08 (0.02 to 0.33)	0.19	0.00
Salmonella							
Luminex xTAG	0.85 (0.80 to 0.90)	0.97 (0.92 to 0.99)	0.97 (0.95 to 0.98)	33 (11 to 100)	0.15 (0.11 to 0.21)	0.14	96.61
FilmArray	0.94 (0.84 to 0.98)	1.00 (0.99 to 1.00)	1.00 (0.98 to 1.00)	210 (110 to 400)	0.06 (0.02 to 0.16)	0.15	73.03
STEC stx1/stx2							
Luminex xTAG	0.92 (0.81 to 0.97)	0.99 (0.99 to 1.00)	0.99 (0.96 to 1.00)	130 (65 to 270)	0.08 (0.03 to 0.19)	0.03	41.95
FilmArray	0.96 (0.85 to 0.99)	0.99 (0.99 to 1.00)	1.00 (0.96 to 1.00)	190 (100 to 350)	0.04 (0.01 to 0.15)	0.25	89.16
Shigella or Shigella/EIEC							
Luminex xTAG	0.95 (0.88 to 0.98)	0.99 (0.97 to 0.99)	1.00 (0.99 to 1.00)	76 (36 to 160)	0.06 (0.02 to 0.12)	0.98	95.69
FilmArray	0.95 (0.87 to 0.98)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)	440 (170 to 1200)	0.05 (0.02 to 0.13)	0.15	35.89
Yersinia enterocolitica							
Luminex xTAG	0.48 (0.31 to 0.65)	1.00 (0.99 to 1.00)	0.91 (0.81 to 1.00)	230 (45 to 1200)	0.53 (0.35 to 0.69)	0.93	72.88
Adenovirus 40/41							
Luminex xTAG	0.70 (0.42 to 0.88)	0.99 (0.99 to 1.00)	0.96 (0.94 to 0.99)	96 (53 to 160)	0.30 (0.12 to 0.58)	0.78	2.23
FilmArray	0.90 (0.69 to 0.97)	0.99 (0.98 to 1.00)	0.99 (0.94 to 1.00)	100 (55 to 180)	0.10 (0.03 to 0.31)	0.04	86.80
Norovirus GI/GII							
Luminex xTAG	0.88 (0.82 to 0.93)	0.98 (0.95 to 0.99)	0.97 (0.96 to 0.99)	37 (16 to 85)	0.12 (0.08 to 0.19)	0.85	89.74
FilmArray	0.92 (0.86 to 0.95)	0.99 (0.98 to 1.00)	0.99 (0.97 to 1.00)	120 (61 to 230)	0.08 (0.05 to 0.14)	0.85	71.76
Rotavirus A							
Luminex xTAG	0.93 (0.90 to 0.96)	0.99 (0.98 to 1.00)	0.99 (0.99 to 1.00)	100 (52 to 200)	0.07 (0.04 to 0.10)	0.74	88.05
FilmArray	0.93 (0.75 to 0.98)	0.99 (0.97 to 0.99)	1.00 (0.96 to 1.00)	76 (35 to 160)	0.07 (0.02 to 0.25)	0.21	92.42

Continued

Table 2 Continued

Test	Sensitivity (95% CI)	Specificity (95% CI)	AUROC (95% CI)	LR+ (95% CI)	LR- (95% CI)	Publication bias	I^2 (%)
Cryptosporidium							
Luminex xTAG	0.82 (0.63 to 0.92)	0.99 (0.97 to 1.00)	0.98 (0.89 to 1.00)	96 (22 to 410)	0.18 (0.08 to 0.37)	0.01	37.52
FilmArray	0.92 (0.68 to 0.98)	1.00 (0.99 to 1.00)	1.00 (0.92 to 1.00)	230 (110 to 490)	0.08 (0.02 to 0.32)	0.15	0.00
Entamoeba histolytica							
Luminex xTAG	0.70 (0.33 to 0.92)	0.99 (0.97 to 0.99)	0.99 (0.85 to 1.00)	59 (18 to 160)	0.30 (0.08 to 0.68)	0.18	0.00
Giardia lamblia							
Luminex xTAG	0.81 (0.52 to 0.94)	0.98 (0.95 to 0.99)	1.00 (0.95 to 1.00)	36 (13 to 85)	0.19 (0.06 to 0.49)	0.22	64.59
FilmArray	0.91 (0.69 to 0.98)	1.00 (0.99 to 1.00)	1.00 (0.93 to 1.00)	200 (100 to 390)	0.09 (0.02 to 0.31)	0.08	0.00
Astrovirus							
FilmArray	0.96 (0.85 to 0.99)	1.00 (0.98 to 1.00)	0.99 (0.91 to 1.00)	300 (55 to 1600)	0.04 (0.01 to 0.15)	0.08	90.16
Sapovirus							
FilmArray	0.96 (0.83 to 0.99)	0.99 (0.99 to 1.00)	1.00 (0.99 to 1.00)	170 (66 to 430)	0.04 (0.01 to 0.17)	0.35	84.54

AUROC, area under the receiver operating characteristic curve; E. coli, *Escherichia coli*; EIEC, Enteroinvasive *Escherichia coli*; ETEC, Enterotoxigenic *Escherichia coli*; LR-, negative likelihood ratio; LR+, positive likelihood ratio; STEC, Shiga-like Toxin producing *Escherichia coli*.

standard real-time PCR does not distinguish between adenovirus species⁹; therefore, it is likely that real-time PCR can detect adenovirus species other than adenovirus type 40/41, resulting in a falsely low sensitivity. For *Y. enterocolitica*, the low sensitivity (48%) may be impacted by the lowest sensitivity report from Claas *et al*; the cause of this low sensitivity needs further verification.

In acute gastroenteritis, careful history questioning the characteristics of the illness and potential exposures can provide powerful diagnostic clues. Clinical features such as shorter duration of illness and frequent vomiting may suggest a viral aetiology. However, an observational study found that there are only a few differences in presentation caused by viral and bacterial pathogens.²⁴ Therefore, epidemiological and clinical evaluation are not always reliable methods to differentiate between viral and bacterial etiologies but should be used to guide diagnostic testing. Nowadays, stool culture is the primary diagnostic tool for bacterial gastroenteritis. However, bacterial culture is time-consuming, laborious and costly^{25–29} and requires selective agars or serologic testing to then identify and confirm the pathogens. Stool culture also has a low positive yield and relatively poor sensitivity,³⁰ limiting its use in a clinical setting. faecal leucocyte testing (FLT) is another tool often used to screen for infectious diarrhoea.⁶ Although the presence of stool cellular exudates has been long regarded as a sign of infectious diarrhoea, there is evidence questioning the value of FLT.³¹ Investigations show that FLT cannot distinguish between noninfectious gastroenteritis and infectious gastroenteritis inpatient. A study found that in 25 patients with infectious gastroenteritis, only 32% of patients had positive FLT.³² FLT has also been stated to be a poor predictor of *C. difficile* infection.³³ In fact, the 2017 Infectious Diseases Society of America Clinical Practice Guidelines does not recommend using FLT to establish the cause of acute infectious diarrhoea.⁶ The inability to determine the specific causative pathogen vastly hinders effective clinical management.

Compared with conventional diagnostic techniques, multiplex technology permits rapid organism-specific diagnostic testing that can curb inappropriate antibiotic use as use of broad-spectrum antibiotics may facilitate the emergence of multidrug resistant bacteria. More importantly, outcomes of some bacterial diarrhoeal illness may worsen with the use of antibiotics. A prospective cohort study found a strong association between antibiotic treatment and the development of the hemolytic-uremic syndrome in children with *Escherichia coli* O157:H7 infections.³⁴ Multiplex assays allow clinicians to make informed decisions and judicious use of antibiotics. Identification of specific pathogens also has public health implications. For instance, infected food workers cause about 70% of reported norovirus outbreaks from contaminated food. The Centers for Disease Control and Prevention, therefore, recommends food service workers stay home not only at the onset of GI symptoms but also for at least 48 hours after symptoms have resolved. Community

**Table 3** The calculation of post-test probabilities

Pathogens	Study(n)	Pre-test probability (%)	Test kit	Likelihood ratio	Post-test probability (%)
Campylobacter	11	5.6	Luminex	LR+: 55 (21-140) LR-: 0.06 (0.03-0.12)	77 0
	5	3.6	FilmArray	LR+: 120 (47-330) LR-: 0.05 (0.02-0.13)	82 0
Clostridium difficile	8	5.5	Luminex	LR+: 49 (24-100) LR-: 0.06 (0.04-0.09)	74 0
	4	10.9	FilmArray	LR+: 35 (26-47) LR-: 0.03 (0.01-0.11)	81 0
E. coli O157	7	0.8	Luminex	LR+: 150 (72-330) LR-: 0.13 (0.05-0.28)	55 0
ETEC	5	1.2	Luminex	LR+: 60 (13-290) LR-: 0.13 (0.03-0.38)	42 0
	3	1.4	FilmArray	LR+: 150 (80-280) LR-: 0.08 (0.02-0.33)	68 0
Salmonella	11	5.3	Luminex	LR+: 33 (11-100) LR-: 0.15 (0.11-0.21)	65 1
	5	3.5	FilmArray	LR+: 210 (110-400) LR-: 0.06 (0.02-0.16)	88 0
STEC stx1/stx2	6	2.1	Luminex	LR+: 130 (65-270) LR-: 0.08 (0.03-0.19)	74 0
	4	3.3	FilmArray	LR+: 190 (100-350) LR-: 0.04 (0.01-0.15)	87 0
Shigella/EIEC	11	4.3	Luminex	LR+: 73 (37-150) LR-: 0.07 (0.04-0.13)	77 0
	4	4.8	FilmArray	LR+: 440 (170-1200) LR-: 0.05 (0.02-0.13)	96 0
Yersinia enterocolitica	3	2.1	Luminex	LR+: 230 (45-1200) LR-: 0.53 (0.35-0.69)	83 1
Adenovirus 40/41	9	2	Luminex	LR+: 96 (53-160) LR-: 0.30 (0.12-0.58)	66 1
	5	3.8	FilmArray	LR+: 100 (55-180) LR-: 0.10 (0.03-0.31)	80 0
Norovirus GI/GII	10	6.1	Luminex	LR+: 37 (16-85) LR-: 0.12 (0.08-0.19)	71 1
	6	6.8	FilmArray	LR+: 120 (61-230) LR-: 0.08 (0.05-0.14)	90 1
Rotavirus A	11	5.7	Luminex	LR+: 100 (52-200) LR-: 0.07 (0.04-0.10)	86 0
	6	2.9	FilmArray	LR+: 76 (35-160) LR-: 0.07 (0.02-0.25)	69 0
Cryptosporidium	7	0.7	Luminex	LR+: 96 (22-410) LR-: 0.18 (0.08-0.37)	40 0
	3	1.2	FilmArray	LR+: 230 (110-490) LR-: 0.08 (0.02-0.32)	74 0

Continued

Table 3 Continued

Pathogens	Study(n)	Pre-test probability (%)	Test kit	Likelihood ratio	Post-test probability (%)
Entamoeba histolytica	6	0.2	Luminex	LR+: 59 (18-160)	11
				LR-: 0.30 (0.08-0.68)	0
Giardia lamblia	7	0.9	Luminex	LR+: 36 (13-85)	25
				LR-: 0.19 (0.06-0.49)	0
	4	1.3	FilmArray	LR+: 200 (100-390)	72
				LR-: 0.09 (0.02-0.31)	0
Astrovirus	3	2.7	FilmArray	LR+: 300 (55-1600)	89
				LR-: 0.04 (0.01-0.15)	0
Sapovirus	3	5.6	FilmArray	LR+: 170 (66-430)	91
				LR-: 0.04 (0.01-0.17)	0

fecal-oral outbreaks or waterborne outbreaks, on the other hand, have been associated with *Giardia*, *Cryptosporidium* and norovirus.³⁵ The high rule-out value of FilmArray GI panel means that it can quickly detect highly communicable pathogens and prevent widespread transmission.

It has to be noted that most cases of acute gastroenteritis are of infectious aetiology and resolve with symptomatic treatment alone.⁶ It is neither practical nor cost-effective to perform an extensive laboratory evaluation for every patient presenting with diarrhoeal illness. It is crucial, however, to make accurate microbial identification and enact specific directed therapy in patients who are more likely to have a bacterial infection or who would need treatment once the organism is identified; this includes patients with signs of severe illness (dehydration, severe abdominal pain) or inflammatory diarrhoea (bloody stools, fevers) and patients with high-risk features, comorbidities and immunocompromised conditions.³⁶ For example, in patients with clinically significant diarrhoea, suspected *C. difficile* infection, laboratory approach with nucleic acid amplification testing (NAAT) alone or multistep algorithm including initial EIA screening for glutamate dehydrogenase antigen and toxins A and B arbitrated by NAAT is recommended in recent guidelines.³⁷ Furthermore, in patients with severe or fulminant colitis, multiplex assays may improve outcomes as early surgical consultation and timely operative management result in a shorter hospital length of stay if a patient's clinical course worsens.³⁸ Implementing multiplex assays remarkably reduces the time to initial identification of pathogens. Randomised controlled trials in patients with shigellosis have demonstrated that appropriate use of antimicrobial therapy shortens the average duration of diarrhoea by 2.4 days or more, decreases the duration of fever and tenesmus and reduces the excretion of infectious organisms.³⁹ Altogether, prompt pathogen-specific diagnosis through multiplex assays could greatly influence clinical courses by earlier initiation of appropriate therapy and thereby preventing potential complications

in the most vulnerable patients. In addition to generating more favourable clinical outcomes, multiplex assays can also optimise infection control, allowing for implementation of timely measures to mitigate nosocomial transmission and outbreaks.⁴⁰

Although this meta-analysis includes more than 7000 samples with robust statistical analysis following the Cochrane guideline, there are still several limitations. First, the relative few data on FilmArray did not allow us to perform subgroup analyses for some rare but deadly pathogens (eg, *Vibrio cholerae*, *Enteroaggregative E. coli*, *Enteropathogenic E. coli*, *Cyclospora cayatanensis* and *E. histolytica*). Second, the patient characteristics varied among the included studies in age, travel history and symptoms, and the number of the studies may be insufficient to perform several sensitivity analyses. Third, the accuracy of the nucleic acid test reflected by our study does not reflect active infection. Laboratory results should always be interpreted with a high degree of clinical correlation.⁴¹ Fourth, five studies included discordant analysis which may increase the sensitivity and specificity due to the potential elevation of true positive and true negative cases. In addition, although the FilmArray GI panel shows a higher overall summary AUROC than xTAG GI panel (AUROC 0.99 vs 0.98, $p=0.03$), the result should only be viewed as a statistical significance instead of clinical meaning. Despite these limitations, our results yield valuable insight into the accuracy of xTAG GPP and FilmArray GI panel and their utility in clinical practice.

CONCLUSION

In summary, this is the first systematic review and meta-analysis comparatively evaluating the performance of the novel multiplex PCR-based tests Luminex xTAG GPP and FilmArray GI panel in detecting each pathogen. Compared with conventional methodologies, xTAG GPP and FilmArray GI panel can detect more than 90% of the common enteropathogens with high sensitivity, specificity and a shorter turnaround time. In addition, FilmArray



has higher sensitivity and post-test probability than xTAG GPP for most of the pathogens except for Rotavirus A (the post-test probability for positive test is 69% for FilmArray, 86% for xTAG). Multiplex platforms can clearly have a significant impact on patient management with the potential to (1) reduce the time to first identification of a pathogen, (2) influence patient outcome through early initiation of therapy, (3) alter antimicrobial stewardship and (4) optimise infection control. It is important, however, to account for the variable rule-out accuracy of xTAG GPP and its suboptimal diagnostic accuracy for parasites. However, five studies included in our evaluation had discordant analysis which may increase the sensitivity and specificity due to the potential elevation of true positive and true negative cases. Regardless, this will be an exciting area of development and research as multiplex technology becomes increasingly integrated into everyday clinical practice in the future.

Further reading

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revision of the manuscript. S-TC and H-PW reviewed the manuscript and provided insights in the contents. All investigators contributed to the design or execution of the study, and approved the final version.

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Accuracy and Comparison of Two Rapid Multiplex PCR Tests for Gastroenteritis Pathogens- a Systematic Review and Meta-analysis

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Supplementary Materials S1-detailed search strategy

The search term combination was: (Gastroenteritis OR diarrhea OR feces OR Gastrointestinal Diseases) OR (gastrointestinal OR stool OR enteric OR feces OR faeces OR diarrhea) AND (multiplex polymerase chain reaction) OR multiplex pcr OR (multiplex pcr analysis) OR (multiplex pcr assay) OR (multiplex polymerase chain reaction assay) OR (xtag OR Luminex OR Filmarray OR biofire) OR (Faecal Pathogens B OR Faecal Panel B OR ausdiagnostics) OR (gastrointestinal pathogen panel OR gastrointestinal infection panel).

Embase search strategy 2016-2019

#1	'gastroenteritis'/exp
#2	'diarrhea'/exp
#3	feces*
#4	gastroenteritis*
#5	'gastrointestinal diseases*'
#6	gastrointestin* OR stool* OR enteric* OR 'feces'/exp OR feces OR 'faeces'/exp OR faeces OR 'diarrhea'/exp OR diarrhrea
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	'multiplex polymerase chain reaction'/exp
#9	xtag OR 'luminex'/exp OR luminex OR 'filmarray'/exp OR filmarray OR biofire
#10	'faecal pathogens b' OR 'faecal panel b' OR ausdiagnostics
#11	'multiplex polymerase chain reaction'/exp OR 'multiplex pcr' OR 'multiplex pcr analysis' OR 'multiplex pcr assay' OR 'multiplex polymerase chain reaction' OR 'multiplex polymerase chain reaction assay'
#12	'gastrointestinal pathogen panel' OR 'gastrointestinal infection panel'
#13	#8 OR #9 OR #10 OR #11 OR #12
#14	#7 AND #13
#15	#7 AND #13 AND [2016-2019]/py

Downloaded 927

Web of Science search strategy: 2016-2019

#1	TI= (multiplex* and (PCR or polymerase chain reaction or assay* or panel* or test*)) AND TS= (gastrointestin*)
#2	TS=(“gastrointestinal pathogen panel” or “gastrointestinal infection panel”)
#3	TI= (xtag or Luminex or Filmarray or biofire or “Faecal Pathogens B” or “Faecal Panel B” or ausdiagnostics) AND TS= (gastro*)
#4	#3 OR #2 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

#5	#3 OR #2 OR #1	Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=2016-2019
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Downloaded: 104

Pubmed search strategy: 2016-2019

((((((("Gastroenteritis"[Mesh]) OR diarrhea*) OR feces) OR Gastroenteritis*) OR "Gastrointestinal Diseases"[Mesh]) OR ((gastrointestin[Text Word] OR stool*[Text Word] OR enteric*[Text Word] OR feces[Text Word] OR faeces[Text Word] OR diarrhea[Text Word]))) AND (((("Multiplex Polymerase Chain Reaction"[Mesh]) OR (xtag[Text Word] OR Luminex[Text Word] OR Filmarray[Text Word] OR biofire[Text Word])) OR (("Faecal Pathogens B"[Text Word] OR "Faecal Panel B"[Text Word] OR ausdiagnostics[Text Word])) OR "multiplex polymerase chain reaction" OR "multiplex pcr" OR "multiplex pcr analysis" OR "multiplex pcr assay" OR "multiplex polymerase chain reaction" OR "multiplex polymerase chain reaction assay") OR ((gastrointestinal pathogen panel[Text Word] OR gastrointestinal infection panel[Text Word])))) AND ("2016"[Date - Completion] : "3000"[Date - Completion])

Downloaded: 546

Ovid medline search strategy: 2016-2019

Ovid MEDLINE® and In-Process & Other Non-Indexed Citations 1946 to Present

1	exp Gastroenteritis/
2	exp *Diarrhea/
3	exp *Feces/
4	exp *Gastroenteritis/
5	exp *Gastrointestinal Diseases/
6	(gastrointestin* or stool* or enteric* or feces or faeces or diarrh?ea).tw.
7	1 or 2 or 3 or 4 or 5 or 6
8	Multiplex Polymerase Chain Reaction/
9	(xtag or Luminex or Filmarray or biofire).tw.
10	("Faecal Pathogens B" or "Faecal Panel B" or ausdiagnostics).tw.
11	(multiplex* adj4 (PCR or polymerase chain reaction or assay* or panel* or test*)).tw.
12	(gastrointestinal pathogen panel or gastrointestinal infection panel).tw.
13	13. 8 or 9 or 10 or 11 or 12
14	14. 7 and 13
15	limit 14 to yr="2016 - 2019"

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Supplementary Materials S2-Guidance notes for study assessment using tailored Quality Assessment of Diagnostic Accuracy Studies-2

Risk of bias should be judged as low for each domain only if all questions are answered with 'yes'. The risk of bias should be classed as 'high' if one or more signalling question is answered with 'no'. If at least one question is answered with 'unclear', the risk of bias should be judged 'unclear'.

<i>Domain 1: patient selection</i>
<i>risk of bias</i>
Was a consecutive or random sample of patients enrolled?
Was a case-control design avoided?
Did the study avoid inappropriate exclusions?
Was only one sample per episode included in the study?
<i>Concerns regarding applicability:</i> If the samples are collected from diarrhea patients, then the concerns regarding applicability should be judged as 'low'. If the study population is questionable or unconcerned, then the concerns regarding applicability should be classed as 'unclear'. If the samples are test-negative samples of conventional test, the concerns regarding applicability should be judged as 'high'. If the samples are from mixed population (such as travellers, immunocompromised patients, children aged ≤ 5 years etc.), the concerns are low. If the samples are from travellers or immunocompromised patient only, then the concerns are high.
<i>Domain 2: index test</i>
<i>risk of bias</i>
Were the index test results interpreted without knowledge of the results of the comparator and verification method?
If a threshold was used, was it explicitly pre-specified?
Did all samples receive the index test?
Was the index test undertaken as recommended by the manufacturer?
<i>Concerns regarding applicability:</i> If the GI panel test is used according to the manufacturer's instructions, the concern of applicability of the index test is 'low'.
<i>Domain 3: reference standard</i>
<i>risk of bias</i>
Were the reference standard results interpreted without knowledge of the results of the index test and verification method?

Is the reference standard(comparator) likely to correctly classify the target condition?
If a threshold was used, was it explicitly pre-specified?
Concerns regarding applicability: The question evaluated whether or not the target condition identified by the reference standard matches the target condition of interest in the review. The target condition for this assessment is the pathogen causing symptoms of diarrhea. If the reference standard detects pathogen DNA/RNA at levels that are unlikely to cause symptoms or detect dead organisms, then the applicability concern is high. Therefore, the concerns regarding applicability of the reference standard are 'high' if discrepant results were investigated with PCR-based methods and the comparator methods for at least some pathogens were conventional non-PCR microbiology tests. Furthermore, PCR and sequencing are not common daily practice due to their higher price, then the concerns regarding applicability are high.
Domain 4: flow and timing
risk of bias
Was there an appropriate interval between index test(s) and reference standard?
Did all discordant samples receive a reference standard?
Did all patients receive the same reference standard?
Did all samples receive the comparator methods for all pathogens considered in the study?
Were all patients included in the analysis?

Supplementary Materials S3- Characteristics of the 11 included studies (21 data sets)

Characteristic	n (data sets) (%)
Age	
Children	2 (10%)
Adult	1 (5%)
Mixed	12(56%)
Unclear	6 (29%)
Index test	
Luminex xTAG GI panel	15(71%)
FilmArray GI panel	6 (29%)
Reference standard	
Sequencing or real-time PCR	6 (29%)
Conventional standard microbiology techniques (including culture, C. difficile toxin study, enzyme immunoassay (EIA) or microscopy)	6 (29%)
Mixed (including PCR and conventional standard microbiology techniques)	9 (42%)
Specimen type	
Stool	21(100%)
Study design	
Prospective	15(71%)
Retrospective	4 (19%)
mixed	2 (10%)
Country	
United States	9 (42%)

Netherlands	5 (23%)
Spain	2 (10%)
Vietnam	2 (10%)
United Kingdom	1 (5%)
France	1 (5%)
China	1 (5%)

Supplementary Materials S4- Comparison of characteristics between two FDA-approved multiplex platforms for the detection of gastrointestinal pathogens. (10)

Feature	Luminex	FilmArray
Technology	PCR plus xTAG (fluorescent bead-based detection)	Nested PCR plus melting curve
Processing time per run (min)	45	2
Separate extraction required (min)	Yes (~45)	No
Time/run (h)	~3.5	~1
Throughput (no. specimens/run)	96	1
Maximum no. of targets	15	22
targets	<ul style="list-style-type: none"> ● <i>Campylobacter</i> (<i>C. jejuni</i>, <i>C. coli</i>和<i>C. lari</i>) ● <i>Clostridium difficile</i> (<i>C. difficile</i>) toxin A/B ● <i>Escherichia coli</i> (<i>E. coli</i>) O157 ● Enterotoxigenic <i>Escherichia coli</i> (ETEC) LT/ST ● <i>Salmonella</i> ● Shiga-like Toxin producing <i>E. coli</i> (STEC) stx 1/stx 2 ● <i>Shigella</i> (including <i>S. boydii</i>, <i>S. sonnei</i>, <i>S. flexneri</i> and <i>S. dysenteriae</i>) ● <i>Vibrio cholerae</i> (<i>V. cholerae</i>) cholera toxin gene (ctx) ● <i>Yersinia enterocolitica</i> ● Adenovirus 40/41 ● Norovirus GI/GII ● Rotavirus A ● <i>Cryptosporidium</i> (<i>C. parvum</i> and <i>C. hominis</i>) ● <i>Entamoeba histolytica</i> ● <i>Giardia lamblia</i> 	<ul style="list-style-type: none"> ● <i>Campylobacter</i> (<i>C. jejuni</i>/<i>C. coli</i>/<i>C. upsaliensis</i>) ● <i>Clostridium difficile</i> (<i>C. difficile</i>) toxin A/B ● <i>Plesiomonas shigelloides</i> ● <i>Salmonella</i> ● <i>Vibrio</i> (<i>V. parahaemolyticus</i>/<i>V. vulnificus</i>/<i>V. cholerae</i>) ● <i>Vibrio cholerae</i> ● <i>Yersinia enterocolitica</i> ● Enteroaggregative <i>Escherichia coli</i> (EAEC) ● Enteropathogenic <i>Escherichia coli</i> (EPEC) ● Enterotoxigenic <i>Escherichia coli</i> (ETEC) lt/st ● Shiga-like toxin-producing <i>Escherichia coli</i> (STEC) stx1/stx2 ● <i>E. coli</i> O157 ● <i>Shigella</i>/ Enteroinvasive <i>Escherichia coli</i> (EIEC) ● Adenovirus F 40/41 ● Astrovirus ● Norovirus GI/GII ● Rotavirus A

Feature	Luminex	FilmArray
		<ul style="list-style-type: none"> ● Sapovirus (Genogroups I, II, IV and V) ● <i>Cryptosporidium</i> ● <i>Cyclospora cayetanensis</i> ● <i>Entamoeba histolytica</i> ● <i>Giardia lamblia</i>
Open or closed system	Open	Closed
Results	Qualitative	Qualitative
Footprint size	Moderate	Small
List price per instrument (\$)	37,000	39,500
List price reagent cost per specimen (\$)	80–90	155

Supplementary Materials S5-detailed characteristics of 11 included studies

I D	Author, year, country	Number and characteristics of samples and patient	Patient age	Patient inclusion criteria	Specimen type	Routine testing methods	Adjudication methods for discordant results	Index test (multiplex PCR)	<i>pathogens</i>	Sen	Spe
1	Deng J et al., 2015, China	Prospective, 290 stool samples from 290 patient. 70 inpatients and 220 outpatients, and pediatric outpatients were the most common (54.1%). 64.1% male.	Mixed (median age of 25 months and ranging from 11 days to 83 years.)	Diarrheal patients	Stool	Bacterial culture, serotyping for Salmonella and Shigella, real-time reverse transcription-polymerase chain reaction (RT-PCR) assays for viral detection, microscopic examination for parasite detection.	Singleplex PCR and sequencing	Luminex xTAG	<i>Campylobacter</i>	1.00	1.00
									<i>C. difficile toxin A</i>	1.00	0.99
									<i>C. difficile toxin B</i>	0.87	1.00
									<i>E. coli O157</i>	1.00	1.00
									<i>ETEC LT/ST</i>	1.00	1.00
									<i>Salmonella</i>	0.85	0.99
									<i>Shigella</i>	1.00	1.00
									<i>V. cholerae</i>	NA	1.00
									<i>Yersinia enterocolitica</i>	1.00	1.00
									<i>Adenovirus 40/41</i>	1.00	1.00
									<i>Norovirus GI</i>	1.00	1.00
									<i>Norovirus GII</i>	1.00	0.99
2	Chhabra P et al., 2017, USA	Retrospective, 300 stool samples from children and adults	Unclear	Patient with acute	Stool	TAC system, real-time PCR and sequencing	Discordant analysis	Luminex xTAG	<i>Adenovirus 40/41</i>	0.58	1.00
									<i>Norovirus GI/GII</i>	0.78	1.00
									<i>Rotavirus A</i>	0.96	1.00

				gastroenteritis				FilmArray	<i>Adenovirus F 40/41</i>	0.97	0.98
									<i>Astrovirus</i>	0.97	0.99
									<i>Norovirus GI/GII</i>	0.88	1.00
									<i>Rotavirus A</i>	1.00	0.96
									<i>Sapovirus</i>	0.98	1.00
3	Alejo-Cancho I et al., 2017, Spain	Prospective, 95 stool samples were obtained from 95 immunocompromised adult patients.	Adult patient, with a median age of 52 years (46–64).	Acute diarrheal patient	Stool	Routine microbiological techniques, including bacterial culture, <i>C. difficile</i> toxin study, microscopy for parasite, virus antigen.	Second multiplex assay (Allplex, Seegene, Korea)	FilmArray	<i>Campylobacter</i>	1.00	1.00
									<i>C. difficile toxin A/B</i>	1.00	1.00
									<i>Plesiomonas shigelloides</i>	NA	1.00
									<i>Salmonella</i>	1.00	1.00
									<i>Vibrio spp.</i>	NA	1.00
									<i>Vibrio cholerae</i>	NA	1.00
									<i>Yersinia enterocolitica</i>	NA	1.00
									EAEC	1.00	1.00
									EPEC	1.00	0.97
									ETEC lt/st	1.00	1.00
									STEC stx1/stx2	NA	1.00
									<i>E. coli O157</i>	NA	1.00
									<i>Shigella/EIEC</i>	NA	1.00
									<i>Adenovirus F 40/41</i>	0.00	1.00
									<i>Astrovirus</i>	NA	1.00
									<i>Norovirus GI/GII</i>	1.00	1.00

									<i>Rotavirus A</i>	1.00	1.00
									<i>Sapovirus</i>	NA	1.00
									<i>Cryptosporidium</i>	NA	1.00
									<i>Cyclospora cayetanensis</i>	NA	1.00
									<i>Entamoeba histolytica</i>	NA	1.00
									<i>Giardia lamblia</i>	1.00	1.00
4	Duong VT et al., 2016, Vietnam	Retrospective, 479 stool samples were collected from 92 adults (>15 years) and 387 children (≤15 years old) admitted to the hospital with diarrheal disease.	The median age of the adult patients was 50 years (interquartile range [IQR], 33 to 64 years). In children, the median age was 16.5 months (IQR, 6.7 to 20 months).	Diarrheal patients	Stool	Microbiological culture and real-time PCR	Discordant analysis	Luminex xTAG	<i>Campylobacter</i>	0.91	0.99
									<i>C. difficile toxin A</i>	NA	NA
									<i>C. difficile toxin B</i>	NA	NA
									<i>E. coli O157</i>	NA	NA
									<i>ETEC LT/ST</i>	NA	NA
									<i>Salmonella</i>	0.90	0.67
									<i>STEC stx1/stx2</i>	NA	NA
									<i>Shigella</i>	0.96	0.99
									<i>V. cholerae</i>	NA	NA
									<i>Yersinia enterocolitica</i>	NA	NA
									<i>Adenovirus 40/41</i>	0.92	0.99
									<i>Norovirus GI</i>	0.88	0.99
									<i>Norovirus GII</i>	0.97	0.99
									<i>Rotavirus A</i>	0.93	0.99
									<i>Cryptosporidium</i>	NA	NA
									<i>Entamoeba histolytica</i>	NA	NA

									<i>Giardia lamblia</i>	NA	NA
									<i>Campylobacter</i>	0.90	0.92
									<i>Salmonella</i>	0.95	0.61
									<i>Shigella</i>	1.00	0.88
6	Khare R et al., 2014, USA	Prospective and retrospective, 230 prospectively collected samples	Unclear	Stool samples submitted to laboratory for routine GI testing.	Stool	Routine testing (e.g., culture, microscopy, antigen testing, and/or individual real-time PCR)	Discordant analysis	Luminex xTAG	<i>Campylobacter</i>	1.00	1.00
									<i>C. difficile toxin A/B</i>	0.96	0.97
									<i>E. coli O157</i>	NA	1.00
									<i>ETEC LT/ST</i>	1.00	1.00
									<i>Salmonella</i>	1.00	1.00
									<i>STEC stx1/stx2</i>	NA	1.00
									<i>Shigella</i>	1.00	1.00
									<i>V. cholerae</i>	NA	1.00
									<i>Yersinia enterocolitica</i>	NA	1.00
									<i>Adenovirus 40/41</i>	1.00	1.00
									<i>Norovirus GI/GII</i>	1.00	0.91
									<i>Rotavirus A</i>	NA	0.99
									<i>Cryptosporidium</i>	1.00	1.00
									<i>Entamoeba histolytica</i>	NA	1.00
									<i>Giardia lamblia</i>	1.00	1.00
6	Khare R et al., 2014, USA	Prospective and retrospective, 270 additional previously characterized samples	Unclear	Stool samples submitted to laboratory	Stool	Routine testing (e.g., culture, microscopy, antigen testing, and/or	Discordant analysis	Luminex xTAG	<i>Campylobacter</i>	0.79	1.00
									<i>C. difficile toxin A/B</i>	0.92	0.98
									<i>E. coli O157</i>	0.91	1.00

				y for routine GI testing.		individual real-time PCR)			<i>ETEC LT/ST</i>	NA	NA
									<i>Salmonella</i>	0.83	1.00
									<i>STEC stx1/stx2</i>	0.96	1.00
									<i>Shigella</i>	0.82	NA
									<i>V. cholerae</i>	NA	NA
									<i>Yersinia enterocolitica</i>	0.48	1.00
									<i>Adenovirus 40/41</i>	0.80	1.00
									<i>Norovirus GI/GII</i>	0.93	0.86
									<i>Rotavirus A</i>	0.93	1.00
									<i>Cryptosporidium</i>	1.00	1.00
									<i>Entamoeba histolytica</i>	1.00	1.00
									<i>Giardia lamblia</i>	1.00	1.00
6	Khare R et al., 2014, USA	Prospective, <u>230 prospectively collected samples</u>	Unclear	Stool samples submitted to laboratory for routine GI testing.	Stool	Routine testing (e.g., culture, microscopy, antigen testing, and/or individual real-time PCR)	Discordant analysis	FilmArray	<i>Campylobacter</i>	1.00	1.00
									<i>C. difficile toxin A/B</i>	1.00	0.97
									<i>Plesiomonas shigelloides</i>	NA	1.00
									<i>Salmonella</i>	1.00	1.00
									<i>Vibrio spp.</i>	NA	1.00
									<i>Vibrio cholerae</i>	NA	1.00
									<i>Yersinia enterocolitica</i>	NA	1.00
									<i>EAEC</i>	NA	NA
									<i>EPEC</i>	NA	NA
									<i>ETEC lt/st</i>	1.00	1.00

									<i>STEC stx1/stx2</i>	NA	1.00
									<i>E. coli O157</i>	NA	1.00
									<i>Shigella/EIEC</i>	1.00	1.00
									<i>Adenovirus F 40/41</i>	1.00	1.00
									<i>Astrovirus</i>	1.00	NA
									<i>Norovirus GI/GII</i>	0.92	1.00
									<i>Rotavirus A</i>	NA	1.00
									<i>Sapovirus</i>	1.00	NA
									<i>Cryptosporidium</i>	1.00	1.00
									<i>Cyclospora cayetanensis</i>	NA	1.00
									<i>Entamoeba histolytica</i>	NA	1.00
									<i>Giardia lamblia</i>	1.00	1.00
									<i>Aeromonas spp.</i>	1.00	1.00
6	Khare R et al., 2014, USA	Prospective, 270 <u>additional previously characterized samples</u>	Unclear	Stool samples submitted to laboratory for routine GI testing.	Stool	Routine testing (e.g., culture, microscopy, antigen testing, and/or individual real-time PCR)	Discordant analysis	FilmArray	<i>Campylobacter</i>	0.97	1.00
									<i>C. difficile toxin A/B</i>	0.92	0.98
									<i>Plesiomonas shigelloides</i>	1.00	1.00
									<i>Salmonella</i>	1.00	1.00
									<i>Vibrio spp.</i>	NA	NA
									<i>Vibrio cholerae</i>	NA	NA
									<i>Yersinia enterocolitica</i>	1.00	1.00
									<i>EAEC</i>	NA	NA

									<i>EPEC</i>	NA	NA
									<i>ETEC lt/st</i>	NA	NA
									<i>STEC stx1/stx2</i>	1.00	0.99
									<i>E. coli O157</i>	1.00	1.00
									<i>Shigella/EIEC</i>	0.91	1.00
									<i>Adenovirus F 40/41</i>	0.90	0.99
									<i>Astrovirus</i>	1.00	1.00
									<i>Norovirus GI/GII</i>	0.93	1.00
									<i>Rotavirus A</i>	1.00	1.00
									<i>Sapovirus</i>	0.90	1.00
									<i>Cryptosporidium</i>	1.00	1.00
									<i>Cyclospora cayetanensis</i>	NA	NA
									<i>Entamoeba histolytica</i>	NA	1.00
									<i>Giardia lamblia</i>	1.00	1.00
									<i>Aeromonas spp.</i>	0.24	1.00
7	Buss SN et al., 2015, USA	Prospective, 1556 stool samples from 584 adult (older than 21 years old [38%]) and 972 pediatric (younger than or equal to 21 years old [62%]) populations	Unclear	Stool samples submitted with orders by the provider for stool culture	Stool	Stool culture, PCR	Discordant analysis	FilmArray	<i>Campylobacter</i>	0.97	0.98
									<i>C. difficile toxin A/B</i>	0.99	0.97
									<i>Plesiomonas shigelloides</i>	1.00	0.99
									<i>Salmonella</i>	1.00	1.00
									<i>Vibrio spp.</i>	NA	1.00
									<i>Vibrio cholerae</i>	NA	1.00

									<i>Yersinia enterocolitica</i>	NA	1.00
									<i>EAEC</i>	0.99	0.98
									<i>EPEC</i>	0.99	0.97
									<i>ETEC lt/st</i>	1.00	0.99
									<i>STEC stx1/stx2</i>	1.00	1.00
									<i>E. coli O157</i>	1.00	0.97
									<i>Shigella/EIEC</i>	0.96	1.00
									<i>Adenovirus F 40/41</i>	0.96	1.00
									<i>Astrovirus</i>	1.00	1.00
									<i>Norovirus GI/GII</i>	0.95	0.99
									<i>Rotavirus A</i>	1.00	0.99
									<i>Sapovirus</i>	1.00	0.99
									<i>Cryptosporidium</i>	1.00	1.00
									<i>Cyclospora cayetanensis</i>	1.00	1.00
									<i>Entamoeba histolytica</i>	NA	1.00
									<i>Giardia lamblia</i>	1.00	1.00
8	Claas EC et al., 2013, Netherlands	Prospective, 901 stool specimens from both pediatric and adult patients	Unclear	Stool collected in four hospitals	Stool	Routine testing (e.g., culture, microscopy, EIA/DFA, or real-time PCR)	Discordant analysis	Luminex xTAG	<i>Campylobacter</i>	1.00	0.82
									<i>C. difficile toxin A/B</i>	1.00	0.91
									<i>E. coli O157</i>	0.83	0.99
									<i>ETEC LT/ST</i>	NA	1.00
									<i>Salmonella</i>	0.97	0.95

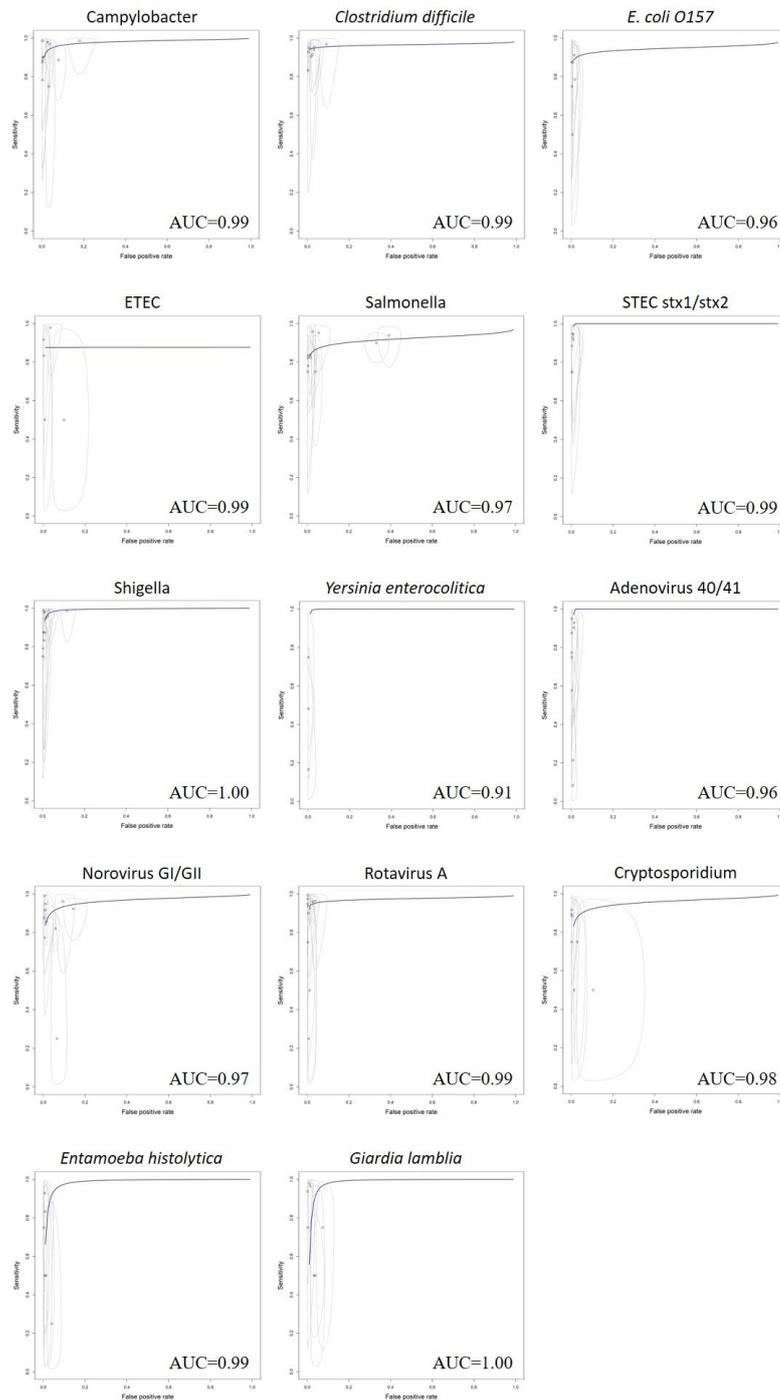
									<i>STEC stx1/stx2</i>	1.00	1.00
									<i>Shigella</i>	0.97	0.98
									<i>V. cholerae</i>	NA	1.00
									<i>Yersinia enterocolitica</i>	0.00	1.00
									<i>Adenovirus 40/41</i>	1.00	1.00
									<i>Norovirus GI</i>	NA	1.00
									<i>Norovirus GII</i>	1.00	0.99
									<i>Rotavirus A</i>	0.00	1.00
									<i>Cryptosporidium</i>	NA	1.00
									<i>Entamoeba histolytica</i>	NA	1.00
									<i>Giardia lamblia</i>	NA	0.96
									<i>Adenovirus F 40/41</i>	0.20	0.99
									<i>Astrovirus</i>	1.00	1.00
									<i>Norovirus GI/GII</i>	0.93	0.98
									<i>Rotavirus A</i>	1.00	1.00
									<i>Cryptosporidium</i>	0.91	1.00
									<i>Entamoeba histolytica</i>	1.00	0.99
									<i>Giardia lamblia</i>	1.00	0.99
									<i>Campylobacter</i>	0.97	0.96
									<i>E. coli O157</i>	0.94	0.99
									<i>Salmonella</i>	0.83	0.99
									<i>Shigella</i>	1.00	0.97

									<i>V. cholerae</i>	0.00	1.00
									<i>Yersinia enterocolitica</i>	NA	1.00
									<i>Cryptosporidium</i>	0.92	1.00
									<i>Entamoeba histolytica</i>	NA	0.99
									<i>Giardia lamblia</i>	1.00	0.97
									<i>C. difficile toxin A/B</i>	0.97	0.97
									<i>ETEC lt/st</i>	NA	0.91
									<i>STEC stx1/stx2</i>	1.00	0.99
									<i>Cryptosporidium</i>	NA	1.00
									<i>Giardia lamblia</i>	NA	1.00
9	Halligan E et al., 2014, UK	Prospective, 2187 diarrhoeal stool samples. 986 (45%) samples originated from inpatients developing symptoms in the first 4 days of admission or from outpatient clinics, and the remaining 1201 (55%) samples were from inpatients on day 4 or more of admission.	Unclear	Diarrheal patients	Stool	Conventional tests including microbiological culture, microscopy, microwell enzyme immunoassay, immunochromatographic test	Discordant analysis	Luminex xTAG	<i>Campylobacter</i>	1.00	0.97
									<i>C. difficile toxin A/B</i>	0.95	0.99
									<i>E. coli O157</i>	1.00	1.00
									<i>ETEC LT/ST</i>	NA	NA
									<i>Salmonella</i>	1.00	0.97
									<i>STEC stx1/stx2</i>	NA	NA
									<i>Shigella</i>	1.00	0.99
									<i>V. cholerae</i>	NA	NA
									<i>Yersinia enterocolitica</i>	NA	NA
									<i>Adenovirus 40/41</i>	1.00	0.99
									<i>Norovirus GI/GII</i>	0.83	0.94

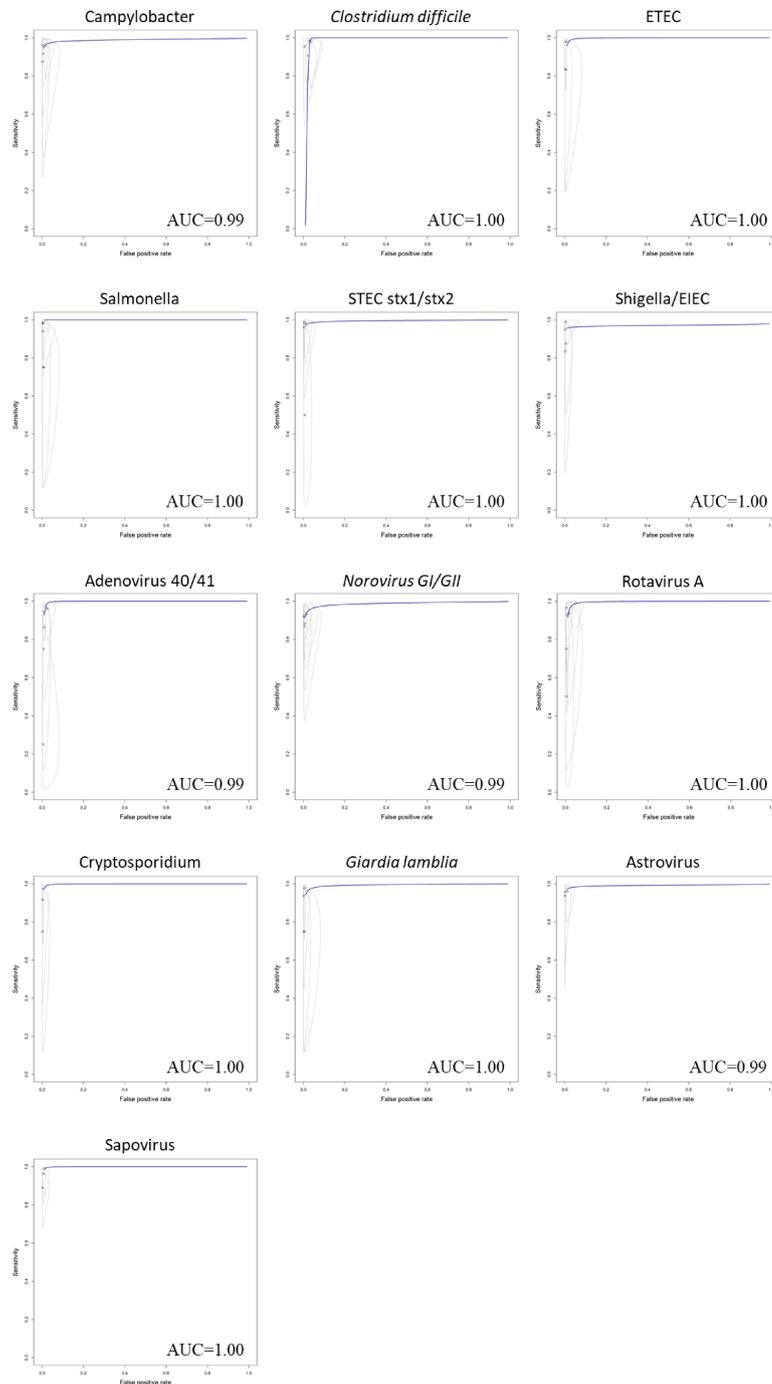
									<i>Rotavirus A</i>	1.00	0.96
									<i>Cryptosporidium</i>	1.00	0.97
									<i>Entamoeba histolytica</i>	0.00	0.96
									<i>Giardia lamblia</i>	1.00	0.93
10	Mengelle C et al., 2013, France	Prospective, 440 stool samples collected from 329 diarrhoeic patients	Three groups included immunosuppressed hospitalized patients: 102 adult organ transplant recipients (mean age, 50.6; median, 56; range, 17–75), 50 immunosuppressed children (mean age, 5; median, 7; range, 0–14) and 56 children attending the neonatal unit (aged under 1 year). The 121 children attending the	Diarrheal patients	Stool	Routine diagnostic methods (e.g., culture, microscopy, immunochromatographic assay, and multiplex PCR)	Discordant analysis	Luminex xTAG	<i>Campylobacter</i>	1.00	0.97
									<i>C. difficile toxin A/B</i>	1.00	0.98
									<i>E. coli O157</i>	NA	1.00
									<i>ETEC LT/ST</i>	NA	1.00
									<i>Salmonella</i>	0.78	0.96
									<i>STEC stx1/stx2</i>	1.00	0.99
									<i>Shigella</i>	1.00	1.00
									<i>V. cholerae</i>	NA	1.00
									<i>Yersinia enterocolitica</i>	NA	1.00
									<i>Adenovirus 40/41</i>	0.00	1.00
									<i>Norovirus GI/GII</i>	0.00	0.94
									<i>Rotavirus A</i>	0.97	0.97
									<i>Cryptosporidium</i>	NA	0.99
									<i>Entamoeba histolytica</i>	NA	1.00
									<i>Giardia lamblia</i>	NA	1.00

			emergency unit (mean age, 2.80; median, 9; range, 0–16) were considered to be outpatients.								
1	Zboromyrska Y et al., 2014, Spain	Prospective, 185 stool samples from patients with traveller's diarrhea.	Unclear	Patients with traveller's diarrhea	Stool	Routine diagnostic methods (e.g., culture, microscopy, mass spectrometry, and multiplex PCR)	Conventional PCR and bidirectional sequencing	Luminex xTAG	<i>Campylobacter</i>	1.00	1.00
									<i>C. difficile toxin A/B</i>	NA	1.00
									<i>E. coli O157</i>	1.00	1.00
									<i>ETEC LT/ST</i>	1.00	0.97
									<i>Salmonella</i>	1.00	1.00
									<i>STEC stx1/stx2</i>	1.00	1.00
									<i>Shigella</i>	1.00	0.99
									<i>V. cholerae</i>	NA	NA
									<i>Yersinia enterocolitica</i>	NA	NA
									<i>Adenovirus 40/41</i>	NA	NA
									<i>Norovirus GI/GII</i>	NA	0.99
									<i>Rotavirus A</i>	NA	1.00
									<i>Cryptosporidium</i>	NA	NA
									<i>Entamoeba histolytica</i>	1.00	0.99
									<i>Giardia lamblia</i>	1.00	0.99
			Unclear		Stool				<i>Campylobacter</i>	0.92	1.00

1 2	Huang RS et al., 2016, USA	98 retrospective and 54 prospective samples collected from pediatric patients with signs and symptoms of acute gastroenteritis.		Patient with acute gastroenteritis		Conventional testing including stool cultures, immunochromatographic rapid tests, and singleplex RT-PCR	Discordant analysis	Luminex xTAG	<i>Salmonella</i>	0.79	1.00
									<i>STEC stx1/stx2</i>	0.92	1.00
									<i>Shigella</i>	1.00	1.00
									<i>Norovirus GI/GII</i>	0.90	1.00
									<i>Rotavirus A</i>	1.00	1.00
1 2	Huang RS et al., 2016, USA	98 retrospective and 54 prospective samples collected from pediatric patients with signs and symptoms of acute gastroenteritis.	Unclear	Patient with acute gastroenteritis	stool	Conventional testing including stool cultures, immunochromatographic rapid tests, and singleplex RT-PCR	Discordant analysis	FilmArray	<i>Campylobacter</i>	1.00	1.00
									<i>Salmonella</i>	0.96	1.00
									<i>STEC stx1/stx2</i>	1.00	1.00
									<i>Shigella</i>	1.00	1.00
									<i>Norovirus GI/GII</i>	0.95	0.99
<i>Rotavirus A</i>	1.00	0.99									



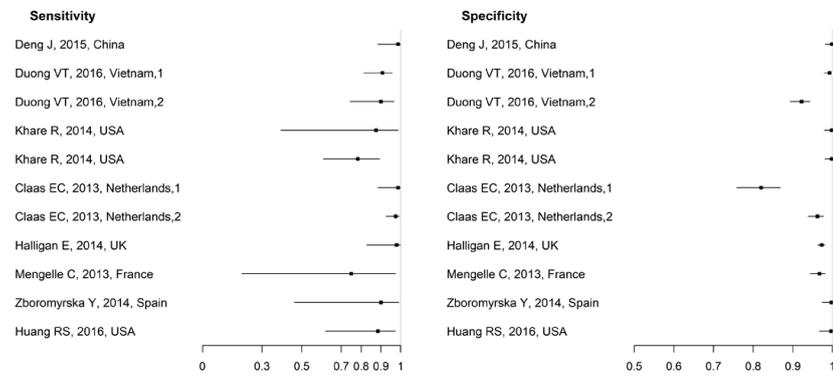
Supplementary materials S6. Receiver operating curve (ROC) analysis of Luminex xTAG GI panel for detection of different pathogens. The blue lines indicate the receiver operating curve. The blue lines indicate the receiver operating curve. The grey dots represent estimates of individual studies and grey circles around the dots represent the 95% confidence interval.



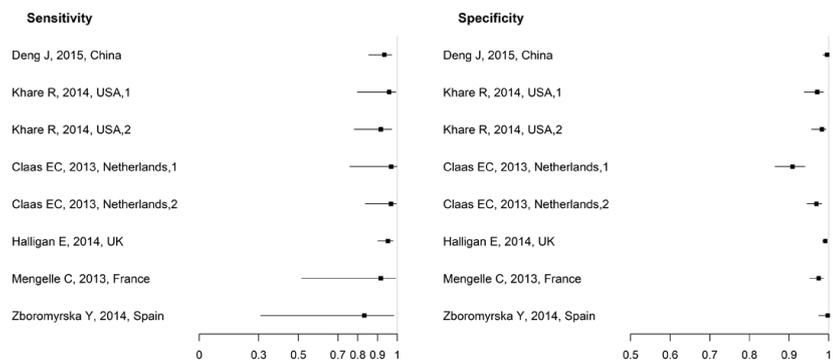
Supplementary materials S7. Receiver operating curve (ROC) analysis of FilmArray GI panel for detection of different pathogens. The blue lines indicate the receiver operating curve. The blue lines indicate the receiver operating curve. The grey dots represent estimates of individual studies and grey circles around the dots represent the 95% confidence interval.

(A)

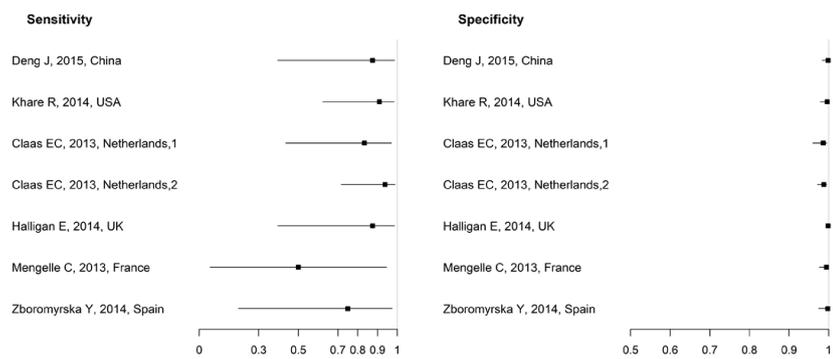
Campylobacter



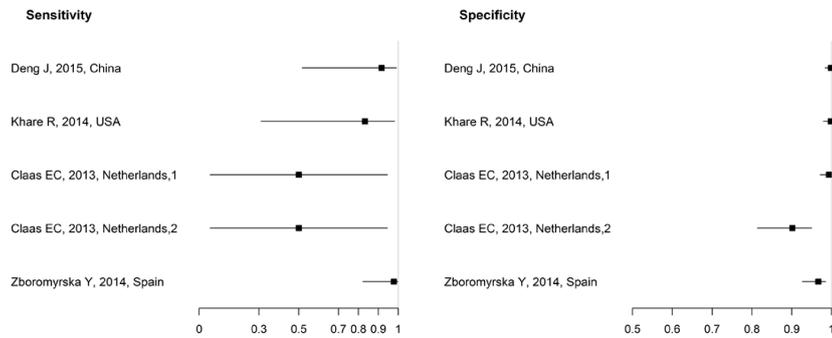
Clostridium difficile



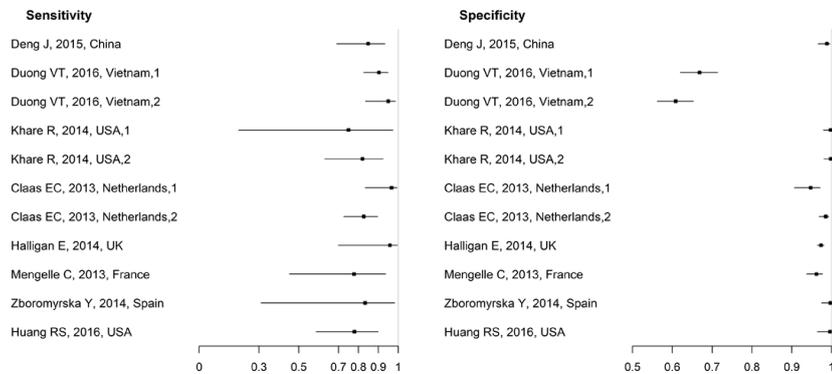
E. coli O157



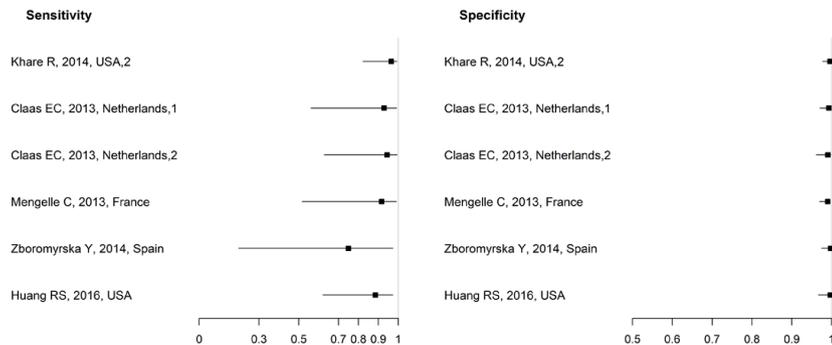
ETEC



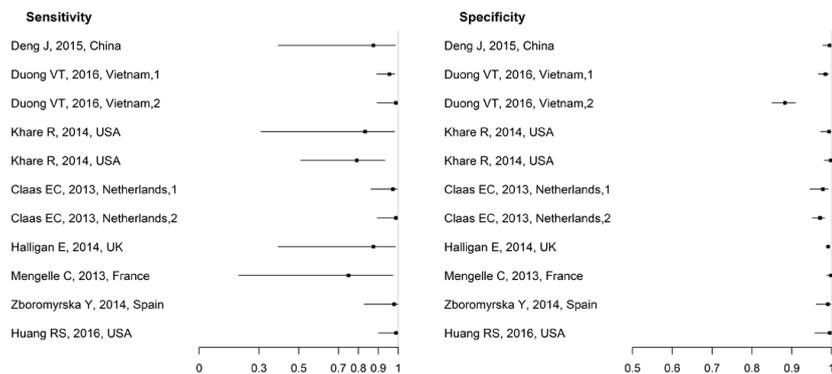
Salmonella



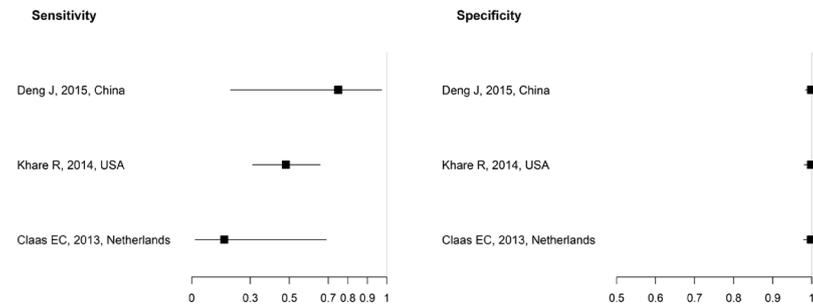
STEC stx1/stx2



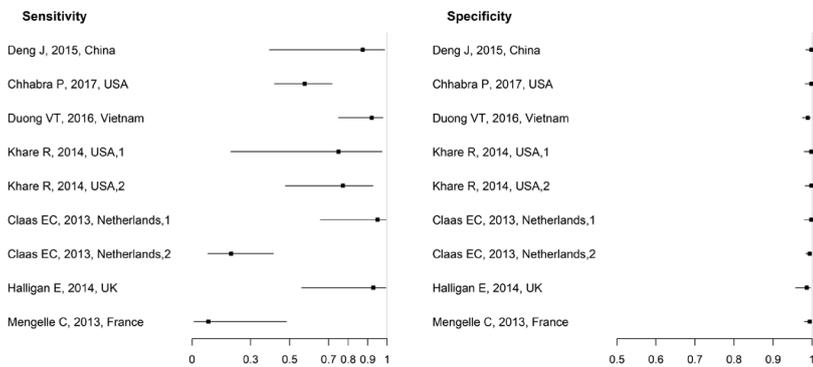
Shigella



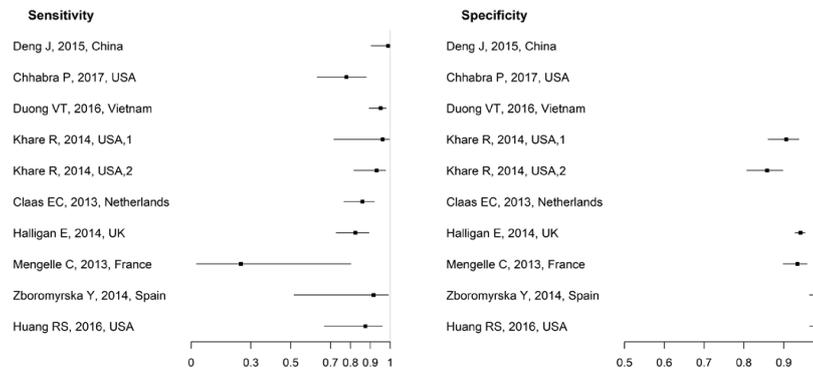
Yersinia enterocolitica



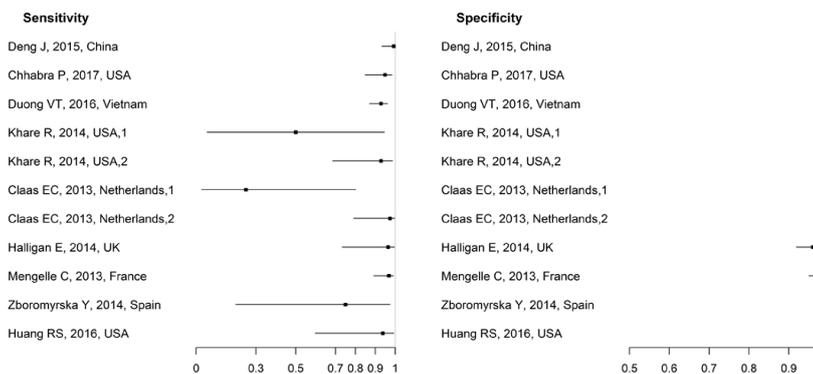
Adenovirus 40/41



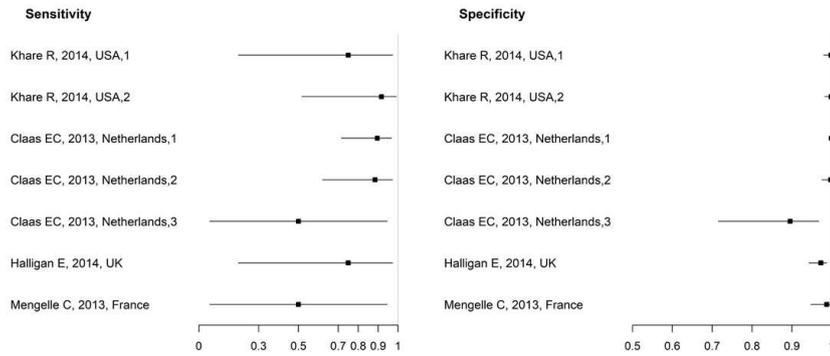
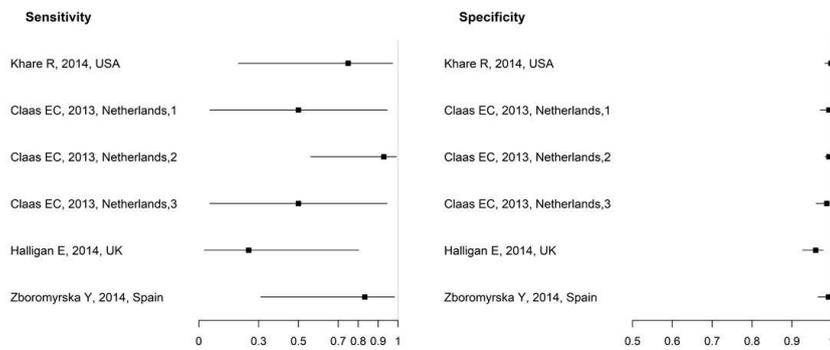
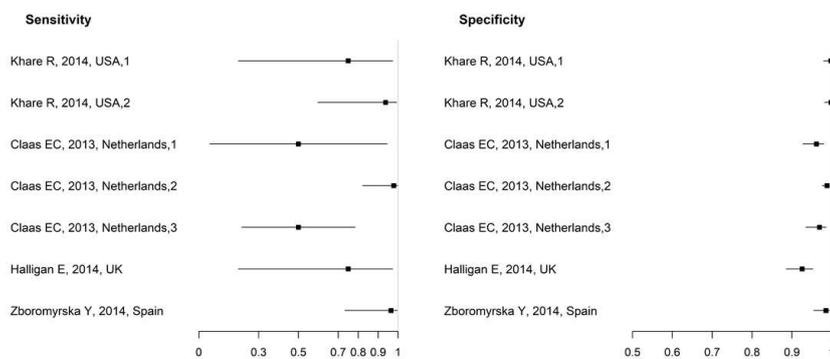
Norovirus GI/GII



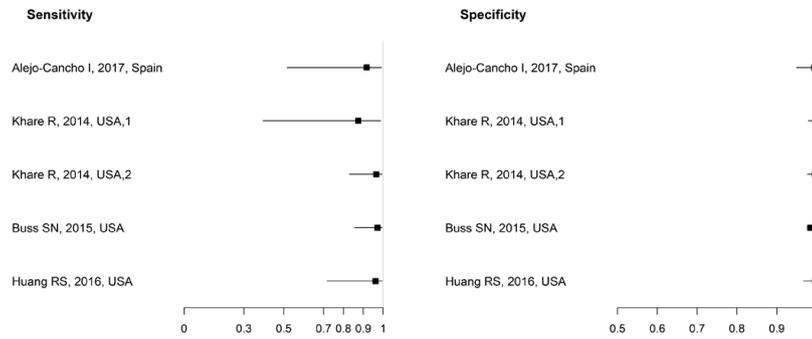
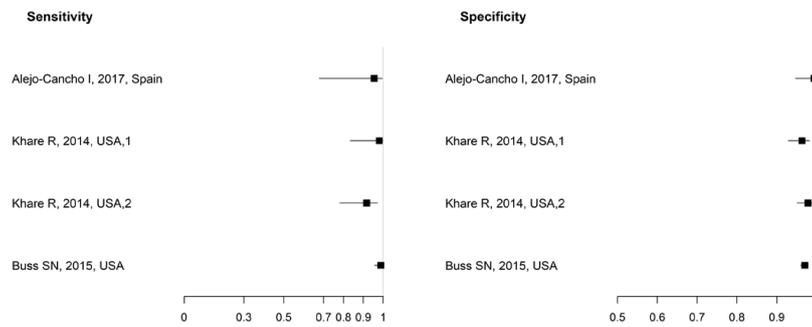
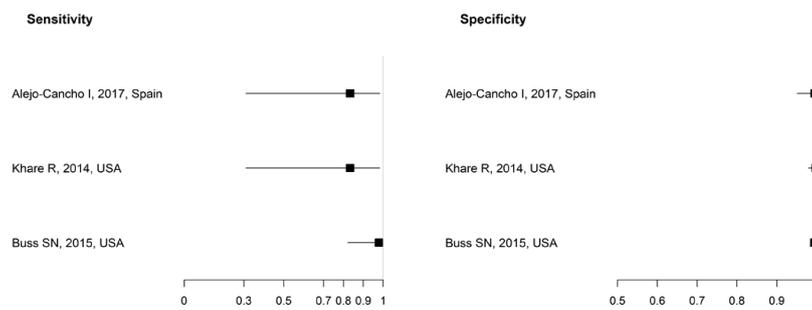
Rotavirus



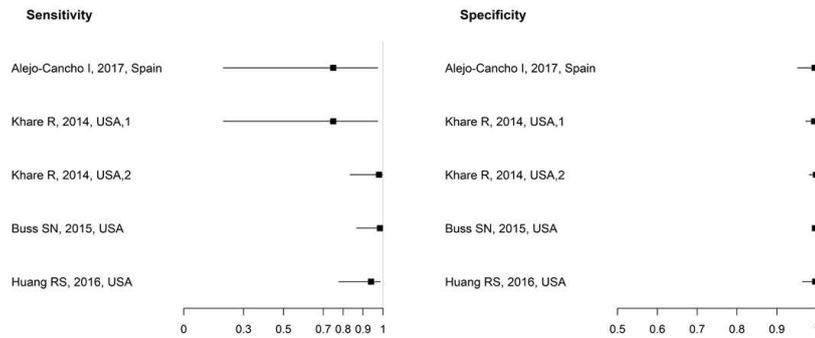
Cryptosporidium

*Entamoeba histolytica**Giardia lamblia*

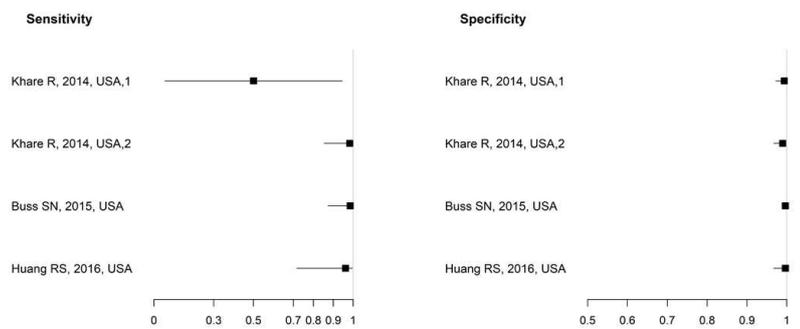
(B)

Campylobacter**Clostridium difficile****ETEC**

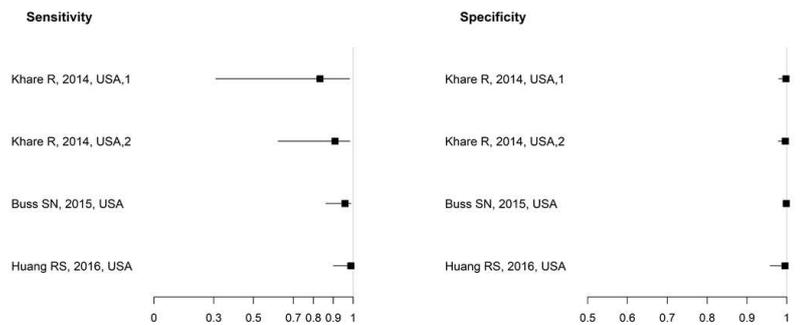
Salmonella



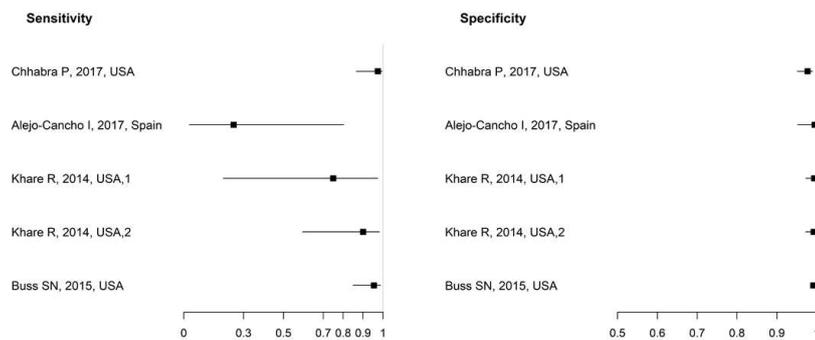
STEC stx1/stx2



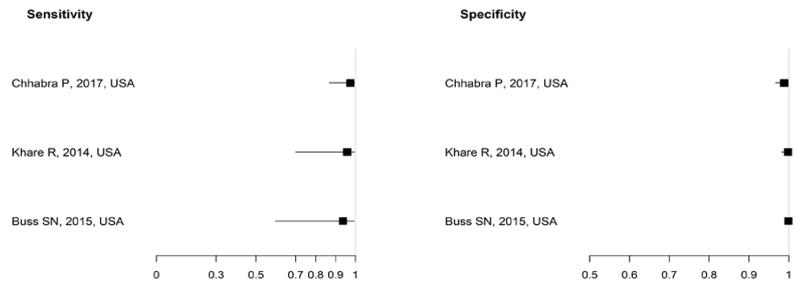
Shigella/EIEC



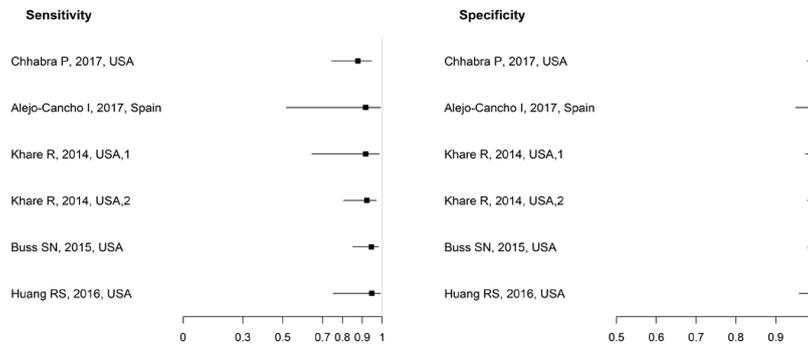
Adenovirus



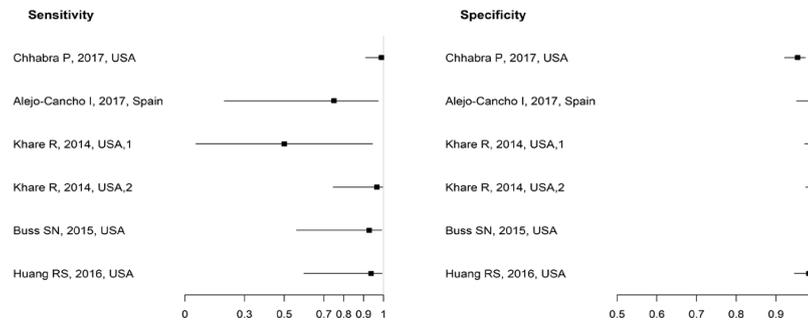
Astrovirus



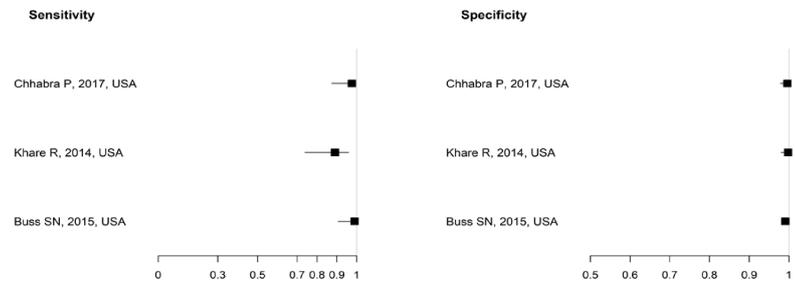
Norovirus GI/GII



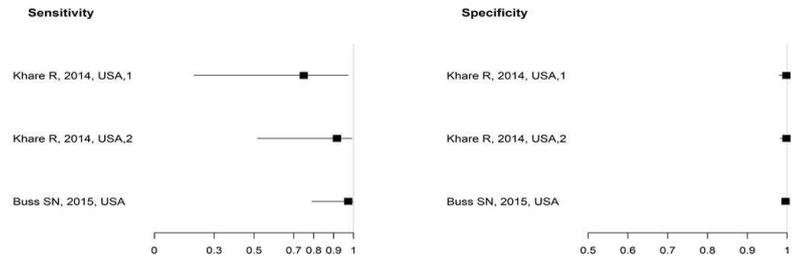
Rotavirus



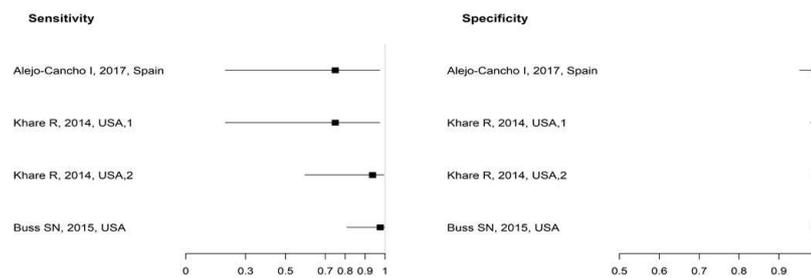
Sapovirus



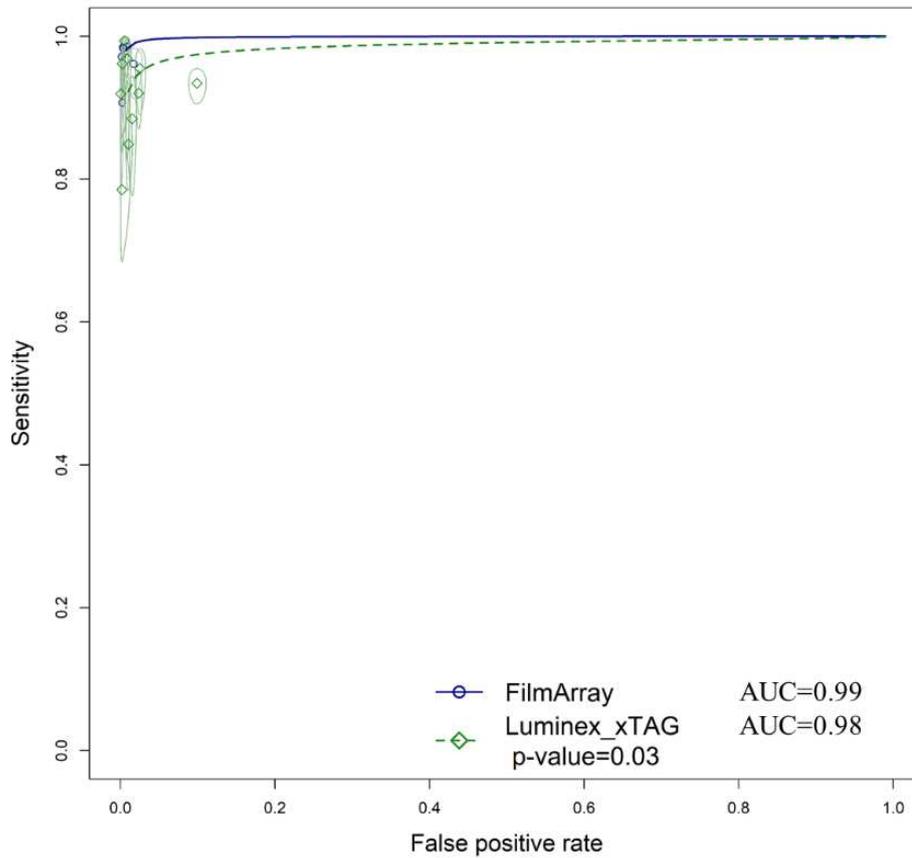
Cryptosporidium



Giardia lamblia



Supplementary materials S8. (A) Forest plot of the estimated sensitivity and specificity (black squares) of the Luminex xTAG GI panel for each pathogen, and its 95% confidence intervals (horizontal black lines) of each study. (B) Forest plot of the estimated sensitivity and specificity (black squares) of the FilmArray GI panel for each pathogen, and its 95% confidence intervals (horizontal black lines) of each study.



Supplementary materials S9. Summary receiver operating characteristic (SROC) curve. Dots and diamonds represent estimates of individual studies for FilmArray and Luminex, respectively. Circles represent the 95% confidence interval. SROC curves are the lines passing through summary points.

Supplementary material S10. Subgroup analysis for GI panel sensitivity and specificity when tested with different gold standards.

Test	Studies number	Sensitivity (95% confidence interval)	Specificity (95% confidence interval)	AUC (95% confidence interval)	P value (compared with overall data)
Campylobacter					
Culture	4	0.96(0.89-0.98)	0.96(0.93-0.97)	0.99(0.96-1.00)	0.901
PCR/sequencing	2	NA	NA	NA	NA
Culture and PCR/sequencing	5	0.84(0.73-0.92)	1.00(0.99-1.00)	0.99(0.97-1.00)	0.631
Overall(Culture or PCR/sequencing)	11	0.92(0.86-0.96)	0.98(0.95-0.99)	0.99(0.98-1.00)	ref
Shigella					
Culture	4	0.95(0.72-0.99)	0.98(0.91-1.00)	0.99(0.95-1.00)	0.942
PCR/sequencing	2	NA	NA	NA	NA
Culture and PCR/sequencing	5	0.92(0.75-0.98)	0.99(0.99-1.00)	1.00(0.98-1.00)	0.865
Overall(Culture or PCR/sequencing)	11	0.95(0.88-0.98)	0.99(0.97-0.99)	1.00(0.99-1.00)	ref
Rotavirus A					
Virus antigen detection	5	0.93(0.80-0.98)	0.98(0.96-0.99)	0.99(0.94-1.00)	0.956
PCR/sequencing	4	0.93(0.88-0.96)	0.99(0.96-0.99)	0.99(0.98-1.00)	0.550
Virus antigen detection and PCR/sequencing	2	NA	NA	NA	NA

Overall (Virus antigen detection or PCR/sequencing)	11	0.93(0.90-0.96)	0.99(0.98-1.00)	0.99(0.99-1.00)	ref
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