

# UMETNA INTELIGENCA V MIKROBIOLOGIJI

---

Polona Maver Vodičar, Anja Šterbenc Železnik, Tina Triglav

Inštitut za mikrobiologijo in imunologijo,

Medicinska fakulteta, Univerza v Ljubljani

Likarjev simpozij 2024

# Internet v 90-ih

## **Robert Metcalfe, in *InfoWorld*, 1995:**

---

“I predict the Internet will soon go spectacularly supernova and in 1996 catastrophically collapse.”

---

Just five years in to the web's public availability, Robert Metcalfe, the inventor of Ethernet, gave the whole thing a 12-month life expectancy. Still, he ate his words just two years later when, during the sixth International World Wide Web Conference in 1997, he blended a copy of his column with some water and then consumed the resultant smoothie with a spoon.

# Time to 100 Million Users



Chat GPT

2 months



9 months



Instagram

2.5 years



Snapchat

3 years



WhatsApp

3.5 years

facebook

4 years



5 years



6 years

NETFLIX

10 years

# Mesto UI v diagnostični mikrobiologiji

## SLIKOVNE ANALIZE

## PREDVIDEVANJE ODPORNOSTI



Mikroskopiranje



Kultivacija



Testiranje  
občutljivosti



MALDI-TOF MS

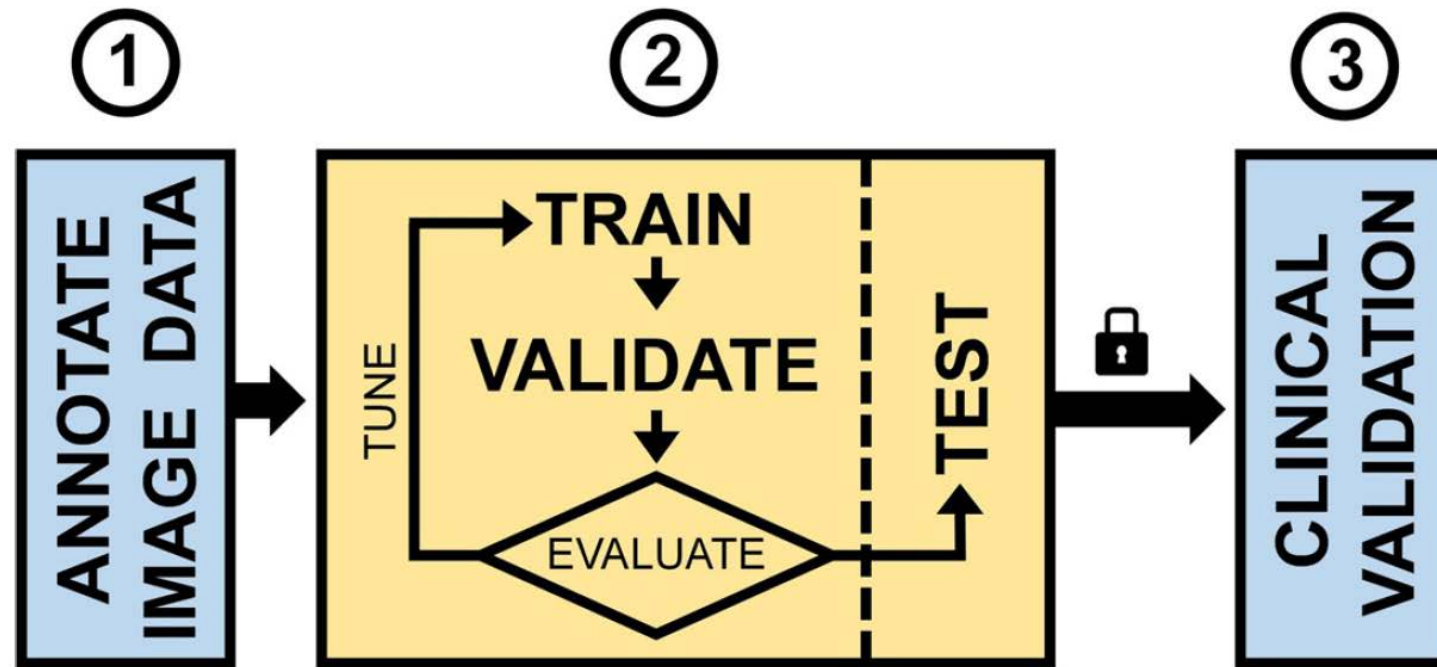


Sekvenciranje

ANALIZA MASNIH  
SPEKTROV

ANALIZA SEKVENC

# Mesto UI v diagnostični mikrobiologiji





# Interpretacija slikovnih podatkov - mikroskopiranje



# Automated Interpretation of Blood Culture Gram Stains by Use of a Deep Convolutional Neural Network

Kenneth P. Smith,<sup>a,b</sup> Anthony D. Kang,<sup>a,b,c</sup> James E. Kirby<sup>a,b</sup>

J Clin Microbiol 2018.

- 25.488 preparatov gramskih razmazov pozitivnih hemokultur, 100.213 slik
- Brez predhodnega pregleda glede primernosti za avtomatizirano mikroskopijo (variabilnost obarvanja, artefakti, porazdelitev)

## → 4 kategorije

- Gr+ KOKI v skupinah
- Gr+ KOKI v verižicah
- Gr- BACILI
- OZADJE

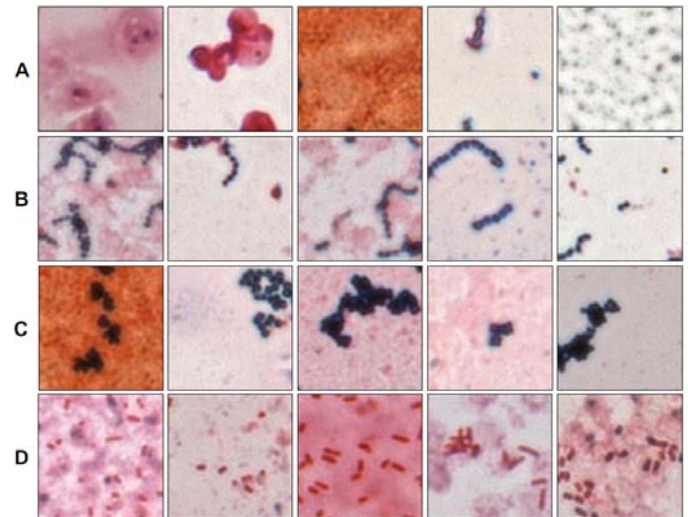


FIG 4 Automatically classified crops. Each image represents a correctly classified crop that was automatically extracted from an image during whole-slide classification. Rows of images represent (A) background, (B) Gram-positive chains/pairs, (C) Gram-positive clusters, or (D) Gram-negative rods. One practical application of the platform would be to present such organism-enriched images to a technologist to expedite smear review.

# Automated Interpretation of Blood Culture Gram Stains by Use of a Deep Convolutional Neural Network

Kenneth P. Smith,<sup>a,b</sup> Anthony D. Kang,<sup>a,b,c</sup> James E. Kirby<sup>a,b</sup>

J Clin Microbiol 2018.

- Natančnost pri testnem setu: 94.9%, ROC analiza krivulje 0.98
- Uporaba na 189 novih preparatih brez človeške intervencije:

**TABLE 1** Confusion matrix of whole-slide classification results

Human classification	Predicted classification ( <i>n</i> )				% sensitivity (CI) <sup>a</sup>	% specificity (CI) <sup>a</sup>
	Gram negative	Gram-positive pairs or chains	Gram-positive clusters	Background		
Gram negative	51	1	0	17	98.1 (94.3–100)	96.3 (93.7–98.9)
Gram-positive pairs or chains	3	27	6	4	75.0 (60.9–89.0)	98.4 (90.8–100)
Gram-positive clusters	1	1	70	8	97.2 (93.4–100)	93.2 (89.7–96.6)

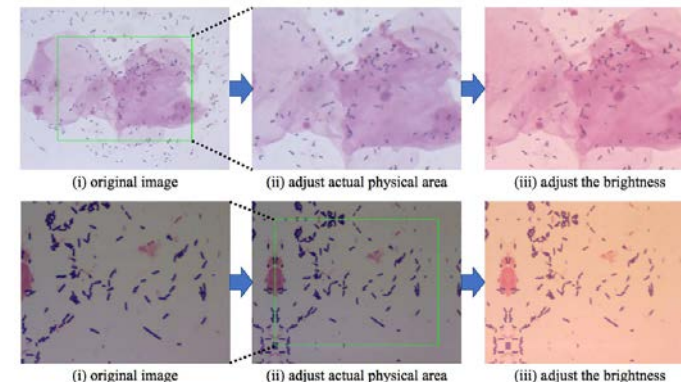
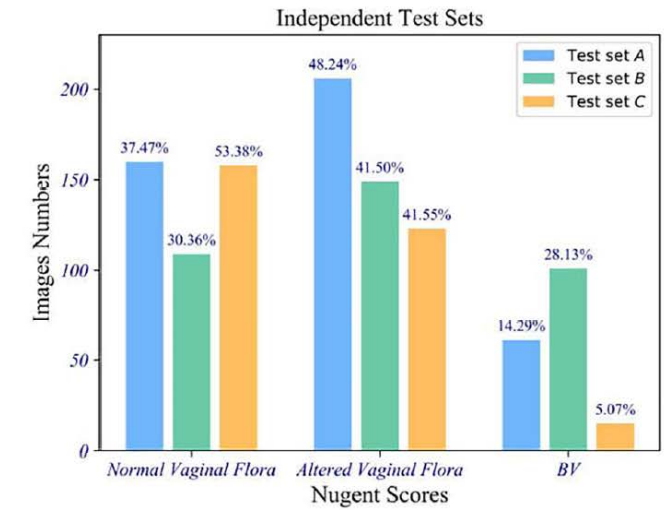
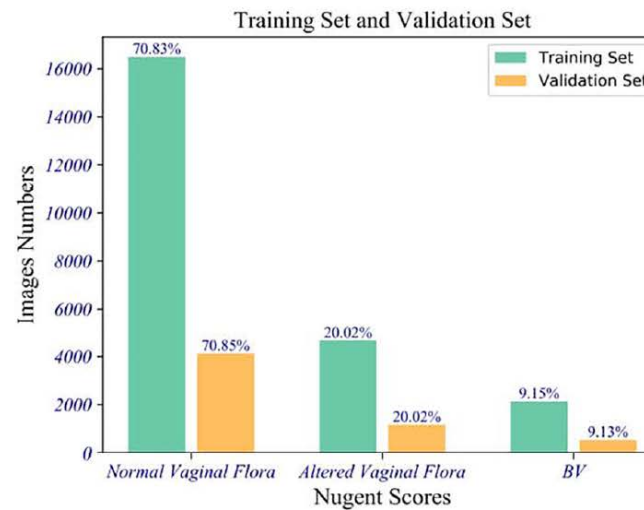
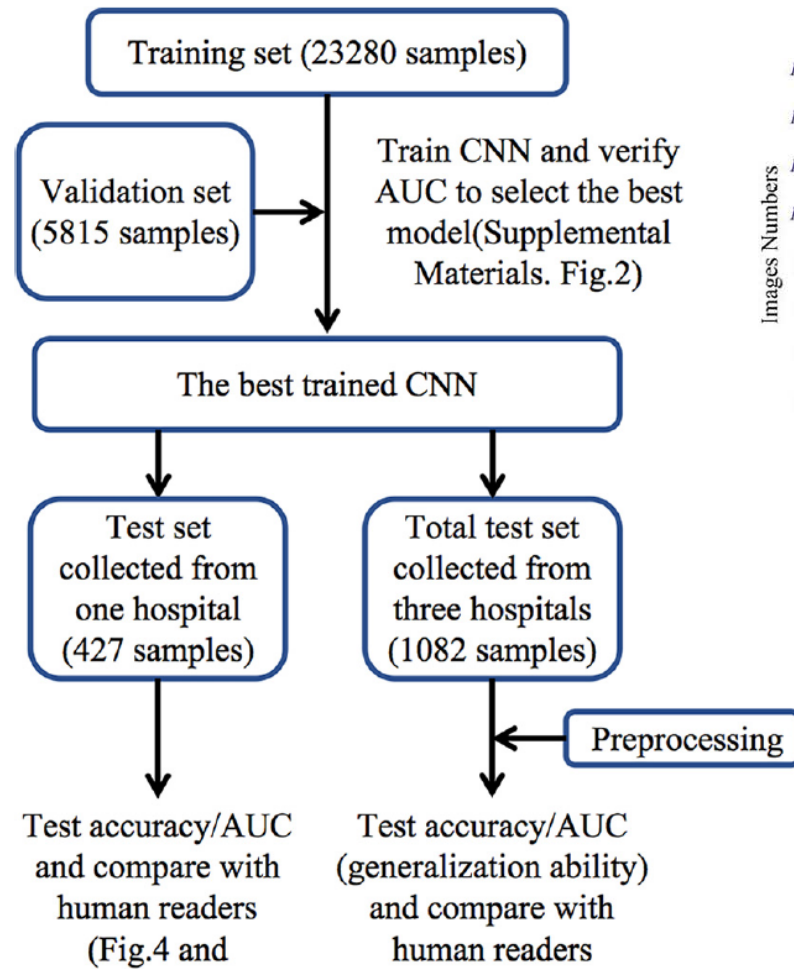
<sup>a</sup>Data were determined based on slides where bacteria were detected. CI, 95% confidence interval.



# Deep Neural Networks Offer Morphologic Classification and Diagnosis of Bacterial Vaginosis



J Clin Microbiol 2021; 59: e02236-20

✉ Zhongxiao Wang,<sup>b</sup> Lei Zhang,<sup>a</sup> Min Zhao,<sup>h</sup> Ying Wang,<sup>a</sup> Huihui Bai,<sup>g</sup> Yufeng Wang,<sup>a</sup> Can Rui,<sup>i</sup> Chong Fan,<sup>i</sup> Jiao Li,<sup>j</sup> Na Li,<sup>j</sup> Xinhuan Liu,<sup>k</sup> Zitao Wang,<sup>f</sup> Yanyan Si,<sup>n</sup> Andrea Feng,<sup>m</sup> Mingxuan Li,<sup>c,d</sup> ✉ Qiongqiong Zhang,<sup>a,q</sup> Zhe Yang,<sup>o</sup> Mengdi Wang,<sup>l</sup> Wei Wu,<sup>c,d</sup> Yang Cao,<sup>c,d</sup> Lin Qi,<sup>e</sup> Xin Zeng,<sup>i</sup> Li Geng,<sup>k</sup> Ruifang An,<sup>j</sup> Ping Li,<sup>i</sup> Zhaohui Liu,<sup>g</sup> Qiao Qiao,<sup>f</sup> Weipei Zhu,<sup>e</sup> Weike Mo,<sup>c,d,p</sup> Qinping Liao,<sup>a,q</sup> Wei Xu<sup>b</sup>



# Deep Neural Networks Offer Morphologic Classification and Diagnosis of Bacterial Vaginosis

J Clin Microbiol 2021; 59: e02236-20

 Zhongxiao Wang,<sup>b</sup> Lei Zhang,<sup>a</sup> Min Zhao,<sup>h</sup> Ying Wang,<sup>a</sup> Huihui Bai,<sup>g</sup> Yufeng Wang,<sup>a</sup> Can Rui,<sup>i</sup> Chong Fan,<sup>i</sup> Jiao Li,<sup>j</sup> Na Li,<sup>j</sup> Xinhuan Liu,<sup>k</sup> Zitao Wang,<sup>f</sup> Yanyan Si,<sup>n</sup> Andrea Feng,<sup>m</sup> Mingxuan Li,<sup>c,d</sup>  Qiongqiong Zhang,<sup>a,q</sup> Zhe Yang,<sup>o</sup> Mengdi Wang,<sup>l</sup> Wei Wu,<sup>c,d</sup> Yang Cao,<sup>c,d</sup> Lin Qi,<sup>e</sup> Xin Zeng,<sup>i</sup> Li Geng,<sup>k</sup> Ruifang An,<sup>j</sup> Ping Li,<sup>i</sup> Zhaohui Liu,<sup>g</sup> Qiao Qiao,<sup>f</sup> Weipei Zhu,<sup>e</sup> Weike Mo,<sup>c,d,p</sup> Qinping Liao,<sup>a,q</sup> Wei Xu<sup>b</sup>


**TABLE 1** Results of the best model and five human readers for the total independent test set with 1,082 samples<sup>a</sup>

Method or reader	No. of samples with Nugent score:				Sensitivity (%)	Specificity (%)	Three-category accuracy (%)
	0–3 (negative)	4–10 (positive)	4–6	7–10			
Gold standard	427	655	478	177	NA	NA	NA
Best point (AI)	363	583	356	94	89.0	85.0	75.1
High sensitivity (AI)	296	637	379	94	97.3	69.3	71.1
Technologist 1	256	635	338	140	97.0	60.0	67.8
Technologist 2	260	624	335	135	95.3	60.9	67.5
Technologist 3	280	637	342	139	97.3	65.6	70.3
Obstetrician 1	401	618	375	99	94.4	93.9	80.9
Obstetrician 2	396	592	359	96	90.4	92.7	78.7
Avg (technologists)	265.3	632	338.3	138	96.5	62.2	68.5
Avg (human readers)	318.6	621.2	349.8	121.8	94.9	74.6	73.0

<sup>a</sup>“Best point” refers to maximizing the sum of sensitivity and specificity; “high sensitivity” refers to setting sensitivity equal to the best result of human readers; AI is our best model; NA is 100%.

# Evaluation of MetaSystems Automated Fluorescent Microscopy System for the Machine-Assisted Detection of Acid-Fast Bacilli in Clinical Samples

J Clin Microbiol 2022; 60: e0113122.

Gianna Tomasello,<sup>a</sup> Farnaz Foroughi,<sup>a</sup> Danielle Padron,<sup>a</sup> Angel Moreno,<sup>b</sup>  Niaz Banaei<sup>a,b,c</sup>

- Preparati, barvani z avraminom
  - 133 kultura pozitivni
  - 363 kultura negativni
- NEON Metafer AFB Module, MetaSystems Mycobacteria Scanner

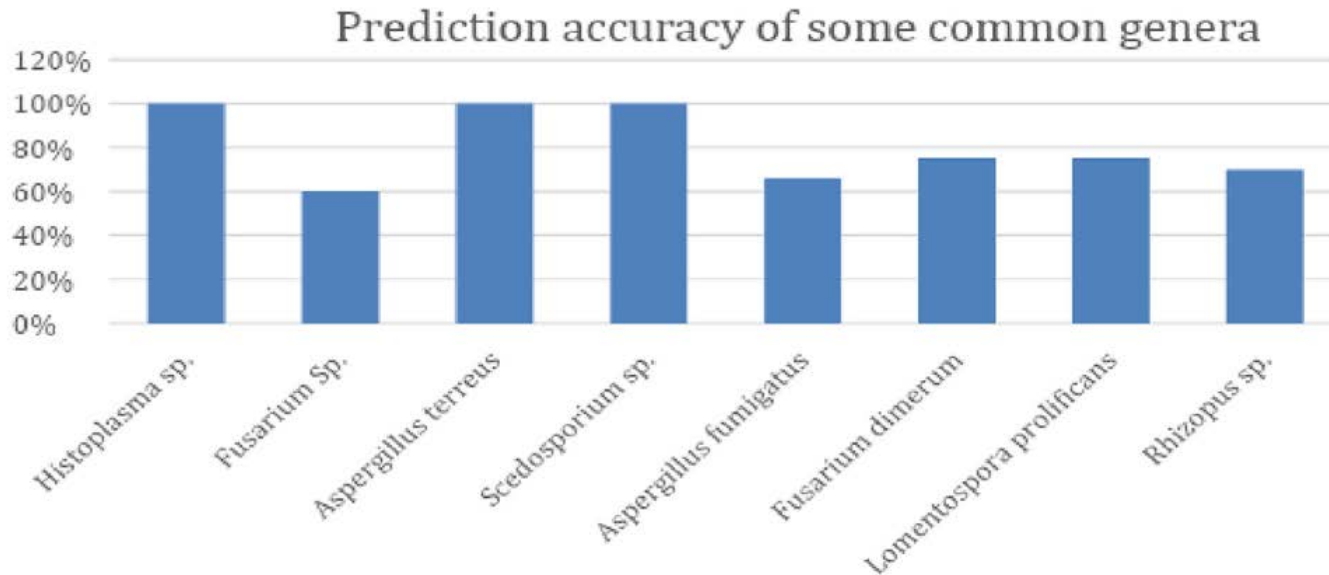
**TABLE 1** Performance of MetaSystems automated AFB microscopy

Microscopy method evaluated	Reference standard	
	Culture	
	Sensitivity (n <sup>a</sup> /N <sup>b</sup> ; 95% CI)	Specificity (n/N; 95% CI)
Manual	79.7% (106/133; 71.9–86.2)	98.6% (358/363; 96.8–99.6)
MetaSystems automated	97.0% (129/133; 92.5–99.2)	12.7% (46/363; 9.4–16.5)
MetaSystems automated assisting CLS	70.7% (94/133; 62.2–78.3)	89.0% (323/363; 85.3–92.0)

## Classification of fungal genera from microscopic images using artificial intelligence

Md Arafatur Rahman <sup>c,d</sup>, Madelyn Clinch <sup>c,e</sup>, Jordan Reynolds <sup>a</sup>, Bryan Dangott <sup>a,c</sup>, Diana M. Meza Villegas <sup>a,b</sup>, Aziza Nassar <sup>a</sup>, D. Jane Hata <sup>a,b</sup>, Zeynetin Akkus <sup>a,c,\*</sup>

J Pathol Inform. 2023.



Učenje 6 obstoječih CNN, vključenih 89 glivnih rodov (1079 slik)



3 faze: učenje, validacija, testiranje v razmerju 7:1:2

- Slabša celokupna napovedna natančnost predvsem zaradi majhnega števila slik redkejših glivnih rodov, boljši rezultati za pogostejše patogene (več slik!)
  - Zvišanje napovedne natančnosti za 10% v primeru obogatitve baze podatkov
- Najbolj učinkovit CNN model = DenseNet s celokupno natančnostjo 65,35% za 1 najboljšo napoved in 75,19% za 3 najboljše napovedi



# Automated detection of superficial fungal infections from microscopic images through a regional convolutional neural network

Taehan Koo<sup>1</sup>, Moon Hwan Kim<sup>2</sup>, Mihn-Sook Jue<sup>1\*</sup>

PLoS One. 2021;16(8):e0256290.

Učenje CNN YOLO v4 na mikroskopskih slikah (100- in 40-kratna povečava) s KOH obdelanih vzorcev kože in nohtov za detekcijo hif

- 1.255 slik v učnem naboru
- 1.645 slik v testnem naboru

Model poda interpretacijo (poz/neg) in s pravokotnikom označi predel preparata, kjer se nahaja hifa → možnost pregleda

Občutljivost in specifičnost (100x): 95,2% in 100%  
Občutljivost in specifičnost (40x): 99% in 86,6%  
Skupna občutljivost in specifičnost (100+40x): 93,2% in 89%

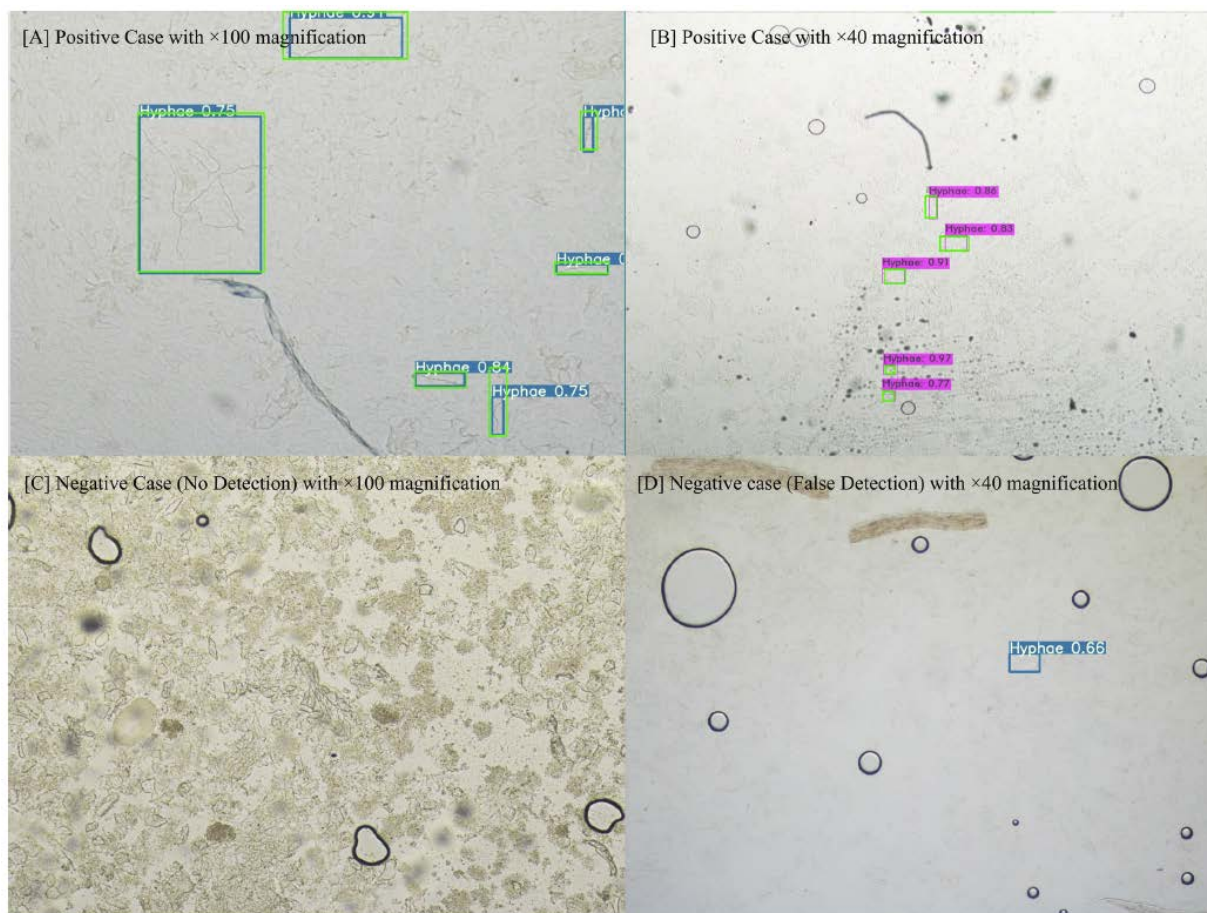
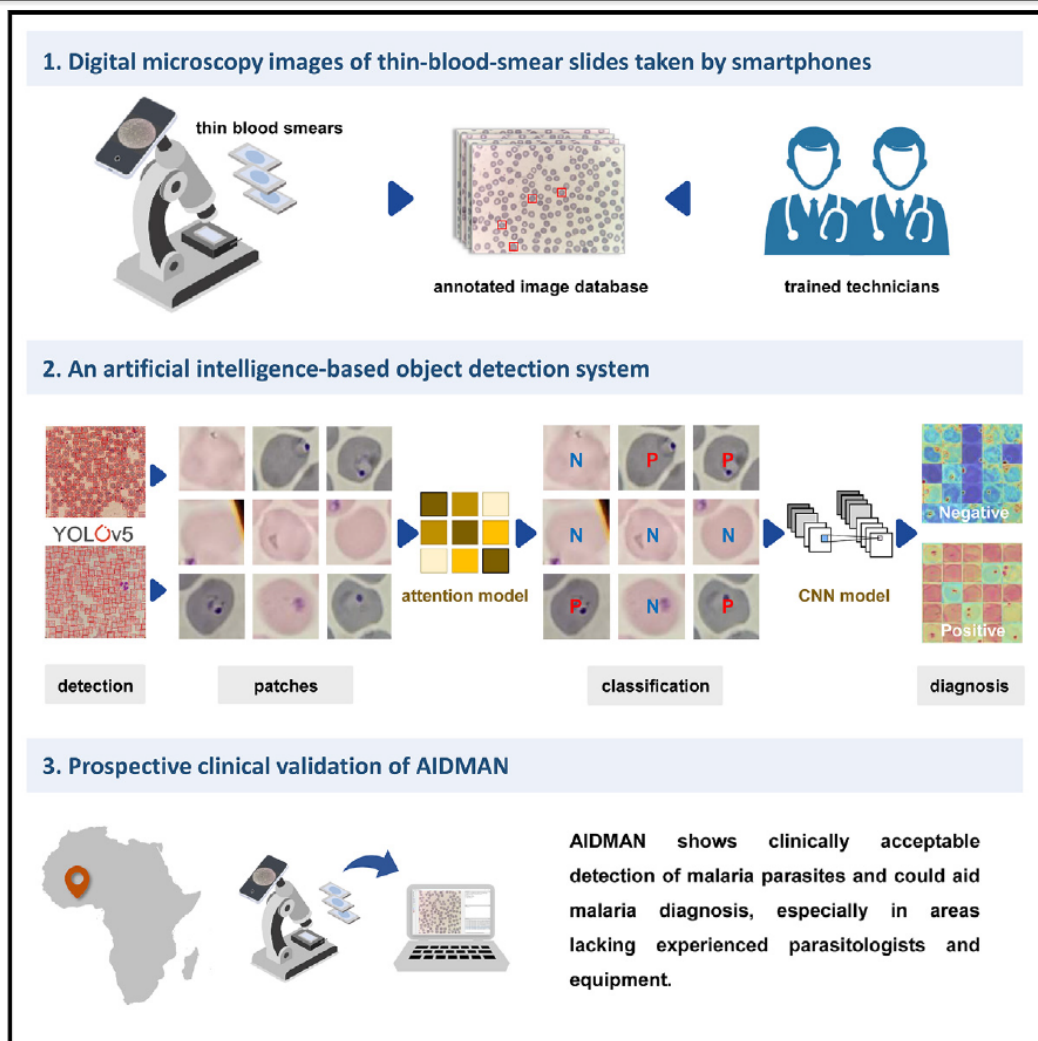


Fig 3. Example images of the autodetection of hyphae with bounding box. (A) positive case with 100x magnification, (B) positive case with 40x magnification, (C) negative case with 100x magnification, and (D) negative case (false detection) with 40x magnification. The ground truth were marked with a green box in positive case (A, B).



# AIDMAN: An AI-based object detection system for malaria diagnosis from smartphone thin-blood-smear images

Liu R, et al. Patterns 2023; 4:100806.



Klinična validacija na 64 bolnikih:

**Table 2. Comparison of the accuracies of different malaria diagnosis methods**

Detection method		No. patients		Total	Accuracy, %
		Positive	Negative		
Microscopic examination	positive	34	0	34	100
	negative	0	30	30	
RDTs	positive	32	1	33	95.31
	negative	2	29	31	
AIDMAN	positive	33	0	33	98.44
	negative	1	30	31	

# Detection of Intestinal Protozoa in Trichrome-Stained Stool Specimens by Use of a Deep Convolutional Neural Network

J Clin Microbiol. 2020.

Blaine A. Mathison,<sup>a</sup> Jessica L. Kohan,<sup>a</sup> John F. Walker,<sup>b</sup> Richard Boyd Smith,<sup>b</sup> Orly Ardon,<sup>a,c</sup> Marc Roger Couturier<sup>a,c</sup>

**TABLE 1** Total number of unique slides per class, and total number of examples per class used for training the model

Category (class)	No. of unique slides per class	No. of examples per class
<i>Giardia duodenalis</i> cyst	23	6,499
<i>Giardia duodenalis</i> trophozoite	21	2,191
<i>Blastocystis</i> sp.	61	23,566
<i>Dientamoeba fragilis</i>	29	12,764
<i>Entamoeba non-hartmanni</i> trophozoite	34	4,307
<i>Entamoeba hartmanni</i> trophozoite	10	1,394
<i>Chilomastix mesnili</i> trophozoite	15	4,064
<i>Endolimax nana</i> / <i>Iodamoeba buetschlii</i> trophozoite	36	7,914
Red blood cells	18	8,482
White blood cells	31	2,099
Yeast	94	13,450

**TABLE 2** Contingency table and slide-level agreement calculations comparing the CNN model to the gold-standard O&P examination for 87 true-positive specimens and 106 true-negative specimens<sup>a</sup>

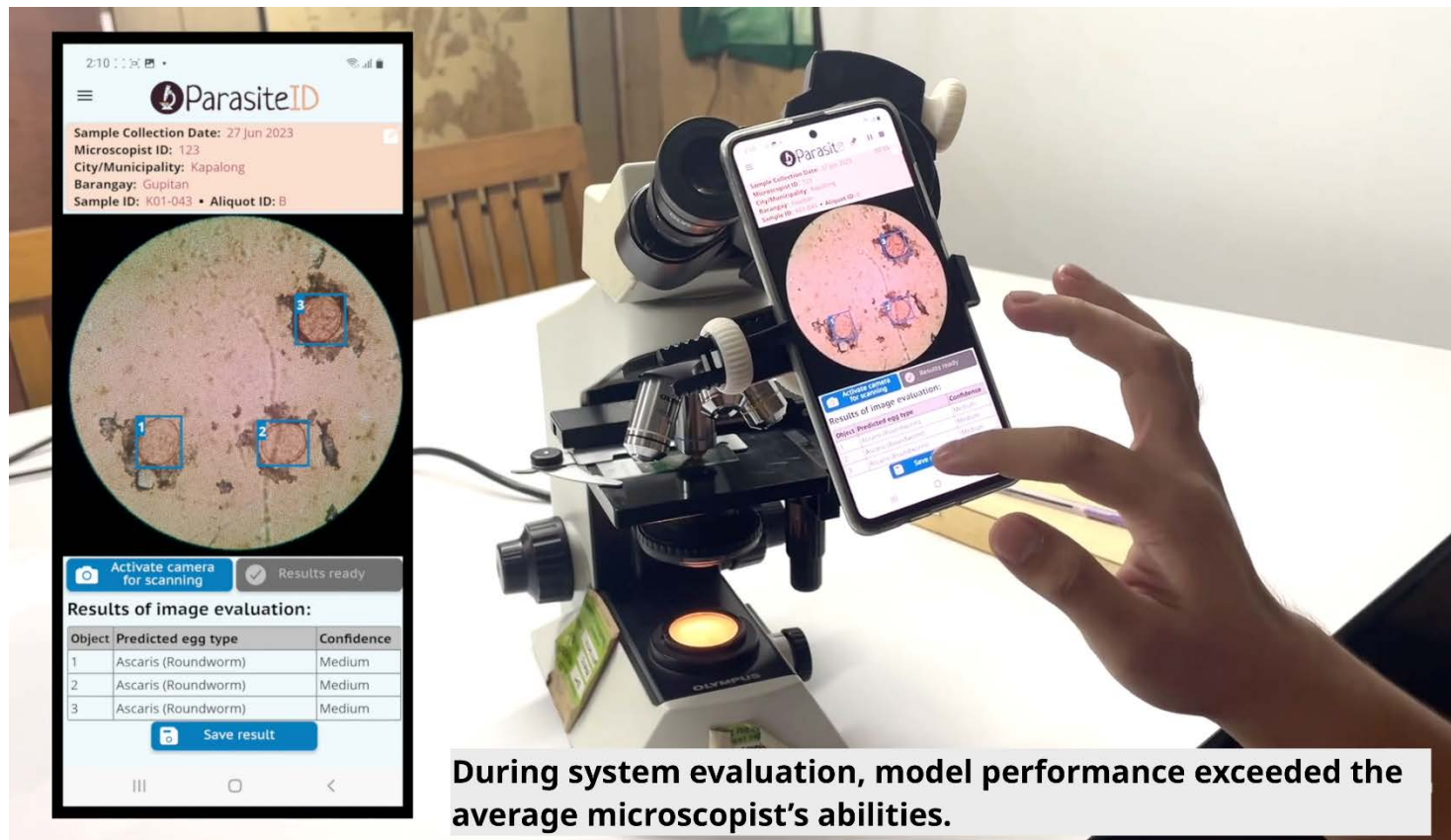
CNN model analysis result	O&P examination result (n)	
	Positive	Negative
Positive	86	2
Negative	1	104

<sup>a</sup>Positive percent agreement, 98.88% (95% CI, 93.76% to 99.98%); negative percent agreement, 98.11% (95% CI 93.35% to 99.77%).

Velika večina vzorcev blata (>95%) mikroskopsko negativnih → cilj razviti občutljiv sistem, ki bi omogočil avtomatsko izločanje negativnih in opozarjanje v primeru sumljivih vzorcev blata, ki potrebujejo ročni pregled/potrditev.

Meja detekcije: model pogosteje zazna vzorce z nizkim bremenom parazitov kot mikroskopist

- do 5 serijskih dilucij višja analitična občutljivost za *G. duodenalis* in *Blastocystis* spp.)



„During field surveillance activities, egg species type is identified in stool using a mobile app enabled by AI. The app can transmit data to enable storage and aggregation of results by time and location in cloud databases, and data can be displayed in near real-time in web-accessible dashboards.“

**Aplikacija Parasite ID deluje brez internetne povezave → zlasti uporabno na področjih z nestabilno internetno povezavo.**

<https://parasite.id/>

# Interpretacija slikovnih podatkov - kultivacija



# Avtomatizacija interpretacije bakterijske kulture

- Programske opreme za avtomatsko digitalno analizo – **URINOKULTURA**
  - COPAN WaspLAB: PhenoMatrix
  - BD Kiestra: Urine Culture App
  - Clever Culture Systems APAS (prvi imeli FDA dovoljenje za aplikacijo za urinokulture)
- **Odsotnost rasti**
- **Mešana rast ali kontaminacija**
- **Semikvantifikacija**

Glasson J, et al. Ann Lab Med 2017. (APAS)  
Faron ML, et al. J Clin Microbiol 2020. (COPAN)  
Dauwalder O, et al. Clin Microbiol Infect 2021. (COPAN)  
Patel P, et al. Open Forum Infect Dis 2019. (Kiestra)  
Uwamino Y, et al. Diagn Microbiol Infect Dis 2022. (Kiestra)



# Avtomatizacija interpretacije bakterijske kulture

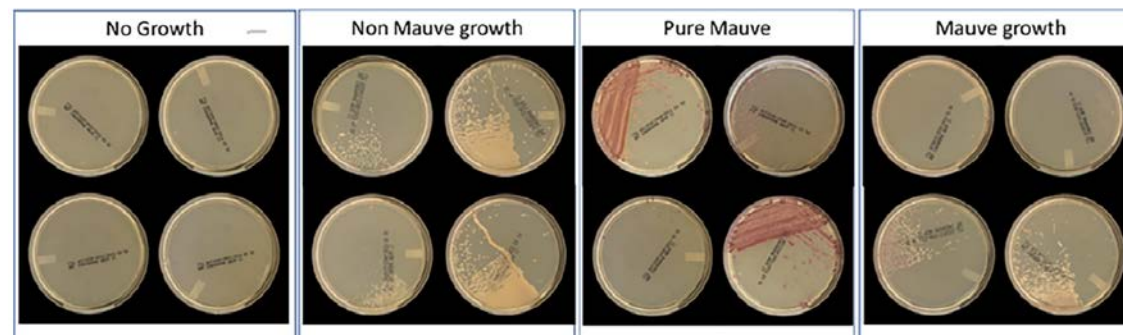
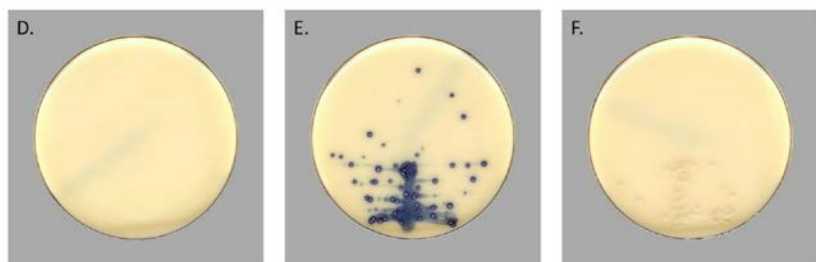
Algoritmi za avtomatsko digitalno analizo – **KROMOGENA GOJIŠČA**

## Detekcija VRE:

- Faron ML, et al. J Clin Microbiol 2016. (COPAN)
- Cherkaoui A, et al. Front Cell Infect Microbiol 2019. (COPAN)

## Detekcija MRSA:

- Faron ML, et al. J Clin Microbiol 2016. (COPAN)
- Gammel N, et al. J Clin Microbiol 2021 (APAS)
- McElvania E, et al. J Clin Microbiol 2024 (KIESTRA)



# Avtomatizacija interpretacije bakterijske kulture

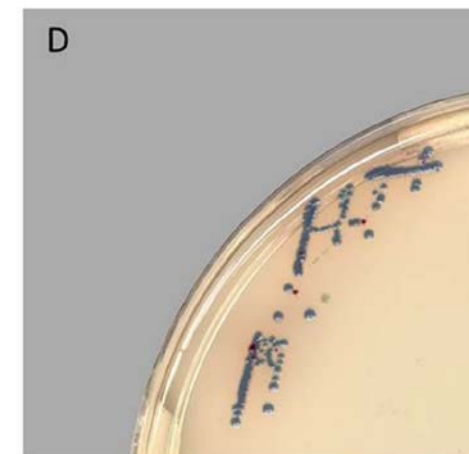
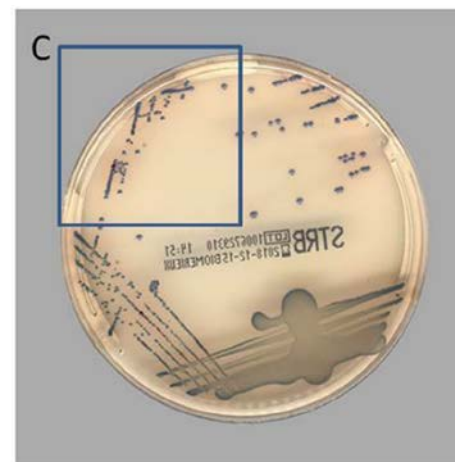
Algoritmi za avtomatsko digitalno analizo – **KROMOGENA GOJIŠČA**

## Detekcija streptokoka B:

- Foschi C, et al. Diagn Microbiol Infect Dis 2021 (COPAN)
- Baker J, et al. J Clin Microbiol 2020. (COPAN)

## Detekcija Streptokoka A:

- Van TT, et al. J Clin Microbiol 2019. (COPAN)



# Development and evaluation of an artificial intelligence for bacterial growth monitoring in clinical bacteriology

Damien Jacot,<sup>1</sup> Shkllqim Gizha,<sup>1</sup> Cedrick Orny,<sup>2</sup> Mathieu Fernandes,<sup>2</sup> Carmelo Tricoli,<sup>2</sup> Raphael Marcelpoil,<sup>2</sup> Guy Prod'hom,<sup>1</sup> Jean-Marc Volle,<sup>2</sup> Gilbert Greub,<sup>1,3</sup> Antony Croxatto<sup>1,4</sup>

J Clin Microbiol 2024; 62: e0165123

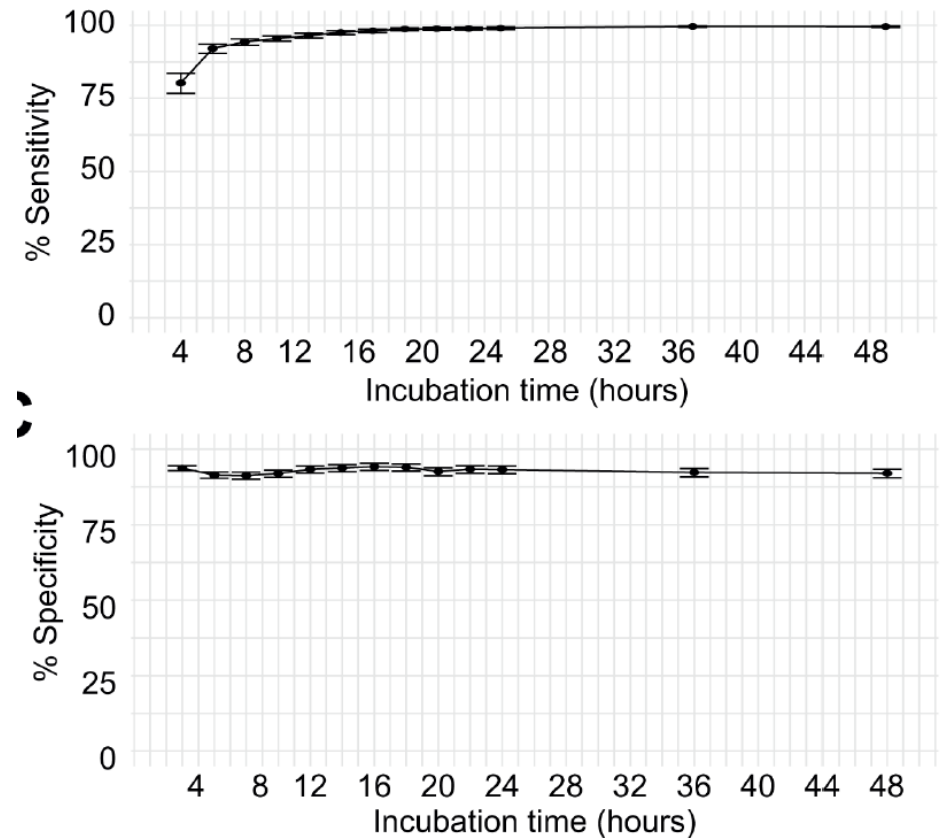
- Algoritem za detekcijo rasti
  - Različni klinični vzorci
  - 5 najpogostejših gojišč
  - 15 časovnih točk (do 48h)
- Skupno 3.844 gojišč
  - Pregledala 2 mikrobiologa (naključno in neodvisno)  
→ 99.944 človeških „temeljnih resnic“

# Development and evaluation of an artificial intelligence for bacterial growth monitoring in clinical bacteriology

Damien Jacot,<sup>1</sup> Shkllqim Gizha,<sup>1</sup> Cedrick Orny,<sup>2</sup> Mathieu Fernandes,<sup>2</sup> Carmelo Tricoli,<sup>2</sup> Raphael Marcelpoil,<sup>2</sup> Guy Prod'hom,<sup>1</sup> Jean-Marc Volle,<sup>2</sup> Gilbert Greub,<sup>1,3</sup> Antony Croxatto<sup>1,4</sup>

J Clin Microbiol 2024; 62: e0165123

- Po 48 urah:
  - OBČUTLJIVOST 99.80 % (5/3844 LN)
  - SPECIFIČNOST 91.97%
  - **MOŽNOST PRIORITIZACIJE!**
- Rast zaznana že po 4h, po 6h rast pri polovici pozitivnih gojišč  
→ **PRIMARNO STERILNI VZORCI**



1-Urine 48 h      2-Urogenital 48 h      3-Urogenital 48 h      4-Respiratory 48 h      5-Tissue and Pus 48 h



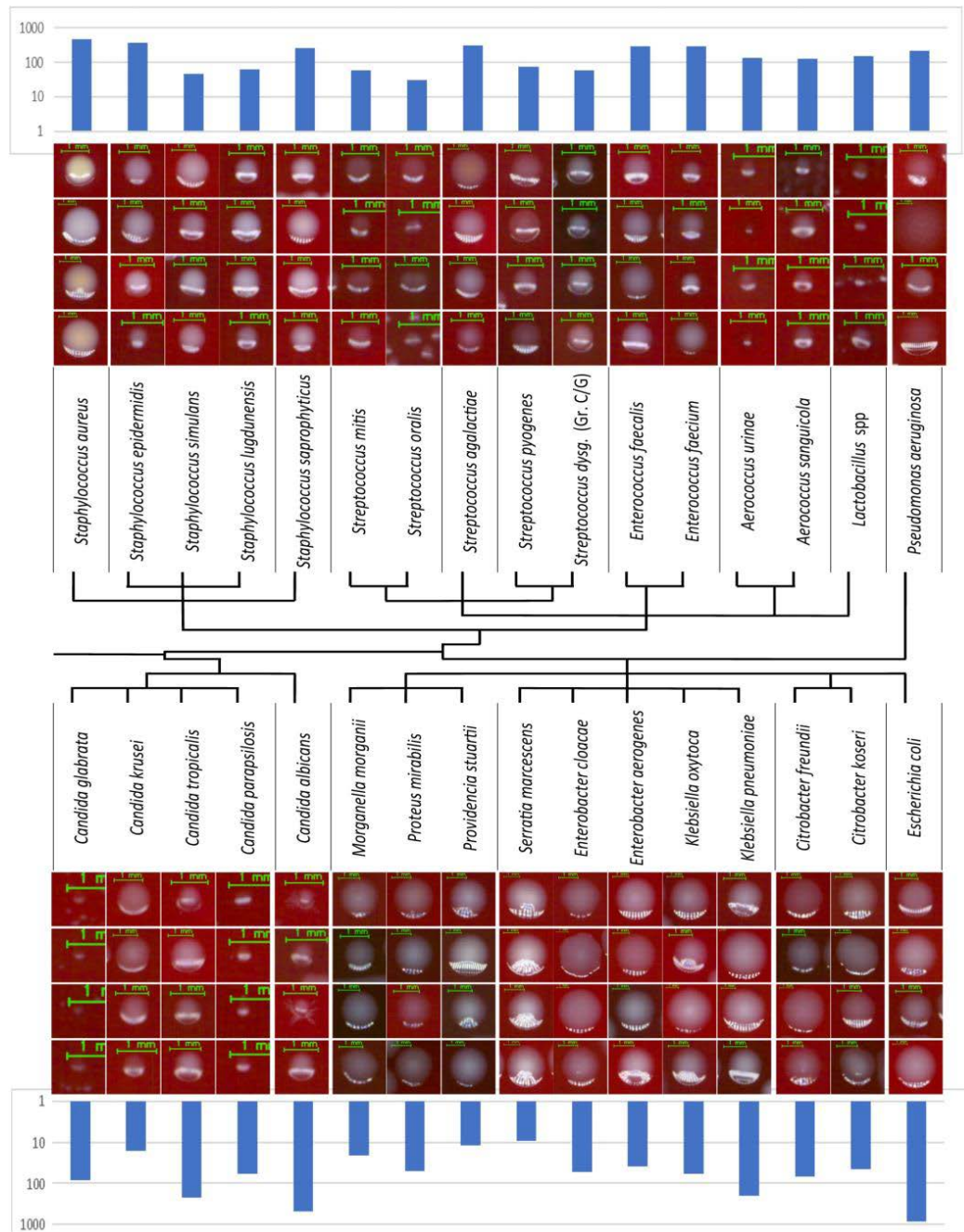
# Hierarchical AI enables global interpretation of culture plates in the era of digital microbiology

Alberto Signoroni <sup>1,2,6</sup> , Alessandro Ferrari<sup>3,4,6</sup>, Stefano Lombardi <sup>1,3</sup>,  
Mattia Savardi <sup>1,2</sup>, Stefania Fontana <sup>3</sup> & Karissa Culbreath<sup>5</sup>

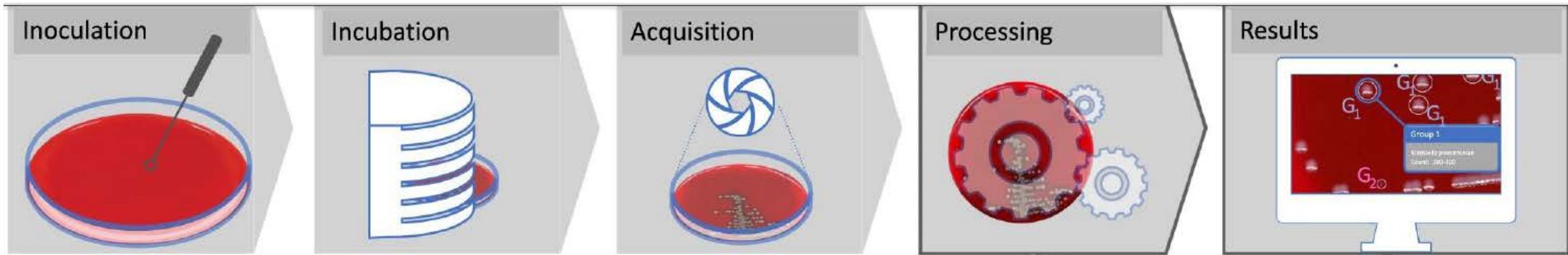
Nature Communications, 2023

- Globalna interpretacija bakterijskih kultur, vključno z identifikacijo patogenov
- Dekompozicija problema v hierarhijo kompleksnih podnalog
- Obdelava podnalog z ***DeepColony*** – hierarhična multimreža z arhitekturo, ki je sposobna obravnavati vse stopnje identifikacije, kvantifikacije in interpretacije od posamezne kolonije do celega gojišča

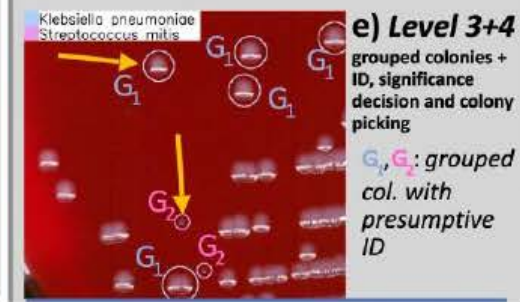
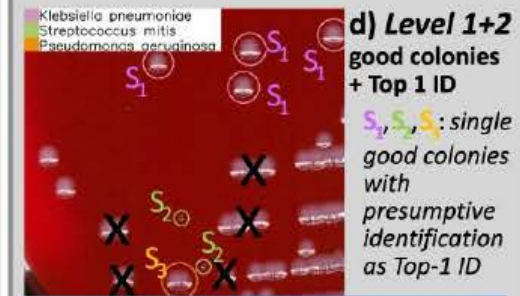
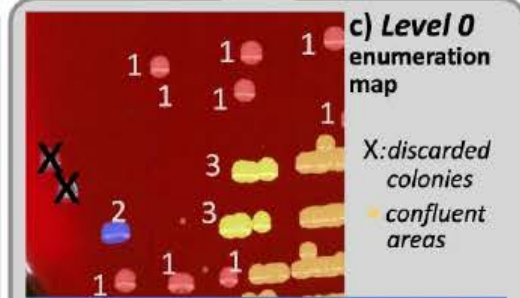
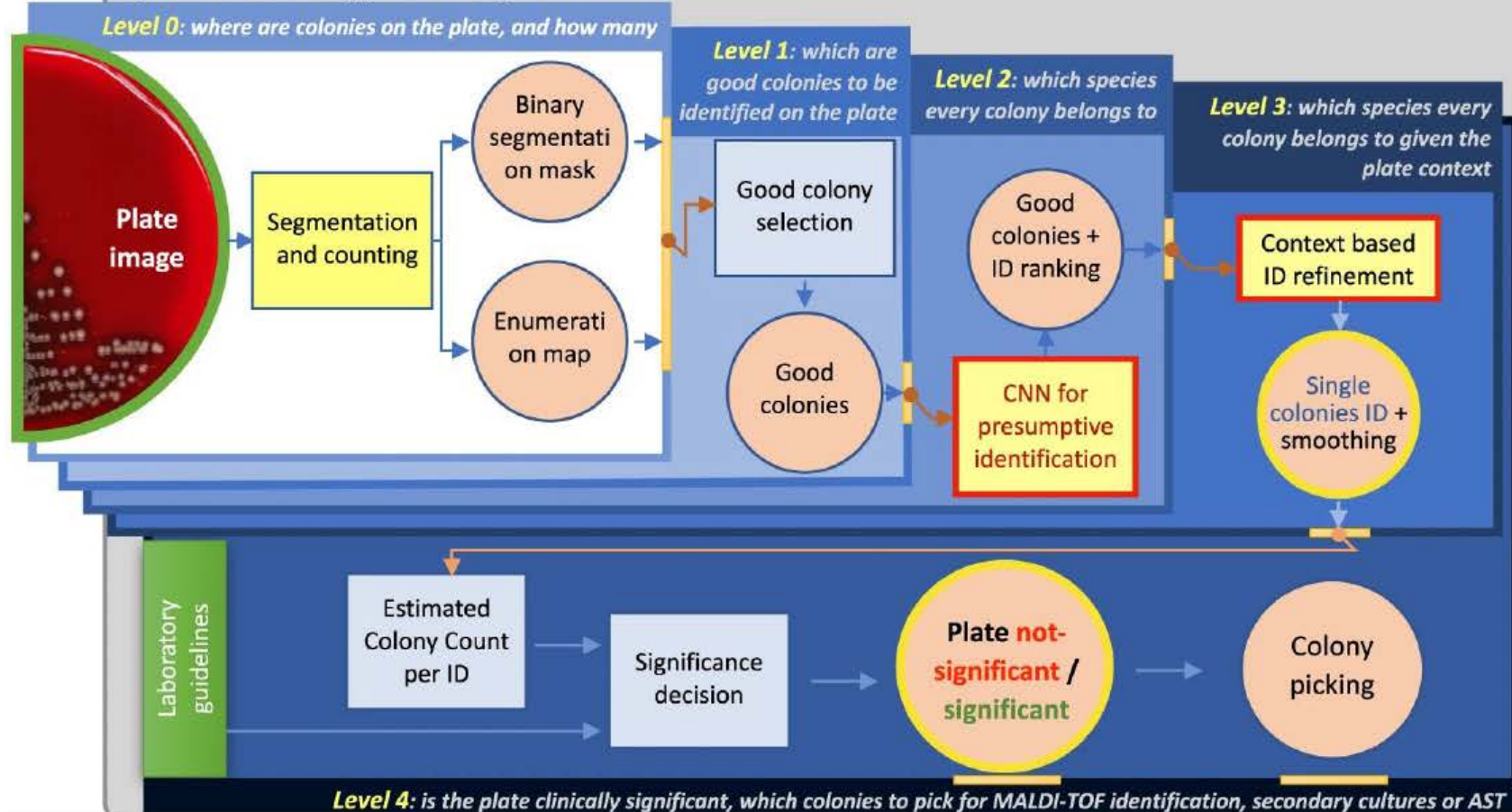








- Velika baza kliničnih podatkov, set 32 patogenov → urinokulture (98% vseh vrst patogenov v 3 mesecih diagnostike UTI)
- 26.213 slik posameznih kolonij
- Učni nabor: 200.000 parov slik
- Validacijski nabor: 10.000 slik



**b) Decision making process diagram**



# Hierarchical AI enables global interpretation of culture plates in the era of digital microbiology

Alberto Signoroni <sup>1,2,6</sup> , Alessandro Ferrari<sup>3,4,6</sup>, Stefano Lombardi <sup>1,3</sup>,  
Mattia Savardi <sup>1,2</sup>, Stefania Fontana <sup>3</sup> & Karissa Culbreath<sup>5</sup>

Nature Communications, 2023

Testni nabor: 5.051 urinokultur iz velikega laboratorija v ZDA

Ujemanje med *DeepColony* in ročno interpretacijo:

- 99,2% za negativne urinokulture
- 95,6% za pozitivne urinokulture
- 77,1 % za kontaminacije oz. mešana rast („safety by design“ kriteriji)

# Človek vs. umetna inteligenca

- Odčitavanje plošč v bakteriologiji je večšina, ki zahteva več let usposabljanja
  - Frekvenca odčitavanja plošč → doseganje kompetenc s ponavljanjem
    - Zlasti pomembno pri redkih patogenih in v primeru prisotnosti komenzalne mikrobiote
- Kljub ustreznemu usposabljanju pogosta neskladja med različnimi odčitovalci
- UI in aplikacije za digitalno slikanje omogočajo standardizacijo nekaterih vidikov interpretativne mikrobiologije in s tem zmanjšanje možnosti napak
- Optimizacija časa pri velikem številu negativnih preparatov

# Pomanjkljivosti in omejitve

- Algoritmi so razviti za točno določen niz spremenljivk, ki morajo ostati fiksne → sistem mora biti strogo nadzorovan
  - Primer pri uporabi digitalnih slikovnih aplikacij: sprememba osvetlitve, kamere ali pogojev zajema slike (npr. kot) bo ustvarilo „novo“ sliko, kar lahko vpliva na zanesljivost dobljenih rezultatov
  - Vsakršna sprememba v pogojih (npr. nov način nacepitve vzorca) mora biti natančno preverjen in validiran
- Sistemi, ki temeljijo na UI, manj zanesljivi pri kategorizaciji vzorcev, opredeljenih kot „kontaminacija“
- Problematična identifikacija fenotipskih različic istega mikroorganizma



# Predvidevanje odpornosti – analiza masnih spektrov



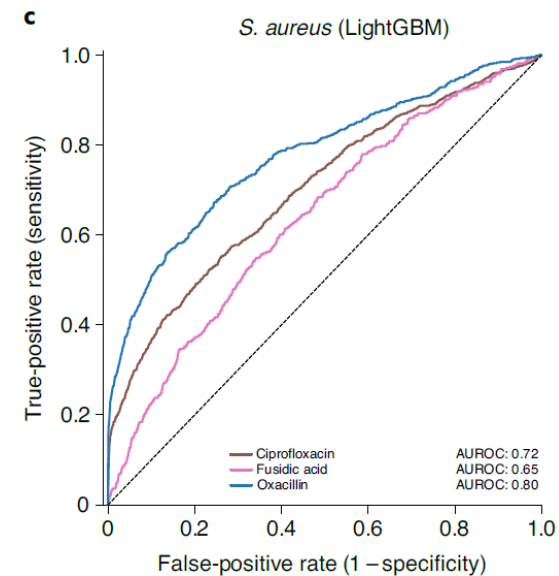
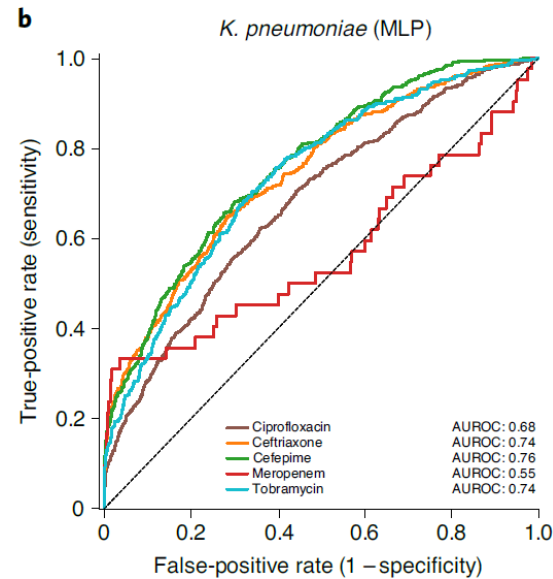
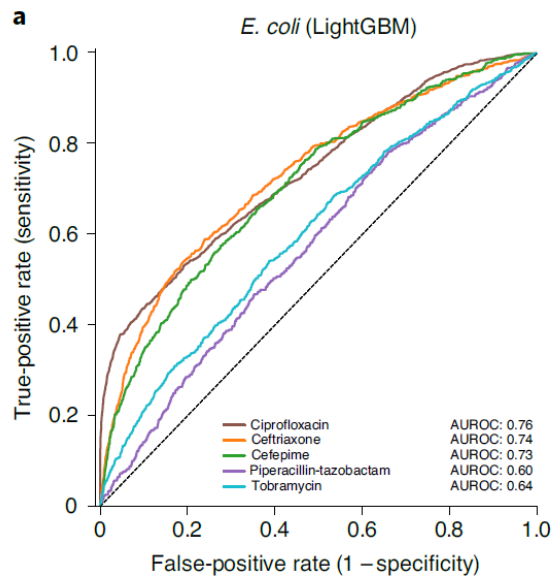
# Direct antimicrobial resistance prediction from clinical MALDI-TOF mass spectra using machine learning

Caroline Weis <sup>1,2</sup> , Aline Cuénod<sup>3,4</sup>, Bastian Rieck <sup>1,2</sup>, Olivier Dubuis<sup>5</sup>, Susanne Graf<sup>6</sup>, Claudia Lang<sup>5</sup>, Michael Oberle<sup>7</sup>, Maximilian Brackmann <sup>8</sup>, Kirstine K. Søgaard<sup>3,4</sup>, Michael Osthoff<sup>9,10</sup>, Karsten Borgwardt <sup>1,2,11</sup>  and Adrian Egli <sup>3,4,11</sup> 

- Baza kliničnih izolatov s povezanimi fenotipi občutljivosti
  - 300.000 masnih spektrov
  - >750.000 AMR fenotipov, 803 bakterijskih in glivnih vrst
  - 4 medicinski centri v Švici
- Validacija na klinično pomembnih patogenih:
  - *S. aureus*
  - *E. coli*
  - *K. pneumoniae*

# Validacija na klinično pomembnih patogenih

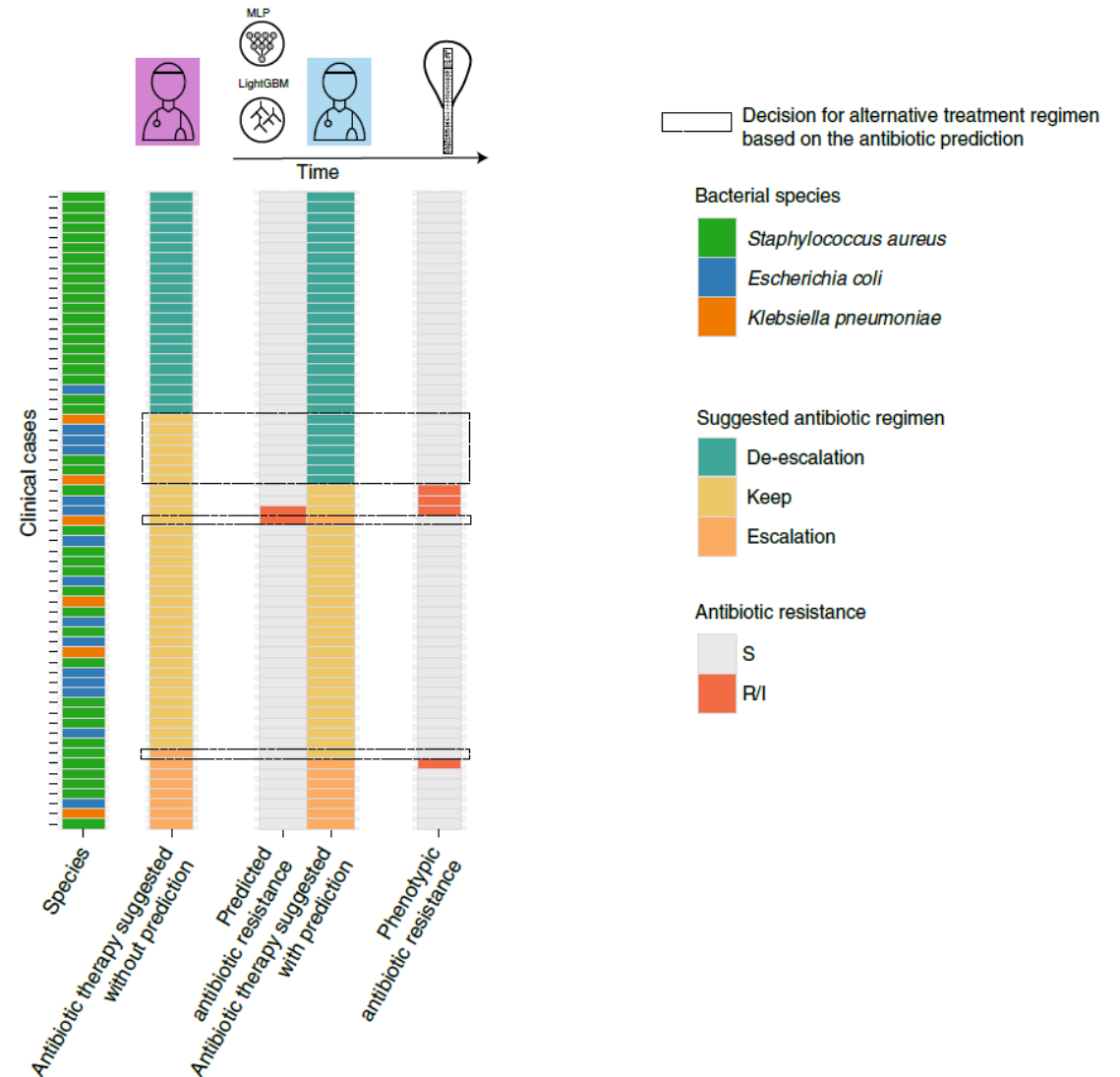
- *E. coli* – ceftriakson: AUROC 0,74
- *K. pneumoniae* – ceftriakson: AUROC 0,74
- *S. aureus* – oksacilin: AUROC 0,80



# Retrospektivna študija na kliničnih primerih

63 bolnikov z resno bakterijsko okužbo:

- V 51/63 primerih algoritem podprl predpisano terapijo
- V 3 primerih algoritem napovedal S, čeprav v resnici R (terapija se ne bi spremenila)

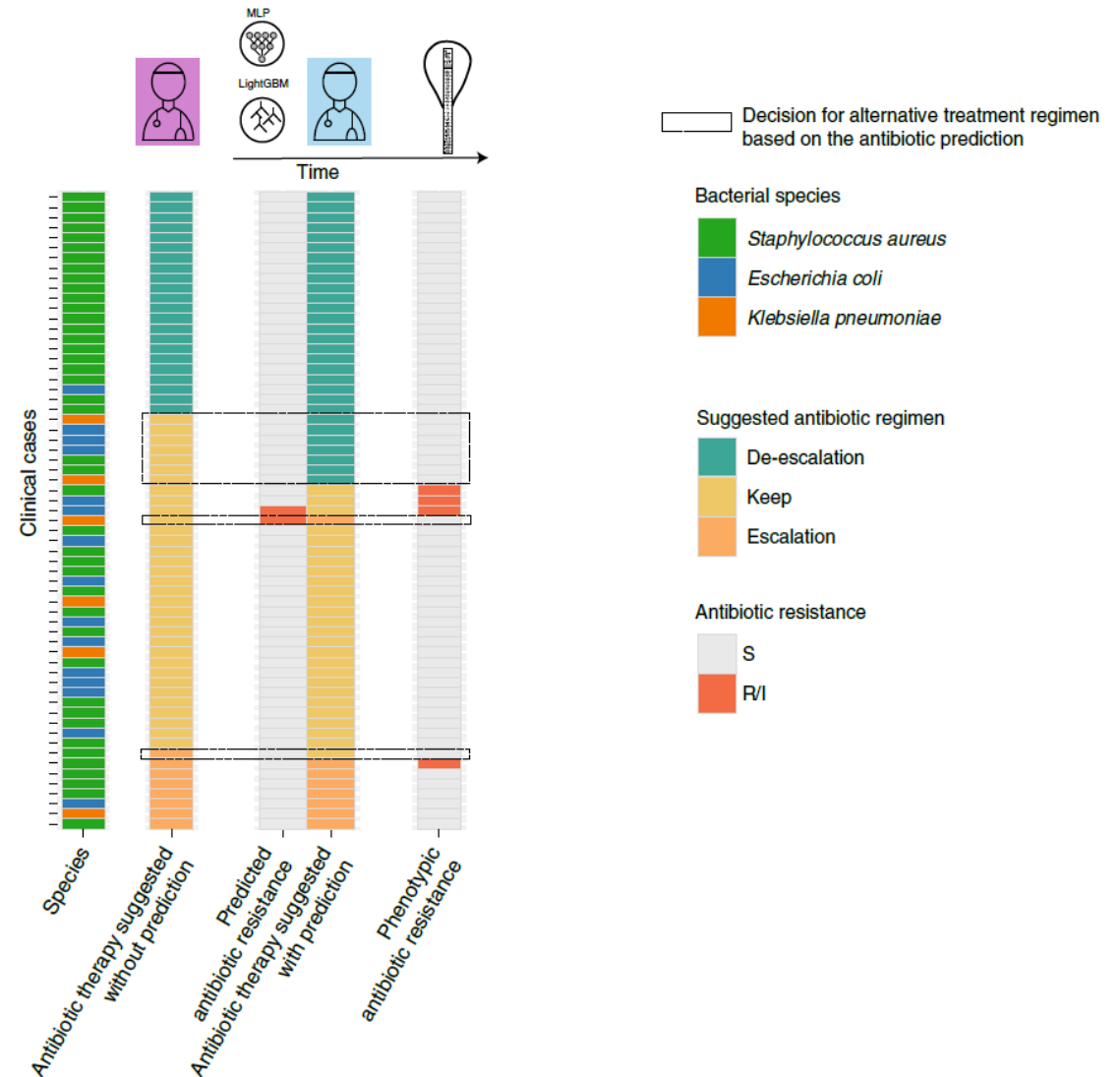


# Retrospektivna študija na kliničnih primerih

V 9 primerih bi z algoritmom prišlo do spremembe terapije:

- 7 primerov: DE-ESKALACIJA
- 1 primer: nadaljevanje terapije namesto spremembe (klinik po nepotrebnem predpisal širši atb)
- 1 primer: NEPOTREBNA ESKALACIJA

V 8/9 primerov koristna sprememba z uporabo algoritma





# Predvidevanje odpornosti – analiza sekvenc

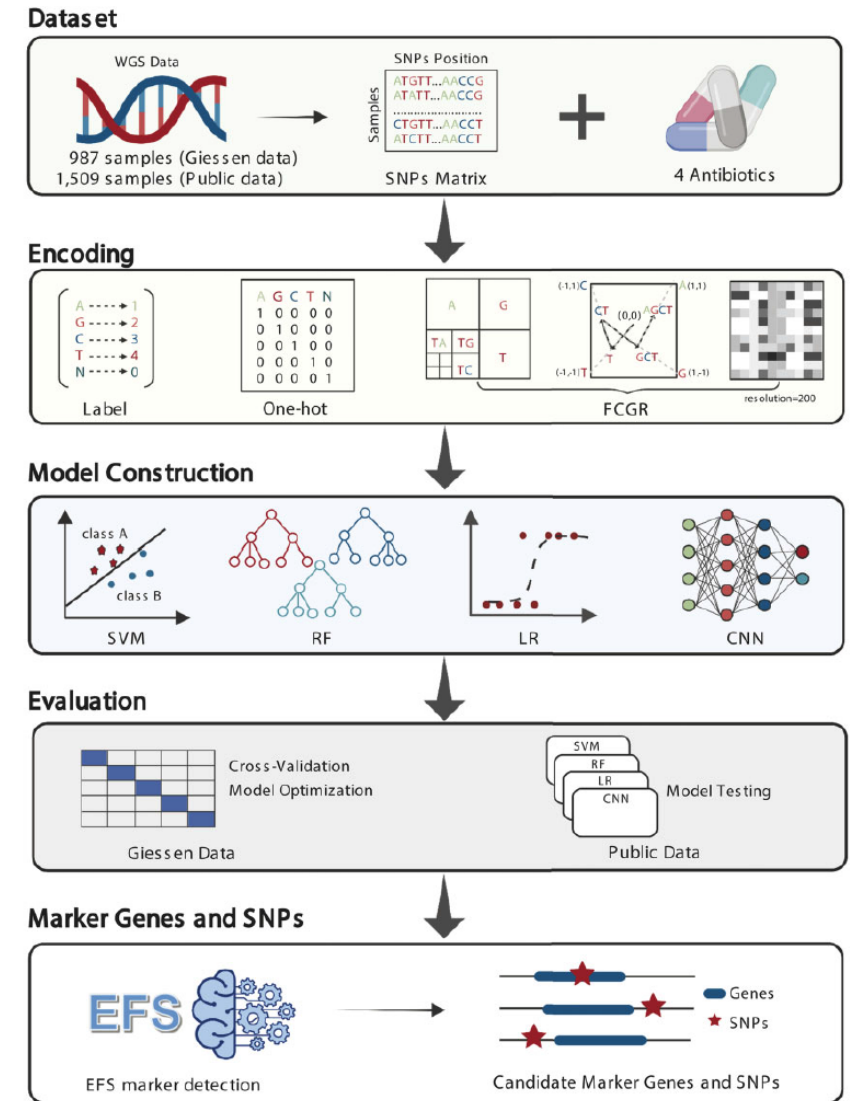


# Prediction of antimicrobial resistance based on whole-genome sequencing and machine learning

Yunxiao Ren<sup>1</sup>, Trinad Chakraborty<sup>2,3</sup>, Swapnil Doijad<sup>2,3</sup>, Linda Falgenhauer<sup>3,4,5</sup>, Jane Falgenhauer<sup>2,3</sup>, Alexander Goesmann<sup>3,6</sup>, Anne-Christin Hauschild<sup>1</sup>, Oliver Schwengers<sup>3,6</sup> and Dominik Heider<sup>1,\*</sup>

## Napoved odpornosti proti antibiotikom: *E. coli* (CIP, CTX, CAZ, GEN)

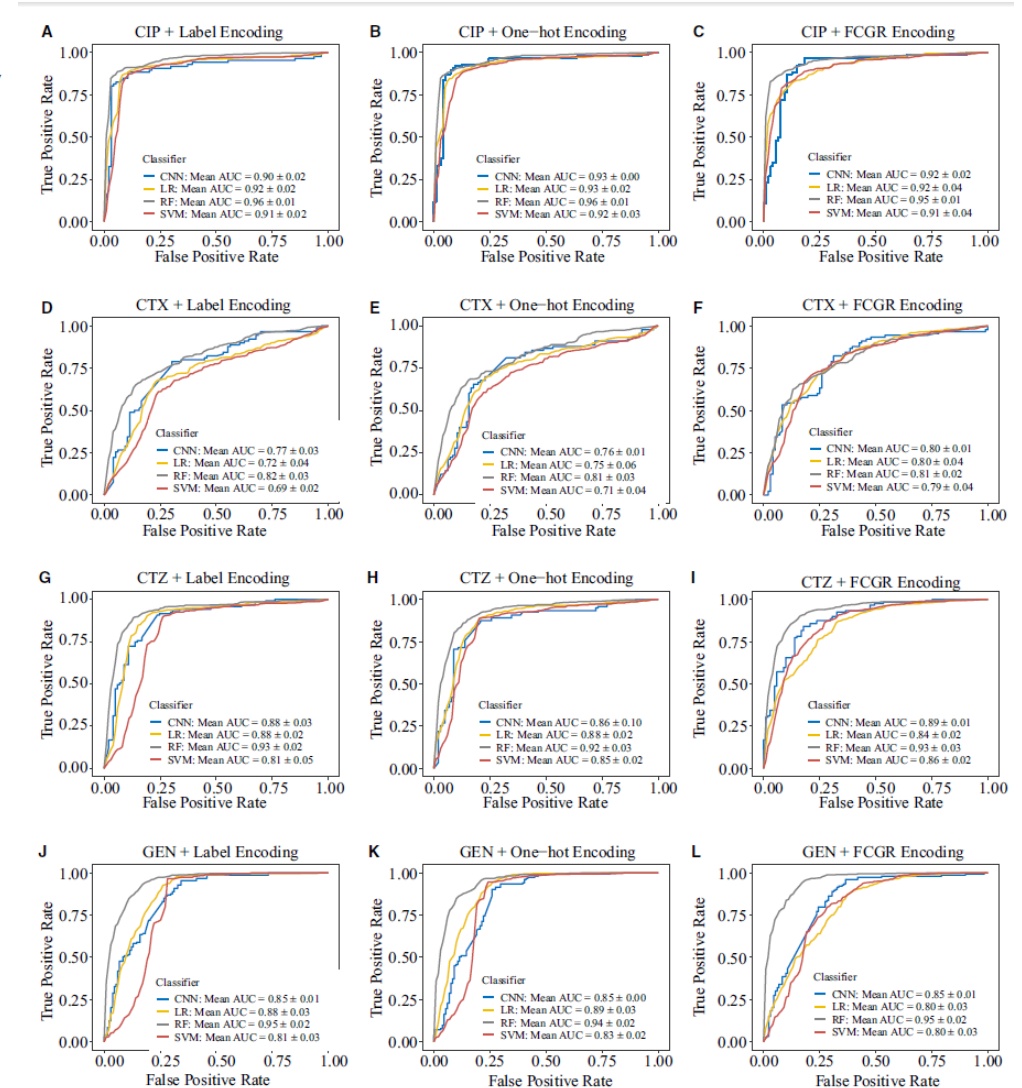
- WGS, 2 seta podatkov:
  - 987 sevov *E. coli* z znano fenotipsko odpornostjo
  - 1509 sevov *E. coli* z znano fenotipsko odpornostjo (javna baza)
- 4 metode strojnega učenja: logistic regression (LR), support vector machine (SVM), random forest (RF), convolutional neural network (CNN), 3 različne kodirne sheme
- Identifikacija (sekundarnih) mutacij izven rezistenčnih genov, povezanih z odpornostjo (SNPs)



# Prediction of antimicrobial resistance based on whole-genome sequencing and machine learning

Yunxiao Ren<sup>1</sup>, Trinad Chakraborty<sup>2,3</sup>, Swapnil Doijad<sup>2,3</sup>, Linda Falgenhauer<sup>3,4,5</sup>, Jane Falgenhauer<sup>2,3</sup>, Alexander Goesmann<sup>3,6</sup>, Anne-Christin Hauschild<sup>1</sup>, Oliver Schwengers<sup>3,6</sup> and Dominik Heider<sup>1,\*</sup>





- Vsi modeli so učinkovito predvideli odpornost proti antibiotikom
- Analize brez znanih genov za odpornost – sekundarne mutacije -> pristop, ki ne potrebuje strokovnjaka z znanjem o odpornosti





# Predicting antimicrobial resistance in *Pseudomonas aeruginosa* with machine learning-enabled molecular diagnostics

EMBO Mol Med 2020.

Ariane Khaledi<sup>1,2,†</sup>, Aaron Weimann<sup>2,3,4,†</sup> , Monika Schniederjans<sup>1,2,†</sup>, Ehsaneddin Asgari<sup>3,5,†</sup>, Tzu-Hao Kuo<sup>3</sup>, Antonio Oliver<sup>6</sup>, Gabriel Cabot<sup>6</sup>, Axel Kola<sup>7</sup>, Petra Gastmeier<sup>7</sup>, Michael Hogardt<sup>8</sup>, Daniel Jonas<sup>9</sup>, Mohammad RK Mofrad<sup>5,10</sup>, Andreas Bremges<sup>3,4</sup> , Alice C McHardy<sup>3,4,§,\*</sup>  & Susanne Häussler<sup>1,2,§,\*\*</sup> 

- Visoka (0.8-0.9) ali zelo visoka (>0.9) občutljivost in napovedna vrednost
- Transkriptomski podatki pomembno izboljšali napoved za vse atb razen za CIP
- Znane rezistenčne determinante in novi biomarkerji

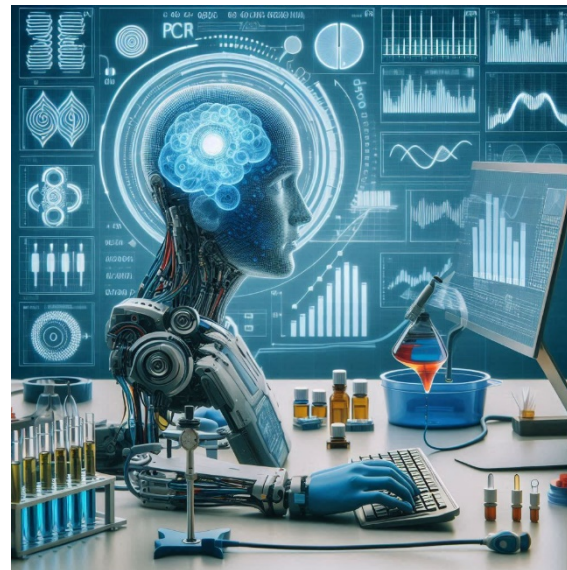
Table 1. Performance of support vector machine (SVM) classifier to predict sensitivity or resistance to four different antibiotics.

Antibiotic	Markers used	Sensitivity (resistance)	Sensitivity (susceptibility)	Predictive value (resistance)	Predictive value (susceptibility)	F1-score	Number of markers*
CAZ	GPA+EXPR	0.83 ± 0.02	0.81 ± 0.02	0.81 ± 0.02	0.83 ± 0.01	0.82 ± 0.01	37
TOB	GPA+EXPR	0.89 ± 0.01	0.94 ± 0.01	0.88 ± 0.01	0.95 ± 0.01	0.92 ± 0.01	59
MEM	GPA+EXPR	0.91 ± 0.02	0.86 ± 0.01	0.93 ± 0.01	0.81 ± 0.03	0.87 ± 0.01	93
CIP	SNPs	0.92 ± 0.01	0.87 ± 0.01	0.91 ± 0.01	0.90 ± 0.01	0.90 ± 0.01	50

\*The number of markers indicates the number of (combined) features that resulted in the least complex SVM model within one standard deviation of the peak performance, i.e., with the best macro F1-score and as few as possible features for each drug.



# Analize v molekularni diagnostiki



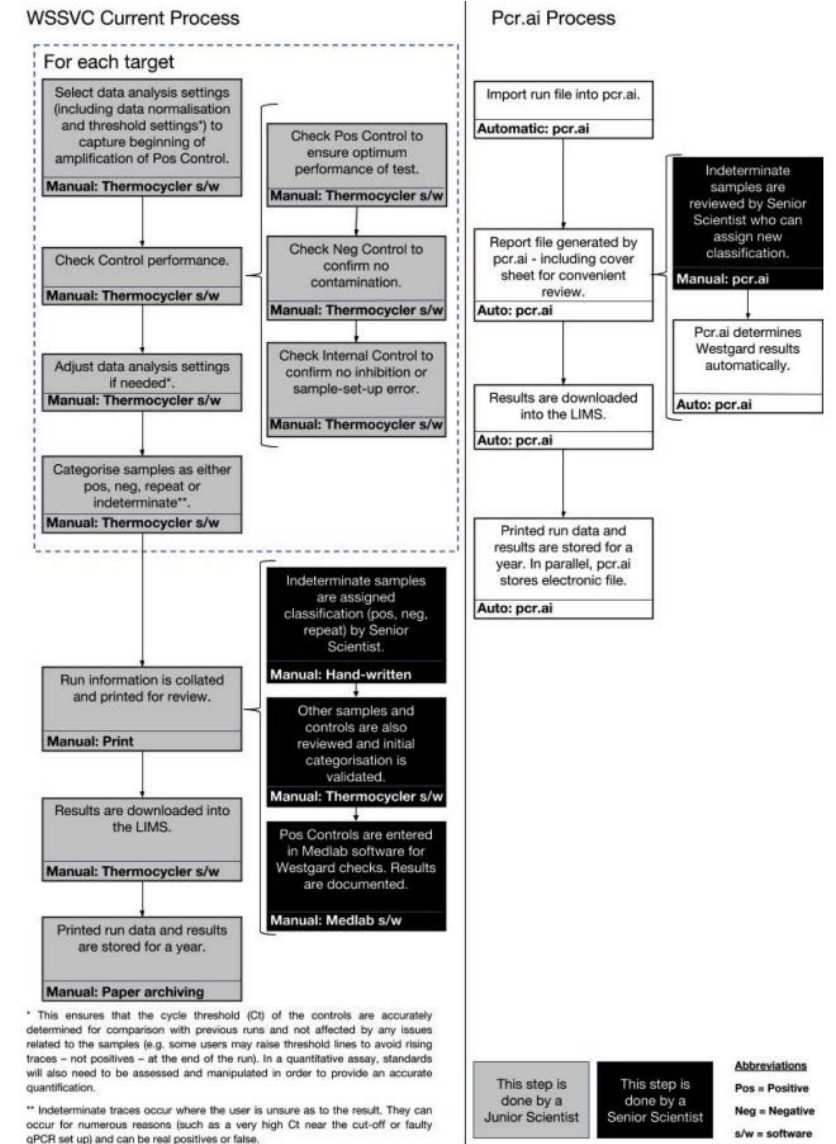
# Automation and standardisation of clinical molecular testing using PCR.Ai – A comparative performance study

A.R. MacLean\*, R. Gunson

Journal of Clinical Virology 120 (2019) 51–56



West of Scotland Specialist Virology Centre, New Lister Building, Glasgow Royal Infirmary, 10–16 Alexandra Parade, Glasgow, G31 2ER, United Kingdom

- PCR.ai = sistem, oblikovan za avtomatsko in hitro interpretacijo krivulj in-house PCR
- Prospektivna klinična študija – evalvacija PCR.ai na >22.000 interpretacijah PCR za respiratorne patogene (20.400) in norovirus (1800)
- 100 % ujemanje z metodo ročne rutinske analize
  - Manjše število razlik pri napakah IC
- Pomemben prihranek časa:
  - 45 min na postopek za respiratorne viruse
  - 32 min na postopek za noroviruse



OPEN

# The application of a deep learning system developed to reduce the time for RT-PCR in COVID-19 detection

Yoonje Lee<sup>1,2,6</sup>, Yu-Seop Kim<sup>3,6</sup>, Da-in Lee<sup>3</sup>, Seri Jeong<sup>4</sup>  , Gu-Hyun Kang<sup>1,2</sup>, Yong Soo Jang<sup>1,2</sup>, Wonhee Kim<sup>1,2</sup>, Hyun Young Choi<sup>1,2</sup>, Jae Guk Kim<sup>1,2</sup> & Sang-hoon Choi<sup>2,5</sup>

Scientific Reports 2022

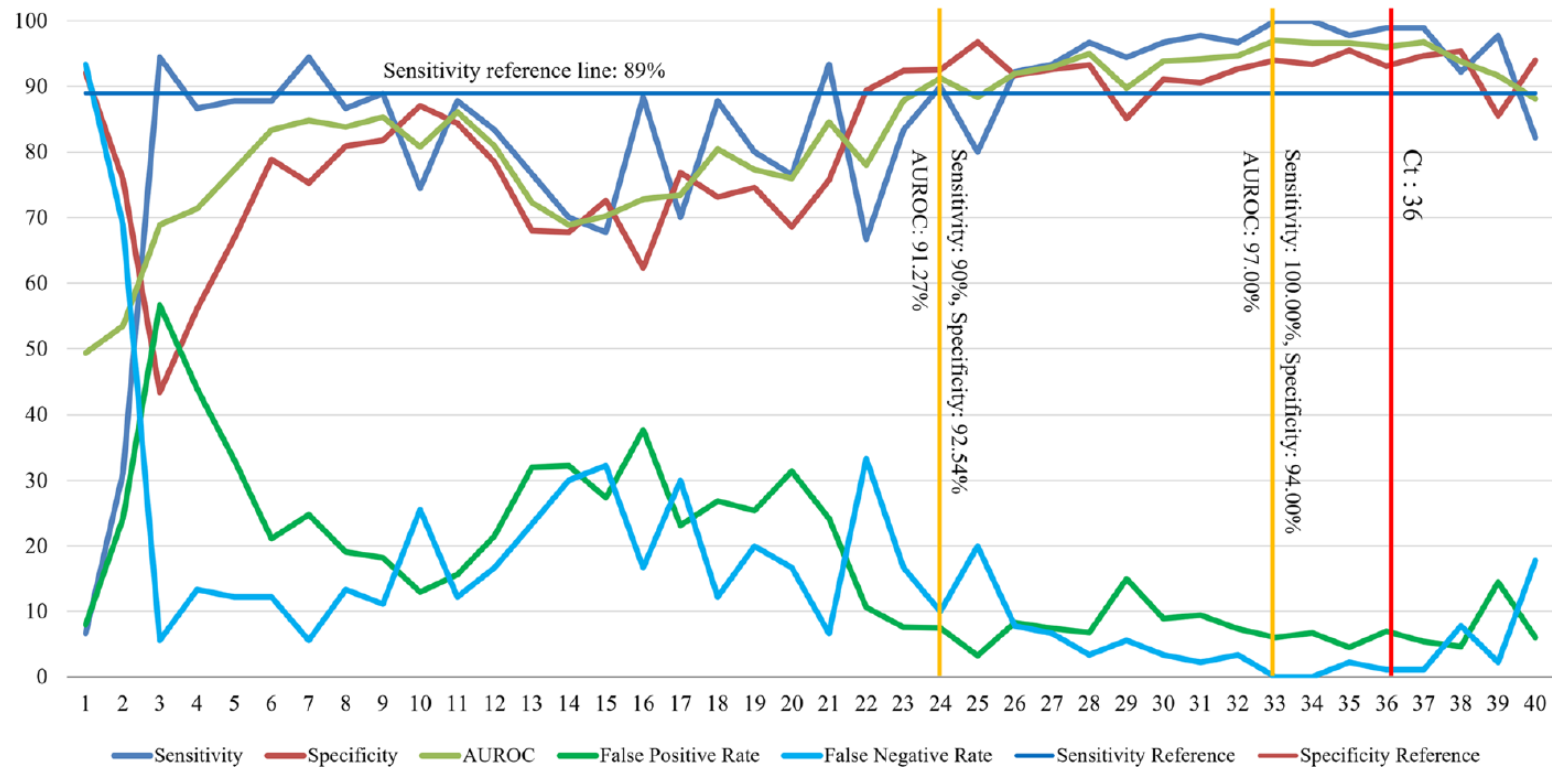
- Ali lahko čas do rezultata skrajšamo z modelom strojnega učenja?
  - Vrednosti fluorescence v vsakem izmed 40 ciklov
- ↓
- 40 modelov DL (long short-term memory)
  - Najboljše razmerje med občutljivostjo, specifičnostjo in AUROC
  - PPV, NPV in natančnost glede na prevalenco okužb (ZDA, Italija, Južna Koreja)

OPEN

# The application of a deep learning system developed to reduce the time for RT-PCR in COVID-19 detection


Scientific Reports 2022

Yoonje Lee<sup>1,2,6</sup>, Yu-Seop Kim<sup>3,6</sup>, Da-in Lee<sup>3</sup>, Seri Jeong<sup>4</sup>✉, Gu-Hyun Kang<sup>1,2</sup>, Yong Soo Jang<sup>1,2</sup>, Wonhee Kim<sup>1,2</sup>, Hyun Young Choi<sup>1,2</sup>, Jae Guk Kim<sup>1,2</sup> & Sang-hoon Choi<sup>2,5</sup>



## Machine Learning-Assisted Real-Time Polymerase Chain Reaction and High-Resolution Melt Analysis for SARS-CoV-2 Variant Identification

Sutossarat Promja, Jiratchaya Puenpa, Titipat Achakulvisut, Yong Poovorawan, Su Yin Lee, Pornpat Athamanolap,\* and Benchaporn Lertanantawong\*

 Cite This: *Anal. Chem.* 2023, 95, 2102–2109

 Read Online

- Spletna aplikacija, ki s pomočjo strojnega učenja identificira različice SARS-CoV-2
  - analiza talilne krivulje
- ↓
- Alfa, Delta, divji tip – razlikovanje pri 100 kopij/ $\mu$ l
  - Validacija na 167 NF brisih, občutljivost 95.2%

Identifikacija različic takoj po qPCR, brez potrebe po dodatnih inštrumentih ali človeške interpretacije.

Z vključitvijo več lokusov bi povečali diskriminatorno moč; potencial kot orodje za obsežno presejanje različic.



- Personalizacija zdravljenja
- Integracija in analiza velikih količin podatkov
  - Analiza genomskih podatkov
  - Združevanje različnih virov podatkov
- Podpora pri odločanju in izobraževanje
  - Pomoč pri kliničnih odločitvah
  - Izobraževanje in usposabljanje
- Epidemiologija in spremljanje širjenja bolezni
  - Zgodnje odkrivanje izbruhov
  - Spremljanje in napovedovanje širjenja bolezni

# Zagotavljanje varnosti, učinkovitosti in kakovosti



## Good Machine Learning Practice for Medical Device Development: Guiding Principles

October 2021

<b>Good Machine Learning Practice for Medical Device Development: Guiding Principles</b>	
<b>Multi-Disciplinary Expertise Is Leveraged Throughout the Total Product Life Cycle</b>	<b>Good Software Engineering and Security Practices Are Implemented</b>
<b>Clinical Study Participants and Data Sets Are Representative of the Intended Patient Population</b>	<b>Training Data Sets Are Independent of Test Sets</b>
<b>Selected Reference Datasets Are Based Upon Best Available Methods</b>	<b>Model Design Is Tailored to the Available Data and Reflects the Intended Use of the Device</b>
<b>Focus Is Placed on the Performance of the Human-AI Team</b>	<b>Testing Demonstrates Device Performance During Clinically Relevant Conditions</b>
<b>Users Are Provided Clear, Essential Information</b>	<b>Deployed Models Are Monitored for Performance and Re-training Risks are Managed</b>



„The illiterate of the 21st century will not be those who cannot read and write, but those who cannot learn, unlearn, and relearn.“

- Alvin Toffler, 1928-2016