MOLECULAR DIAGNOSTICS IN CDI: SWITCHING TO NAAT AS SCREENING METHODOLOGY?

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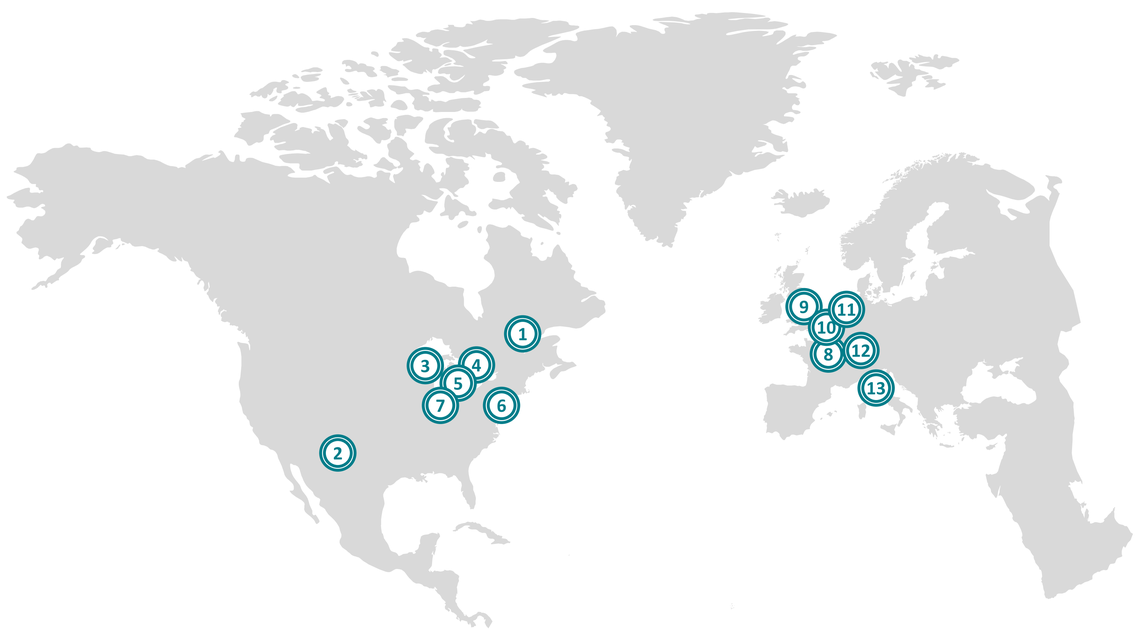
Background: Despite more than a decade of dedicated research on standardization of guidelines, *Clostridium difficile* infections (CDI) still create a tremendous economic burden while complicating proper patient management. The current European guidelines recommend the use of a two-step algorithm with an initial screening test followed by a confirmation test of the positive results. Similar recommendations were recently put in place by the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) for commonly submitted stool specimens for which no pre-agreed institutional criteria are defined. However, if stool specimens are derived from CDI-likely patients using pre-agreed institutional criteria, use of standalone nucleic acid amplification techniques (NAAT) is allowed. Here we report the performance data of the GenePOC™ CDiff assay obtained from two separate multicenter evaluations; one in the US and one in Europe.

Materials/Methods: Consecutive diarrheal stool samples from hospitalized patients were assessed between January and December 2017. All assays (GDH, Toxin A&B, NAAT) were performed in alignment with the manufacturer's instructions. Direct toxigenic culture was performed as golden standard method.

Results: Combined, 5080 stool specimens were evaluated in both the US (2461) and Europe (2619). Overall, the GenePOC CDiff assay displayed a good valid result calling with only 2.1% and 4.1% invalid results for the US and Europe, respectively. In total, only 4 samples (< 0.1%) remained invalid after repeat testing. In comparison to direct culture performed on fresh stool specimens the sensitivity and specificity (with respective 95% CI) were: 95.5% [87.3 – 99.1] and 93.4% [91.4 – 95.1]. When compared to the routine CDI diagnostics, standalone GenePOC CDiff testing displayed an excellent agreement as scored by a kappa value of 0.95.

Conclusions: In accordance to both the European and the IDSA/SHEA guidelines, the overall performance of the GenePOC CDiff assay makes it a suitable testing platform that either could be used as screening test or as standalone method.

Clostridium difficile: Study sites



Background information: Study sites

Site*	Location	Reference method**	# Specimens
1	Montreal, CA	Direct (toxigenic) culture	551
2	Albuquerque, US	Direct (toxigenic) culture	85
3	Milwaukee, US	Direct (toxigenic) culture	715
4	Toronto, CA	Direct (toxigenic) culture	79
5	Detroit, US	Direct (toxigenic) culture	145
6	Baltimore, US	Direct (toxigenic) culture	176
7	Indianapolis, US	Direct (toxigenic) culture	710
8	Paris, FR	Direct (toxigenic) culture	308
9	Swindon, UK	GDH-TOX-NAAT	296
10	Brussels, BE	Direct (toxigenic) culture	189
11	Veldhoven, NL	Direct (toxigenic) culture	386
12	Lucerne, CH	NAAT	736
12	Lucerne, CH	GDH/TOX-NAAT	298
13	Bologna, IT	GDH-TOX-NAAT	407

**Sites 1 – 7 were part of GenePOC's clinical trails phase of which the results are readily available in the GenePOC Cdiff package insert. Site 8: Laboratoire associé "Clostridium difficile", Hôpital Saint-Antoine, AP-HP, Paris, France. Site 9: Great Western Hospitals Foundation Trust, Swindon, UK. Site 10: Belgian Reference Centre for Clostridium difficile, Microbiology Unit Université catholique de Louvain, Brussels, Belgium. Site 11: PAMM laboratories, Department of Medical Microbiology, Veldhoven, The Netherlands. Site 12: Bioanalytica AG and LUKS Cantonal Hospital, Lucerne, Switzerland. Site 13: Unit of Microbiology, The Great Romagna Area Hub Laboratory, Pievesestina di Cesena, Italy.*

**Reference method: Direct (toxigenic) culture was considered the golden standard for the performance calculations. The GDH EIA, TOX EIA and NAAT assay used varied from site to site and where: site 9 – Biomerieux's VIDAS® *C. difficile* GDH and TOX A & B + Cepheid's Xpert® *C. difficile* , site 12a – BD's BD MAX™ Cdiff, site 12b – Alere's C. DIFF QUICK CHEK COMPLETE® (GDH and TOX A & B) + Cepheid's Xpert® *C. difficile,* Site 13: Diasorin's Liaison® *C. difficile* GDH and Toxines A&B + Cepheid's Xpert® *C. difficile.*

GenePOC CDiff Clinical performance*

a. US/Canada

		Direct (Toxigenic) culture		
		POS	NEG	
GenePOC	POS	63	48	111
	NEG	3	683	686
		66	731	797

Sensitivity 95.5%
Specificity 93.4%
Invalid 2.6%
repeat 0.1%

b. Europe

		Direct (Toxigenic) culture		
		POS	NEG	
GenePOC	POS	92	6	98
	NEG	8	777	785
		100	783	883

Sensitivity 92.0%
Specificity 99.2%
Invalid 4.1%
repeat 0.1%

*Clinical performance calculations only includes fresh, loose stool specimens taking the shape of the container. Frozen stool specimens were not taken into account.

EU: GenePOC CDiff in a 2-step algorithm

	GenePOC – TOX EIA	GDH/TOX EIA - GenePOC
***tcdB* strains**		
% CDI	58%	61%
% carriers	42%	39%
Samples (#)	2299	1913
PPA (95% CI)	95.1 (91.8-97.4)	93.0 (88.9-96.0)
NPA (95% CI)	99.5 (99.0-99.7)	99.3 (98.8-99.7)

⇨ **GenePOC CDiff assay can be satisfactorily implemented in the recent European CDI diagnostic guidelines.**

Something to think about…

If your sample arrives at two minutes to ten, then you can have a turnaround time for a negative result in an hour. If it arrives at two minutes past ten, then it's going to be 25 hours.

Infectious disease consultant, UK*

*Preliminary results of a Health Economic evaluation on *Clostridium difficile* infections (supported by GenePOC). Personal communications, data to be published soon.

References and data sources:

Sites 1 – 7: http://www.genepoc-diagnostics.com/about/pi
Site 8: https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=64279
Site 9: https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=64378
Site 10: https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=62782
Site 11: https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=62654
Site 12: https://jmd.amjpathol.org/article/S1525-1578(17)30482-8/pdf
Site 13: https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=62436