Institut für Medizinische Mikrobiologie, Virologie und Hygiene

BS-Experten Netzwerktreffen und refresher, Kassel 10.11.2023

Was bringt uns die syndromische PCR-Diagnostik?

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Leitender Oberarzt

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Director ESCMID AMR Action Committee

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Diagnostischer Paradigmenwechsel in der Mikrobiologie

Das technische Auge der modernen Mikrobiologie hat sich grundlegend verändert:

- Massenspektrometrie (MALDI-TOF)
- Molekulare Assays (Hochdurchsatz, syndromische Panels)
- Beschleunigte Empfindlichkeitsprüfung (RAST)
- Next generation sequencing (WGS, clinical metagenomics)

Chancen und Risiken der Einführung molekularer Testverfahren

Chances	Threats
Schneller Ergebnisse (klinische Signifikanz)	
Reduktion falsch-negativer Befunde	
Gezielte Therapie	

Chancen und Risiken der Einführung molekularer Testverfahren

Chances	Threats
Schneller Ergebnisse (klinische Signifikanz)	**Hohe Kosten**
Reduktion falsch-negativer Befunde	**Falsch-positive / Übertherapie**
Gezielte Therapie	**Nicht indizierte AB Therapien**

Bei der Durchführung syndromorientierter, molekularer Analytik ist die Definition eines “sweet spots” zur Erreichung optimaler Effekte notwendig.

(Syndrombasierte) molekulare Analytik verbessert die diagnostische Sensitivität

Ein erheblicher Teil der Gelenkinfektionen bleibt ätiologisch ungeklärt (d. h. kulturnegativ).

Infektionstyp	% Kultur-negativ	Referenz
Prosthetic joint infection	**5 - 34**	**Tande and Patel, CMR 2014**
Native joint septic arthritis	**15 - 60**	**Richebé et al, BMJ 2022 McBride et al., CID 2020**

Limitations of Broad range PCR approaches to pathogen detection

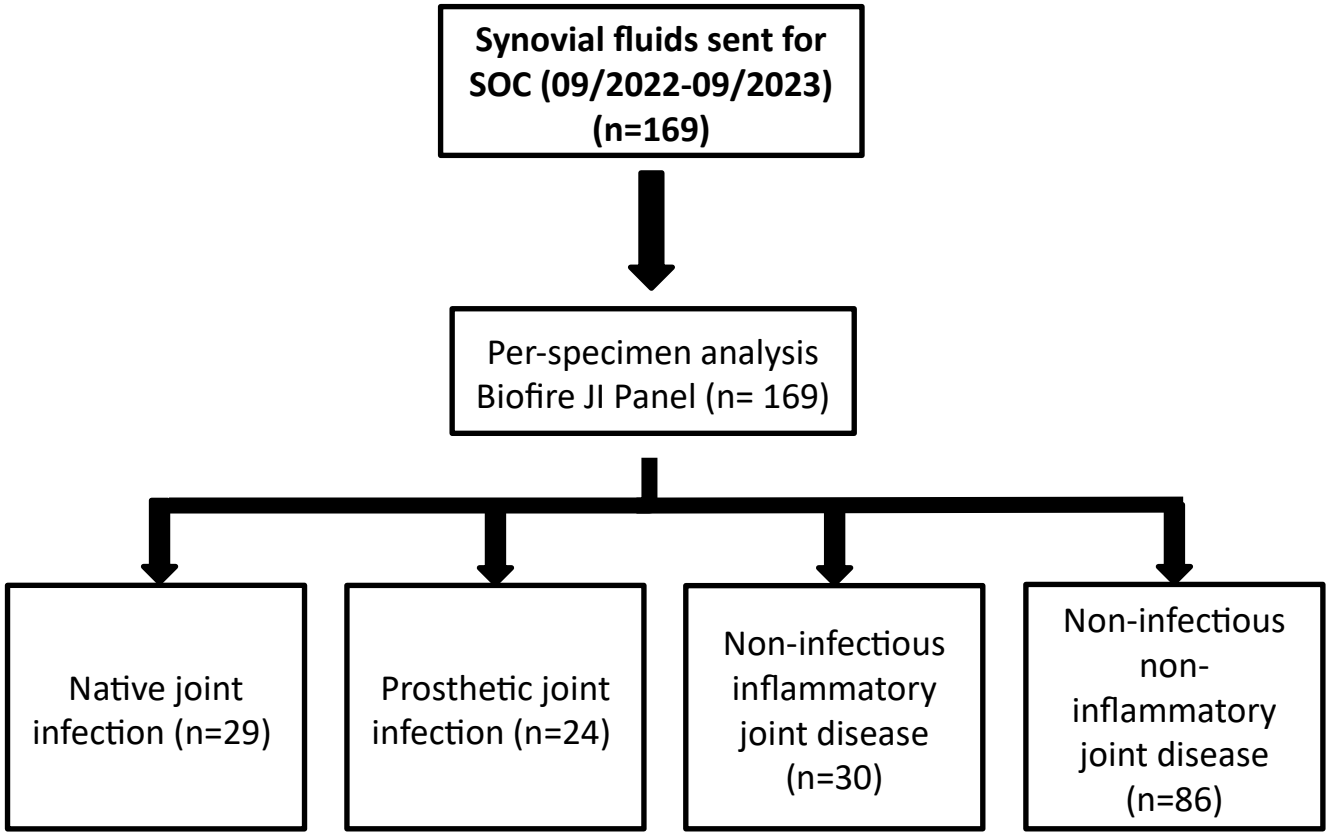
Table 1
Overview of pathogens identified in BJI specimens using SOC or molecular techniques.

Species	Pathogens detected[a] SOC	mPCR	16S rDNA PCR
Monomicrobial infections (n=38)			
S. aureus	11	14	6
CoNS	7	4	2
C. acnes	1	6	0
Enterobacterales (total)	9	8	3
Serratia marcescens	3	2	0
Enterobacter cloacae	4	4	2
Klebsiella pneumoniae	2	2	1
S. dysgalactiae	1	1	1
S. agalactiae	3	3	2
Other (total)	6	1	0
E. faecalis	5	5	1
C. subterminale	1	0	0
Polymicrobial infections (n=2)	2	1	1
S. aureus	1	1	1
P. mirabilis	1	1	1
S. epidermidis	1	0	0
S. haemolyticus	1	0	0

[a] In total, 126 specimens were analyzed by each method.

Berneking, Rohde et al., Int J Infect Dis 2022

Bedeutung eines spPCR Panels bei der Dignostik von Gelenkinfektionen: eine prospektive Kohortenstudie



SOC positive (%)	n=12 (41)	n=15 (62)	n=0	n=0
JI positive (%)	n=16 (55)	n=20 (83)	n=0	n=1

Berinson, Rohde, et al., unpublished data

spPCR / Biofire JI Panel im Kontext der NJSA

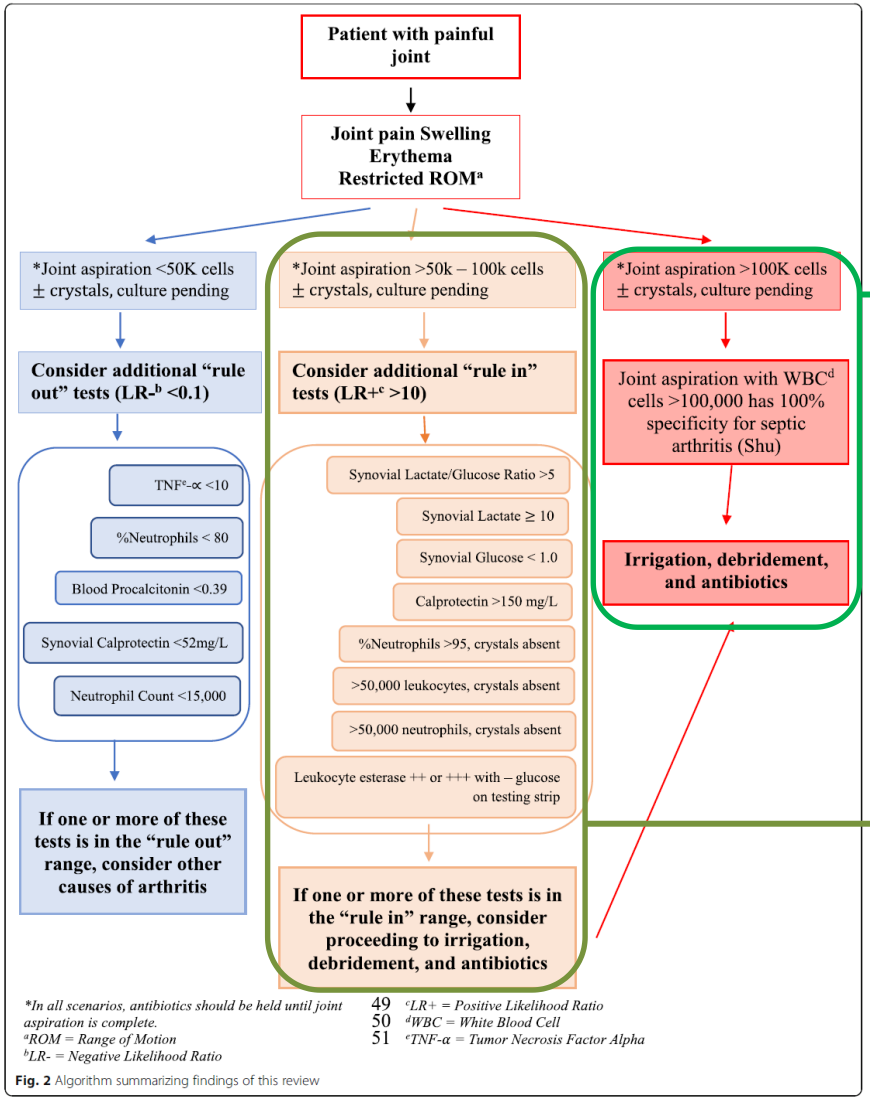


Fig. 2 Algorithm summarizing findings of this review

spPCR als Zusatz zur schnellen und sensitiven Analytik.

spPCR als „rule in" Instrument.

Turner et al., J Exp Orthopedics 2021

Molekulare Diagnostik mittels 16S rDNA PCR: das limit of detection

	Number of colonies		
	<5	5–50	>50
	Available results, $n = 94$		
Culture and mPCR positive concordant results $n = 102$ (%)	13 (13.8)	32 (34.0)	49 (52.2)
	Available results, $n = 65$		
Culture positive and mPCR negative results $n = 115$ (%)	30 (39.4)	21 (37.9)	14 (22.7)

Malandain et al., CMI 2018

Molekulare Diagnostik mittels 16S rDNA PCR: das limit of detection

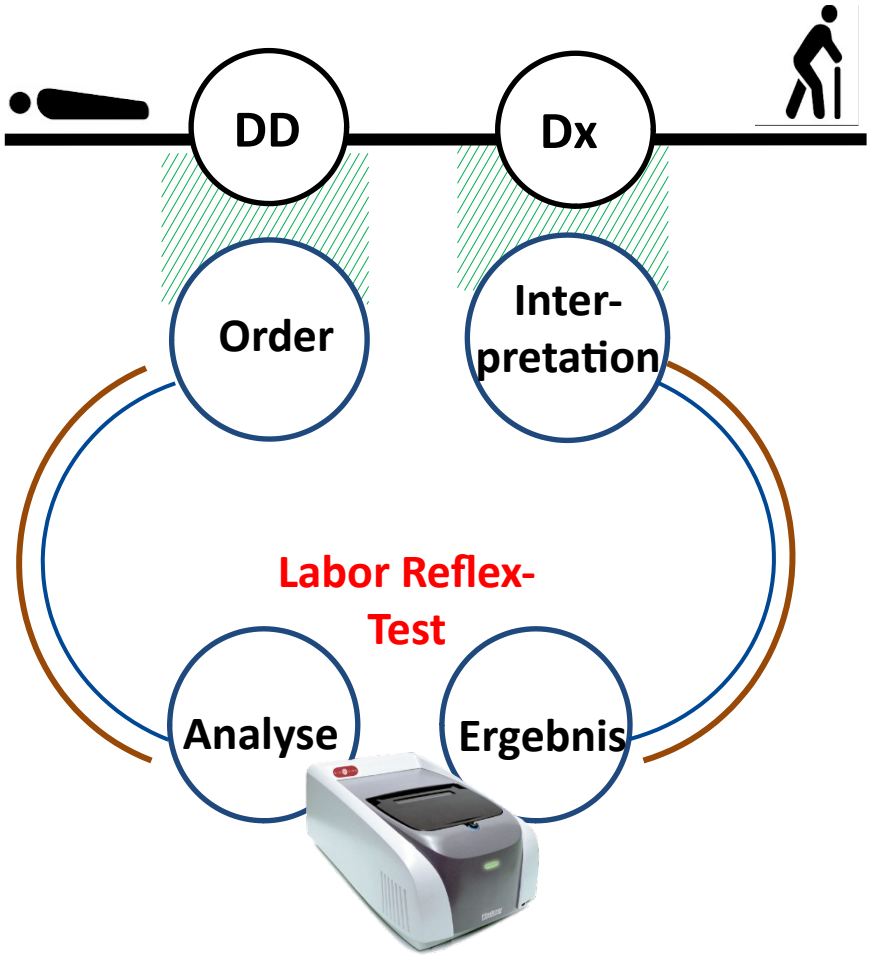
“…..it is essential that local implementation of the (PCR) panels is done in partnership with clinicians to ensure that there is a clear understanding of test characteristics, result interpretation, and appropriate test utilization.“

Hanson, JCM 2016

	Number of colonies		
	<5	5–50	>50
	Available results, $n = 94$		
Culture and mPCR positive concordant results $n = 102$ (%)	13 (13.8)	32 (34.0)	49 (52.2)
	Available results, $n = 65$		
Culture positive and mPCR negative results $n = 115$ (%)	30 (39.4)	21 (37.9)	14 (22.7)

Malandain et al., CMI 2018

Multiplex-PCR Panel können die diagnostische Qualität verbessern



Luz and Sinha (adapted with permission)
Messacar et al., JCM 2017

	UKE-PCR	Biofire	Kultur
E. coli	0	0	0
H. Influenzae	0	0	0
L. monozytogenes	1	1	1
N. meningitidis	3	3	0
S. agalactiae	2	2	0
S. pneumoniae	12	13	6
CMV	0	0	
Enteroviren	6	5	
HSV1	0	0	
HSV2	2	2	
HHV6	3	3	
Parechovirus	0	0	
VZV	3	3	
C. neoformans	1	1	1

Pfefferle, Rohde et al., BMC Infect Dis 2020

Reflex-to-test – optimierte Nutzung von Ressourcen

18 Monate: 4623 Liquorproben

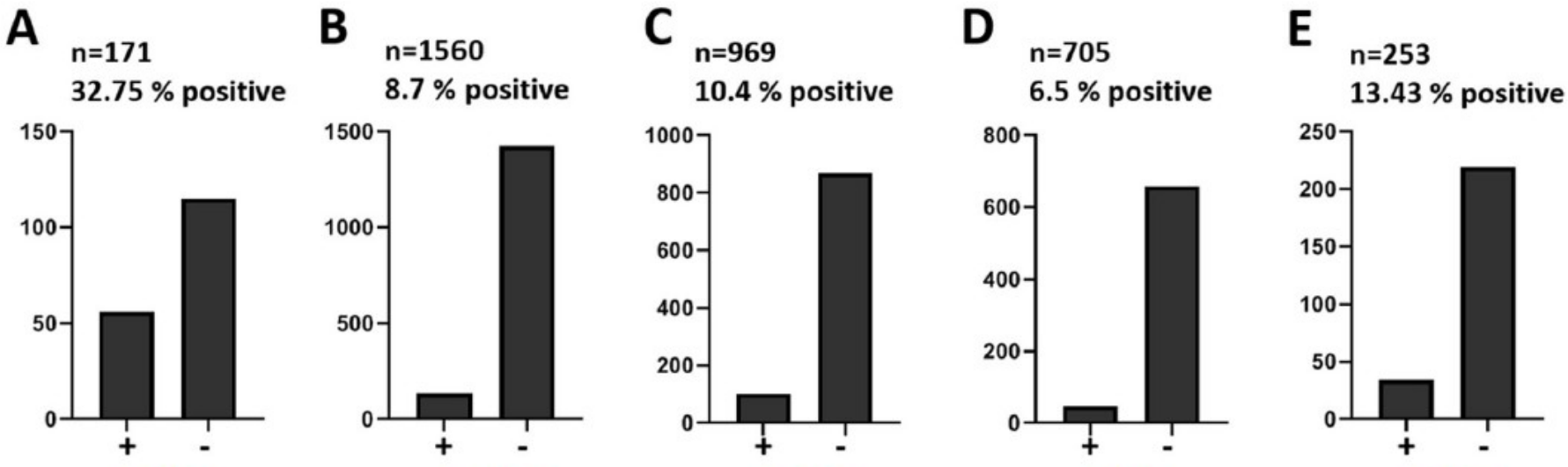
Gramfärbung: Liquorpleozytose?

Biofire Filmarray

Standard-diagnostik (Kultur)

n=171 Proben analysiert

Reflex-to-test – optimierte Nutzung von Ressourcen

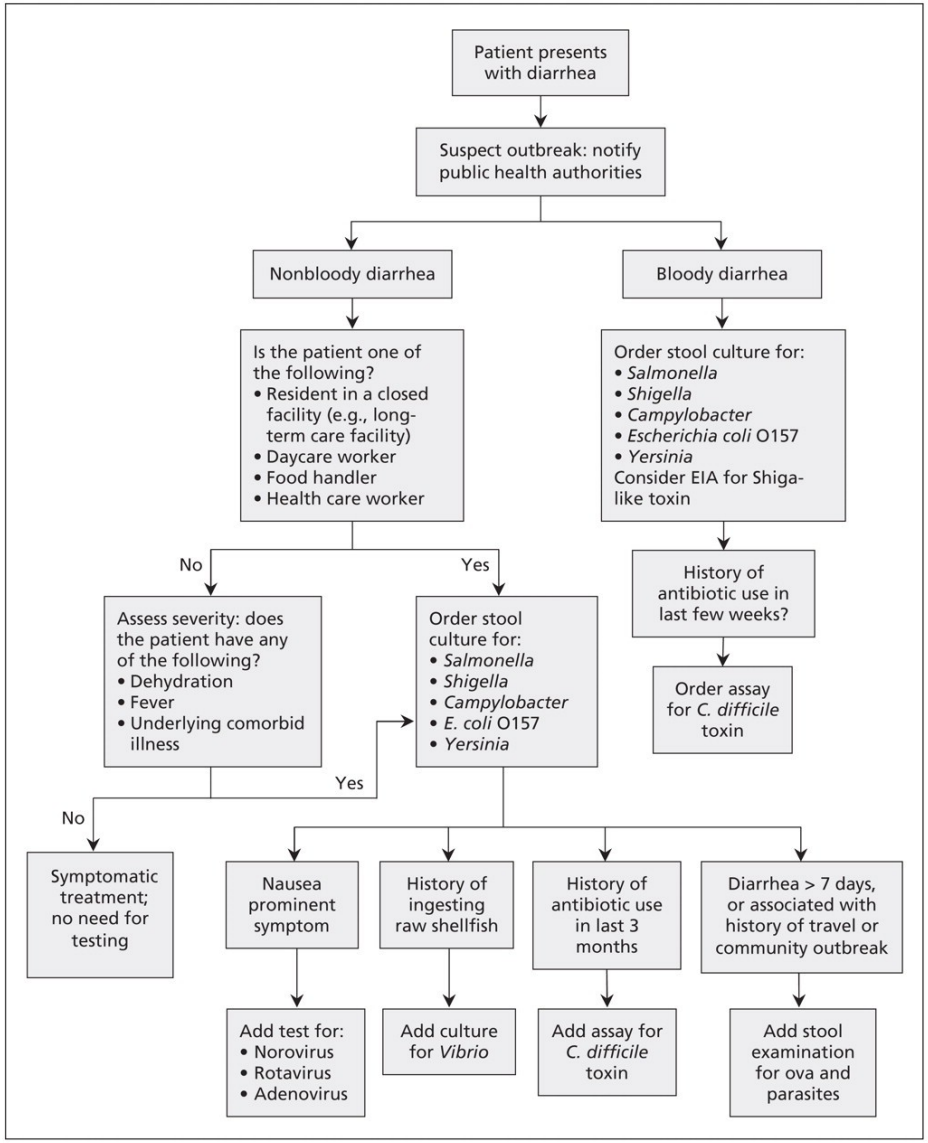


Pfefferle, Rohde et al., BMC Infect Dis 2020

- "...the per-patient yield of the ME panel increased 61.8% from an estimated 11.5% (53/459) positivity rate with no testing restriction to 18.6% (49/263) with criteria in place (P0.01)."

  Broadhurst et al., JCM 2020

Risikoprofil getriebener Algorithmus zum zielgerichteten Einsatz konventioneller Methoden: Anforderer



Für den optimalen Einsatz empfehlen klinische Guidelines selektive Testungen bei GI-Infektionen: à la carte Strategie.

Hatchette und Farina CMAJ 2011

Hatchette und Farina CMAJ 2011

Fehlerhafte / unvollständige Anforderungen: Unkenntnis des Untersuchungsumfangs

In vielen klinischen Kontexten ist die Festlegung der Untersuchungsmethode/ des Untersuchungsumfangs traditionell auf Seite des Klinikers verankert.

Table 2. Unrequisitioned bacteria and parasites detected by xTAG GPP.

Target	No. not requested by physician	% of total additional positives
Salmonella	6	46
Campylobacter	10	40
Shigella	4	24
Clostridium difficile Toxin A/B[a]	32	74
ETEC	12	63
E. coli O157	6	55
STEC	13	81
Yersinia enterocolitica	1	100
Giardia	31	79
Entamoeba histolytica	10	71
Cryptosporidium	12	100
Overall	137	65

[a]18/32 positive specimens collected from subjects <3 years old.

Claas et al., JMB 2013

- **Untersuchungsumfang und Testcharakteristika häufig unbekannt – dies führt zu fehlerhaften / unvollständigen Anforderungen.**

Syndromische multiplex PCR für den Nachweis von gastrointestinalen Pathogenen: one-stop-shop

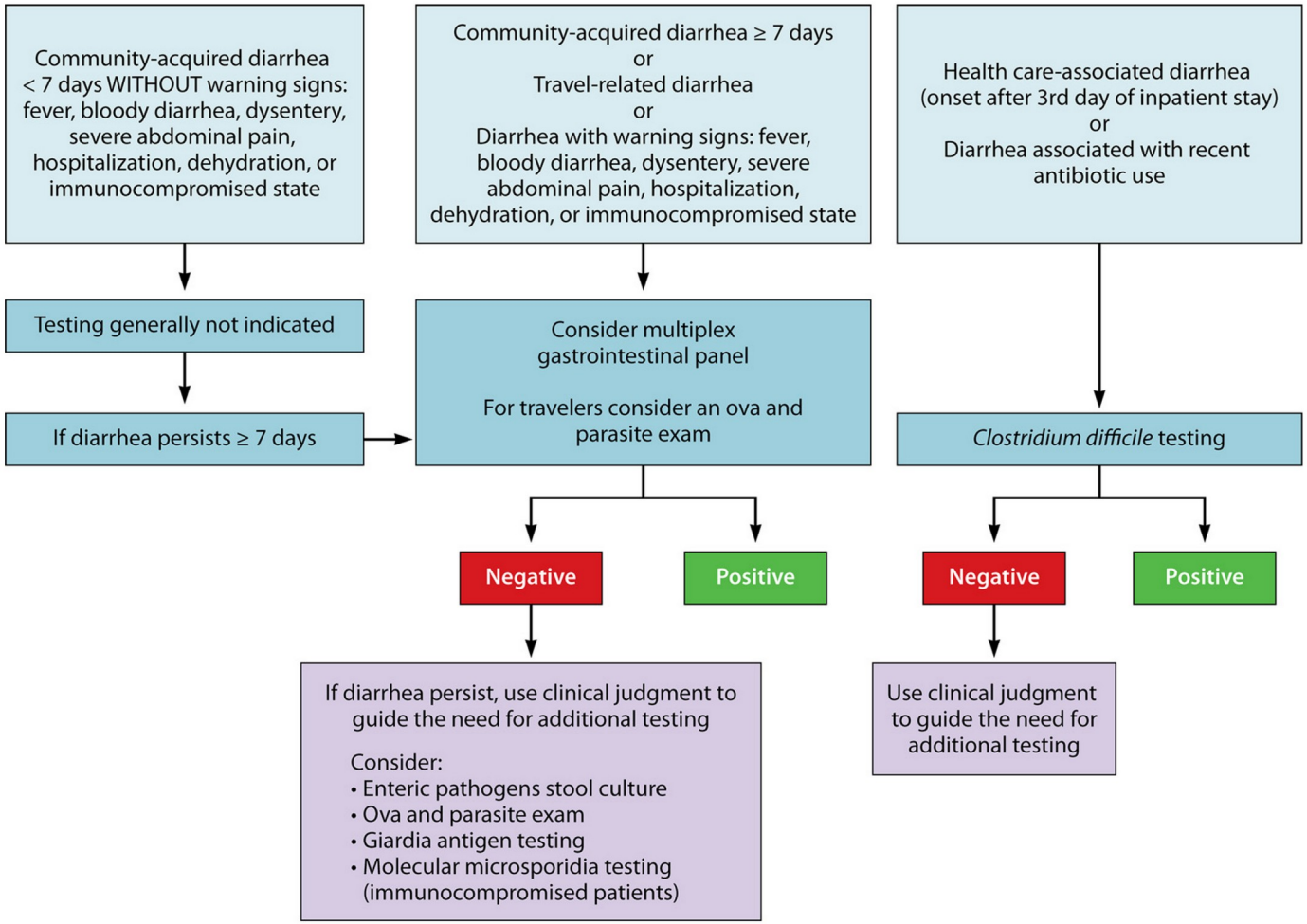
TABLE 4 FDA-approved/cleared multiplex gastrointestinal panels[a]

Parameter	Verigene EP	Luminex GPP	BioFire GIP
Analysis platform	Verigene system	Magpix or Luminex 100/200 system	FilmArray system or FilmArray Torch
Acceptable specimen type	Stool in Cary-Blair medium	Fresh stool or stool in Cary-Blair medium	Stool in Cary-Blair medium
No. of targets	9	14	22
Ability to detect pathogen			
Bacteria			
Campylobacter species	✓	✓	✓
Salmonella species	✓	✓	✓
Shigella species/enteroinvasive *E. coli*[b]	✓	✓	✓
Vibrio species	✓		✓
Vibrio cholerae		✓	✓
Yersinia enterocolitica	✓		✓
Escherichia coli O157		✓	✓
Enterotoxigenic *E. coli*		✓	✓
Enteropathogenic *E. coli*			✓
Enteroaggregative *E. coli*			✓
Plesiomonas shigelloides			✓
Shiga toxin-producing *E. coli* (stx_1-stx_2)	✓[c]	✓	✓
Clostridium difficile (toxin A/B)		✓	✓
Viruses			
Norovirus GI/GII	✓	✓	✓
Rotavirus A	✓	✓	✓
Astrovirus			✓
Adenovirus 40/41		✓	✓
Sapovirus			✓
Parasites			
Cryptosporidium species		✓	✓
Entamoeba histolytica		✓	✓
Giardia lamblia		✓	✓
Cyclospora cayetanensis			✓
No. of samples (throughput)	1–32 (scalable)	24	1–12 (scalable)
Time to result (h)	<2	~5	~1

[a]EP, enteric pathogens; GPP, gastrointestinal pathogen panel; GIP, gastrointestinal panel.
[b]The Verigene EP and Luminex GPP do not specifically target enteroinvasive *E. coli*.
[c]The Verigene EP has separate targets for stx_1 and stx_2.

Ramanan et al., CMI 2017

Syndromische multiplex PCR: vereinfachte Anforderung, transparenteres Output



1. This algorithm should not be used for chronic diarrhea (duration >30 days).
2. For ova and parasite exams, submit 3 stool samples collected on separate days for maximum sensitivity.
3. During the summer, consider molecular detection of Shiga toxin in fecal samples for children with diarrhea even if they do not have bloody diarrhea, are not toxic-appearing, and diarrhea has been present <7 days.

Ramanan et al., CMI 2017

Klinische Konsequenzen einer spPCR auf das Patientenmanagement

Clinical impact of syndromic molecular point-of-care testing for gastrointestinal pathogens in adults hospitalised with suspected gastroenteritis (GastroPOC): a pragmatic, open-label, randomised controlled trial

Nathan J Brendish, Kate R Beard, Ahalya K Malachira, Alex R Tanner, Langizya Sanga-Nyirongo, Markus Gwiggner, J R Fraser Cummings, Helen E Moyses, Tristan W Clark

Single center, UK, Notaufnahme oder stationäre Patienten innerhalb 48h nach Aufnahme

278 Patienten (138 Pat. FilmArray Gastrointestinal Panel (BioFire), 140 Pat. Kontrolle)

Time to result: (BioFire vs. Kont.) (median (IQR)): 1.7 h (1.5–2.0) vs. 44.7 h (21.2 – 66.1),sig

Pat. ohne Erregernachweis (55% in BioFire vs. 74% in Kontrolle):

- **Entisolation (PCR vs. Kont.): 73% vs. 34%, p<0.0001**
- **Zeit bis Entisolation: 0.6 Tage (0.3 – 1.8) vs. 2.2 Tage (1.2 – 3.2), p<0.0001**

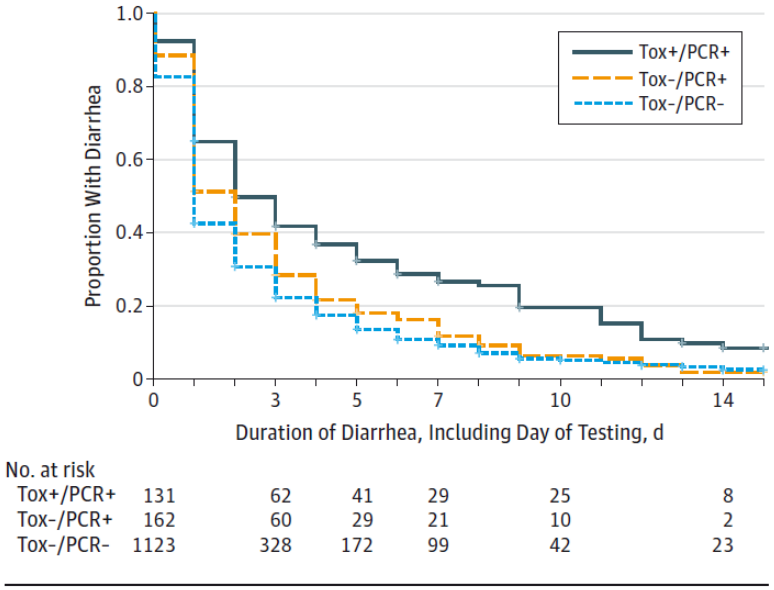
Antibiotikatherapie (BioFire vs. Kont.): 65% vs. 47%, p=0.0028

Klinische Implikationen der Durchführung von syndromischen GI Assays

- Wahrscheinlichkeit des Nachweises von kausalen Pathogenen steigt im Vergleich zur *à la carte* Strategie.
- Ergebnisse sind schneller verfügbar.
- Assays können Einfluss auf das klinische Management nehmen (z.B. Isolationsmaßnahmen).

- Zusätzliche Kosten.
- Klinische Signifikanz von Ergebnissen unklar (Nachweis von > 1 Pathogen [z.B. zusätzliche EPEC Nachweise in 10 – 30 %]).
- Risiko falsch-positiver Befunde.

Polage et al., JAMA Int Med 2015

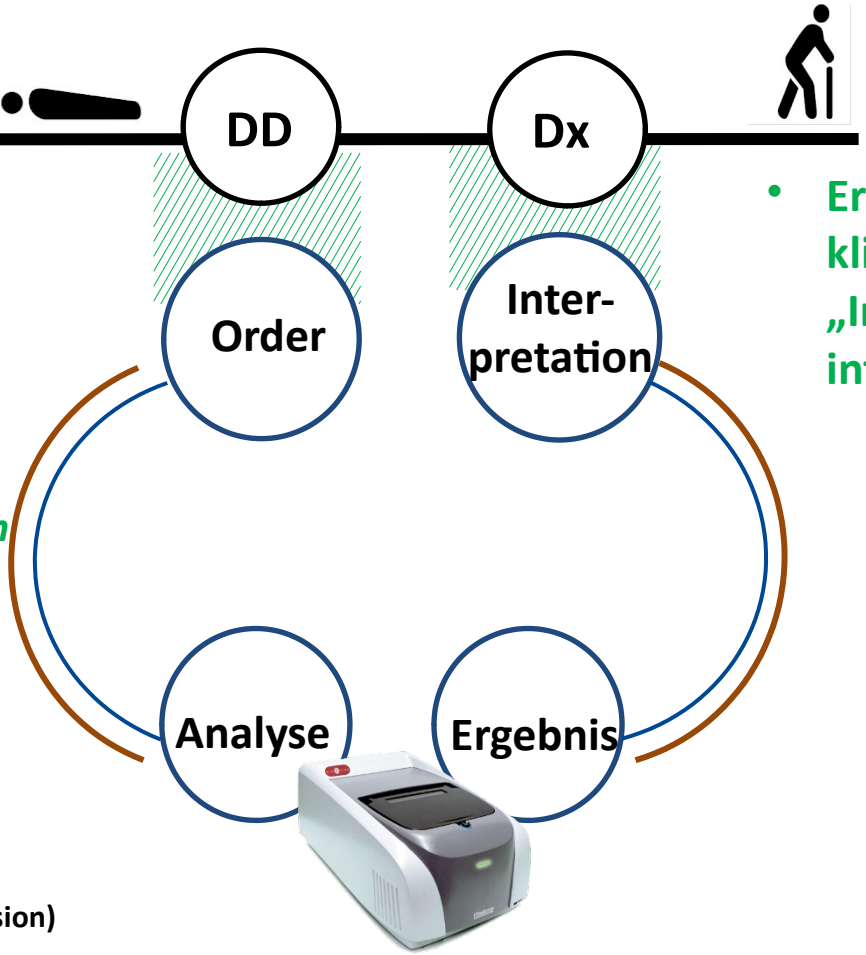


Der breite Einsatz molekularer (multiplex) Diagnostik kann zu einer Erhöhung falsch-positiver Befunde führen: Übertherapie droht.

Messacar et al., JCM 2017

PCR (Panel) Diagnostik: so einfach?

- Indikationsstellung: Verbindliche Festlegung diagnostischer Algorithmen (SOP).
- Kontinuierliche Überwachung des Testeinsatzes und der Performance (*Lab utilization committee*)



- Ergebnisintegration in klinische Handlungsfade: „Intention to test is intention to act“.

Luz and Sinha (adapted with permission)
Messacar et al., JCM 2017

Syndromatische Testung bei Atemwegsinfektionen

TABLE 3 FDA-approved/cleared multiplex respiratory panels[a]

	Parameter	FilmArray	Verigene	x-TAG RVP	x-TAG RVP Fast	NxTAG-RPP	eSensor RVP	ePlex
	Analysis platform	FilmArray system or FilmArray Torch	Verigene system	Luminex 100/200	Luminex 100/200	Luminex Magpix	eSensor	ePlex system
	No. of targets	20	16	12	8	20	14	17
	Ability to detect pathogen							
Virale Erreger	Viruses							
	Adenovirus	✓	✓	✓	✓	✓	✓ (differentiates subgroup B/E from C)	✓
	Coronavirus							✓
	Coronavirus HKU1	✓				✓		
	Coronavirus NL63	✓				✓		
	Coronavirus 229E	✓				✓		
	Coronavirus OC43	✓				✓		
	Human bocavirus					✓		
	Human metapneumovirus	✓	✓	✓	✓	✓	✓	✓
	Influenza A virus	✓	✓	✓	✓	✓	✓	✓
	Subtype H1	✓	✓	✓	✓	✓	✓	✓
	Subtype H3	✓	✓	✓	✓	✓	✓	✓
	Subtype 2009 H1N1	✓					✓	✓
	Influenza B virus	✓	✓	✓	✓	✓	✓	✓
	Parainfluenza virus 1	✓	✓	✓		✓	✓	✓
	Parainfluenza virus 2	✓	✓	✓		✓	✓	✓
	Parainfluenza virus 3	✓	✓	✓		✓	✓	✓
	Parainfluenza virus 4	✓	✓			✓		✓
	Respiratory syncytial virus	✓			✓			
	Respiratory syncytial virus A		✓	✓		✓	✓	✓
	Respiratory syncytial virus B		✓	✓		✓	✓	✓
	Rhinovirus/enterovirus	✓	✓	✓	✓	✓	✓	✓
Bakterien	Bacteria							
	Chlamydophila pneumoniae	✓				✓		✓
	Mycoplasma pneumoniae	✓				✓		✓
	Bordetella pertussis	✓	✓					
	Bordetella parapertussis-Bordetella bronchiseptica		✓					
	Bordetella holmesii		✓					
	Time to result (h)	~1	~2–3	~8	~6	~4	~6	~1.5

[a]The acceptable specimen type for all panels is a nasopharyngeal swab. RVP, respiratory virus panel; RPP, respiratory pathogen panel.

Ramanan et al., CMI 2018

Indikationen und geeignete Materialien bei V.a. tiefe Atemwegsinfektion

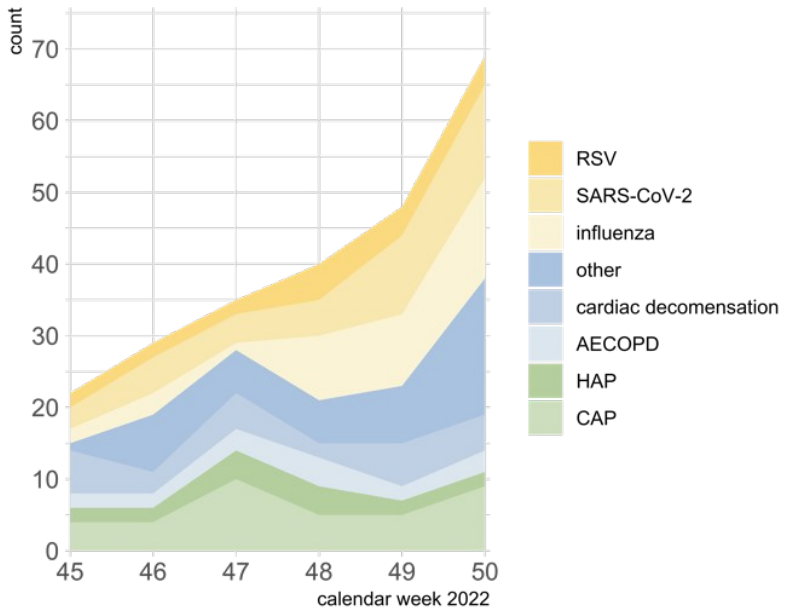
Empfehlungen zur Durchführung mikrobiologischer Analytik bei der CAP

Community-acquired pneumonia: Initial evaluation and site of care based on severity assessment

	Severity score*	Site of care	Microbiologic evaluation
Mild	PSI: I or II or CURB-65: 0¶	Ambulatory care	▪ COVID-19 testing during the pandemic ▪ Influenza testing (when incidence is high and results would change management)Δ ▪ Otherwise, testing is usually not needed
Moderate	PSI: III or IV or CURB-65: 1¶ to 2	General medical ward	▪ Blood cultures ▪ Sputum Gram stain and culture ▪ Urine streptococcal antigen ▪ *Legionella* testing◇ ▪ Respiratory viral panel during respiratory virus season§ ▪ COVID-19 testing¥ ▪ HIV screening‡
Severe	PSI: IV or V or CURB-65: ≥3 and/or Fulfillment of ATS/IDSA criteria for ICU admission†	ICU	▪ Blood cultures ▪ Sputum Gram stain and culture ▪ Urine streptococcal antigen test ▪ *Legionella* testing◇ ▪ Respiratory viral panel§ ▪ Bronchoscopy specimens for Gram stain, fungal stain, aerobic, fungal culture, and molecular testing (when feasible)** ▪ COVID-19 testing¥ ▪ HIV screening‡

Klompas, UpToDate 2021

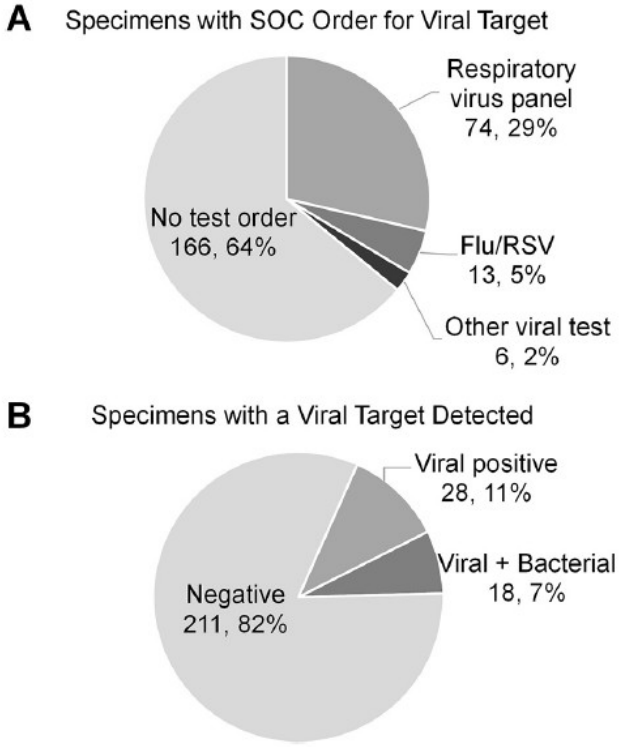
Ungewöhnliche Epidemiologie viraler CAP Erreger Ende 2022



Koch, Rohde, Lütgehetmann, in revision 2023

Nutzen molekularer spPCR Panel bei der Pneumonie-Diagnostik

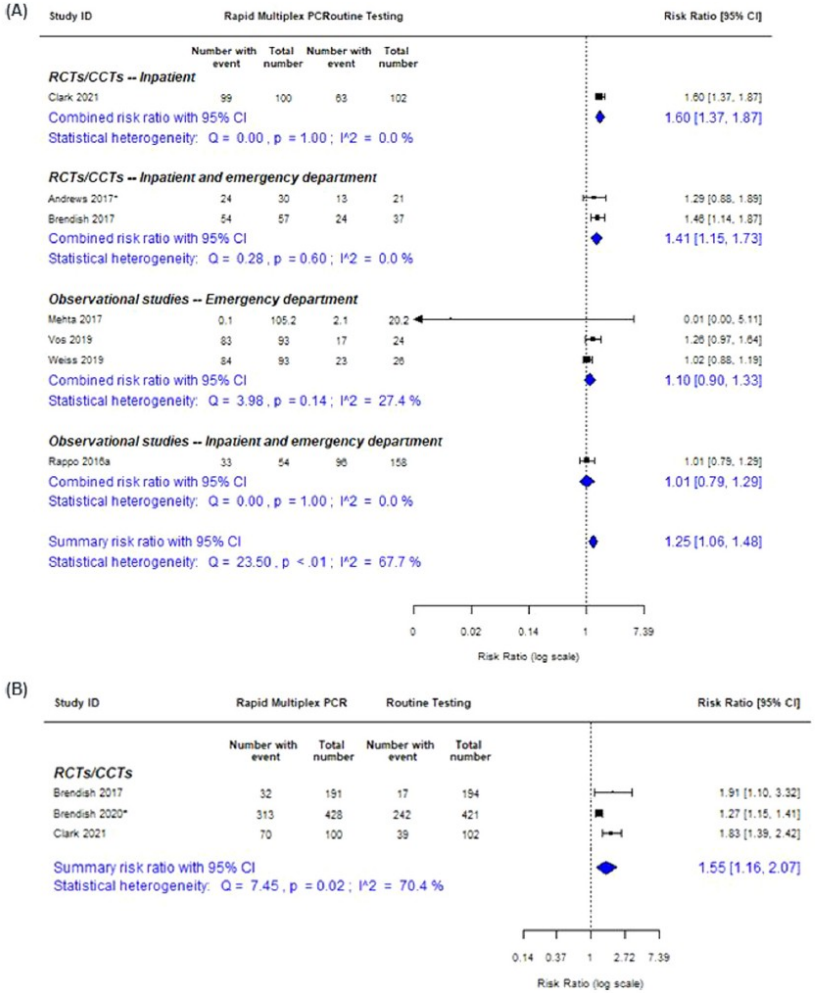
Verbesserte diagnostische Ausbeute



11/46 Virus-positiven Proben wären durch konventionelle Anforderungsstrategien identifiziert worden.

Buchan et al., JCM 2020

Management Konsequenzen



Clarke et al., J Infection 2023

Einsatz Neuraminidaseinhibitoren

Infektionskontroll-maßnahmen

Nutzen molekularer spPCR Panel bei der Pneumonie-Diagnostik

THE LANCET
Respiratory Medicine

Volume 10, Issue 9, September 2022, Pages 877-887

Articles

Fast multiplex bacterial PCR of bronchoalveolar lavage for antibiotic stewardship in hospitalised patients with pneumonia at risk of Gram-negative bacterial infection (Flagship II): a multicentre, randomised controlled trial

Andrei M Darie MD [a], Prof Nina Khanna MD [b c], Kathleen Jahn MD [a], Michael Osthoff MD [d], Prof Stefano Bassetti MD [d], Mirjam Osthoff MD [a], Desiree M Schumann PhD [a], Prof Werner C Albrich MD [f], Prof Hans Hirsch MD [e], Prof Martin Brutsche MD [g], Leticia Grize PhD [a], Prof Michael Tamm MD [a], Prof Daiana Stolz MD [a c h]

- St Gallen, RCT, CAP, **208 Pat**
- Unyvero Hospitalized Pneumonia Panel + Therapieempfehlung
- **Inadäquate ABX (Prim. EP): 47h vs. 86h, sig**
- kein Unterschied Nebenwirkungen, Outcome

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Molecular point-of-care testing for lower respiratory tract pathogens improves safe antibiotic de-escalation in patients with pneumonia in the ICU: Results of a randomised controlled trial

Stephen Poole [a,b,*], Alex R Tanner [b], Vasanth V Naidu [b], Florina Borca [a,c], Hang Phan [c], Kordo Saeed [b,d], Michael P W Grocott [a,d,e], Ahilanandan Dushianthan [a,d,e], Helen Moyses [a], Tristan W Clark [a,b,d,f]

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[b] Department of Infection, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom
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[d] School of Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
[e] General Intensive Care Unit, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom
[f] NIHR Post-Doctoral Fellowship Programme, United Kingdom

- UK Southhampton, RCT, **200 ICU Pat** (68 Pat CAP)
- FilmArray Pneumonia *plus* Panel(BioFire), Mo-Fr Kernarbeitszeit (Befundergebnis: 1.7h vs. 66.7h)
- **Erregernachweis (PCR vs Kont): 71% vs 51%, sig**
- **Deeskalation (PCR vs Kont): 42% vs. 8%, sig**
- kein Unterschied Nebenwirkungen, Outcome

Panelanalytik ist zielführend wenn (messbare) Ziele im klinischen Management definiert worden sind!

The right test	The right patient	The right time
Ist der Test für das klinische Szenario geeignet?	Wird die klinische Versorgung des Patienten durch das Testergebnis beeinflusst?	Wird das Ergebnis rechtzeitig zur Verfügung stehen, um die Behandlung optimal zu beeinflussen?

Workflow optimization by introducing novel approaches to BC processing

BC positive

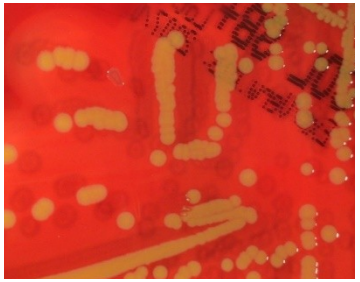
26 - 48 h

Final report

0,5 h

Microscopy

(6) - 24 h



Species ID (MALDI-TOF)

20 - 24 h

Susceptibility testing

Species ID (mass spectrometry, PCR)

Coverage of resistance determinants on the BCID2 panel

Table 1 Targets included in the BCID2 Panel

Gram negatives	Gram positives	Yeast	Antimicrobial resistance markers
A. calcoaceticus-baumannii complex	*Staphylococcus spp.*	*Candida albicans*	*mecA/C*
Bacteroides fragilis	*Staphylococcus aureus*	*Candida auris*	*mecA/C and MREJ (MRSA)*
Haemophilus influenzae	*Staphylococcus epidermidis*	*Candida glabrata*	*van A/B*
Neisseria meningitidis	*Staphylococcus lugdunensis*	*Candida krusei*	*blaCTX-M*
Pseudomonas aeruginosa	*Streptococcus spp.*	*Candida parapsilosis*	*blaKPC*
Stenotrophomonas maltophilia	*Streptococcus agalactiae*	*Candida tropicalis*	*blaIMP*
Enterobacterales spp.	*Streptococcus pyogenes*	*Cryptococcus neoformans/gattii*	*blaOXA-48*
Enterobacter cloacae complex	*Streptococcus pneumoniae*		*blaNDM*
Escherichia coli	*Enterococcus faecalis*		*blaVIM*
Klebsiella aerogenes	*Enterococcus faecium*		*mcr-1*
Klebsiella oxytoca	*Listeria monocytogenes*		
Klebsiella pneumoniae group			
Proteus spp.			
Salmonella			
S. marcescens			

MRSA = Methicillin Resistant *Staphylococcus aureus*

Peri et al., BMC Infect Dis 2022

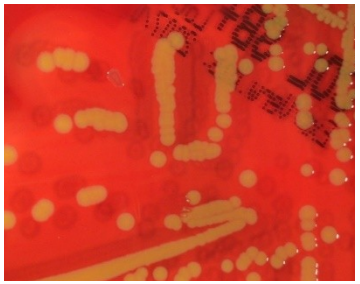
Molekulare Tests der Blutkulturanalytik: Einfluss auf Therapieoptimierung

Blutkultur positiv ..... **26 - 48 h** .....▶ **Endbefund**

0,5 h

Microscopy

(6) - 24 h



Species ID (MALDI-TOF)

20 - 24 h

Susceptibility testing

Antibiotika therapie

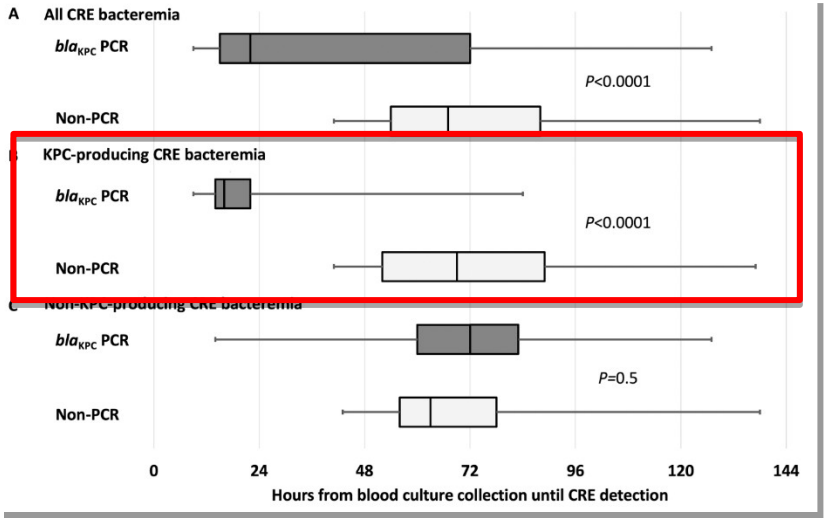
Molecular test for species ID + susceptibility prediction

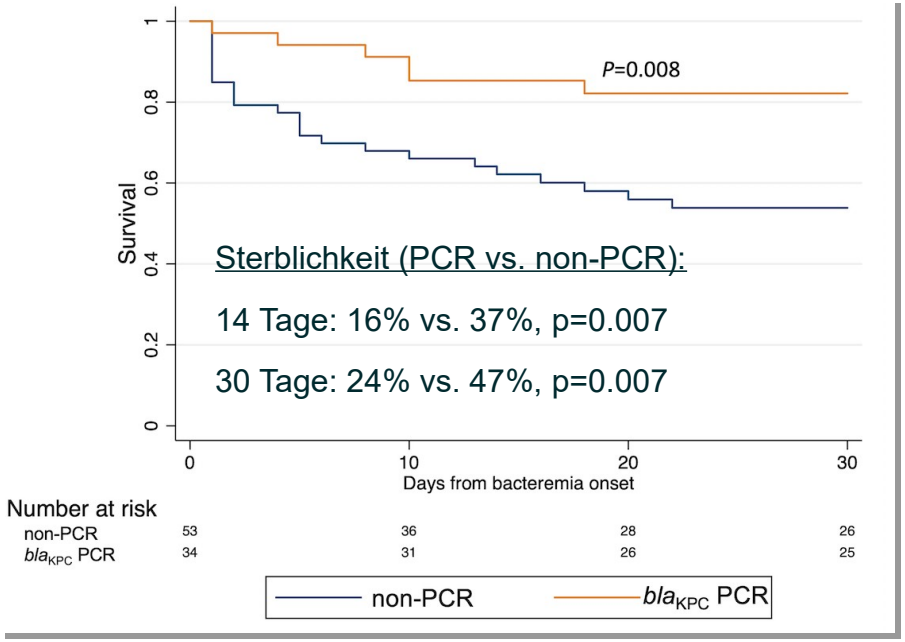
Optimal

Klinischer Impact beschleunigter BK Analytik

- Beobachtungsstudie, 8 Kliniken New York & New Jersey, 2016-2018
- In 3 Kliniken *bla*$_{KPC}$ PCR (BCID, BioFire) etabliert
- 137 Pat mit CRE-BSI (davon 89 Pat. KPC+)
  - → **51 Pat. haben *bla*$_{KPC}$ PCR bekommen**
  - → **32 Pat KPC positiv getestet (1x falsch neg)**

Schnellere Befundmitteilung: 16h vs. 64h





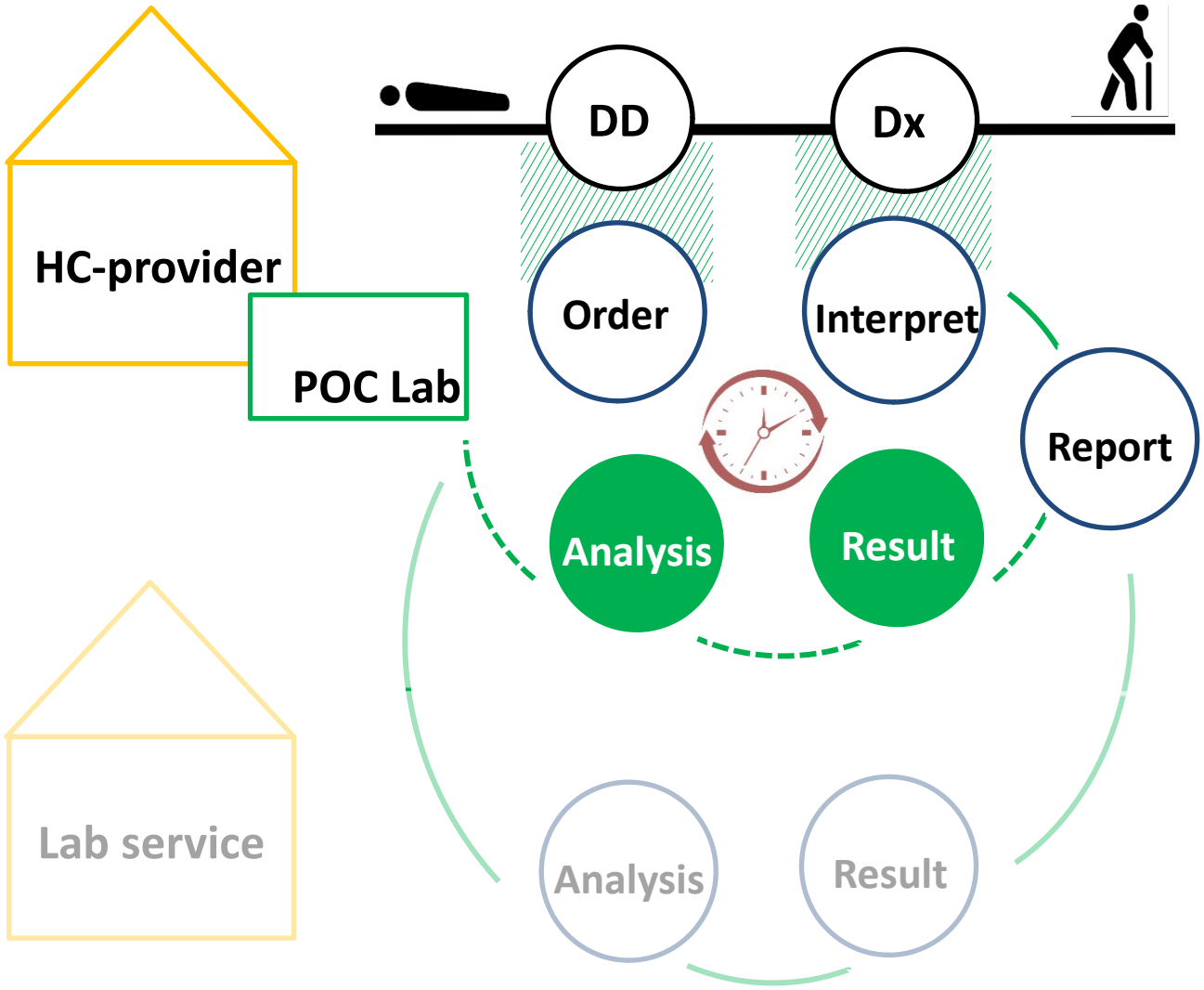
Satlin et al., CID 2022

Zielorientierung bei der Nutzung diagnostischer Verfahren

7.30 a.m. – 1 p.m. Same day: species ID + susceptibility	1 p.m. – 6 p.m. Same day: species ID + MRSA / VRE / Carbapenemases

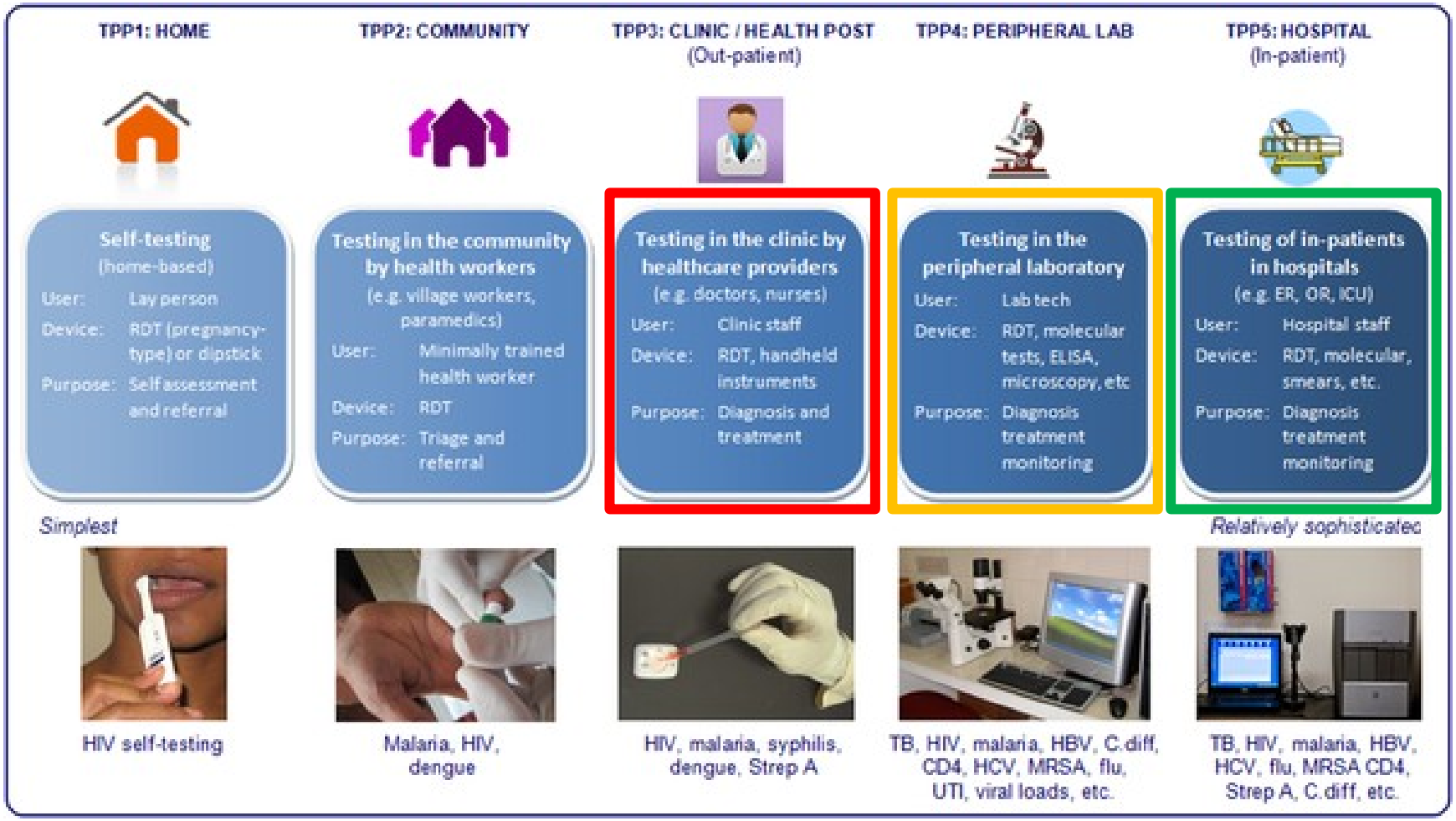
Assay	Pro	Con
Maldi-ToF ID	• **Broad pathogen coverage** • Relatively fast • **Cheap** • **Widely available**	• No valid susceptibility prediction • Labor-intensive • Slow (4 h short incubation)
Multiplex molecular assays	• **Fast** • **Short hands-on-time** • **Easy to use** • Sensitive **MRSA / VRE** prediction	• Limited pathogen coverage • Less sensitive in predicting Gram-negative resistance • Expensive
RAST (EUCAST)	• **Cheap (consumables)** • Reliable • **Broad coverage of resistance mechanisms in Gram-negatives**	• Labor-intensive • Requires at least 4 h incubation time • Restricted to some species

Wie POC spPCR Assays zur Umstrukturierung diagnostischer Strukturen beitragen können



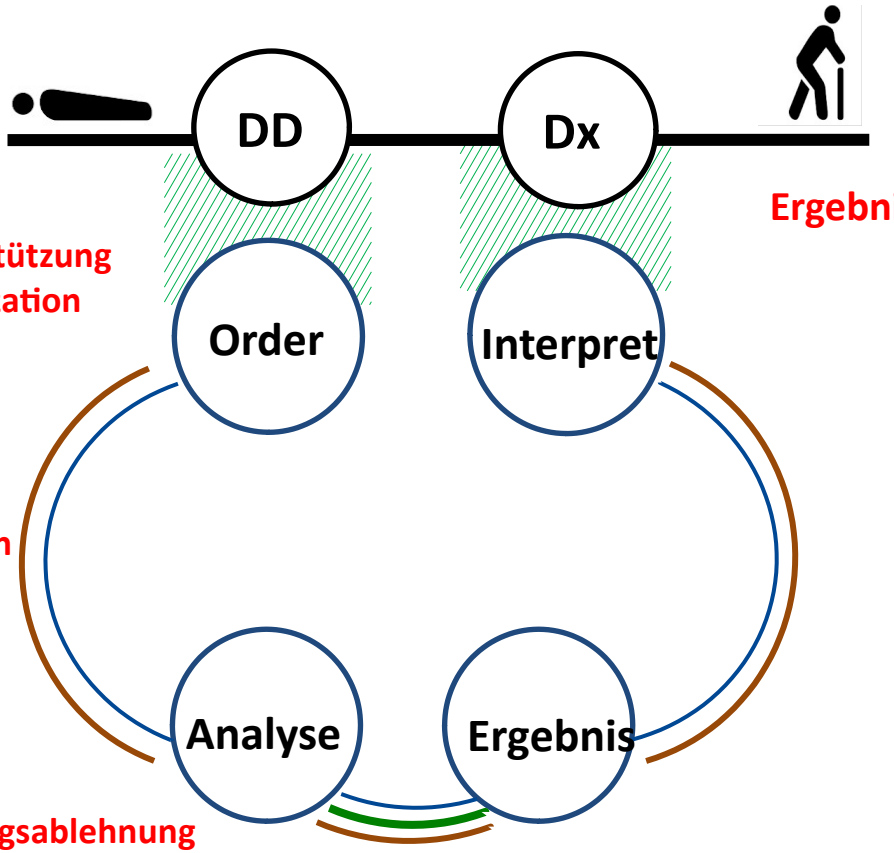
Luz and Sinah (adapted with permission)
Messacar et al., JCM 2017

Molekulare Testsysteme öffnen eine Tür zum POCT in der Infektiologie



Pai et al., Plos One 2012

spPCR Analytik: sinnvoll wenn Ziele definiert und Assays strukturiert in Prozesse integriert werden



- Elektronische Anforderungsunterstützung
- Laboratory test utilization committee

Ergebnisinterpretation

- POCT / dezentrale Lösungen zur Beschleunigung von high impact Diagnostiuk

- Untersuchungsablehnung

Reflex-to-test

Luz and Sinha (adapted with permission)
Messacar et al., JCM 2017

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