폐렴 진료 전략

차세대 진단기법과 정밀 의료 기반 치료

Park Chul MD

Division of Pulmonology and Critical Care Medicine

Department of Internal Medicine

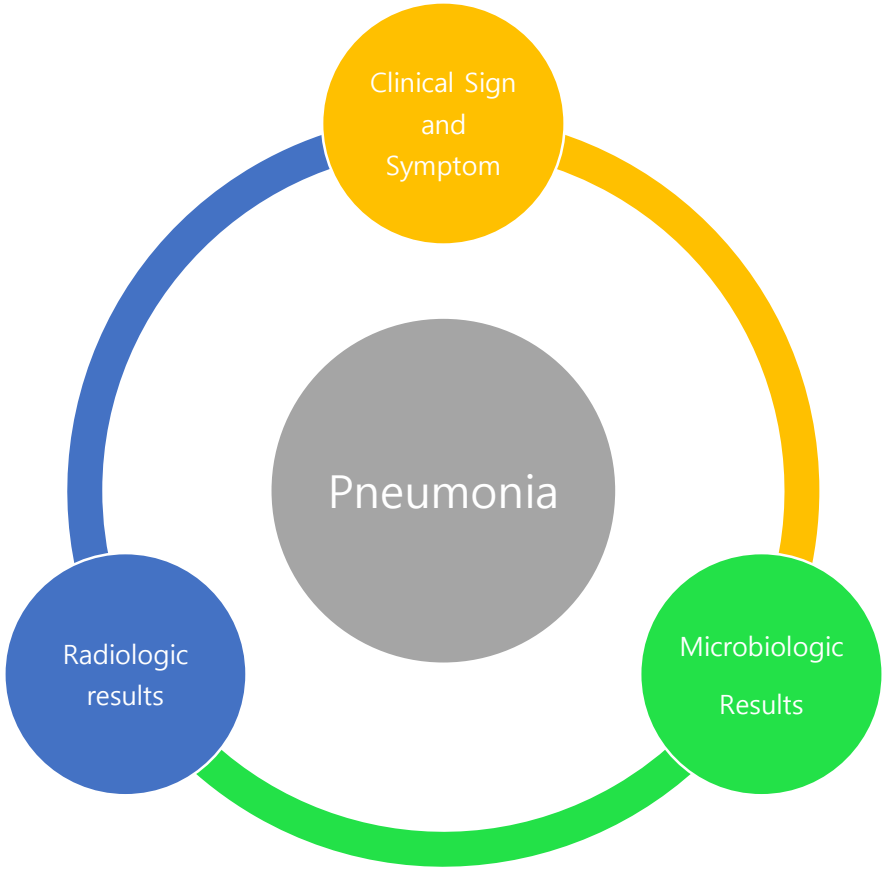
Ulsan University Hospital

Disclosure(s)

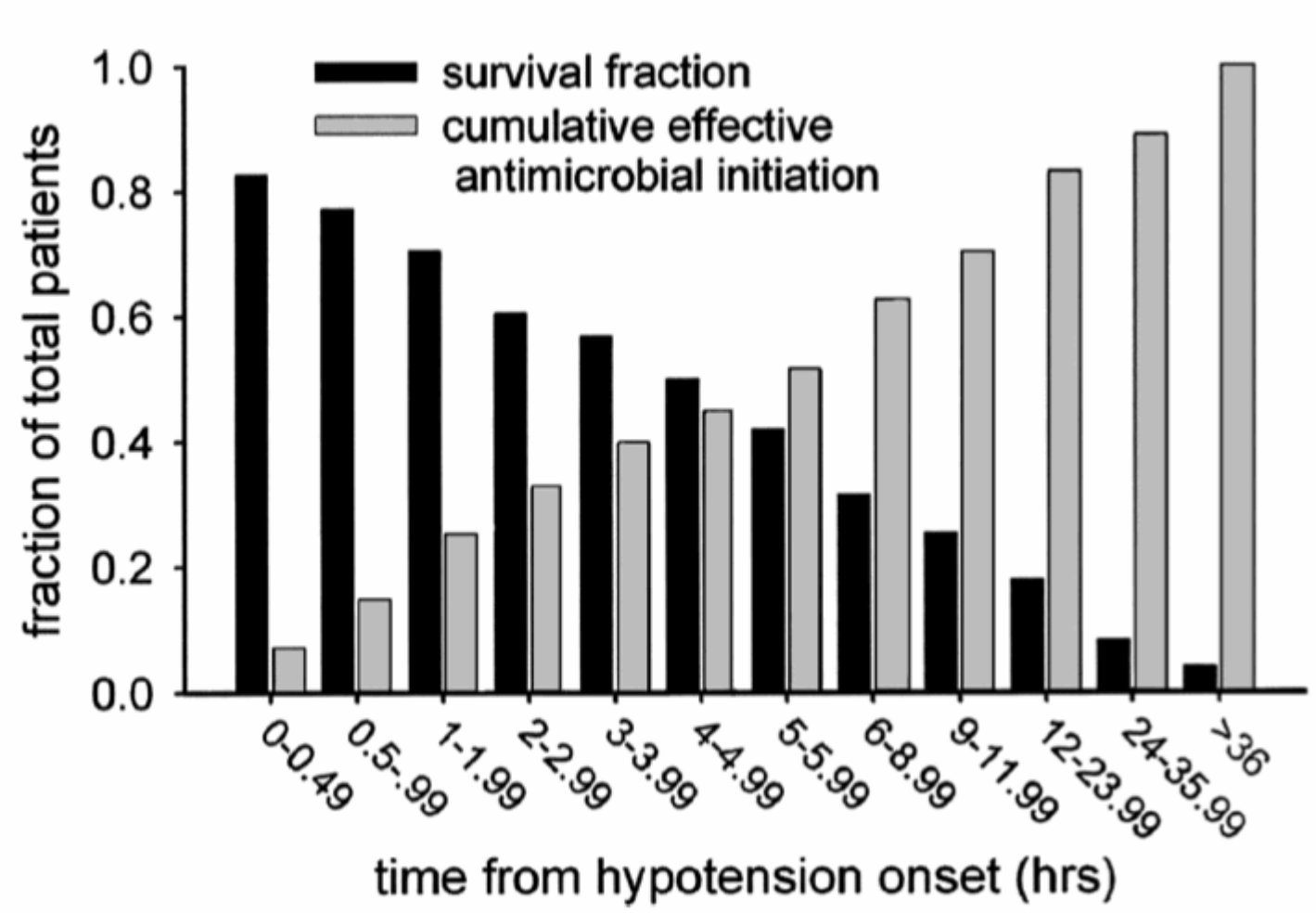
There is no conflict of interest.

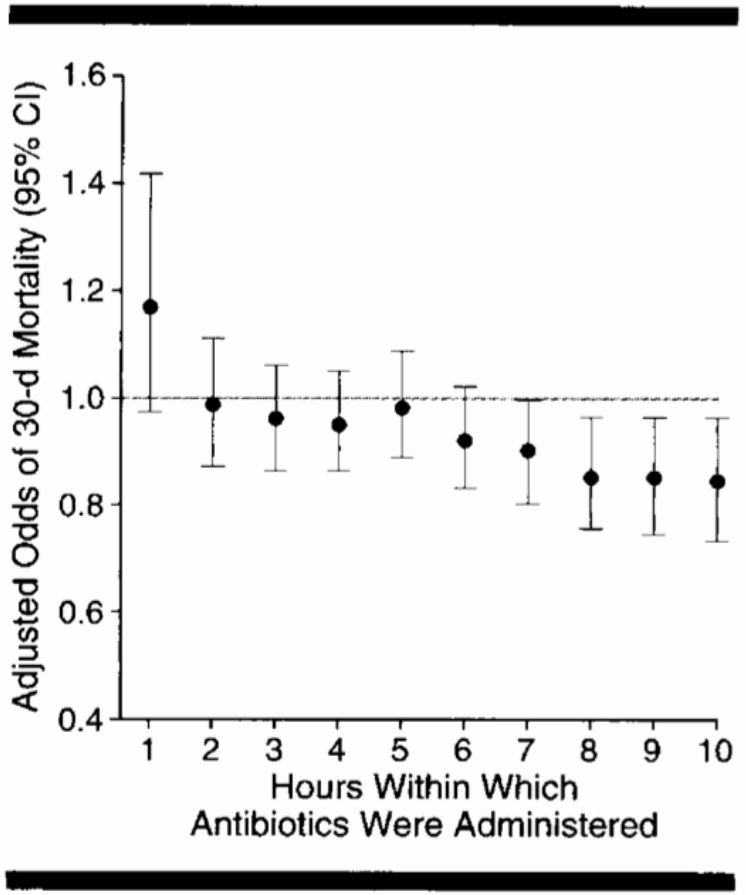
Pneumonia

Infection that inflames the air sacs in one or both lungs



Timing of Antibiotics





Crit Care Med. 2006;34(6):1589-96

Common Pathogen of Etiology and Risk Factors in CAP

위험 인자와 역학적 특성	흔한 원인균
알코올 중독	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae*, *Acinetobacter* species, *Mycobacterium tuberculosis*
만성폐쇄성폐질환, 흡연	*Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Legionella* species, *Streptococcus pneumonia*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*
흡인	Gram-negative enteric pathogens, oral anaerobes
폐농양	Oral anaerobes, *Mycobacterium tuberculosis*, atypical mycobacteria
조류에 노출	*Chlamydophila psittaci* (if poultry: avian influenza)
농장 동물에 노출	*Coxiella burnetii* (Q fever)
인플루엔자 유행	Influenza, *Streptococcus pneumonia*, *Staphylococcus aureus*, *Haemophilus influenzae*
장기간의 기침 또는 기침 후 구토	*Bordetella pertussis*
구조적인 폐 이상(예, 기관지확장증)	*Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Staphylococcus aureus*
주사약물 사용	*Staphylococcus aureus*, anaerobes, *Mycobacterium tuberculosis*, *Streptococcus pneumonia*
기관지 폐색	Anaerobes, *Streptococcus pneumonia*, *Haemophilus infuluenzae*, *Staphylococcus aureus*

Conventional Pneumonia strategy

Empirical Antibiotics Treatment

Surviving Sepsis Campaign 2026

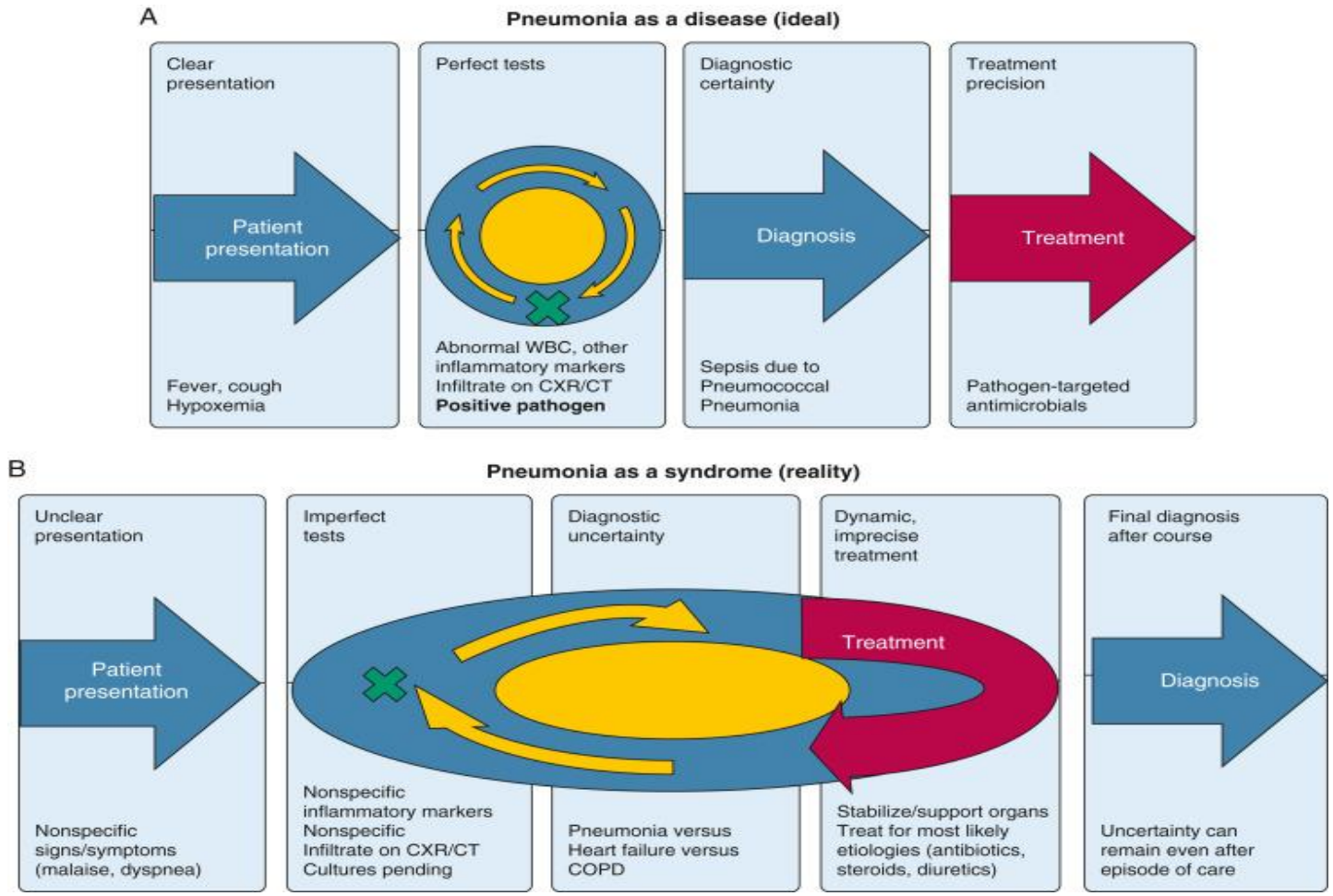
26. For adults with sepsis or septic shock at low risk of infection with a specific **MDR pathogen**, we "suggest **against**" using **empirical antimicrobial** therapy with coverage for this MDR pathogen (conditional recommendation, very low certainty evidence)
27. For adults with sepsis or septic shock, we "suggest **against**" using **empirical antifungal** therapy (conditional recommendation, low certainty evidence)
28. For adults with sepsis or septic shock without risk factors for anaerobic infection, we "suggest" using an **empiric** antibiotic regimen **without anaerobic coverage** (conditional recommendation, very low ce rtainty of evidence)
32. For adults with sepsis or septic shock, we "suggest **against**" using *Candida* fungal biomarkers to guide initiation of **empiric antifungal therapy**

Crit Care Med. 2026;54(4):725-812

Prognostic Factors of Pneumonia

Age	Advanced age	**Pathogen**	Atypical/Fatal pathogen
Frailty	Performance poor	**Clinical Severity**	Hypoxia, Tachypnea, Hypotension, Altered mental status
Comorbidity	COPD, HF, CKD, Malignancy	**Inflammation response**	CRP / Procalcitonin, Lactate
Immune status	Chemotherapy Long term Steroid use	**Treatment response**	Viral/bacterial pathogen

Define Uniformly, Diverse course and outcome



Heterogenous Causes and **Phenotypes**

Need to differentiate viral vs bacteria

Optimizing antimicrobial therapy

Targeting adjunctive and immunomodulatory therapy

Chest. 2025;167(1):27-31

Reason for phenotype classification

Limitations of Pathogen-Based Approaches

Host response heterogeneity

Needs for Precision medicine

Limitations of Pathogen-Based Approaches

	Sputum Gram stain	Sputum Culture	Blood culture	BAL	PSB	Antigen test (urine antigen)	Serologic test
Pathogen						S.pneumoniae Legionella	M pneumoniae C pneumoniae
Characteristics	-세균형태와 염증세포 유무 확인 -결과 보고 빠름 (수십분 이내) -객담 질 평가 가능	-균동정 + 항생제 감수성 검사 (AST) -gold standard microbiologic test	-균혈증 동반 폐렴 확인 -확정적 원인균 진단 가능	-하기도 직접 검체 -contamination 감소 -quantitative culture 가능	-contamination 최소화	-빠른 검사 결과 보고 (수 시간) - 항생제 영향 적음	-atypical pathogen 진단 가능
Limitations	-구강 타액 오염 -항생제 사용 후 민감도 감소 -원인균 확정 불가 -true pathogen 과 colonization 구분 어려움	-결과 보고 시간이 오래 걸림 (48-72 시간) -colonization -contamination 시 의미 없는 결과 -항생제 사용 후 민감도 감소 -비배양성 병원체 검출 불가	-양성률 낮음 (CAP 약 5-14%) -시간 소요 (1-3일) -항생제 노출 시 false negative	-침습적 검사 -중증환자에서 위험 -숙련된 시술자 필요 -결과까지 시간 필요 -$\geq 10^4$ CFU/mL → significant infection	-기술적으로 어려움 -routine clinical practice에서 제한적	-검출 가능한 병원체 제한 -serotype 제한 -colonization 구분 어려움	-acute diagnosis에 부적합 (paired serum 필요) -시간 지연 (2–3주) -임상 활용도 낮음

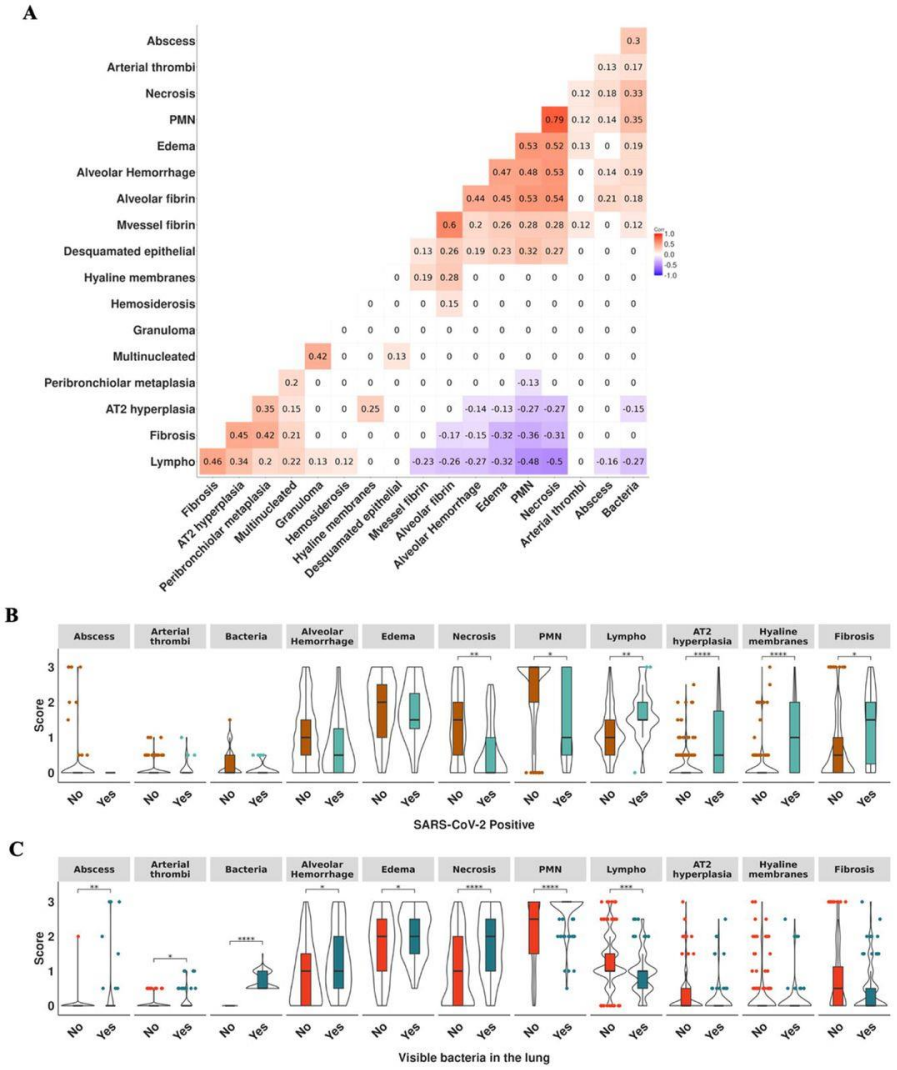
Limitations of Pathogen-Based Approaches

- 진단 시간 지연 배양 검사 중심
- 병원체 다양성 bacteria, virus, fungus etc
- colonization vs infection 문제
- 항생제 사용 후 진단 정확도 감소
- 임상 증상만으로 병원체 구분 불가

미생물 배양 검체[2]	호흡기	객담	706(59.0)
		경기관흡인액(Transtracheal aspirates, TTA)	371(31.0)
		기관지세척액(Bronchial washing fluid)	64(5.4)
		기관지폐포세척액(Bronchoalveolar lavage, BAL)	19(1.6)
	혈액		965(80.7)
	흉수		78(6.5)

Tuberc Respir Dis (2021)

Host response heterogeneity



- Hyper-inflammatory phenotype

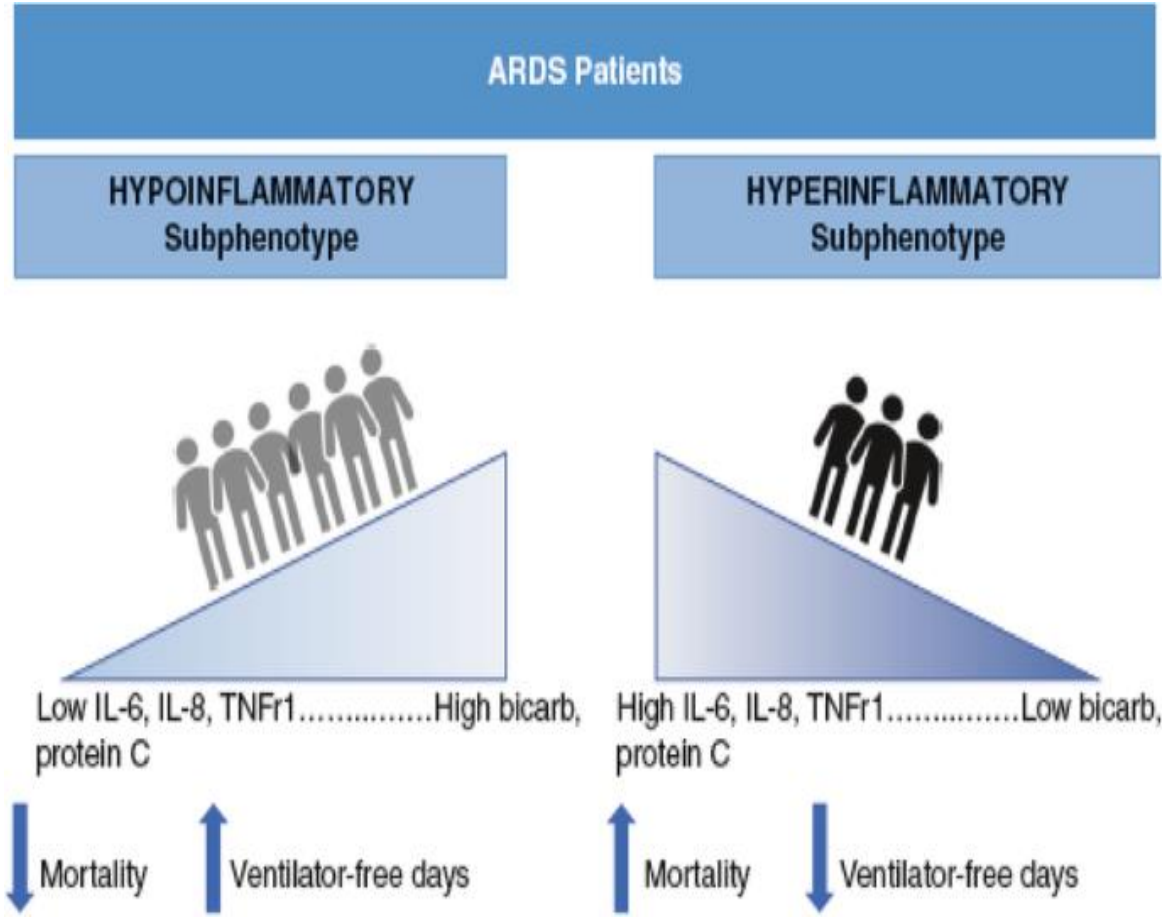
→ cytokine storm, ARDS, shock

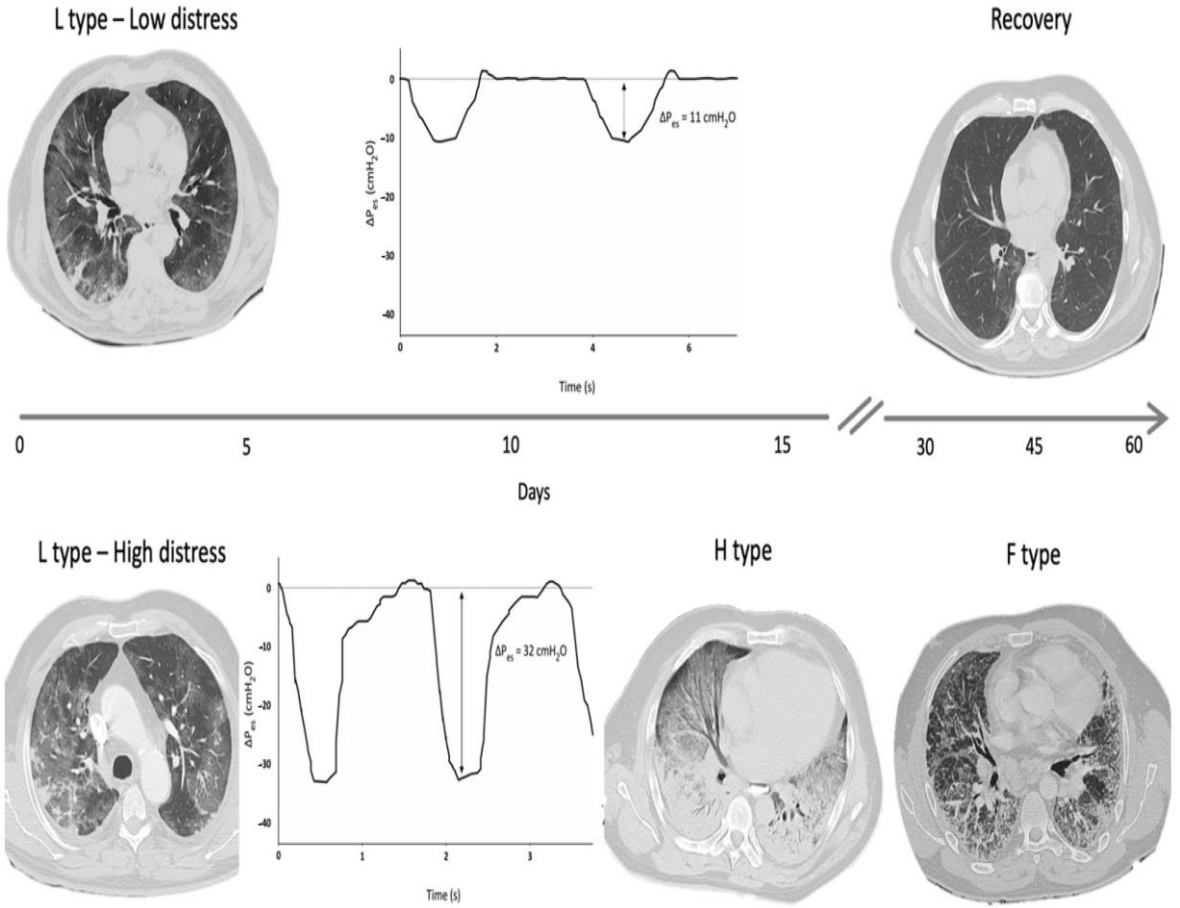
- Hypo-inflammatory / immuno-paralysis phenotype

→ 2ndary infection, Decreased treatment response

bioRxiv. 2025;2025.05.18.654716.

Host response heterogeneity

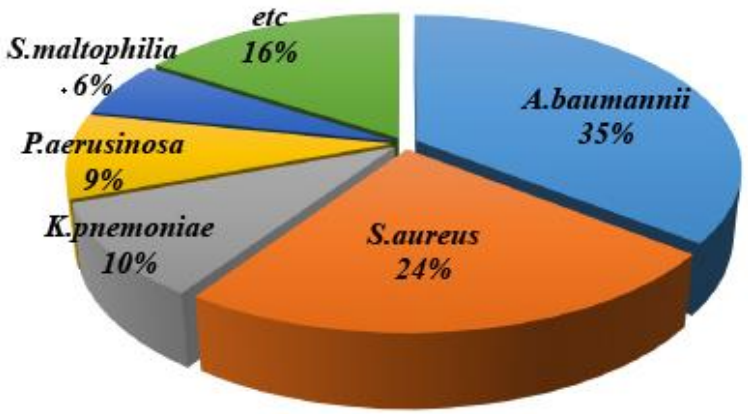


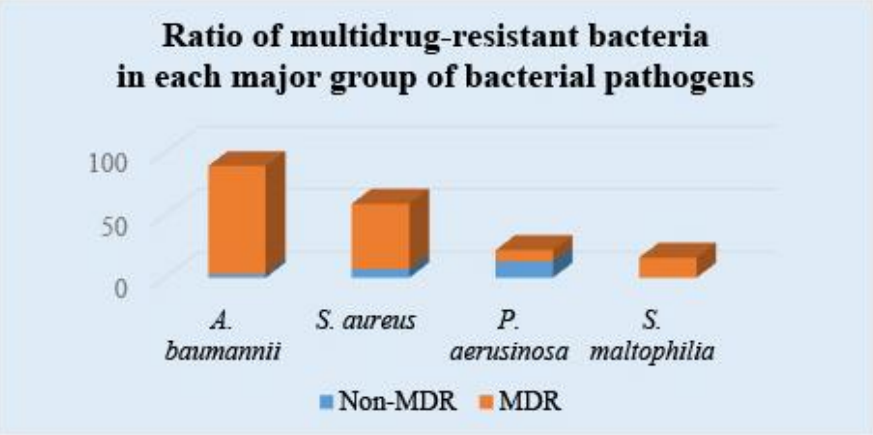


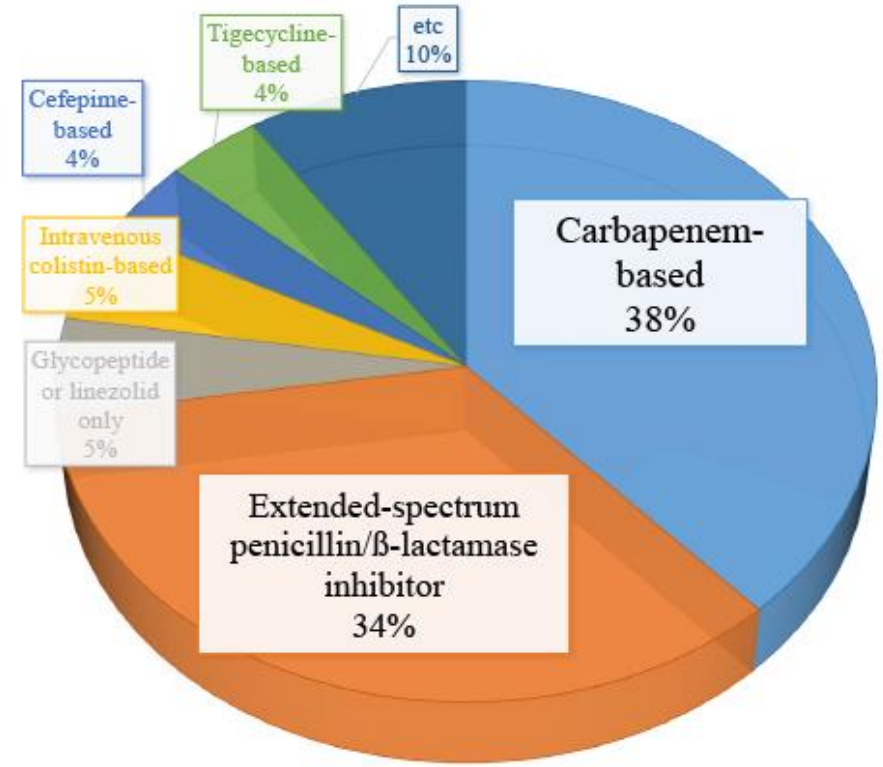
Crit Care 24, 102 (2020)
J. Clin. Med. 2021, 10, 975.

Needs for Precision medicine

- **Discrepancy between major HAP/VAP pathogens and empirical antibiotics**



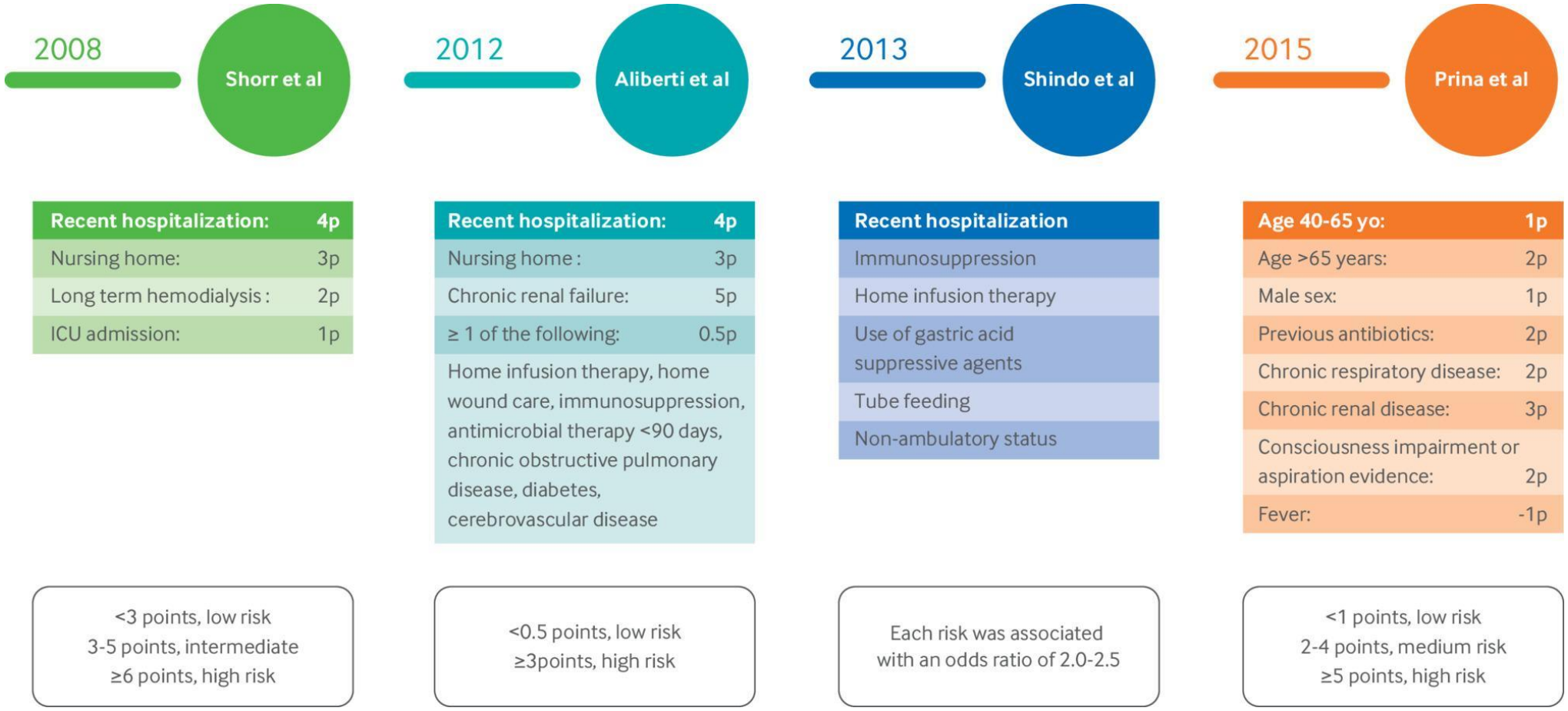




Empirical antibiotics during the first 48 hours

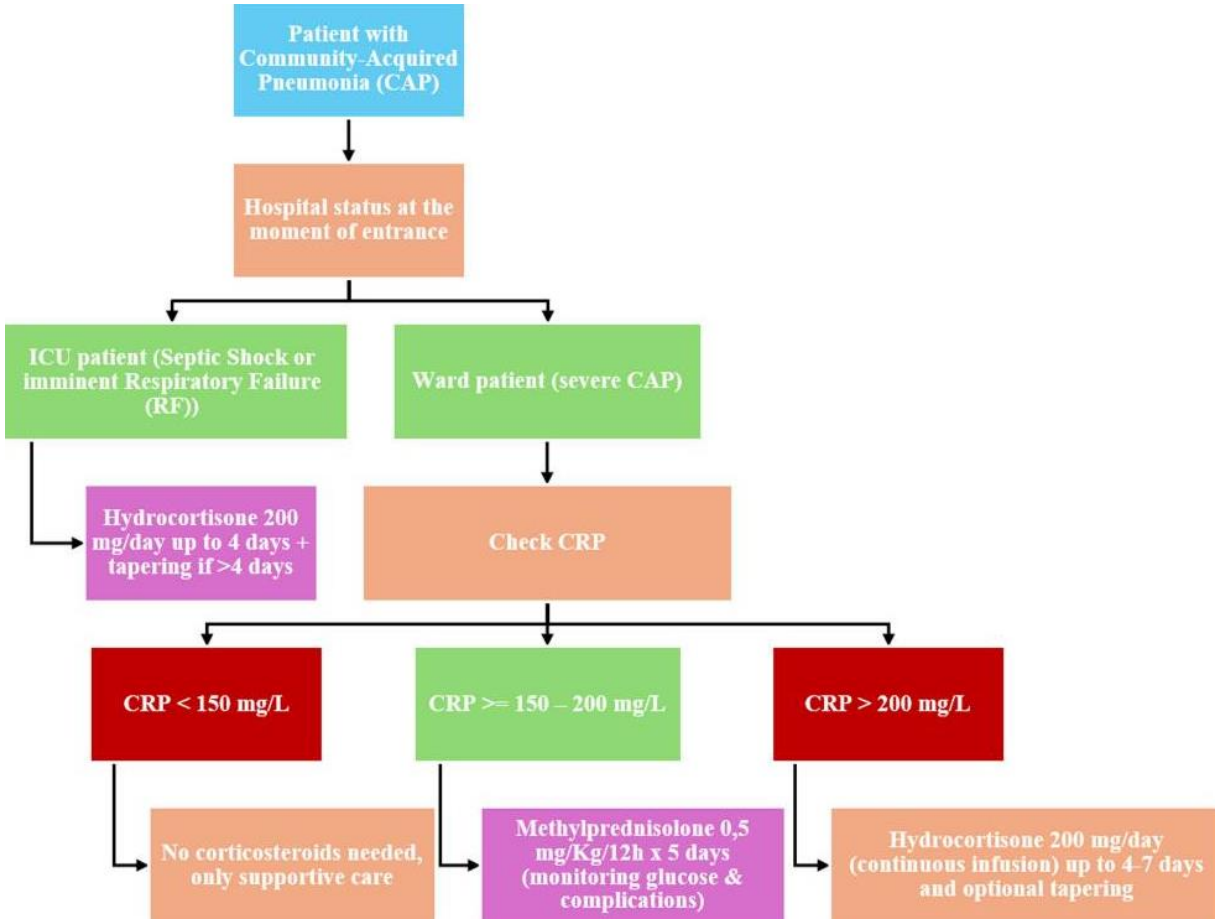
J Korean Med Sci. Oct 25;36(41):e251(2021)

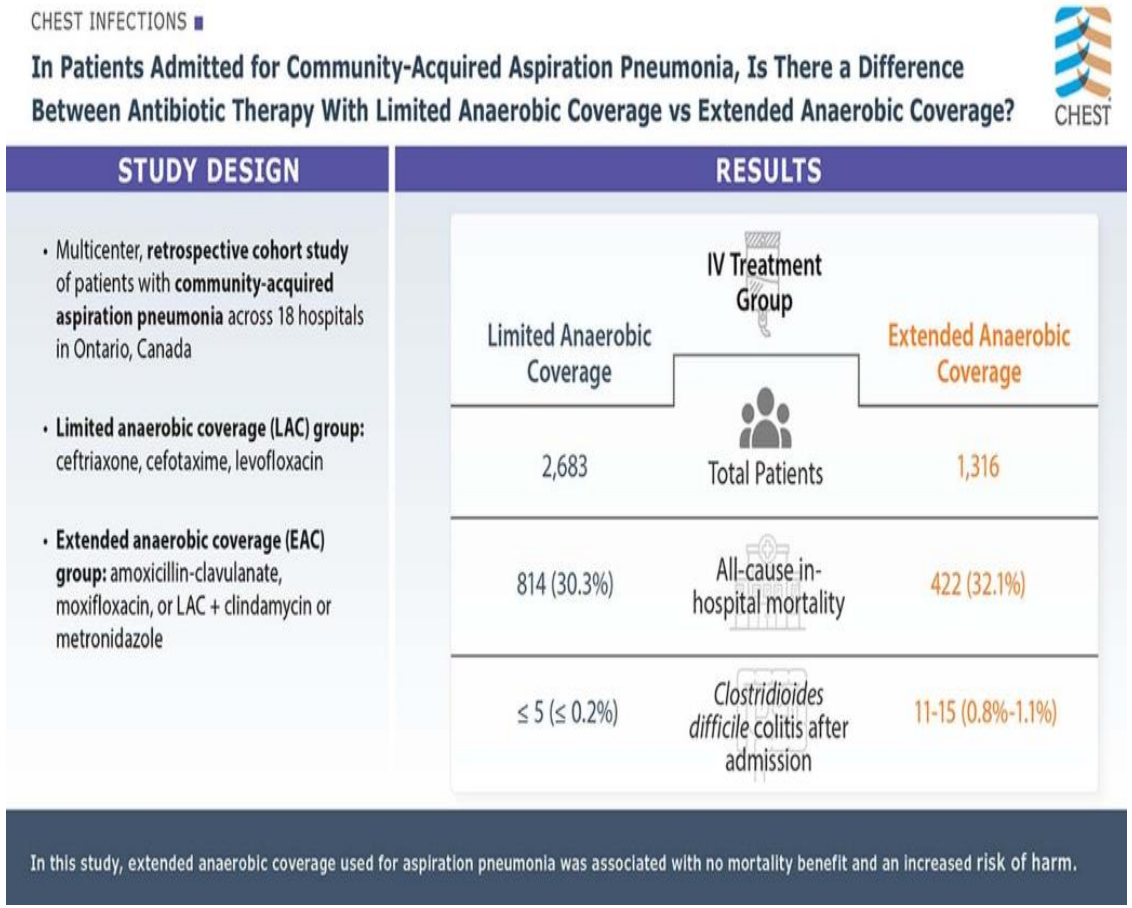
Needs for Precision medicine



BMJ. 2021;375:e065871

Needs for Precision medicine

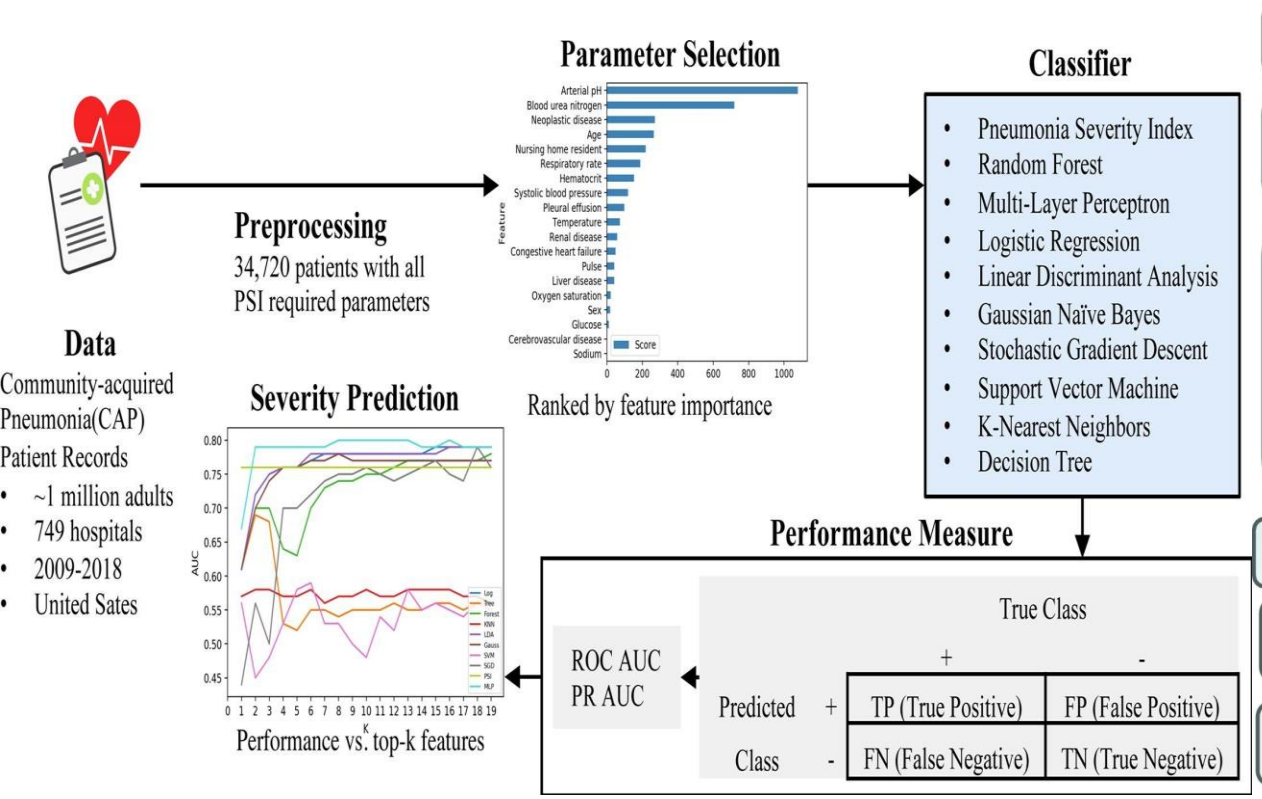


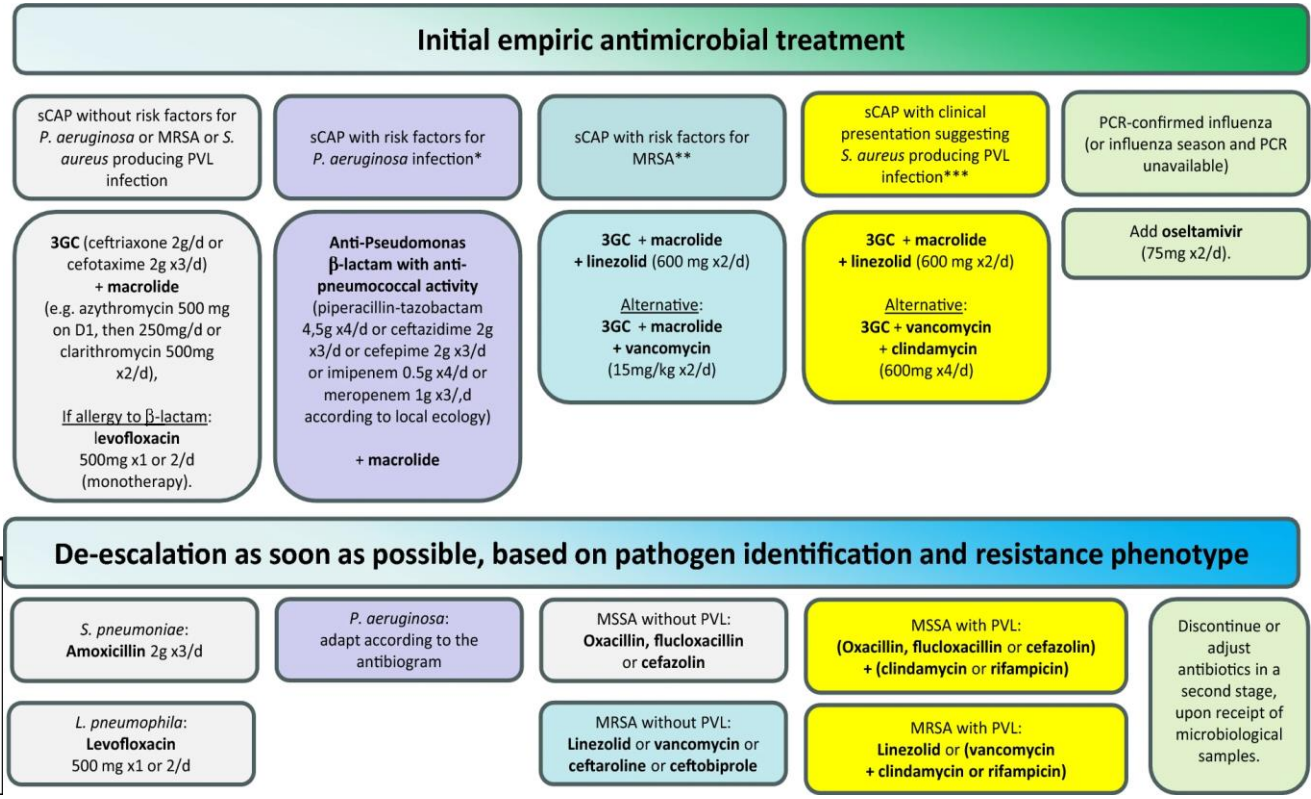


Pneumonia (Nathan). 2026 Feb 25;18(1):4
Chest. 2024;166(1):39-48

Various tip of precise medicine in Pneumonia

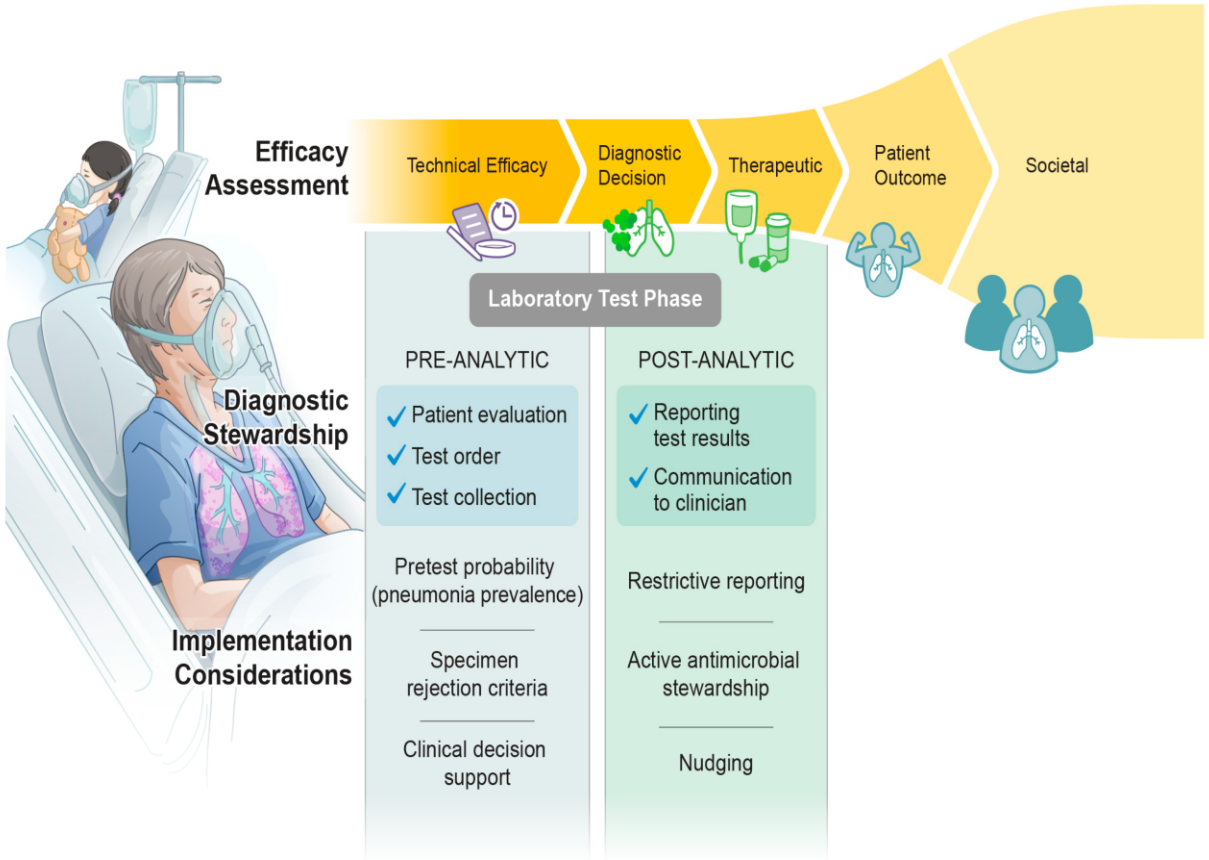
Sx and Sign, Past History, Comorbidity, Prior colonization

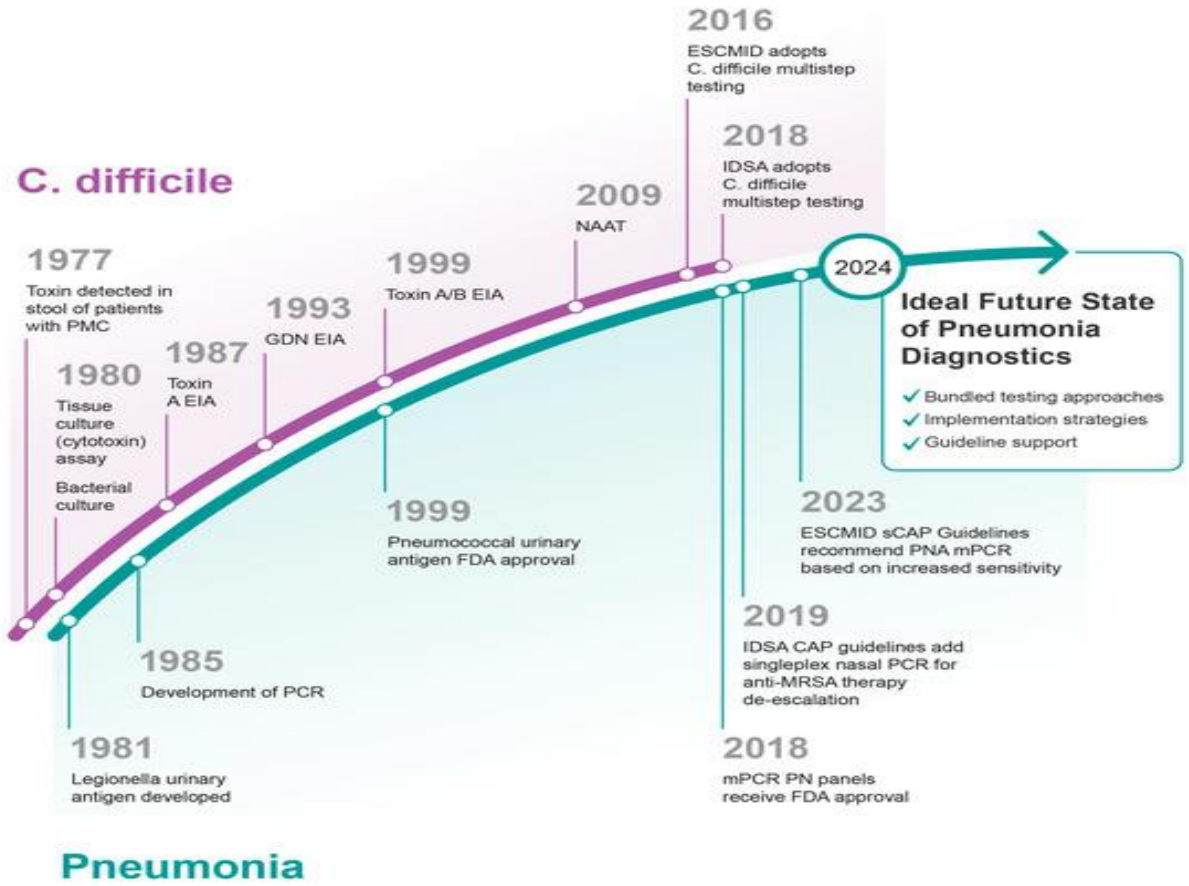




Int J Med Inform. 2022;163:104778
Intensive Care Med **52**, 118–130 (2026)

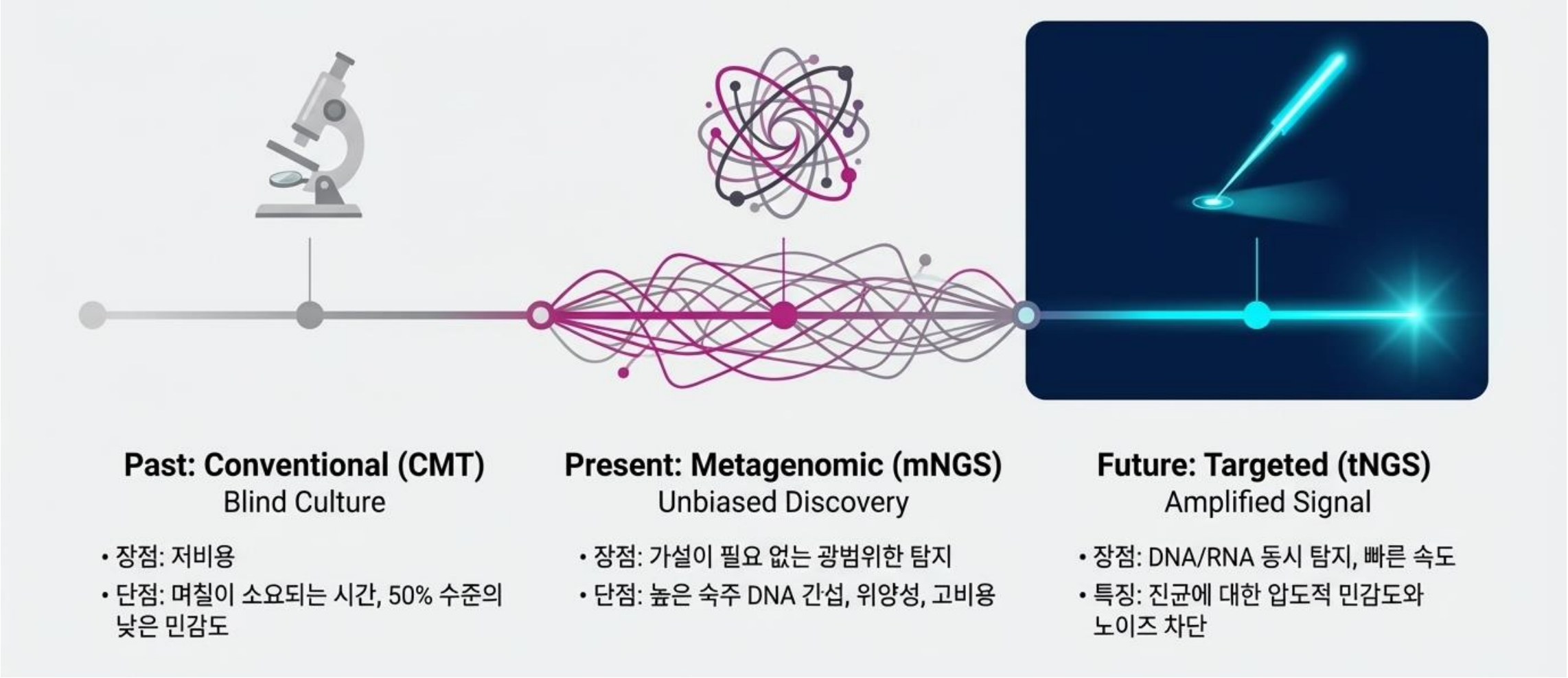
Progression of pneumonia diagnostics efficacy framework





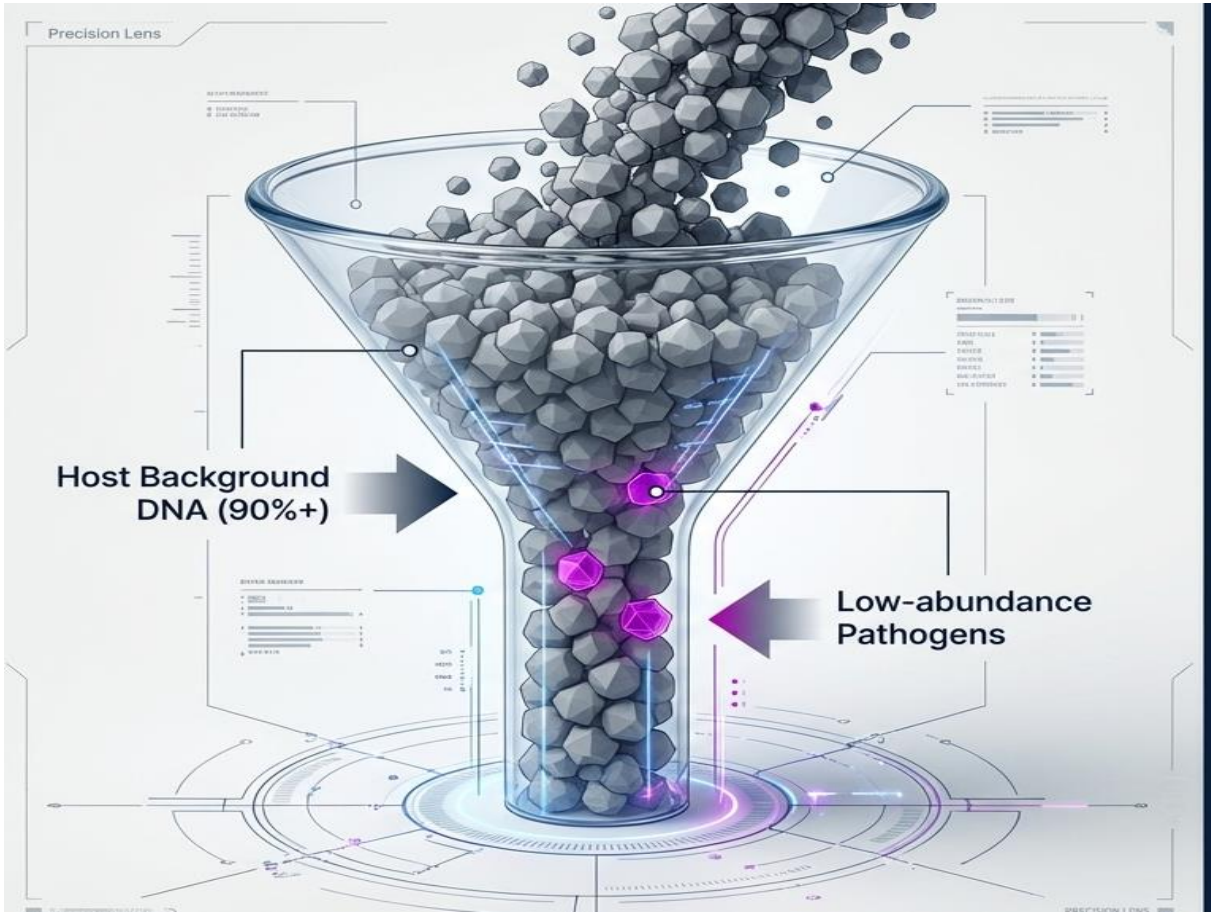
Diagnostics **2024**, *14*(7), 752

Progression of pneumonia diagnostics efficacy framework



Front Microbiol. 2023 Jun 28;14:1186424
Expert Rev Mol Diagn. 2022;22(5):575-582

Progression of pneumonia diagnostics efficacy framework



mNGS의 딜레마: 90%의 숙주 DNA가 병원체 신호를 압도하다

신호 분산의 한계

호흡기 검체(BALF 등)에서 생성되는 압도적인 양의 인간 유래 DNA가 시퀀싱 데이터를 장악합니다.

미량 병원체 누락

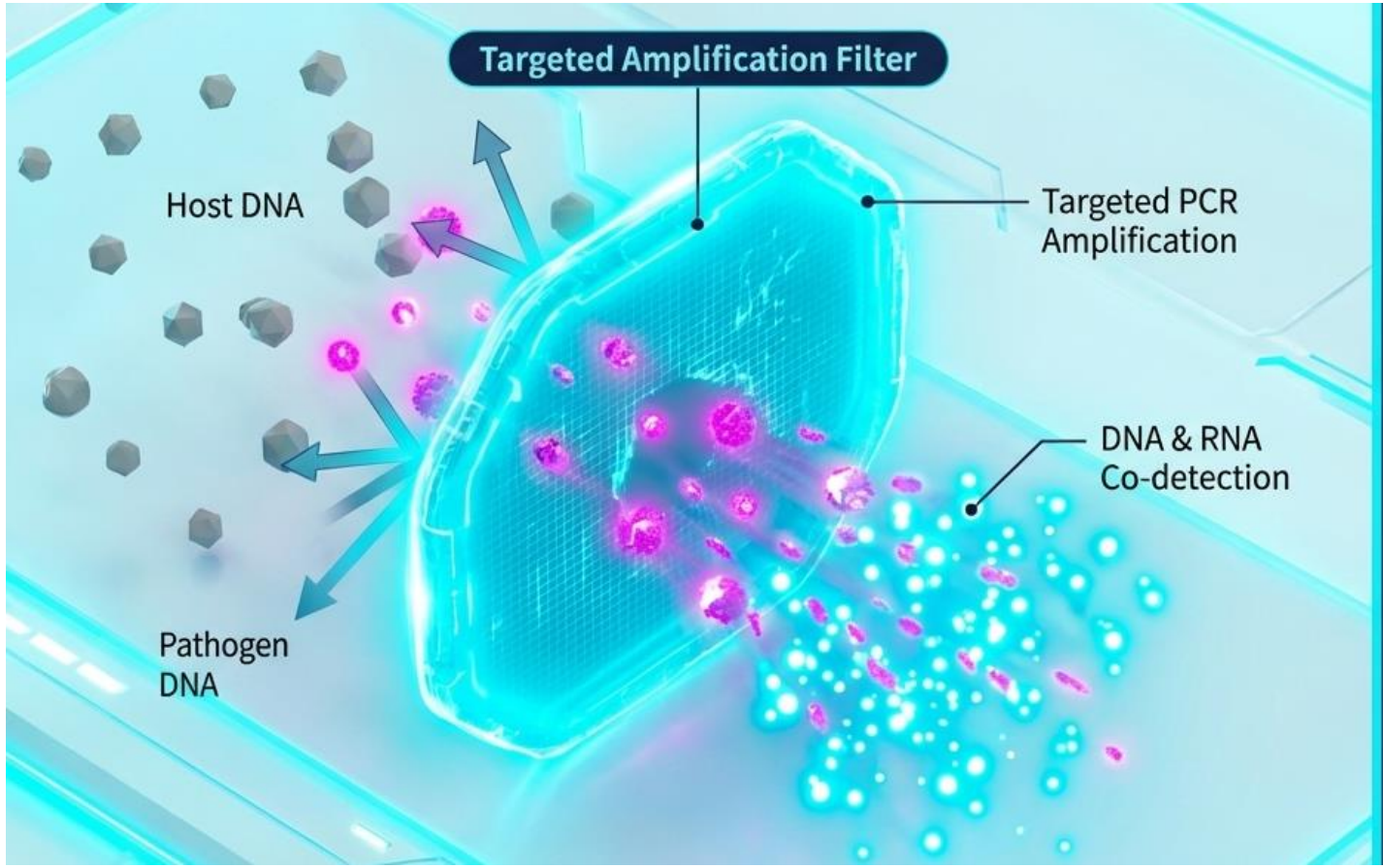
세포 내 병원체(*Mycobacterium* 등)의 미량 세포유리 DNA(cfDNA)는 거대한 숙주 노이즈에 묻혀 검출 임계치를 넘지 못합니다.

핵심 요약

mNGS는 뛰어난 포괄성을 지니지만, 숙주 DNA 비율이 높을 경우 시퀀싱 깊이(Sequencing Depth)가 분산되어 실제 병원체를 놓치는 맹점이 발생합니다.

Front Microbiol. 2023 Jun 28;14:1186424
Expert Rev Mol Diagn. 2022;22(5):575-582

Progression of pneumonia diagnostics efficacy framework



숙주 유전체 원천 차단

초다중(Ultra-multiplex) PCR 증폭을 통해 인간 유전체와 배경 미생물의 간섭을 물리적으로 배제합니다.

단일 프로세스 효율성

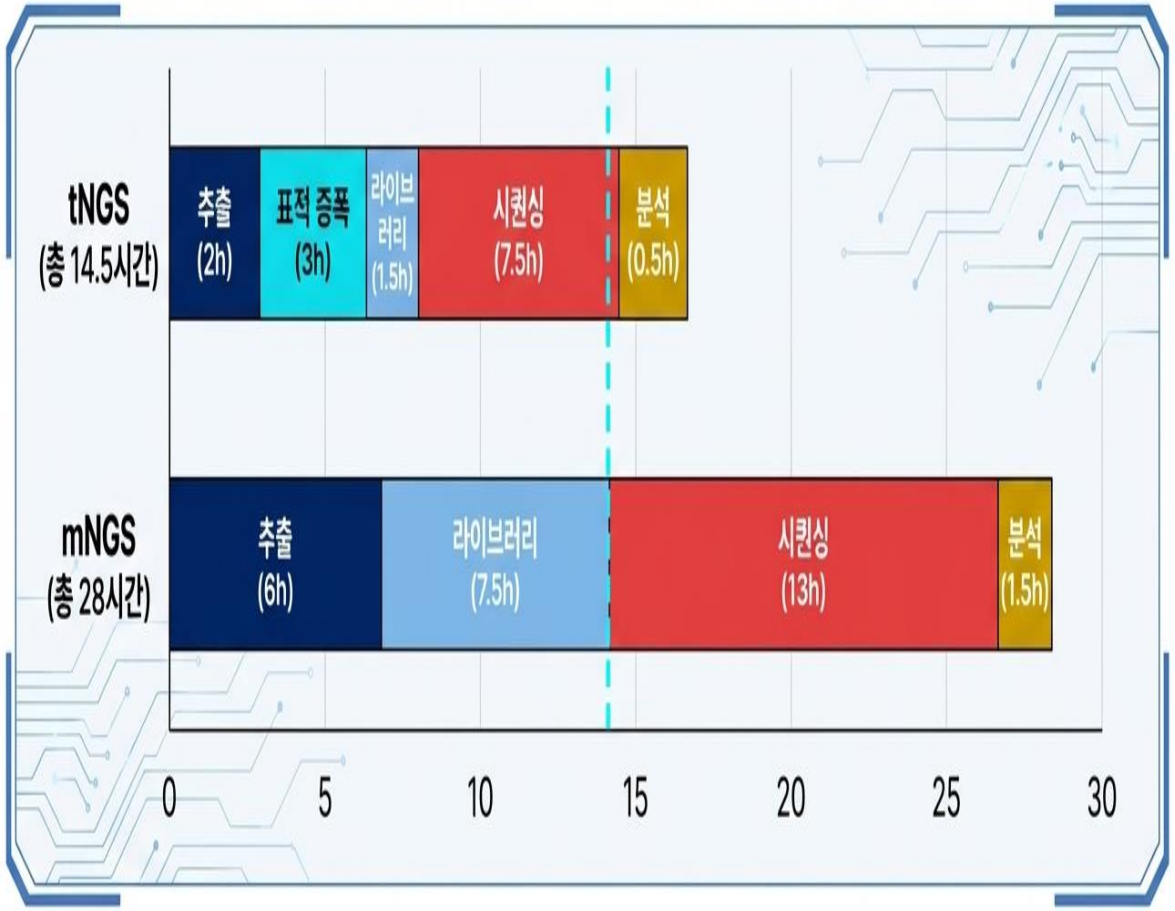
추가 비응과 시간 없이 DNA와 RNA 바이러스를 단일 튜브 프로세스로 동시 검출합니다.

핵심 요약

인간 유전체의 간섭을 차단하여 극미량의 병원체라도 놓치지 않고 수천 배로 증폭시켜 정확하게 식별해냅니다.

Front Microbiol. 2023 Jun 28;14:1186424
Expert Rev Mol Diagn. 2022;22(5):575-582

Progression of pneumonia diagnostics efficacy framework

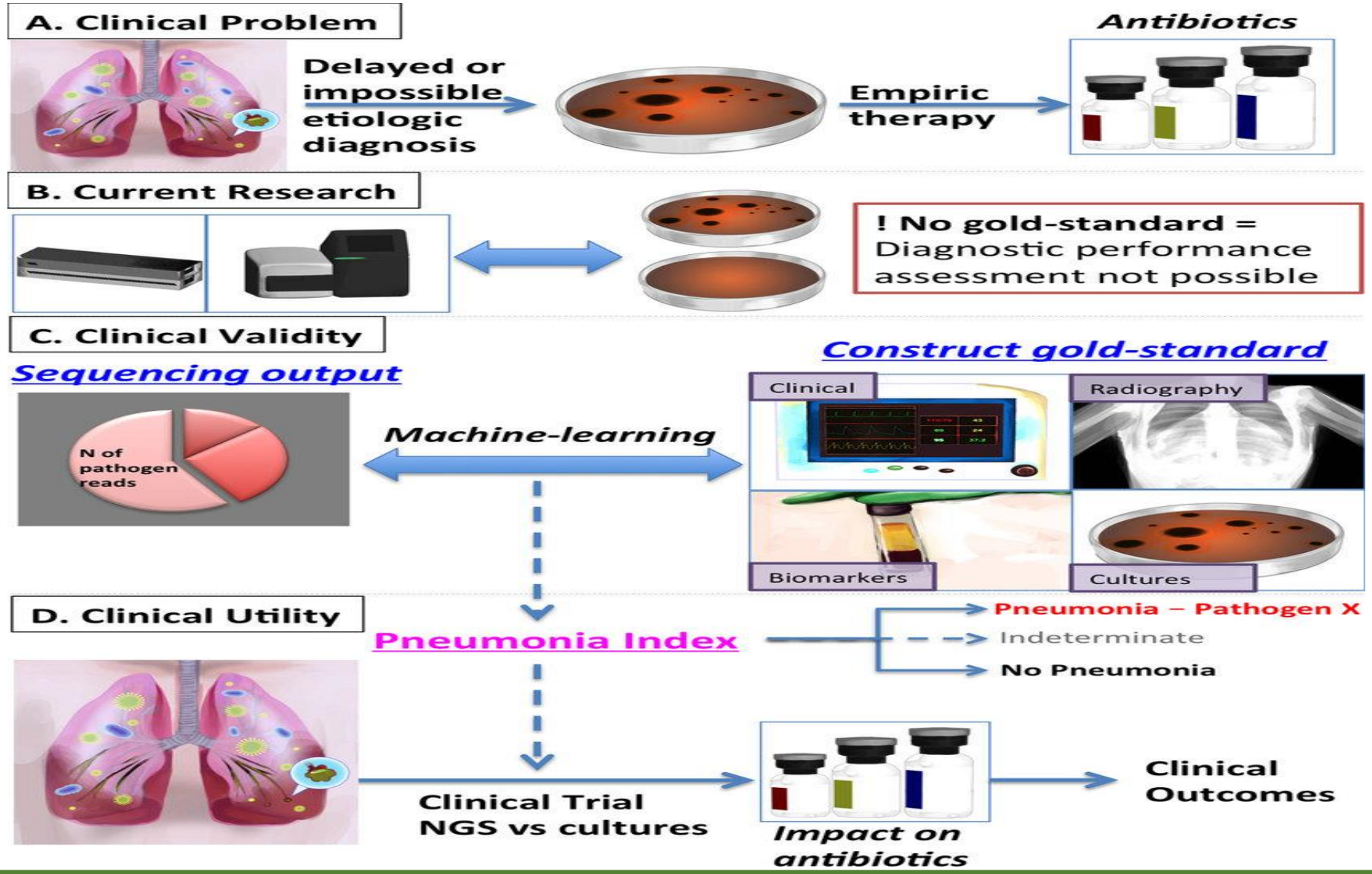


	기존 배양 검사 (CMT)	메타게놈 시퀀싱 (mNGS)	표적 증폭 시퀀싱 (tNGS)
탐지 범위 (Detection Range)	○	●	◑
임상 민감도 (Clinical Sensitivity)	○	◑	●
숙주 DNA 간섭 저항성 (Host DNA Resistance)	N/A	○	●
진균 검출력 (Fungal Efficacy)	○	◑	●
항생제 내성 프로파일 (AMR Profiling)	◑	●	◑
소요 시간 및 비용 효율성 (TAT & Cost)	○	◑	●

꽉 찬 원 = 최고 수준 / 최적, 반 쯤 찬 원 = 우수 / 제한적, 빈 원 = 미흡 / 열위

Front Microbiol. 2023 Jun 28;14:1186424
Expert Rev Mol Diagn. 2022;22(5):575-582

Progression of pneumonia diagnostics efficacy framework



mSystems. 2018 13;3(2):e00153-17

Progression of pneumonia diagnostics efficacy framework

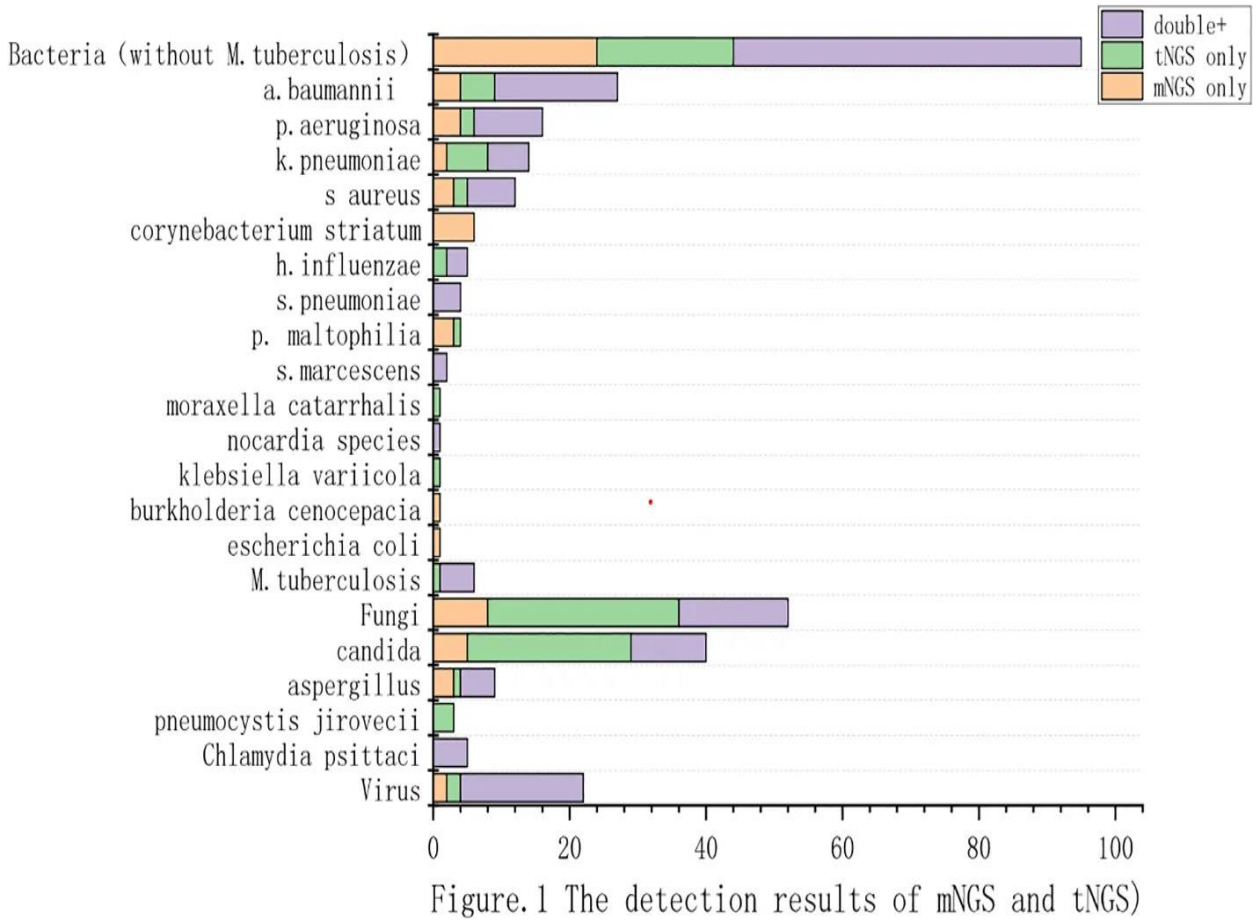
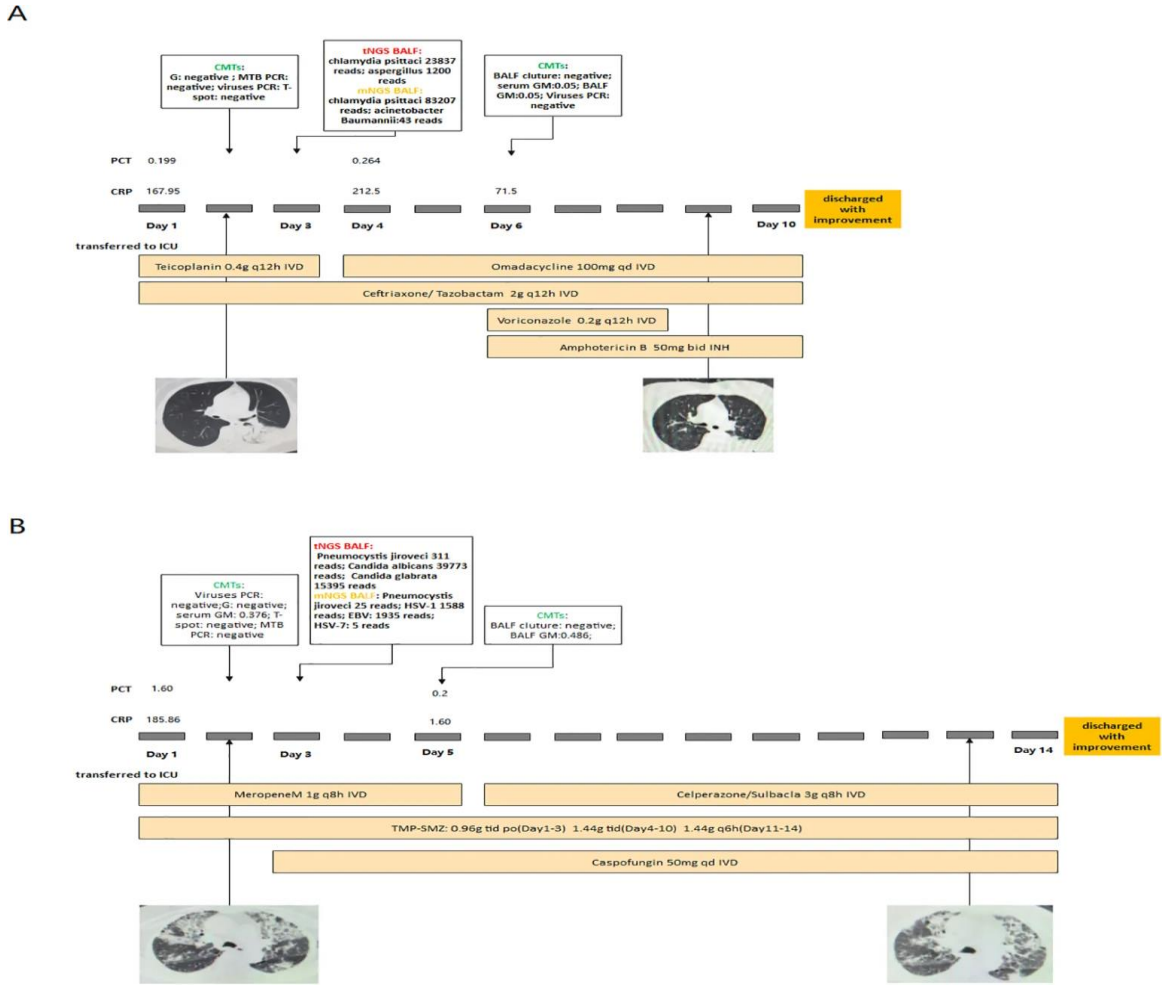
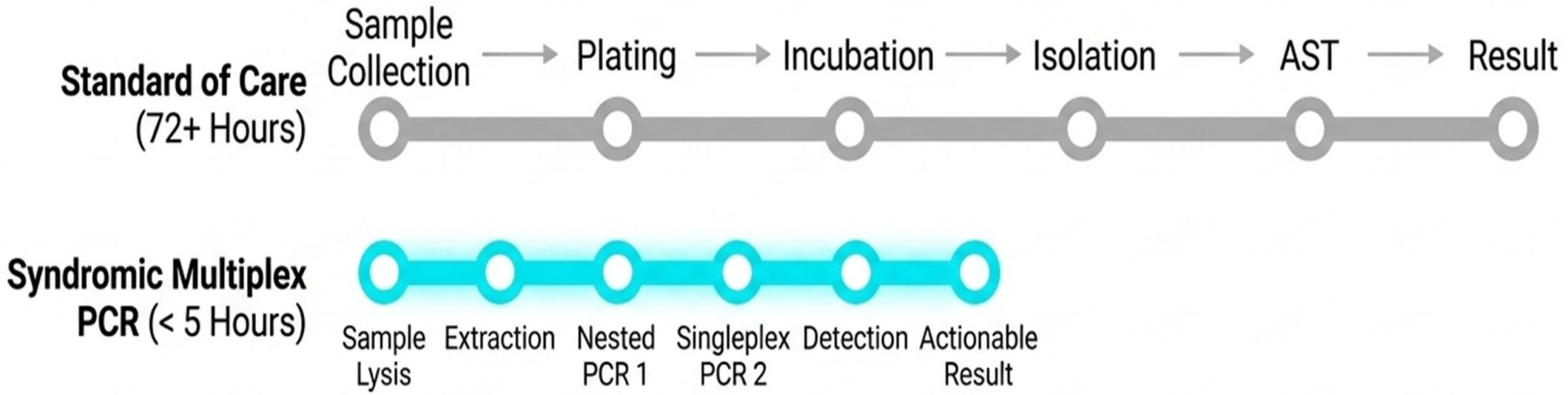


Figure. 1 The detection results of mNGS and tNGS)



Front. Cell. Infect. Microbiol. 15:1578939

The Paradigm Shift: Time to Result Comparison



Key Diagnostic Advantage: Molecular testing bypasses the need for bacterial growth, returning a comprehensive pathogen and resistance profile while the patient is still in the critical early intervention window.

Platform/System

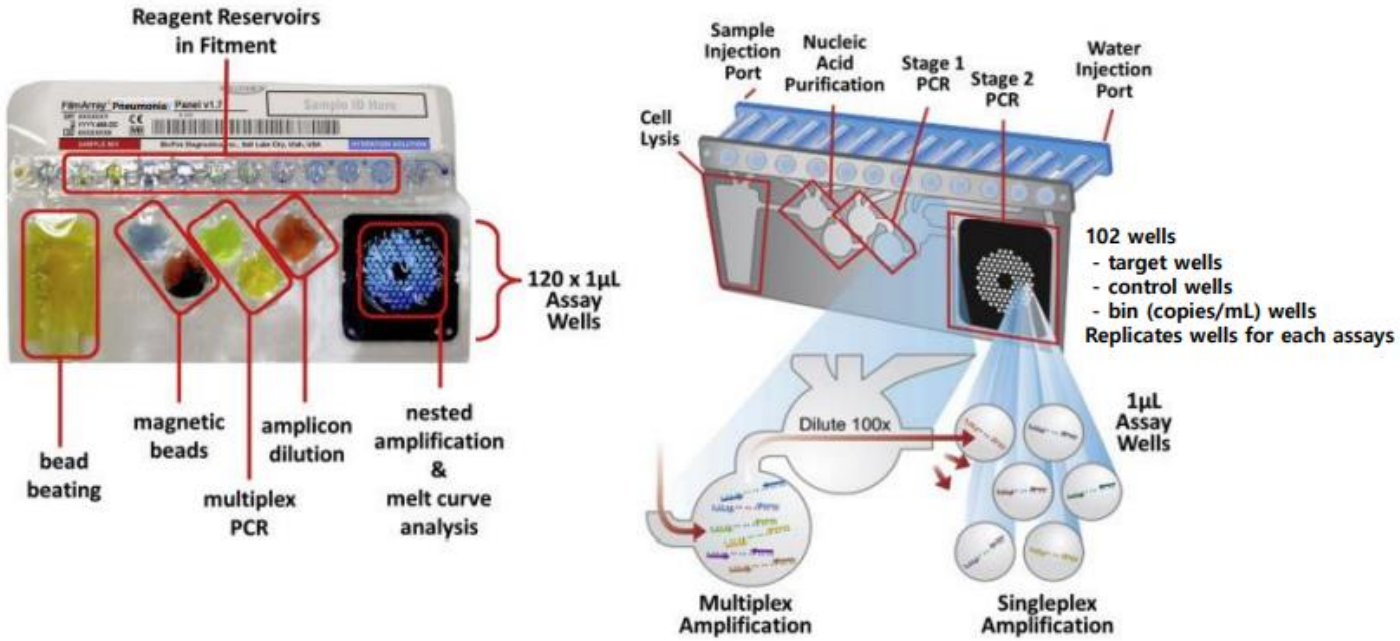
Biofire FilmArray

Cepheid GeneXpert System

Luminex NxTAG Respiratory Pathogen Panel

Unyvero Pneumonia Panel

QIAstat-Dx Respiratory SARS-CoV-2 Panel Cartridge



BIOFIRE® Pneumonia Panel Pouch (Reagent Kit)

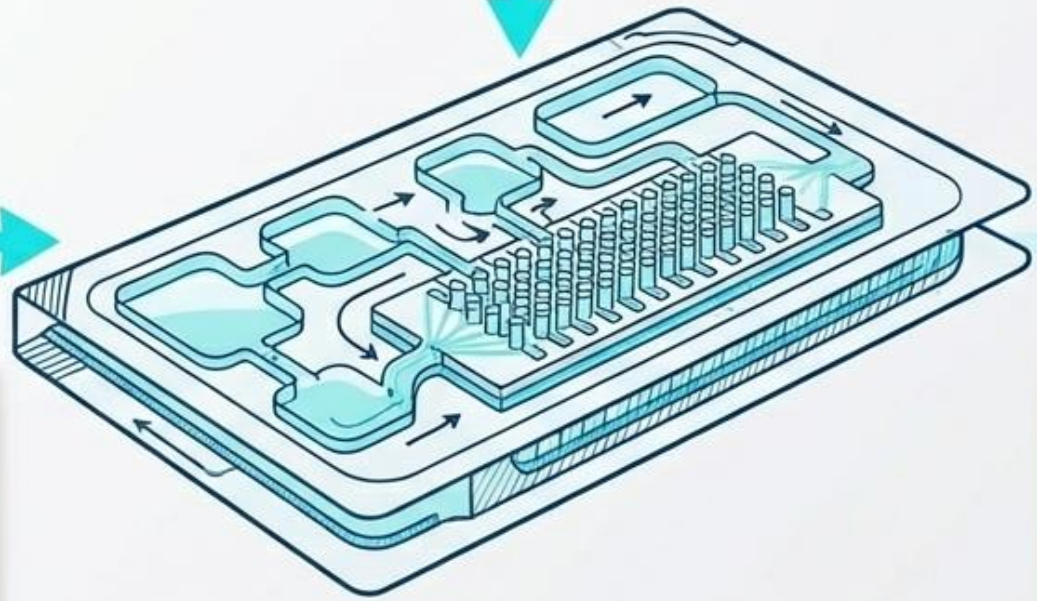
Platform Face-Off: Multiplex Panel

Feature	BioFire FilmArray Pneumonia	Curetis Unyvero (HPN)
Core Technology	Nested Multiplex PCR	Membrane Array Hybridization
Viral Coverage	8 Target Viruses	No Viral Targets
Fungal / Atypical	3 Atypical Bacteria	Includes P. jirovecii
AMR Strategy	7 Transferable Genes	Includes non-transferable gyrA
Reporting Structure	Semi-quantitative (10^4 to 10^7)	Signal intensity bands
E. coli Sensitivity	98.9%	89.6%
K. pneumoniae Sensitivity	98.1%	88.9%

Introducing the Syndromic Approach: BIOFIRE FILMARRAY

Process: Closed-System Automation

1. Lysis via bead beating
2. Magnetic bead extraction
3. Massively-multiplexed RT-PCR 1
4. Singleplex PCR 2 & Melting Curve



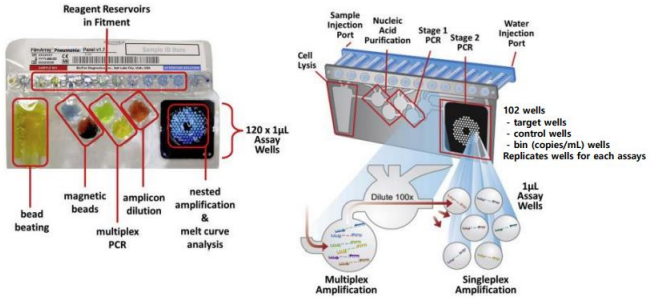
Input: Respiratory Specimens

- **Sputum-like:** Induced, expectorated, endotracheal aspirates (ETA)
- **BAL-like:** Bronchoalveolar lavage (BAL), mini-BAL

Output: Comprehensive Payload

Simultaneous detection of 33 targets from a single specimen, eliminating sequential testing delays.

Microfluidic cartridge 내부 구조



BIOFIRE® Pneumonia Panel Pouch (BIOFIRE® (Reagent Kit)

Wells **여러 개의 작은 홈이 파여 있는 판에서, 각각의 개별적인 실험 공간(작은 용기, 구멍)**을 의미

-102 Wells

1. Target wells: 특정 병원체마다 독립된 PCR 반응이 존재해 검출
2. Replicate well: 신뢰도를 높이기 위해 존재 (false positive/negative 감소, PCR reliability 확보)
3. Control wells: 검사 정확성 확인 (sample processing/PCR/internal control)

-**Bin wells** (정량 정보 제공)

대략적인 균량을 copies/mL 단위로 반정량적으로 보고

Bacterial load	임상적 의미
10^4	colonization 가능성 높음
10^5–10^6	해석 어려움
≥10^7	infection 가능성 높음

Respiratory vs Pneumonia Panel

	Respiratory panel	Pneumonia Panel
Specimen	NP swab (upper)	Sputum/BAL (lower)
Main Target	Virus 대부분 바이러스 중심 + atypical bacteria	Bacteria 세균 중심 + 바이러스 일부
Resistance gene	-	+ (mecA/C (MRSA), CTX-M (ESBL), KPC, NDM, VIM, OXA-48)
Quantitative analysis	-	Semi-quantitative
Reporting time	1시간	1시간

Diagnostic Performance vs. Standard of Care

Positive Percentage Agreement (PPA)

Negative Predictive Value (NPV)

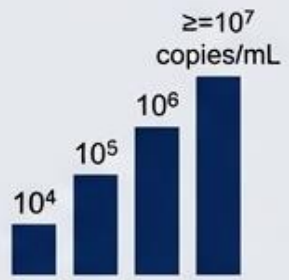
Negative Percentage Agreement (NPA)

The Power of Exclusion

An NPV exceeding 99.6% provides unparalleled clinical confidence to exclude bacterial pneumonia. When typical bacteria are negative and viral targets are positive, clinicians can safely halt broad-spectrum empiric antibiotics.

The Diagnostic Payload: Target Dashboard

15 Typical Bacteria (Semi-Quantitative)



Acinetobacter baumannii complex, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *S. pneumoniae*, and more.

8 Viruses (Qualitative)

Adenovirus, Coronavirus, hMPV, Rhinovirus/Enterovirus, Influenza A, Influenza B, Parainfluenza, RSV.

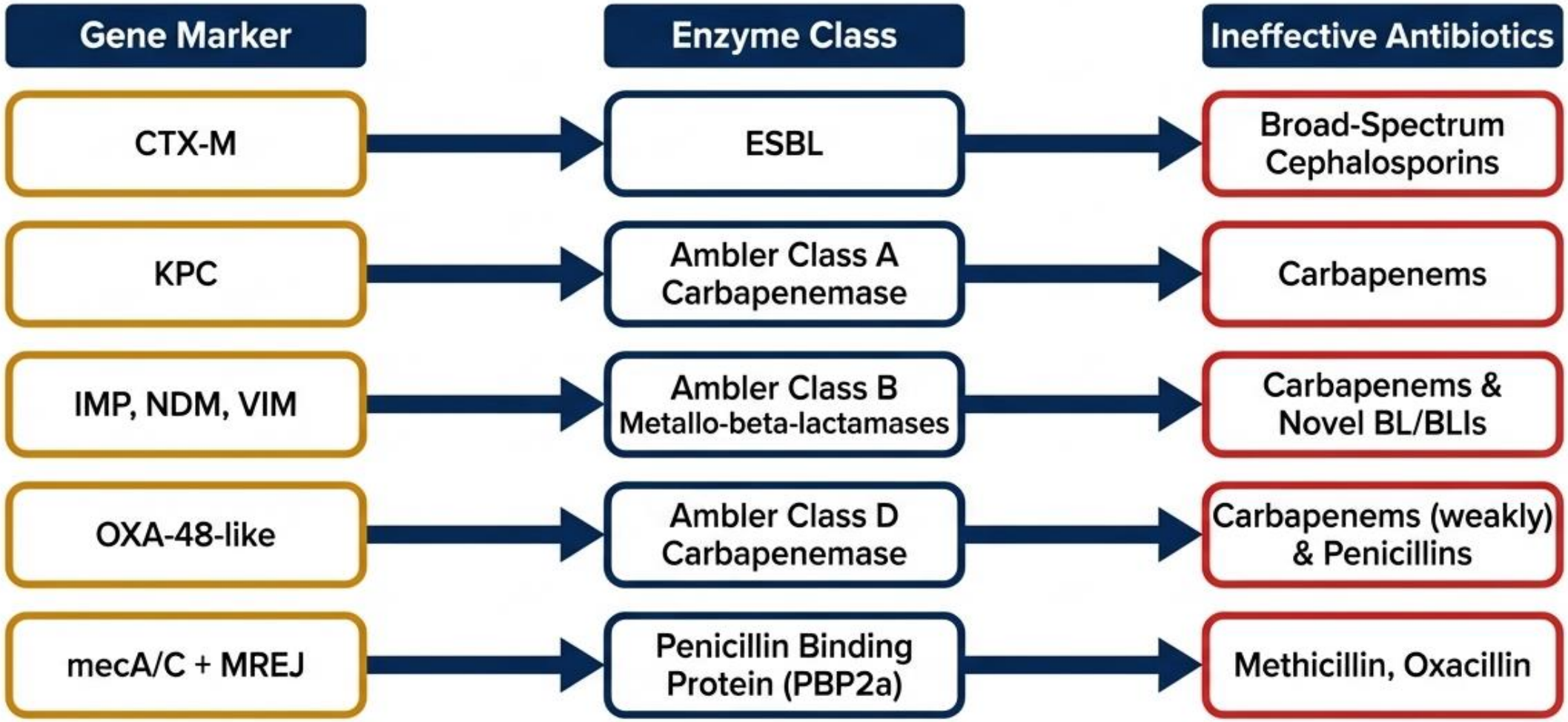
3 Atypical Bacteria (Qualitative)

Chlamydia pneumoniae, *Legionella pneumophila*, *Mycoplasma pneumoniae*.

7 AMR Genes (Qualitative)

CTX-M, IMP, KPC, NDM, OXA-48-like, VIM, *mecA/C* and MREJ.

Decoding Antimicrobial Resistance (AMR)



Clinical Insight: Novel beta-lactam/beta-lactamase inhibitors (e.g., ceftazidime-avibactam) neutralize KPC and OXA-48 but remain ineffective against Metallo-beta-lactamases (NDM/VIM).

Actionable Insights: Bedside Decision Matrix

Scenario 1: Viral Exclusion

Result: Rhinovirus DETECTED, Bacteria NOT DETECTED.

→ **Action:** Safely withhold broad-spectrum antibiotics and halt empiric macrolides.

Scenario 2: Targeted De-escalation

Result: S. pneumoniae DETECTED, mecA/C NOT DETECTED.

→ **Action:** Discontinue empiric MRSA coverage (Vancomycin); step down to targeted amoxicillin.

Scenario 3: Critical Escalation

Result: K. pneumoniae DETECTED, KPC DETECTED.

→ **Action:** Immediately initiate novel therapies (Ceftazidime-avibactam); avoid standard ineffective carbapenems.

The False Positive Paradox

- **Colonization 과 실제 감염을 구분하기 어렵다.**
  - DNA 검출 PCR 기반 검사로 사멸 균도 양성으로 표현
  - 양성 표현: 상기도 colonization/이전 감염 후 잔존 DNA/active infection
  - 특히 문제되는 균주: S aureus, **P aeruginosa, Acinectobacter spp**
  - 특히 문제되는 condition: **bronchiectasis**

The False Positive Paradox

- **객담 검체 질에 크게 영향을 받음**
  - 타액 오염시 구강 세균, 상기도 flora 검출 (+)
  - epithelial cell <10/LPF, neutrophil >25/LPF
  - **PN 의뢰 시 Gram stain + culture 동시 시행이 권고**

The False Positive Paradox

- **반정량 결과 해석이 매우 어려움**
  - Semi-quantitative bin 과 culture CFU가 정확히 일치하지 않음
  - PN panel은 **배양보다 더 높은 균량을 보고하는 경향**

PN panel	의미
10^4	colonization 가능성 높음
10^5–10^6	해석 어려움
≥10^7	infection 가능성 높음

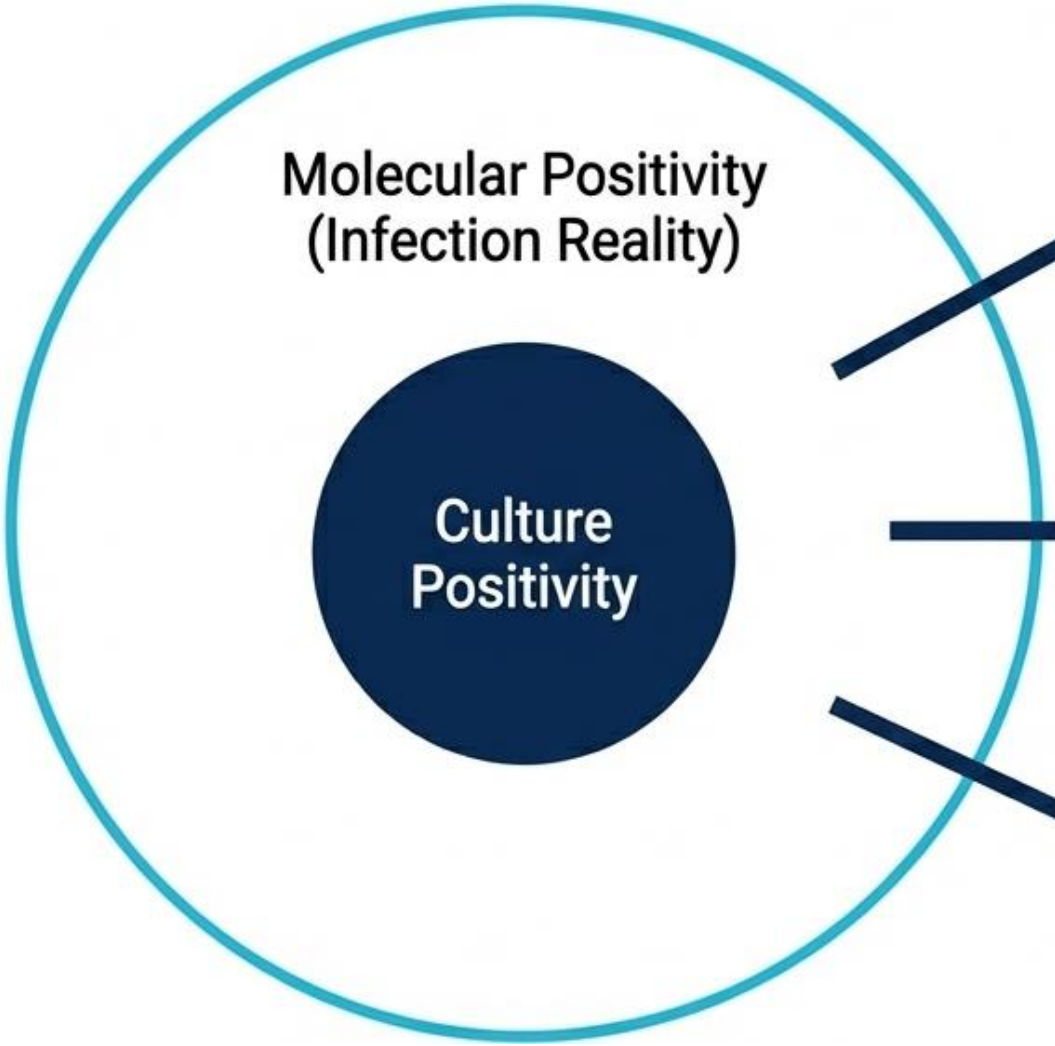
The False Positive Paradox

- **내성 유전자 검출 ≠ 실제 항생제 내성**
  - 유전자 있어도 항상 표현형 내성은 아님: mecA (+)→반드시 MRSA X
  - 유전자 없다고 내성 없는 것도 아님 (다른 내성기전: efflux pump, porin mutation, AmpC overexpression)
  - **최종 항생제 결정은 배양 + AST 기반**

The False Positive Paradox

- **Panel에 없는 병원체는 검출되지 않는다**
  - PN panel=target-based PCR (검사 목록에 있는 병원체만 검출)
  - 검출 불가능 병원체: **Stenotrophomonas maltophilia**, 일부 anaerobe, 일부 fungal pathogen, Nocardia, Mycobacteria
  - **PN panel negative≠ infection 없음**

The False Positive Paradox



Driver 1: Prior Antibiotics

Nearly 50% of culture-negative/PCR-positive results occur because patients received targeted **antibiotics within 72 hours prior** to sampling, neutralizing the culture but leaving pathogen DNA.

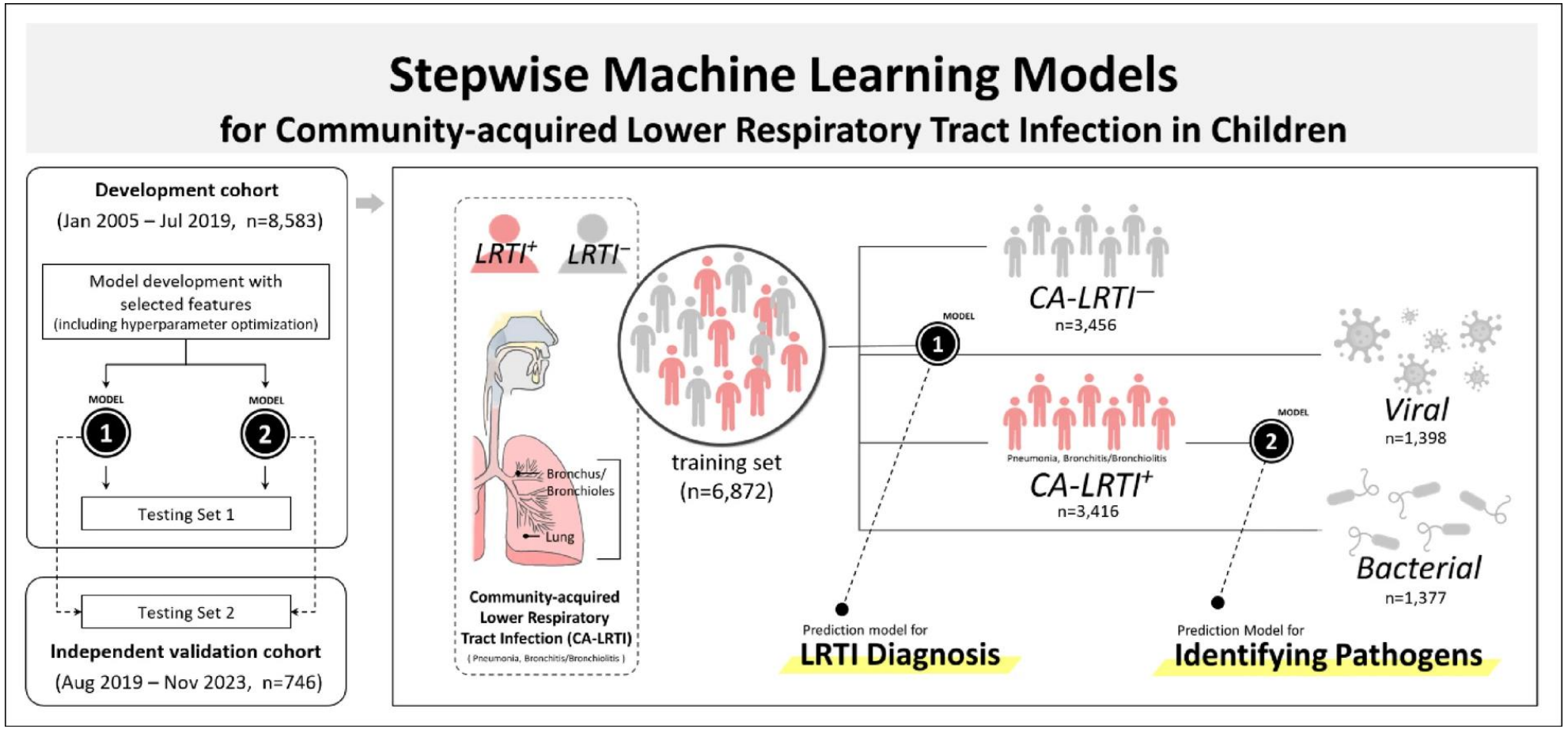
Driver 2: The VBNC State

Clinical stress forces bacteria into a **'Viable But Non-Culturable'** dormant state. They escape traditional plating while retaining severe virulence.

Driver 3: Fastidious Organisms

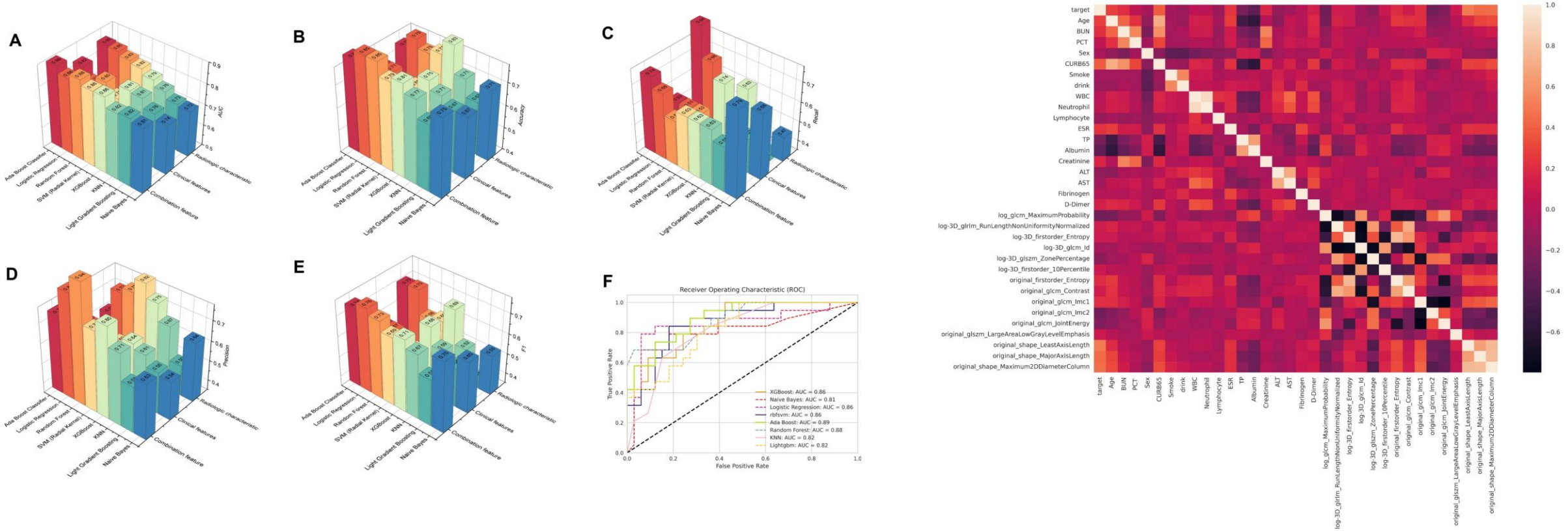
Pathogens outcompeted by normal flora or requiring highly specialized growth conditions are easily missed by standard microbiological protocols.

Machine learning and CDSS



Sci Rep **15**, 41710 (2025)

Machine learning and CDSS



Sci Rep **14**, 21884 (2024)

Take Home Message

- **Pneumonia diagnosis should not rely solely on pathogen identification.**

  → There are significant limitations such as time delay, colonization vs infection issues, and reduced accuracy after antibiotic use.

- **Host phenotype and immune response must be considered.**

  → Hyper- and hypo-inflammatory states influence prognosis and treatment response.

- **Rapid molecular diagnostics are helpful, but careful interpretation is essential.**

  → Results can reflect colonization, dead organisms, or unclear bacterial load.

- **Precision medicine requires an integrated approach.**

  → **Clinical features, microbiology, and host response** should all be combined.

- **Final treatment decisions should still be guided by clinical judgment and culture-based results.**

울산대학교병원
ULSAN UNIVERSITY HOSPITAL

Thank you for your attention

ULSAN
UNIVERSITY
HOSPITAL