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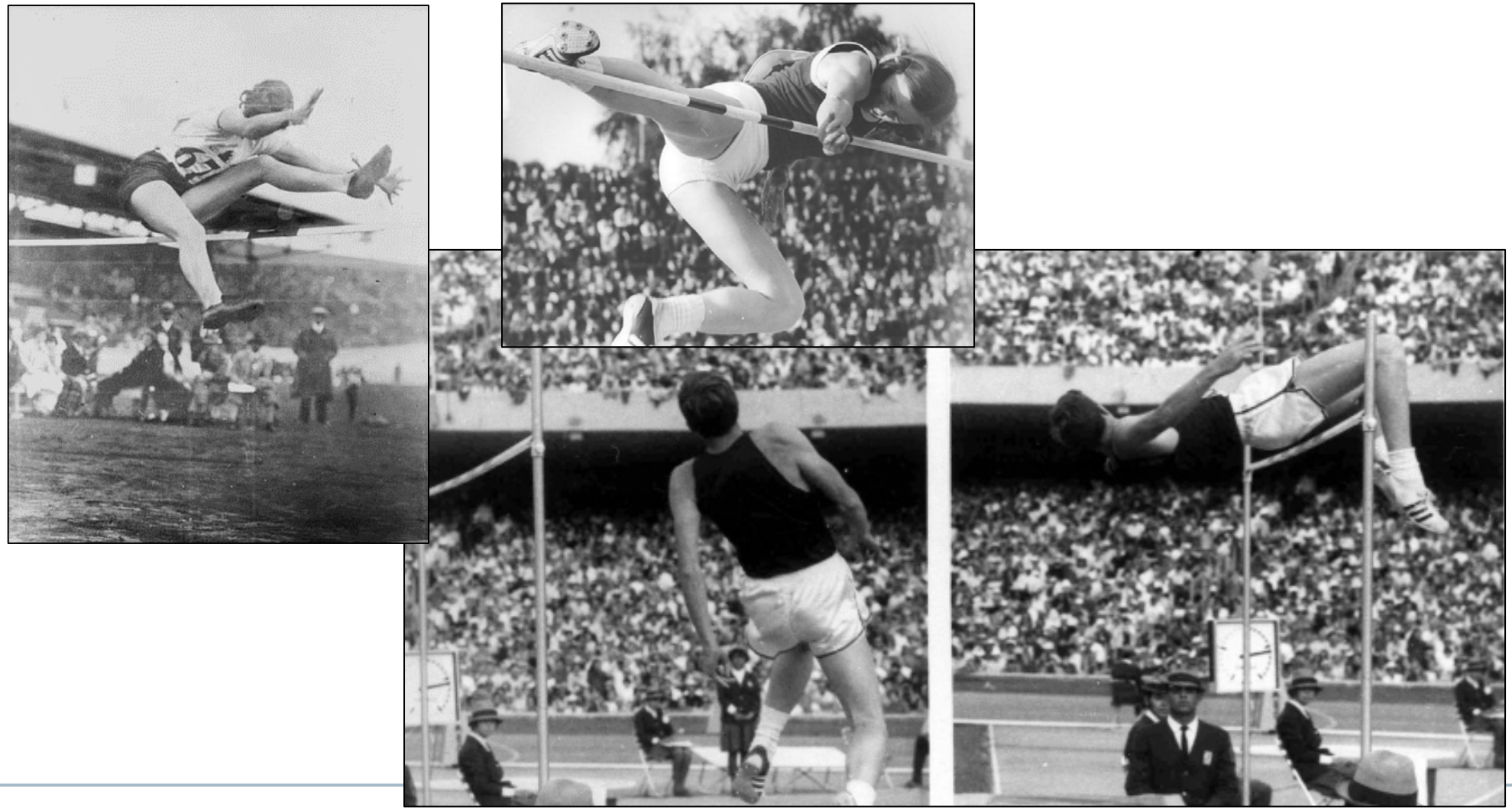
Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB

Next Generation Pathogen Detektion bei Sepsispatienten - ein Gamechanger in der Infektionsdiagnostik?

Kai Sohn | 20. November 2025
BARDa Netzwerk-Treffen, 2025

Disclosure
Co-Founder Noscendo GmbH;
Erfinder von IP diagnostische Algorithmen
und cfDNA-Biomarker

Innovation-driven performance boost



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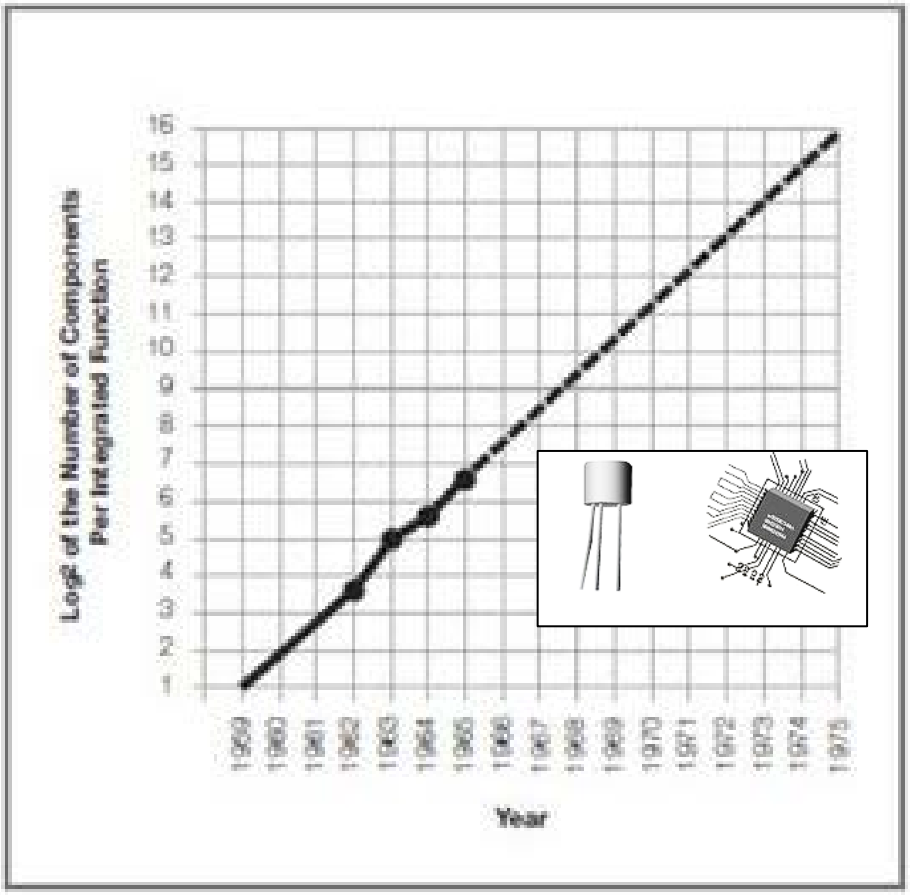
Innovation Integrated Circuits – Moore`s Law



"**Reduced cost** is one of the big attractions of integrated electronics, and the cost advantage continues to increase as the technology evolves toward the production of larger and larger circuit functions on a single semiconductor substrate."
Electronics, Volume 38, Number 8, April 19, 1965

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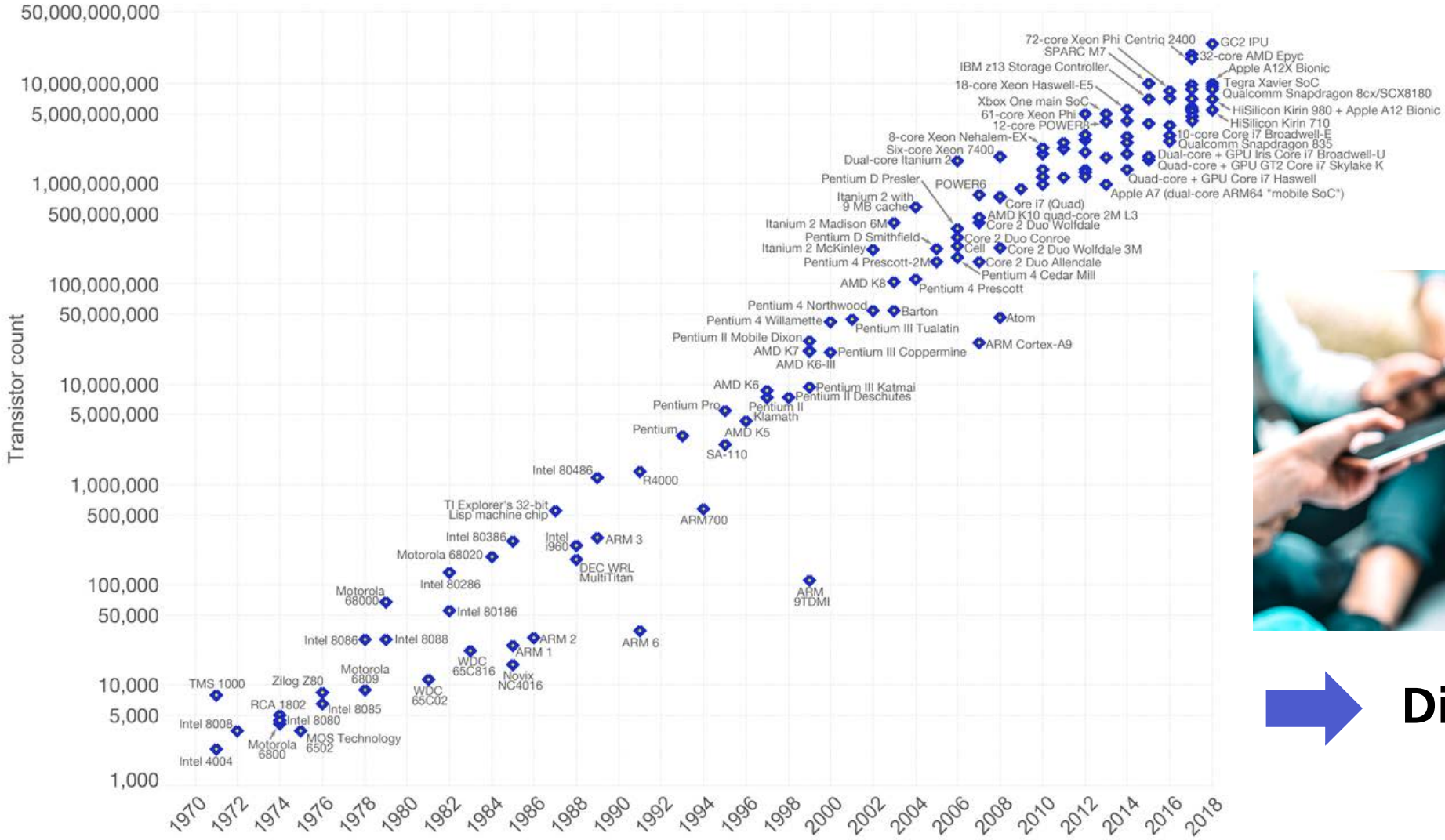
Moore's Law – The number of transistors on integrated circuit chips (1971-2018)

Moore's law describes the empirical regularity that the number of transistors on integrated circuits doubles approximately every two years. This advancement is important as other aspects of technological progress – such as processing speed or the price of electronic products – are linked to Moore's law.

Our World in Data



Digital Revolution

Data source: Wikipedia (https://en.wikipedia.org/wiki/Transistor_count)
The data visualization is available at OurWorldinData.org. There you find more visualizations and research on this topic.

Licensed under CC-BY-SA by the author Max Roser.

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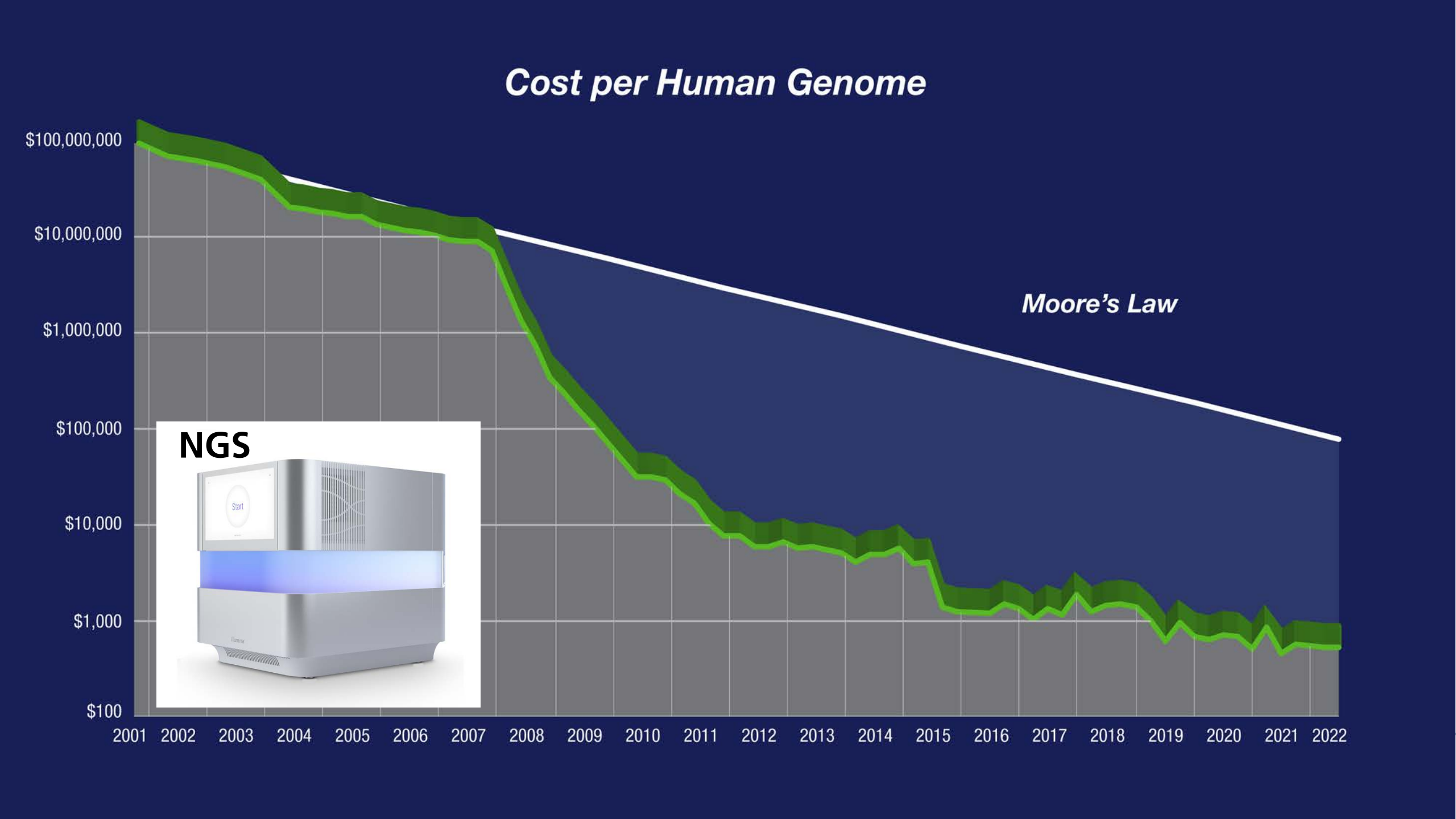
Cost per Human Genome
$100,000,000
$10,000,000
$1,000,000
$100,000
$10,000
$1,000
$100
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
Moore's Law
NGS

Why New Diagnostic Approaches for Systemic Infections?

Background and State-of-the-Art

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01

Sepsis
Clinical Need
Current Limitations

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Blood Culture – a Reasonable Diagnostic Gold Standard?

Patient 08-002

Anamnese
Der 72-jährige Patient ist ein operativer Notfall und war vor der ITS-Aufnahme auf einer internen Normalstation.

Fokus
Am Tag 0 (Sepsis Onset) liegt eine klinisch vermutete, ambulante Sepsis mit urogenitaler Lokalisation, und: urogenital, sowie einem septischen Schock, vor.
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Die Behandlungsdauer auf einer ITS/IMC war 5 Tage. Die Studie wurde vorzeitig an Tag 4 aufgrund von Versterben des Patienten abgebrochen.
Die gesammelten Patientendaten sind vollständig und verifiziert.

Klinischer Verlauf & Labor

	Tag 0	Tag 3
SOFA	8	12
Laktat	2 mmol/l	2.9 mmol/l
CRP	69 - 103 mg/l	72.3 mg/l
PCT	0.23 - 1.12 µg/l	5.41 - 6.14 ng/ml
Leukoz.	5.8 - 10.2 gpt/l	4.5 gpt/l

Antiinfektiva

	vor Onset	Tag 0	Tag 1	Tag 2	Tag 3	nach Tag 3
Aminopenicilline +ß-Laktamaseinhibitor						

NGS & Mikrobiologie

	Tag 0	Tag 3	Andere Zeitpunkte
NGS	**Escherichia coli, Bacteroides vulgatus, Bacteroides fragilis,** Akkermansia muciniphila, **Bacteroides thetaiotaomicron, Proteus mirabilis,**	Escherichia coli, Bacteroides vulgatus, Bacteroides fragilis, **Akkermansia muciniphila, Faecalibacterium prausnitzii, Parabacteroides distasonis, Eubacterium rectale**	n.a.
Blutkultur aerob	Negativ	Negativ	n.a.
Blutkultur anaerob	Negativ	Negativ	n.a.
Andere Proben	Negativ	n.a.	Negativ

Brenner Th, et al., Medicine 2018; 97: 6.

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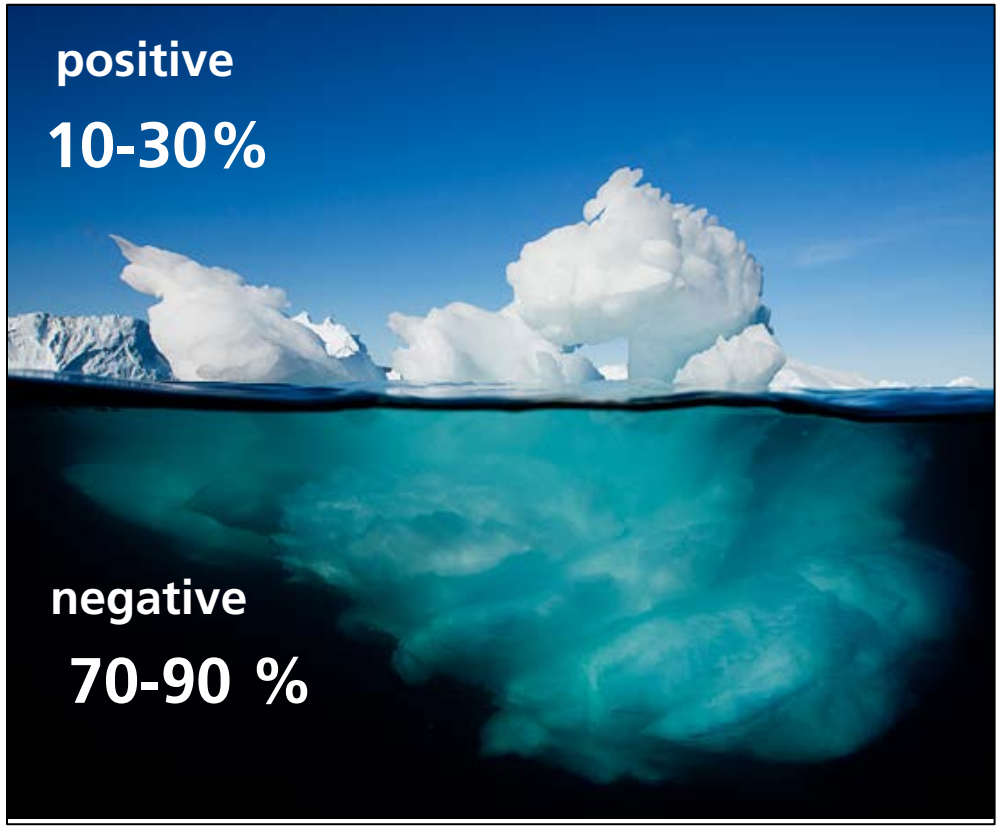
Standard of Care Diagnostics for Bloodstream Infections

Microbial Growth in Blood Cultures



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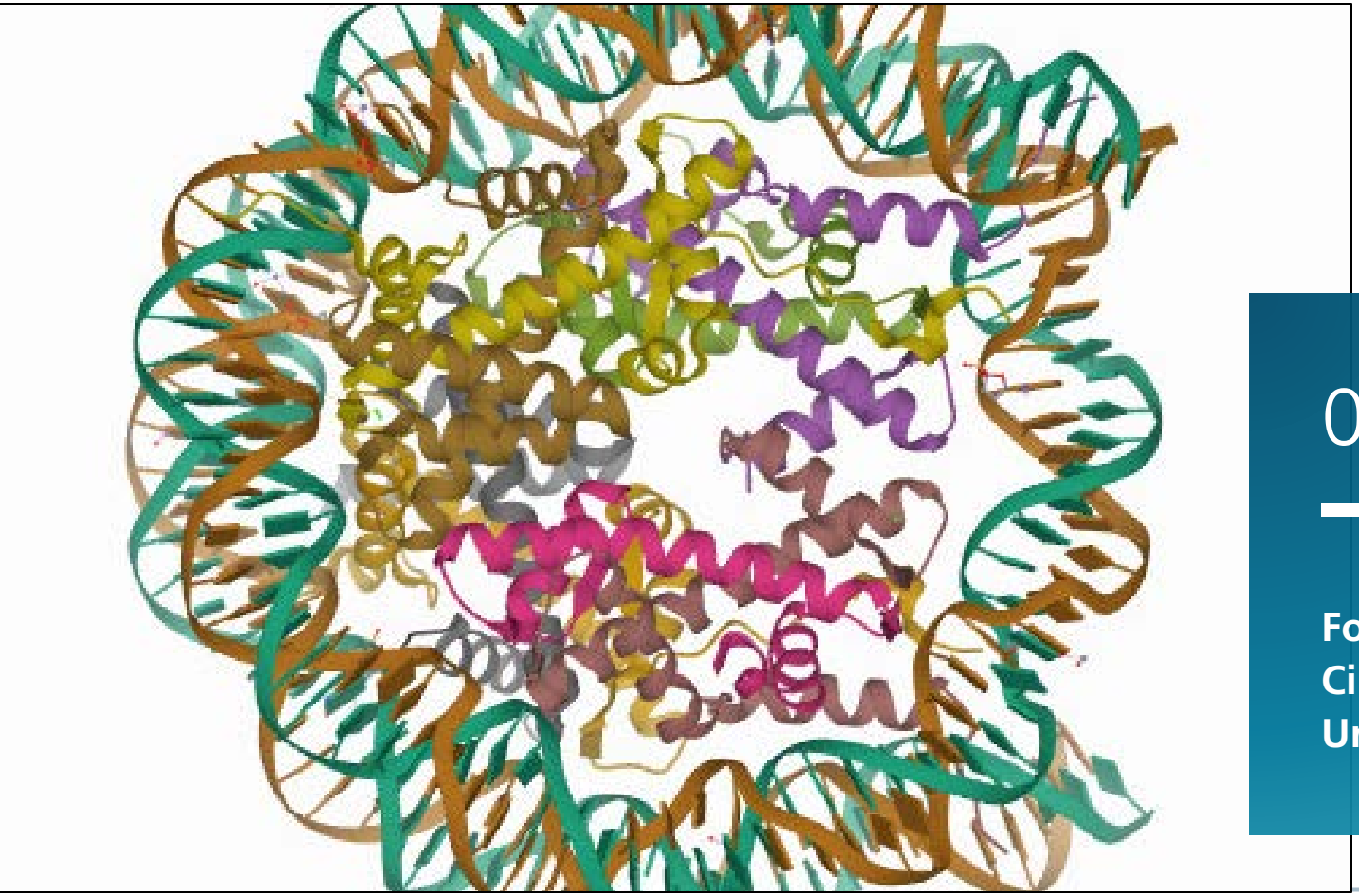
A New Diagnostic Concept Based on Microbial Cell-free DNA



02

Forensic Diagnostics
Circulating cell-free DNA
Unbiased Next Generation Sequencing

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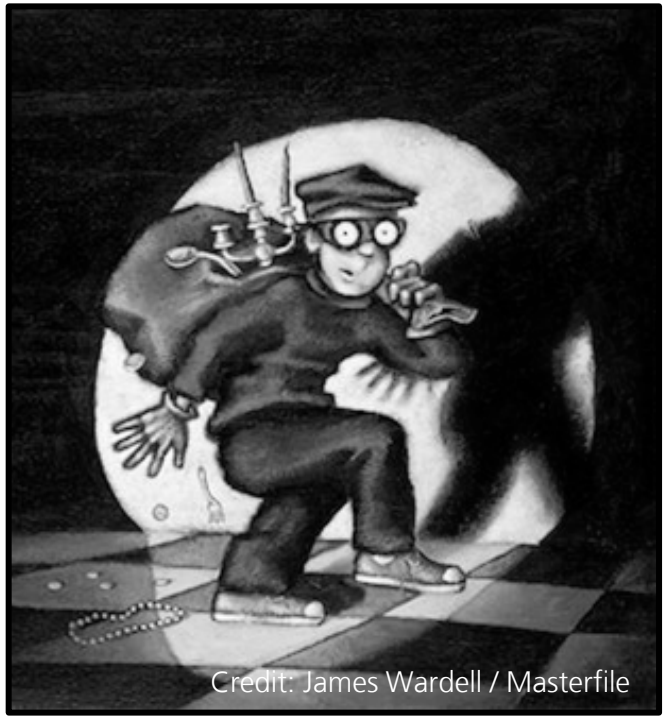
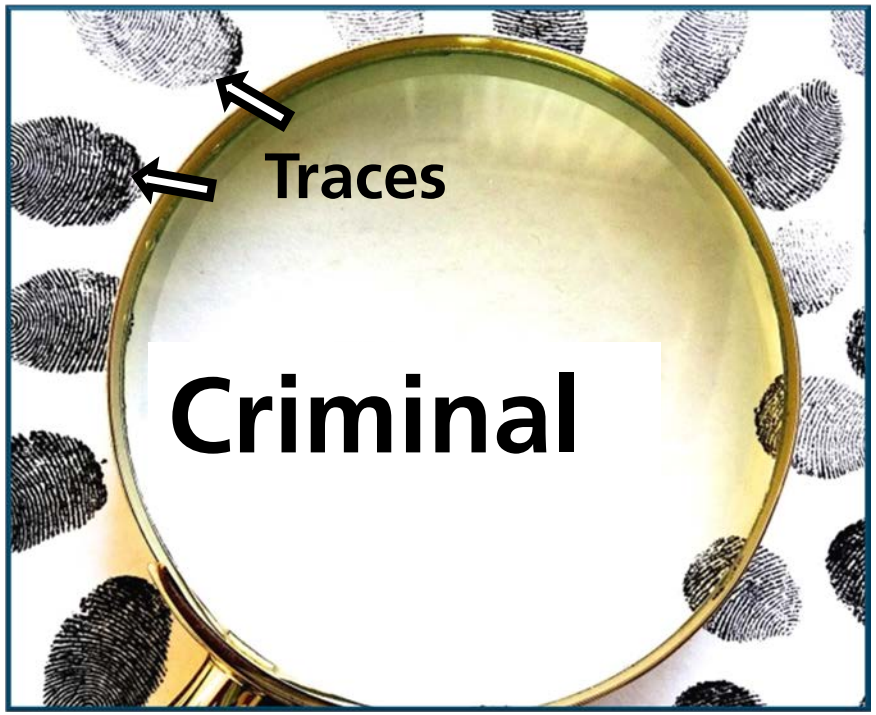
A Forensic Concept

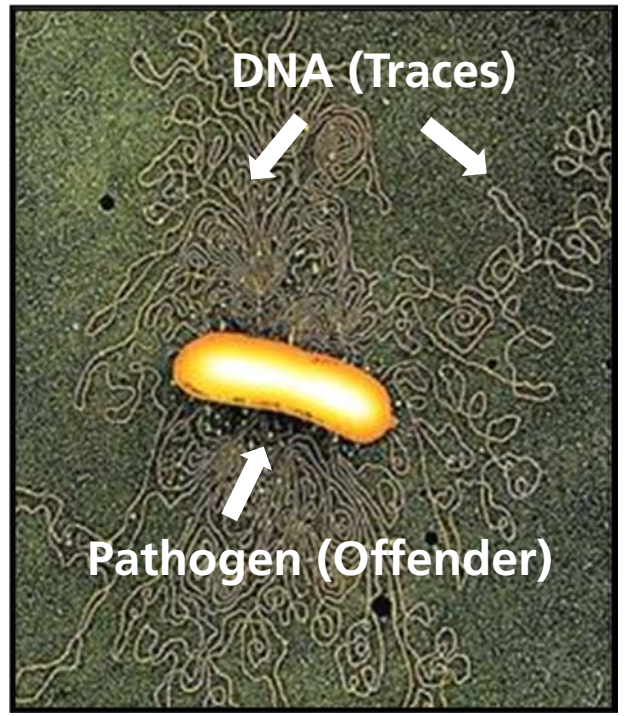
Detection of pathogenic microbes by DNA traces



Caught in the act…



… or by forensics



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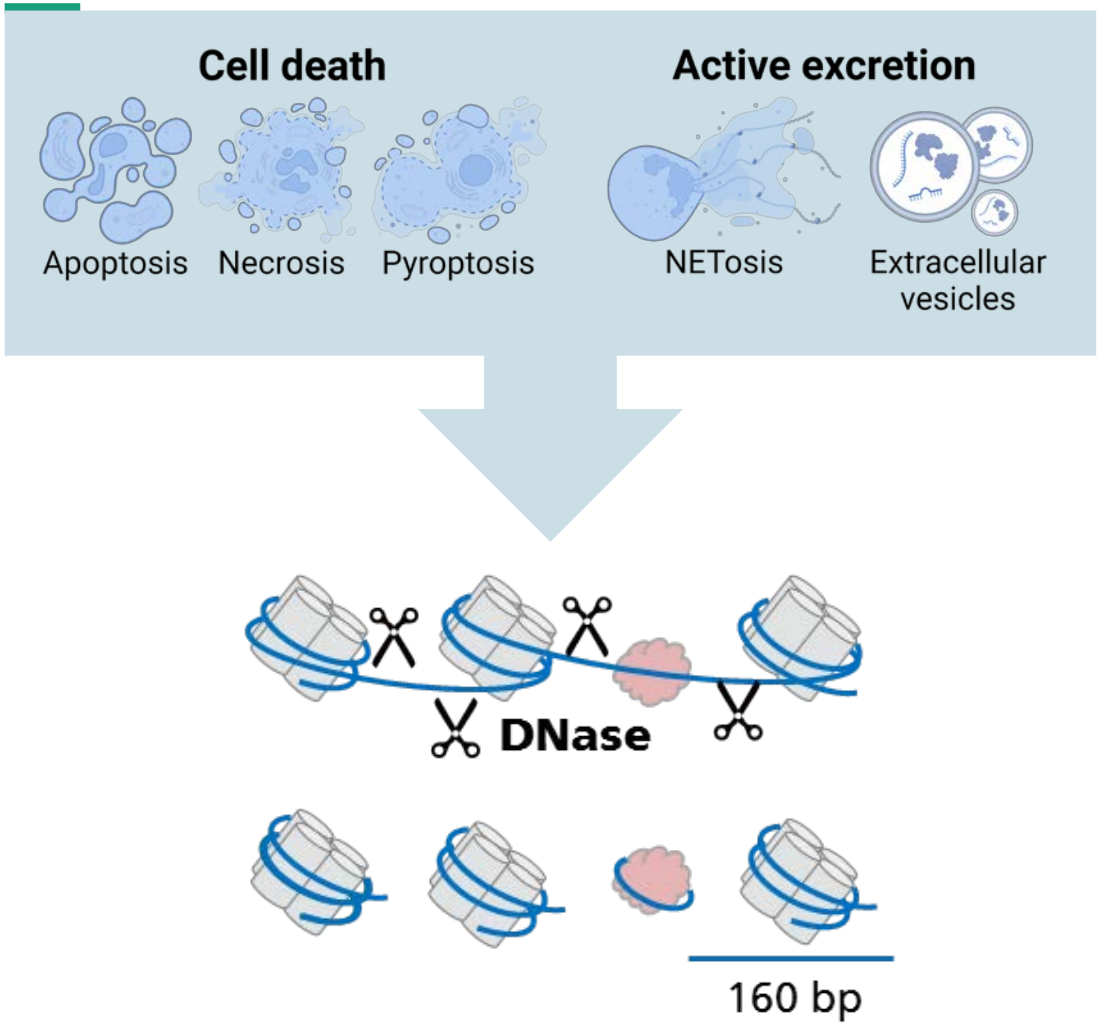
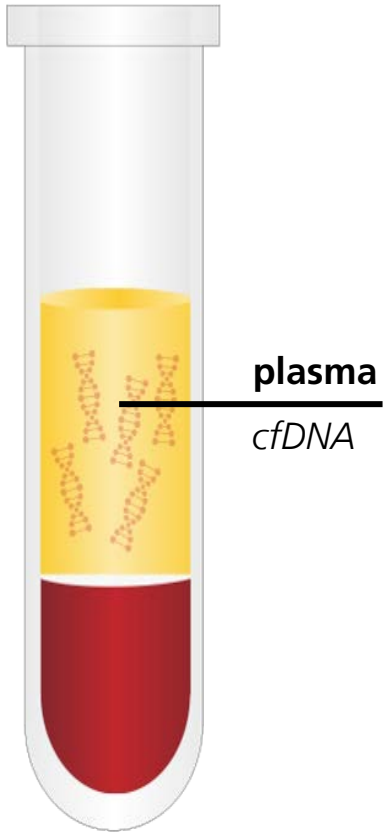
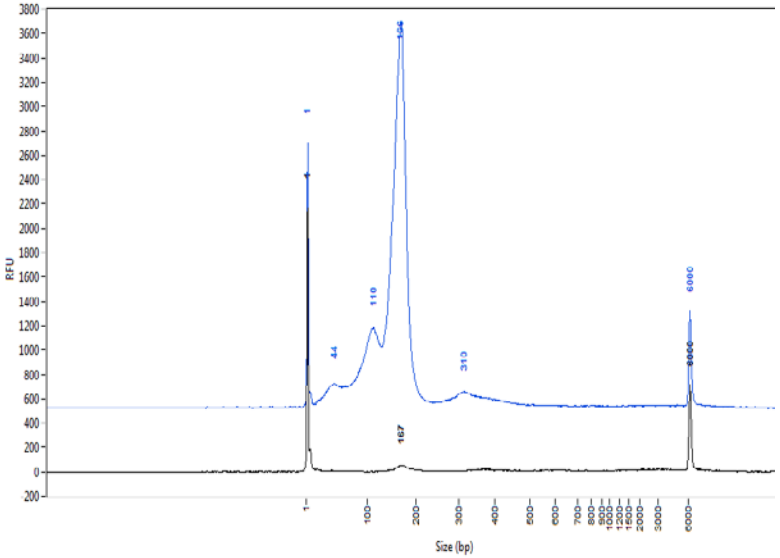
Origin of Cell-Free DNA







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Sequencing of Nucleic Acids from Plasma Diagnostic Approaches

Prenatal

NIPT

Oncology

Liquid Biopsy

Infections

Clinical Metagenomics

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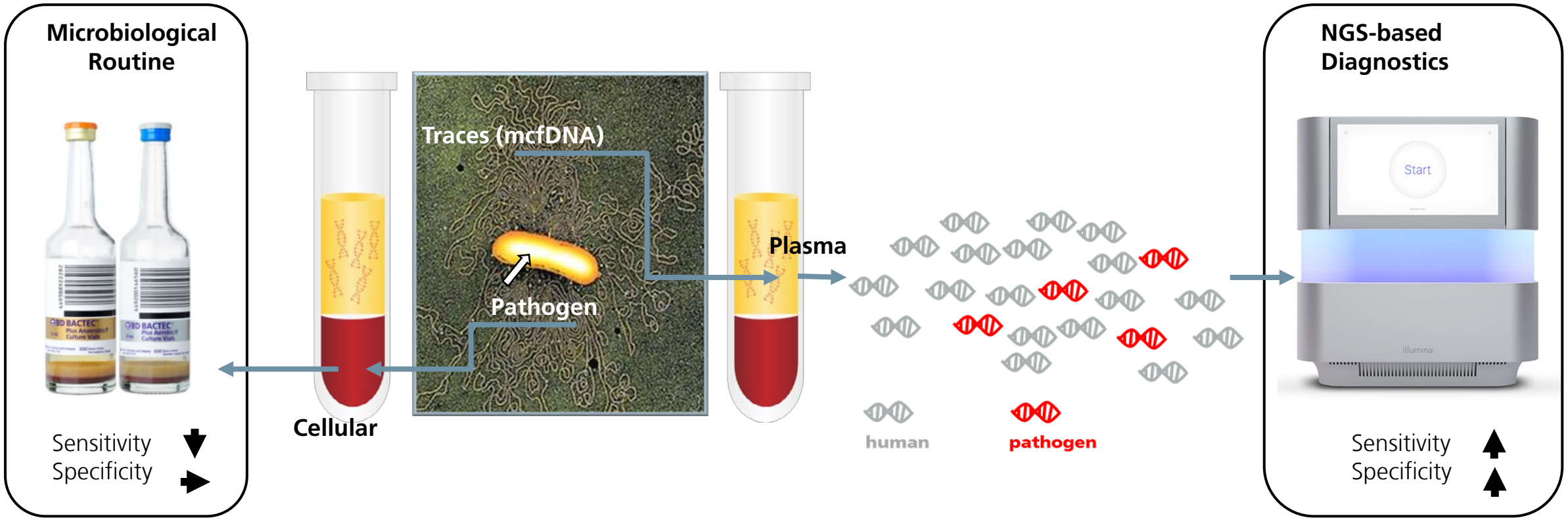
Comparison of Traditional vs. Forensic Diagnostic Concept



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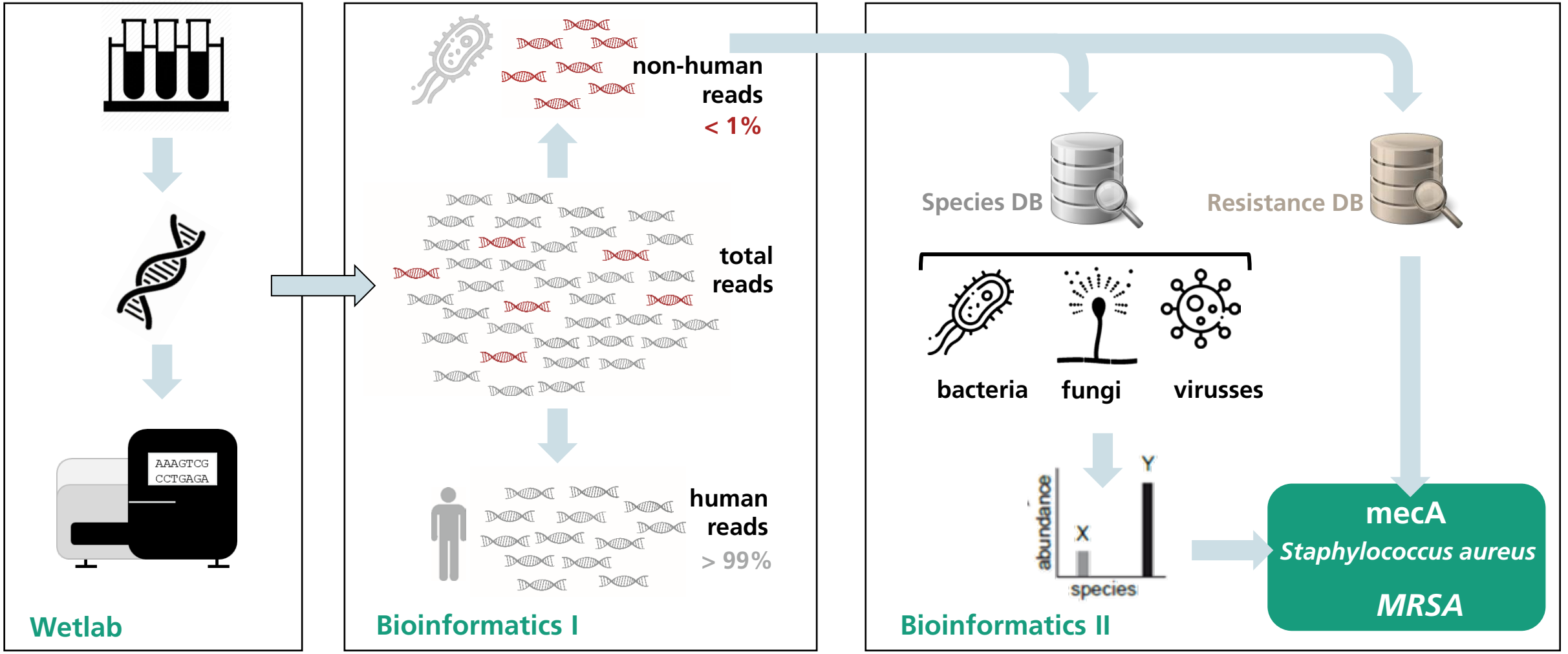
The Complete NGS-based Workflow

Grumaz S., et al. Crit Care Med. 2019 May;47(5):e394-e402.
Grumaz S, Stevens P, et al. Genome Med. 2016 Jul 1;8(1):73.



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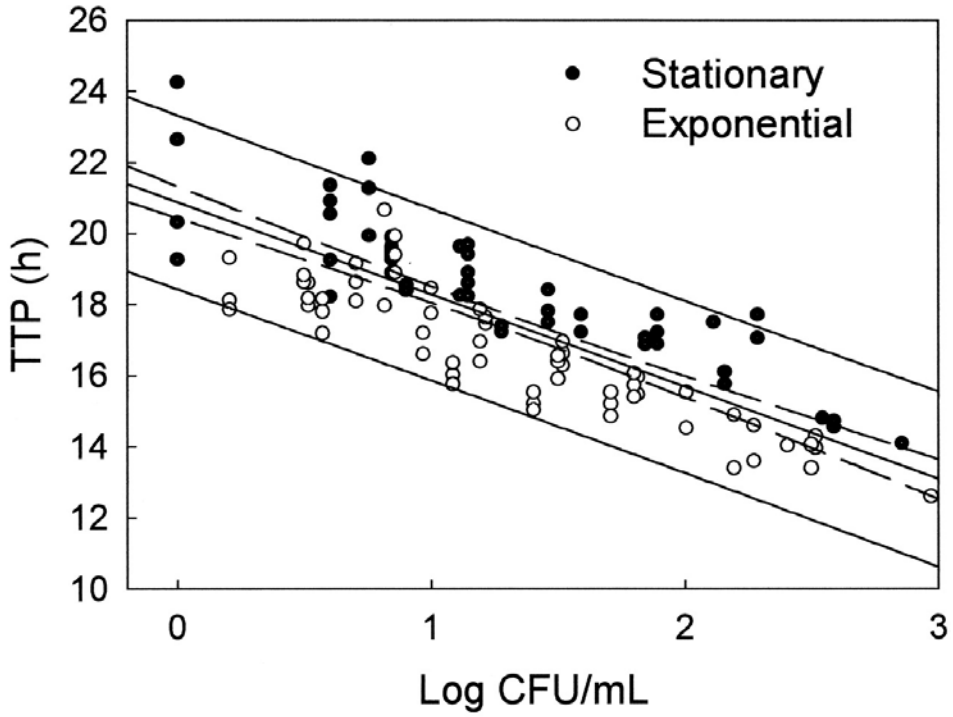
Why Microbial Cell-free DNA?

JOURNAL OF CLINICAL MICROBIOLOGY, Mar. 2002, p. 898–901 Vol. 40, No. 3
0095-1137/02/$04.00+0 DOI: 10.1128/JCM.40.3.898–901.2002
Copyright © 2002, American Society for Microbiology. All Rights Reserved.

Initial Concentration of *Staphylococcus epidermidis* in Simulated Pediatric Blood Cultures Correlates with Time to Positive Results with the Automated, Continuously Monitored BACTEC Blood Culture System

Yishai Haimi-Cohen,[1]† Ernestine M. Vellozzi,[2] and Lorry G. Rubin[1]*

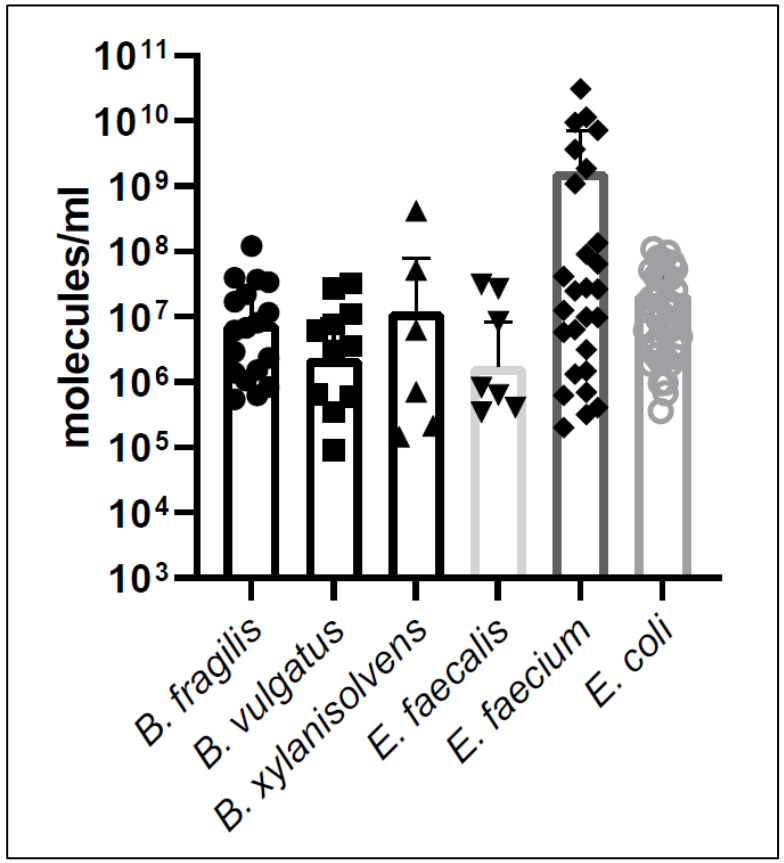


microorganisms MDPI

Article

From Gut to Blood: Spatial and Temporal Pathobiome Dynamics during Acute Abdominal Murine Sepsis

Christina Hartwig [1,2], Susanne Drechsler [3], Yevhen Vainshtein [1], Madeline Maneth [1], Theresa Schmitt [1], Monika Ehling-Schulz [4], Marcin Osuchowski [3,*] and Kai Sohn [1,*]



cfDNA is more abundant

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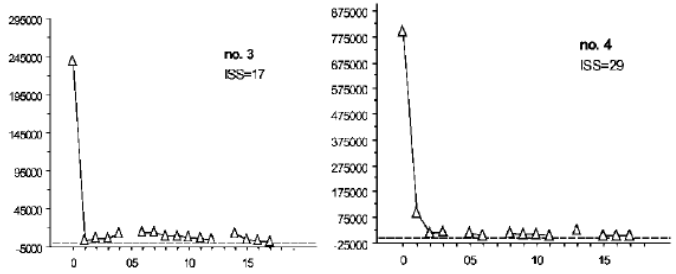
Why Microbial Cell-free DNA?

Clinical Chemistry 49:8
1286–1291 (2003)

Molecular Diagnostics and Genetics

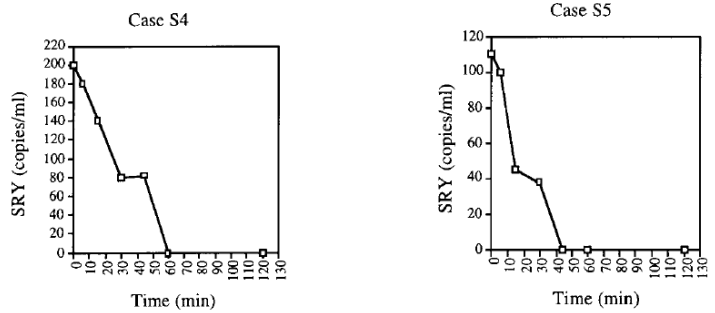
Time Course of Early and Late Changes in Plasma DNA in Trauma Patients

Nicole Y.L. Lam,[1] Timothy H. Rainer,[1] Lisa Y.S. Chan,[2] Gavin M. Joynt,[3] and Y.M. Dennis Lo[2*]



Rapid Clearance of Fetal DNA from Maternal Plasma

Y. M. Dennis Lo,[1] Jun Zhang,[1] Tse N. Leung,[2] Tze K. Lau,[2] Allan M. Z. Chang,[2] and N. Magnus Hjelm[1]



microorganisms

MDPI

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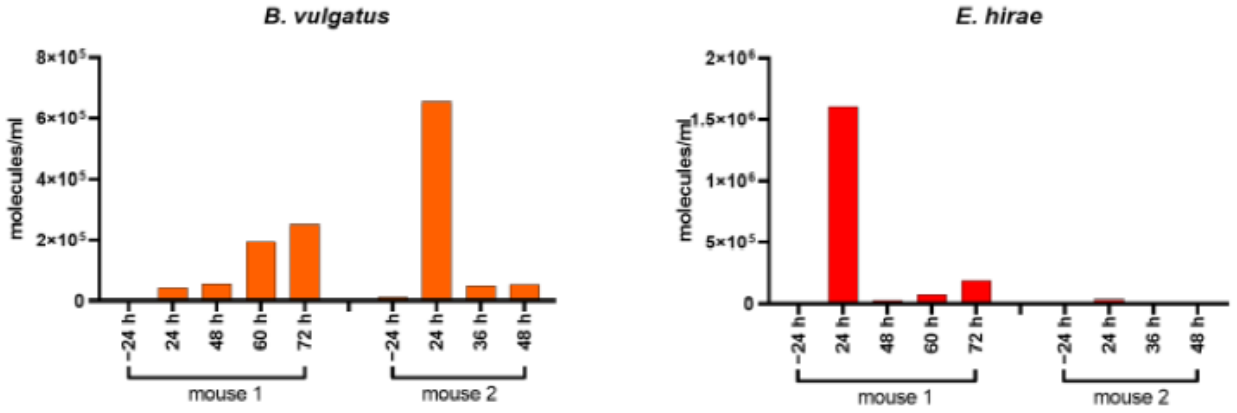

Short half-life of cfDNA

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Performance

Benchmarking against Blood Culture

03

Positivity Rate
Plausibility of NGS

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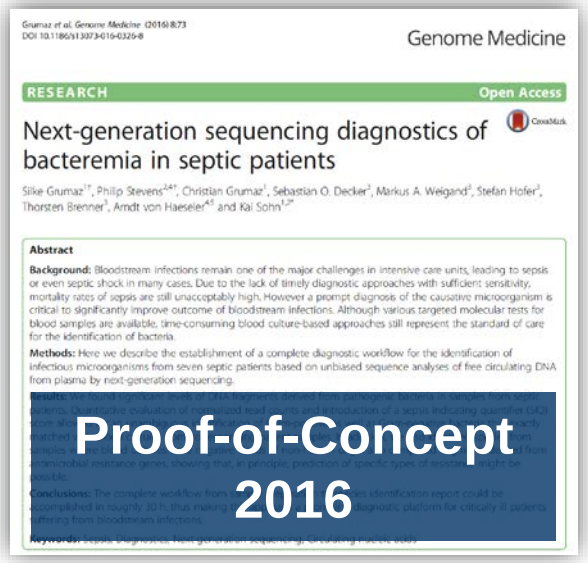
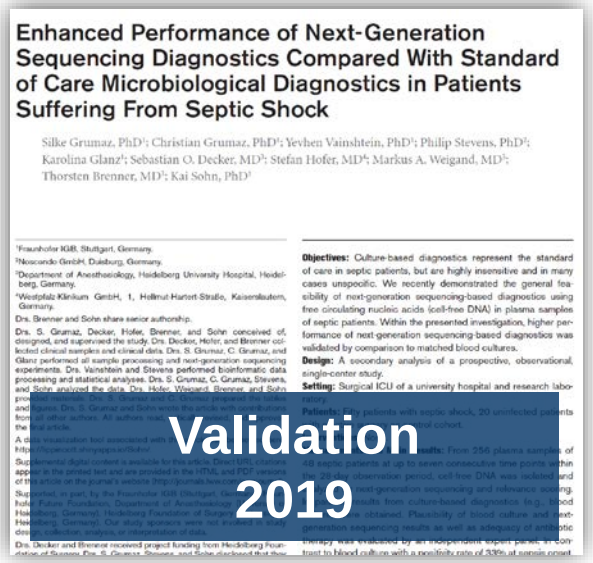
Clinical Validation


Genome Medicine

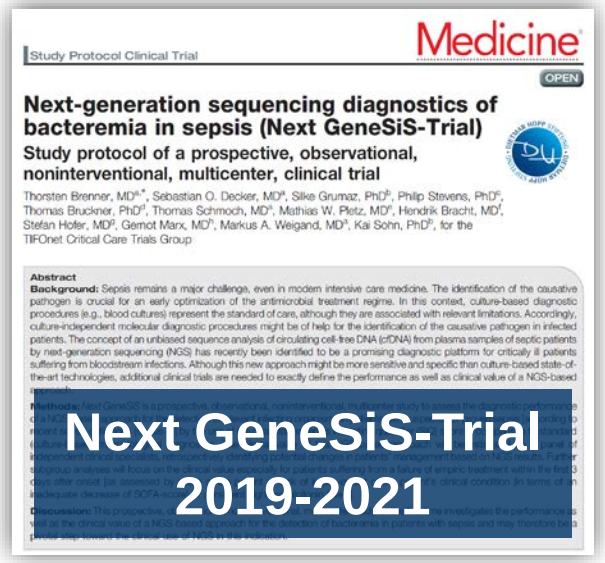
RESEARCH Open Access

Next-generation sequencing diagnostics of bacteremia in septic patients

Proof-of-Concept 2016


Enhanced Performance of Next-Generation Sequencing Diagnostics Compared With Standard of Care Microbiological Diagnostics in Patients Suffering From Septic Shock

Validation 2019


Medicine

Study Protocol Clinical Trial

OPEN

Next-generation sequencing diagnostics of bacteremia in sepsis (Next GeneSiS-Trial)

Study protocol of a prospective, observational, noninterventional, multicenter, clinical trial

Next GeneSiS-Trial 2019-2021

1 Prospective, non-interventional, multicentric study

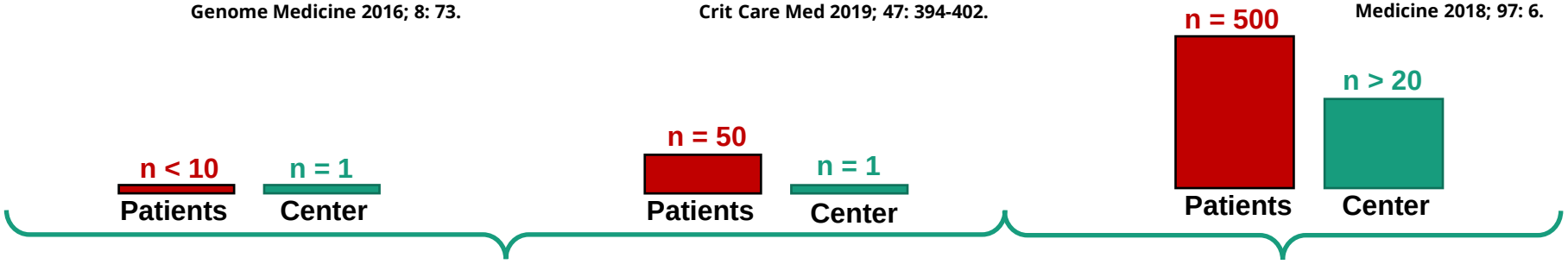
2 Aim
Performance of NGS-based diagnostics compared to gold standard blood culture

3 Number of patients
n = 500

Grumaz S, Brenner Th, Sohn K et al., Genome Medicine 2016; 8: 73.

Grumaz S, Brenner Th, Sohn K et al., Crit Care Med 2019; 47: 394-402.

Brenner Th, Sohn K et al., Medicine 2018; 97: 6.



retrospective, technical/clinical feasibility

Prospective, clinical validity/utility

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Blood Culture – a Reasonable Diagnostic Gold Standard?

Patient 08-002

Anamnese
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NGS & Mikrobiologie

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Blutkultur aerob	Negativ	Negativ	n.a.
Blutkultur anaerob	Negativ	Negativ	n.a.
Andere Proben	Negativ	n.a.	Negativ

Brenner Th, et al., Medicine 2018; 97: 6.

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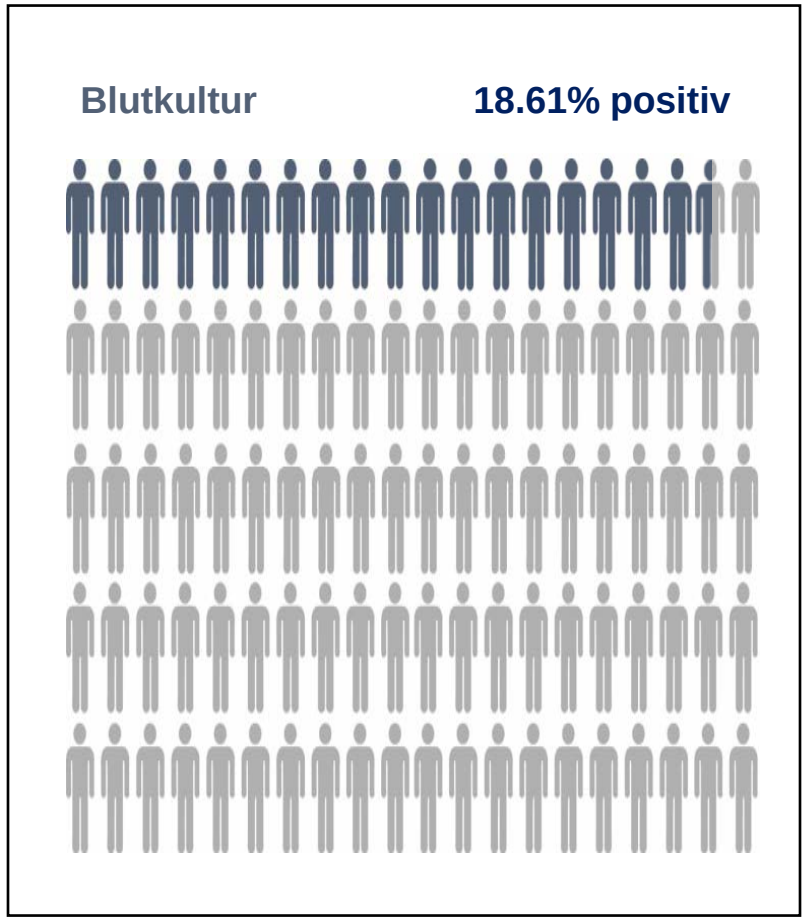
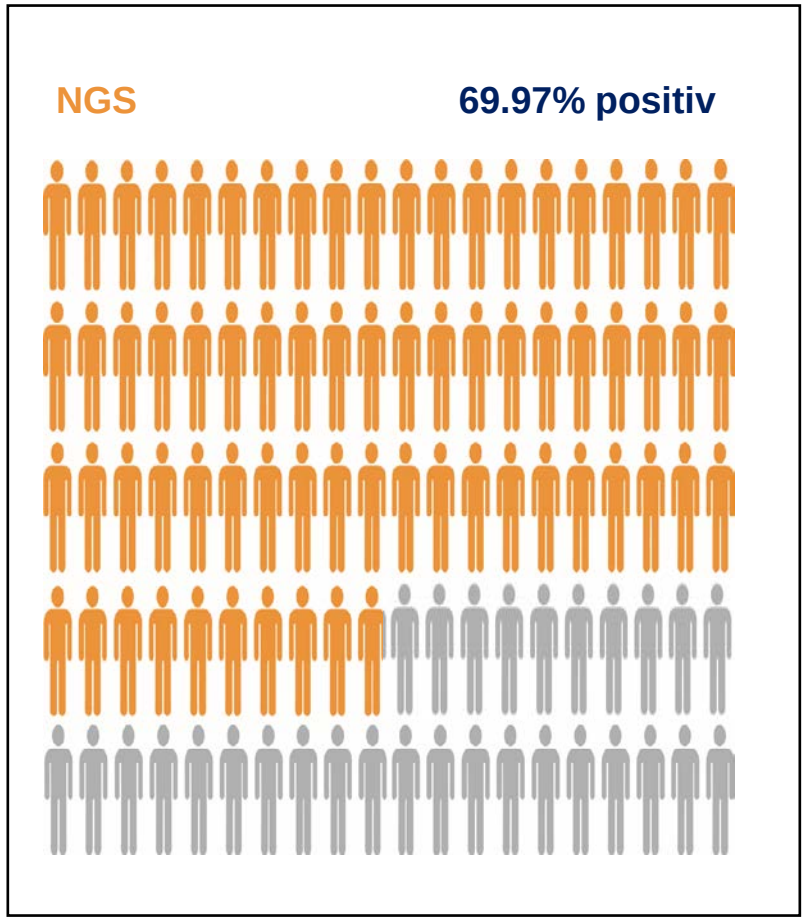
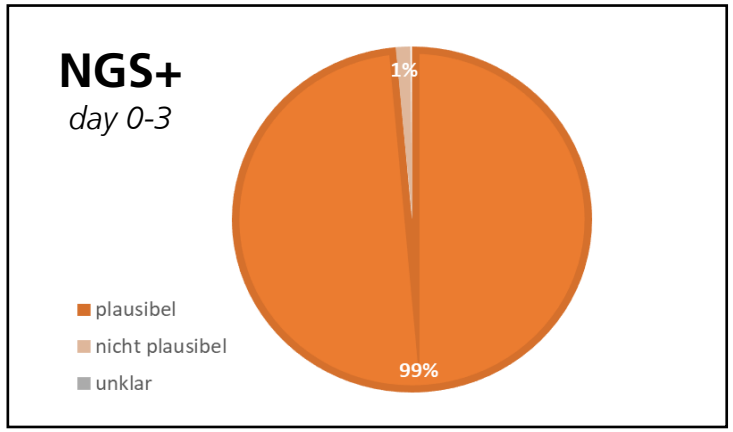
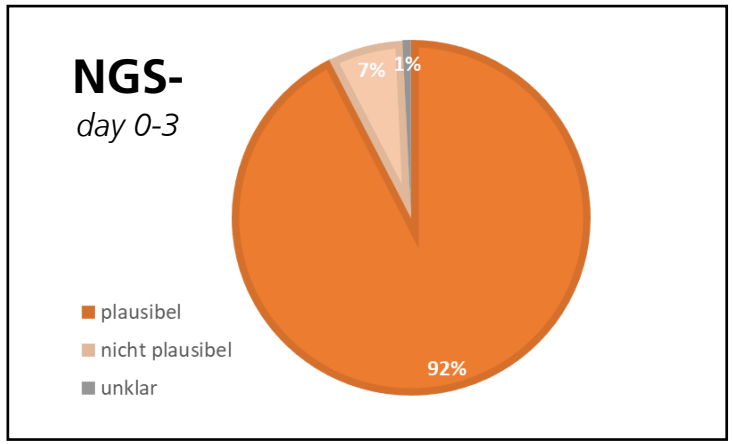
Positivity Rate by Blood Culture and NGS









Unpublished data / Next GeneSiS-Trial.

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Clinical Relevance and Outcome

04

Therapeutic Relevance
Clinical Outcome

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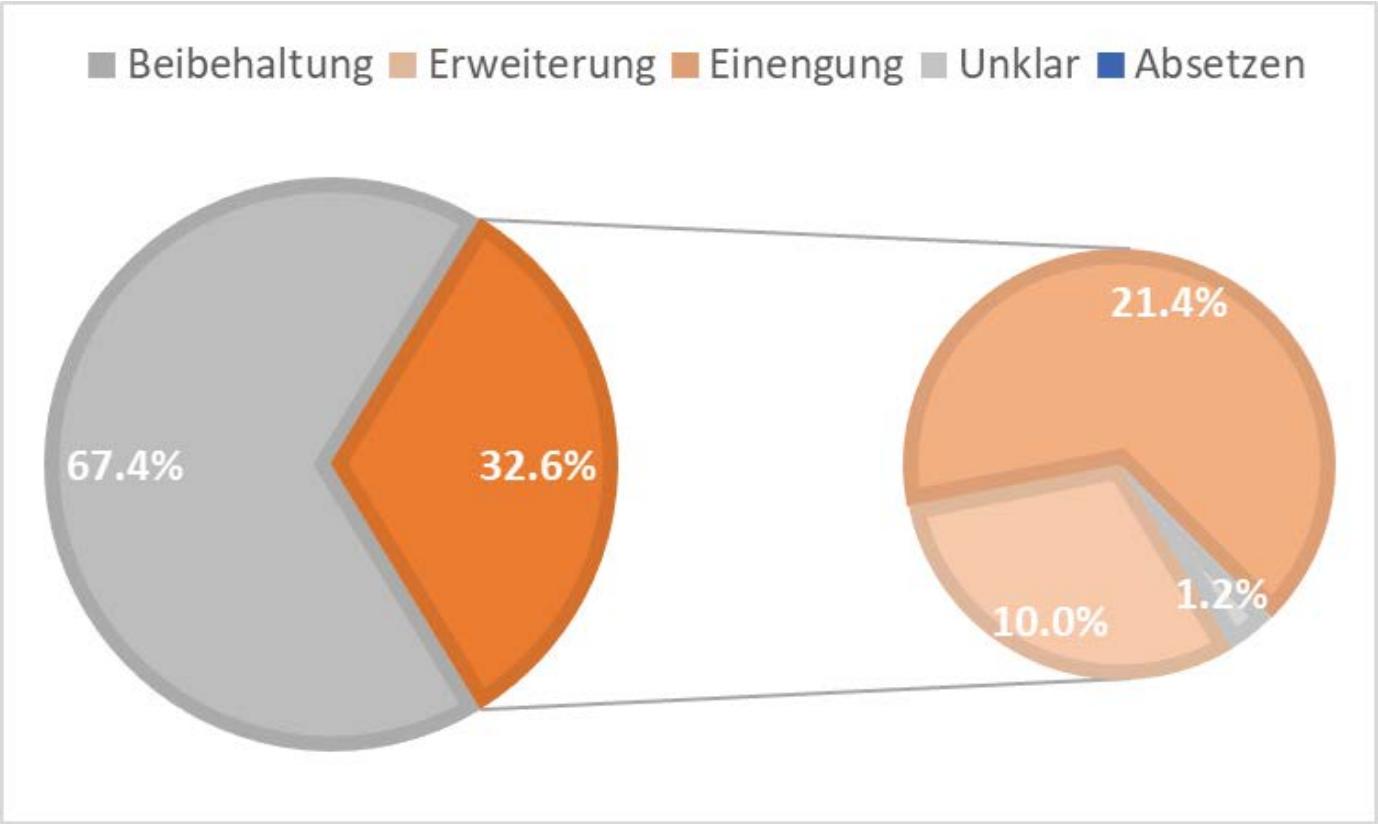
Therapy Relevance of NGS-based Pathogen Identifications



Recommendation for adaptation of antibiotic intervention for approx. 33% of septic patients:

- 2/3 De-escalation
- 1/3 Escalation
- No complete stop!

Outcome-Relevance?

Unpublished data / Next GeneSiS-Trial.

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Outcomes in adequately vs. non-adequately treated patients

Outcome-Relevance in subgroup SIQ+/BC-

Outcome (within 28 days after study inclusion)	Treatment recommendation			p-value
	Maintain (n=112)	Change (n=93)	Total (n=205)	
Length of ICU/IMC stay [days]	12.0±8.4	14.0±9.0	13.0±8.8	**0.026***
Length of mechanical ventilation [days]	5.8±7.3	8.6±9.2	7.1±8.3	**0.018***
Length of antibiotic treatment [days]	12.0±7.4	14.0±8.1	13.0±7.8	**0.038***
Length of antifungal treatment [days]	3.1±6.6	4.4±6.8	3.7±6.7	0.169
Length of antiviral treatment [days]	0.6±2.2	1.8±4.8	1.1±3.7	**0.026***
Length of kidney replacement therapy [days]	1.7±4.8	3.9±8.0	2.7±6.5	**0.021***

Data are by mean ± standard deviation.

Abbreviations: ICU, intensive care unit; IMC, intermediate care

- NGS-based pathogen diagnostics has potential to **prevent over-treatment** with antibiotics and to **optimize clinical outcomes** (LOS at ICU/IMC, length of ventilation, RRT).
- .

Unpublished data / Next GeneSiS-Trial.

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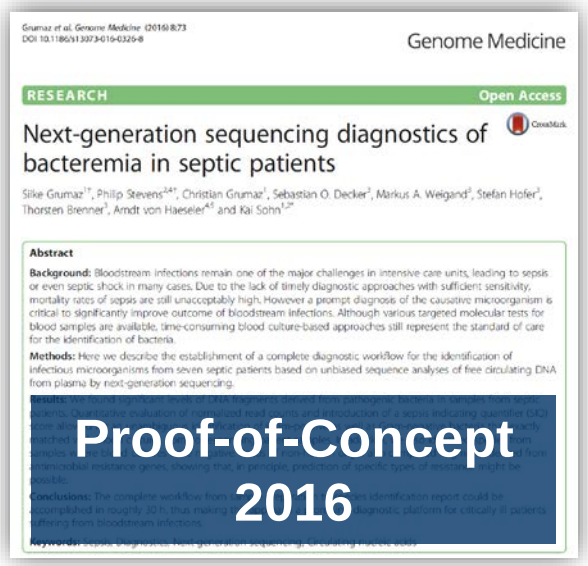
Clinical Utility


Genome Medicine

RESEARCH Open Access

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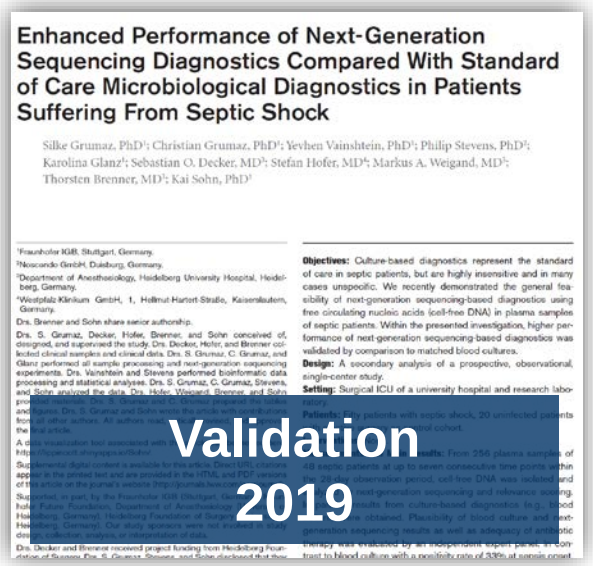
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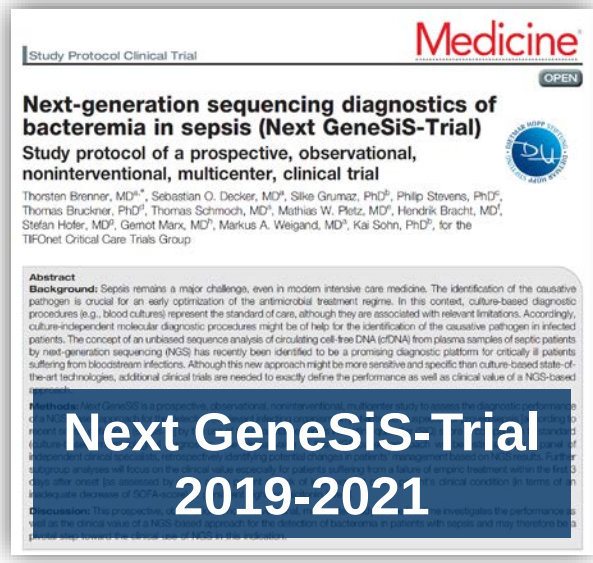

Medicine

Study Protocol Clinical Trial

Next-generation sequencing diagnostics of bacteremia in sepsis (Next GeneSiS-Trial)

Study protocol of a prospective, observational, noninterventional, multicenter, clinical trial

Next GeneSiS-Trial 2019-2021

Brenner Th, Sohn K et al., Medicine 2018; 97: 6.

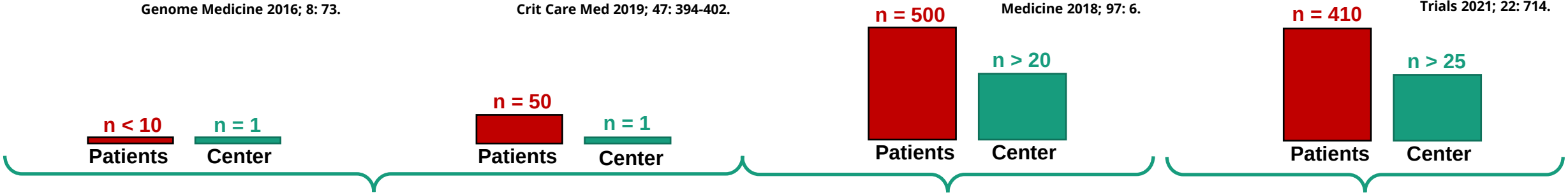
Trials

STUDY PROTOCOL Open Access

Optimization of sepsis therapy based on patient-specific digital precision diagnostics using next generation sequencing (DigiSep-Trial)—study protocol for a randomized, controlled, interventional, open-label, multicenter trial

DigiSep-Trial 2021-2024

Brenner Th, et al., Trials 2021; 22: 714.



retrospective, technical/clinical feasibility

Prospective, clinical validity/utility

Interventional, clinical utility

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Summary and Conclusion

1. Cell-free DNA represents a precise biomarker class for pathogen detection in plasma.

2. NGS-based pathogen diagnostics shows superior performance compared to current gold standard blood culture. Plausibility is confirmed by expert panel evaluation

3. NGS indicates that antibioses for up to 1/3 of patients should be adapted. Clinical trials indicate better outcomes for patients when interventions are optimized accordingly.

4. Tests are already commercially available in Germany.

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Thank you!

Fraunhofer IGB Innovationsfeld In-vitro-Diagnostik

Dr. Yevhen Vainshtein
Jan Müller
Dr. Mehdi Manoochehri
Karolina Glanz

University Vienna

Prof. Arndt von Haeseler

Noscendo

Dr. Silke Grumaz
Dr. Philip Stevens

Universitätsklinikum Essen

Prof. Dr. Thorsten Brenner

Universitätsklinikum Heidelberg

PD Dr. Sebastian O. Decker
Prof. Markus Weigand

Expert Panel

Dr. Wolfgang Krüger
Dr. Christian Lanckohr
Dr. Stefan Hagel

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Dietmar-Hopp-Stiftung
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Prof. Dr. Monika Ehling-Schulz

Ludwig Boltzmann Institut

PD. Dr. Marcin Osuchowski

Fraunhofer IGB

Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB

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