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Machine learning in the clinical microbiology laboratory: has the time come for routine practice?

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NARRATIVE REVIEW

ABSTRACT (295/300 words)

Background

Machine learning (ML) allows the analysis of complex and large data sets and has the potential to improve healthcare. The clinical microbiology laboratory, at the interface of clinical practice and diagnostics, is of special interest for the development of ML systems.

Objectives

This narrative review aims to explore the current use of ML in clinical microbiology.

Sources

References for this review were identified through searches of MEDLINE/PubMed, EMBASE, Google Scholar, biorXiv, arXiv, ACM Digital Library and IEEE Xplore Digital Library up to November 2019.

Content

We found 97 ML systems aiming to assist clinical microbiologists. Overall, 82 (85%) ML systems targeted bacterial infections, 11 (11%) parasitic infections, nine (9%) viral infections and three (3%) fungal infections. Forty (41%) ML systems focused on micro-organisms detection, identification and quantification, 36 (37%) evaluated antimicrobial susceptibility and 21 (22%) targeted the diagnosis, disease classification and prediction of clinical outcomes. The ML systems used very diverse data sources: 21 (22%) used genomic data of micro-organisms, 19 (20%) microbiota data obtained by metagenomic sequencing, 19 (20%) analysed microscopic images, 17 (18%) spectroscopy data, 8 (8%) targeted gene sequencing, 6 (6%) volatile organic compounds, 4 (4%) bacterial colonies photographs, 4 (4%) transcriptome data, 3 (3%) protein structure and 3 (3%) clinical data. Most systems used high-income countries data (n=71, 73%) but a significant number used low- and middle-income countries data (n=36, 37%). Performance measures were reported for the 97 ML systems but no article described the use in clinical practice nor reported impact on processes or clinical outcomes.

Implications

In clinical microbiology, ML has been used with various data sources and diverse practical applications. The evaluation and implementation processes represent the main gap of existing ML systems, requiring a focus on their interpretability and potential integration into real-world settings.

MANUSCRIPT (3970)

INTRODUCTION

During the last decade, the availability of data in the clinical microbiology (CM) laboratory has substantially increased with technological advances such as Matrix-assisted laser desorption ionization - time of flight (MALDI-TOF) mass spectrometry (MS), the rise of whole genome sequencing (WGS) and the access to microbiota data by next-generation sequencing. The optimal analysis and interpretation of this increasingly complex and large data, called 'big data', often outdoes human abilities and requires the use of tools such as machine learning (ML). Unlike expert systems which are based on the programming of a set of rules, ML algorithms are able to define their own rules directly from the data (Figure 1). For example, to differentiate bacteria in the direct Gram stain, an expert system will require humans to program rules (e.g. if the shapes are round, they are cocci), whereas a ML algorithm will find itself a set of rules by analysing a large number of microscopic images labelled with Gram results. However, those rules may have no biological meaning nor may they be accounted for. The ability of the machine to learn, i.e. to define more accurate rules, is driven by the volume and quality of data provided, that is why ML systems are sometimes called data-intensive systems.

ML systems have been sprouting in many fields of medicine and the first FDA approval for an autonomous artificial intelligence system took place in 2018 with a ML system used to detect diabetic retinopathy in retinal fundus photographs.(1) Despite many studies describing the technical performance of ML systems, few are reporting the adoption of such tools in real-life settings,(2,3) confirming the existing gap between the development of innovations in medicine and their adoption in the routine clinical practice.(4,5) In infectious diseases, a recent review reported 60 ML decision support systems among which only three were tested in clinical practice.(6) Moreover, innovations in healthcare have often been implemented without evidence supporting pre-intervention analysis and before an in-depth analysis of the need and requirements, often resulting in a limited uptake in clinical

practice.(7,8) Particularly, clinical microbiologists' needs and expectations from ML systems, and how they can be integrated into the routine practices have not been assessed so far.

The CM laboratory, at the interface of clinical practice and diagnostics, is of special interest for the development of ML tools. This narrative review describes the characteristics, objectives and assessment of ML systems designed to assist clinical microbiologists in the diagnosis of infections, the identification and quantification of micro-organisms and the analysis of antimicrobial susceptibility.

MATERIAL AND METHODS

Search strategy

References for this review were identified through searches of MEDLINE/PubMed, EMBASE, Google Scholar, biorXiv, arXiv, ACM Digital Library and IEEE Xplore Digital Library for articles by use of a combination keywords referring to ML ("artificial intelligence", "artificial learning", "machine learning", "machine intelligence", "supervised learning", "unsupervised learning", "deep learning", "bayesian learning", "statistical learning", "neural network", "probabilistic networks", "knowledge representation") AND clinical microbiology keywords ("microbiology", "bacteriology", "parasitology", "virology", "mycology", "clinic*") AND diagnostics keyword ("diagno*") (Supplementary material). We have included articles resulting from these searches up to November 2019 and added relevant references found in recent reviews.(6,9–14)

Study selection

Prospective and retrospective articles in English that reported original research on ML for microbiological diagnostics were included. We included development reports, implementation studies, clinical trials or qualitative studies of ML systems that could potentially be used in routine by a CM laboratory. We excluded studies that described expert systems (defined by the use of manually programmed rules), ML systems used for research purpose with no relevance in the clinical laboratory, systems for treatment optimisation (e.g. guiding antibiotic

selection) and systems using data not accessible to clinical microbiologists (e.g. biochemical markers).

Analysis of the selected articles

Each article was classified according to its overarching objective into (i) micro-organisms detection, identification and quantification, (ii) evaluation of antimicrobial susceptibility (iii) diagnosis, disease classification and clinical outcomes. We then detailed the precise outcome of the ML system (e.g. prediction of capreomycin resistance in *Mycobacterium* species) and the data sources used by the system (e.g. WGS, MALDI-TOF MS, etc.). We analysed whether the studies described the performance (e.g. sensitivity and specificity) of the diagnostic system, the implementation and adoption of the system in routine clinical microbiology practice or the impact of the system on the microbiology laboratory processes or on patients' clinical outcomes.

Definitions of learning methods

The different ML systems described in the reviewed articles were classified into supervised learning, unsupervised learning and reinforcement learning (Figure 1).(15) Supervised learning refers to algorithms using labelled data, i.e. data in which the outcome of interest is defined, as a training dataset. For example, to train an algorithm for predicting carbapenem resistance, a dataset in which bacteria are already defined as carbapenem resistant or susceptible has to be used. In unsupervised learning, data are used without any predefined outcome of interest and algorithms are left to their own to find patterns and to extract hidden structure from data without any expert labelling. Reinforcement learning involves algorithms discovering actions that yield the greatest rewards through trial and error.(16)

RESULTS

Characteristics of ML systems for clinical microbiology

Among the 141 articles identified and assessed for eligibility, 38 were excluded: 18 with ML system adapted for clinicians, 12 with outcomes not relevant to clinical practice and 8 using data not accessible to clinical microbiologists.

In total, 103 articles with 97 unique ML systems for clinical microbiology were included in the review. Sixty-four articles were found in MEDLINE/PubMed, 14 in IEEE Xplore Digital Library, 14 in free repository of electronic preprints such as arXiv (n = 7) or bioRxiv (n = 7), eight in Google Scholar and three in ACM Digital Library. The general characteristics of the ML systems are summarized in Table 1 and detailed in the supplementary material.

Overall, 82 (85%) ML systems targeted bacterial infections, 11 (11%) parasitic infections, nine (9%) viral infections and three (3%) fungal infections (some ML systems targeted more than one type of micro-organisms). More precisely, 40 (41%) ML systems focused on micro-organisms detection, identification and quantification, 36 (37%) evaluated antimicrobial susceptibility, 21 (22%) targeted diagnosis, disease classification and prediction of clinical outcomes (Table 2).

To achieve these aims, the ML systems used very diverse sources of data: 21 (22%) used WGS of micro-organisms, 19 (20%) microbiota data obtained by shotgun metagenomic sequencing, 19 (20%) analysed microscopic images, 17 (18%) spectroscopy data, eight (8%) targeted gene sequencing, six (6%) volatile organic compounds (the components of odour), four (4%) bacterial colonies photographs, four (4%) transcriptome data, three (3%) protein structure and three (3%) clinical data (Figure 2).

The vast majority of ML systems used supervised learning (n=96, 99%) whereas 6 (6%) used unsupervised learning, all but one in association with supervised learning. No ML system used reinforcement learning. Overall, 34 different ML techniques were used with 40 (41%) systems using more than one ML technique (median 3, IQR 2-4). The most frequent ML techniques were Artificial Neural Network (n=46, 47%) including 15 Convolutional Neural Networks, Support Vector Machine (n=34, 35%), Random Forest (n=28, 29%), and Logistic Regression (n=11, 11%) (Table 1).

Most articles were published using high-income countries (HIC) data (n=71, 73%) but a significant number of ML systems were developed with low- and middle-income countries (LMIC) data (n=36, 37%).

Only one ML system was reported to be used in clinical practice in the UK.(17) This system aimed to screen urine samples in order to decide which ones should be discarded because of a low probability of positivity. The authors analysed 212,554 urine reports including clinical data and described a potential relative workload reduction of 41%. However, the authors did not give any detail on the implementation of the system and its actual impact. The 96 other ML systems only reported performance measures such as sensitivity and specificity.

Micro-organisms detection, identification and quantification

Forty algorithms (41%) aimed to detect, identify or quantify micro-organisms (Table 2). Among them, 15 ML systems analysed data from cultured bacteria including photographs,(18–20) Fourier-transform infrared spectroscopy(21,22) or volatile organic compounds(23,24) of bacterial colonies. Eight ML systems were developed to identify the bacteria by direct analysis of clinical samples, with volatile organic compounds for diabetic foot infection(25) or tuberculosis(24), 16S ribosomal DNA PCR on respiratory samples for LRTI,(26) or fluorescent microscopic images for tuberculosis.(27) However, among these 23 systems the bacteria that could be identified were limited to a small number of species (median 3, IQR 7-15).

Some ML systems aimed to reduce the time between sampling and microbiological diagnosis. Researchers recently reported the use of Raman optical spectroscopy of a single bacterial colony in suspension coupled with ML to identify a micro-organism among 30 bacterial and yeast species.(28) This system could also be used to differentiate between MRSA and MSSA. However, its use with biological liquids rather than with a prepared suspension of bacteria has yet to be evaluated. Andini *et al.* described an internal transcribed spacer high resolution melt assay that can differentiate between 89 bacterial species.(29)

Using ML, they identified the bacterial species in 59 culture-positive monobacterial blood culture samples with 90% accuracy within 3 hours. A recent article described using the same ML system for antimicrobial susceptibility testing (detecting aminoglycosides resistance in *Escherichia coli* and *Staphylococcus aureus*).⁽³⁰⁾

For parasitic diseases, the systems used microscopic images of blood smears to detect *Plasmodium* species^(31–37), mostly *Plasmodium falciparum*, and microscopic images of stools to identify intestinal helminths.^(38,39) Although the reported performances were correct (reported sensitivity between 85% and 99% and specificity between 95% and 99%) for these articles, the exclusion of smears that are difficult to interpret and the use of manually cropped images currently limit the use of ML systems in this field. One article described the use of quantitative phase spectroscopy to detect *P. falciparum* but used one single strain.⁽⁴⁰⁾ Only two ML systems focused on mycology, both using very limited datasets to identify *Candida* species on culture.^(41,42)

In virology, ML systems have been used to identify HPV genotypes⁽⁴³⁾, develop a mobile platform for mumps, measles and HSV diagnosis⁽⁴⁴⁾ and identify viral pathogens in lower respiratory tract infections (LRTI).⁽⁴⁵⁾ Besides, ML could help to identify new viral agents. While conventional bioinformatic methods (based on sequence homology) only permit to discover new variants of already known viruses,^(46,47) a recent work used ML to analyse codon usage bias to identify new putative viral sequences.⁽⁴⁸⁾

Evaluation of antimicrobial susceptibility

Inferring the phenotypic antibiotic susceptibility pattern of microorganisms from genomic data has been a challenge enthusiastically taken up by several groups.⁽⁴⁹⁾ In the early times, predicting the phenotype from the genotype seemed highly feasible for pathogens where acquired resistance was mediated by the acquisition of well-known antibiotic resistance genes. Indeed for such pathogens as *S. aureus*,⁽⁵⁰⁾ *E. coli* and *Klebsiella pneumoniae*,⁽⁵¹⁾ a presence/absence rule-based algorithm yielded excellent performances (91-100%) for inferring the phenotype. However, for species such as *Pseudomonas aeruginosa* where the

antibiotic susceptibility pattern was highly connected to the up or down regulation of the expression of genes, performances were not as good.(52) ML emerged as a potential solution when the knowledge about the precise mutational events associated with antibiotic resistance is not complete enough to be used in genotype-to-phenotype studies. A recent study showed that for *P. aeruginosa*, ML combined with gene expression (RNAseq) and the presence or absence of resistance genes yielded >90% predictive values for predicting resistance to meropenem and tobramycin. Still, poor performances were observed for ceftazidime (81% for predicting resistance and 83% for predicting susceptibility).(53) Similar approaches were described for *C. difficile*,(54) *E. coli*,(55) or *Elizabethkingia* species.(56) Besides genomic data, a number of ML systems analysed MALDI-TOF MS data to extend its potential for diagnostics, e.g. to discriminate between MRSA, MSSA and heterogeneous vancomycin-intermediate *S. aureus*.(57–59) In a recent study, Bhattacharyya *et al.* combined genotypic and phenotypic data to rapidly identify the susceptibility profile of bacterial pathogens.(60) From RNAseq data, they identified gene expression patterns differing between susceptible and resistant strains exposed to antibiotics and used these genes to engineer a quantitative fluorescent hybridization which could work on crude bacterial lysates. The method gave good performances (94-99% correct predictions) in *E. coli*, *K. pneumoniae* and *Acinetobacter baumannii*. The authors provided a proof-of-concept of the test directly from positive blood cultures with a turn-around-time of <4h. Other ML systems used WGS to combine the identification and antibiotic susceptibility testing of micro-organisms: Drouin *et al.* reported a ML system that can identify 12 species and susceptibility to 56 antibiotics,(61) Kim *et al.* 9 species and 29 antibiotics.(62)

One team used ML systems directly to infer the minimal inhibitory concentration (MIC) of nontyphoidal *Salmonella* species or *K. pneumoniae* with WGS data using decision tree-based supervised learning.(63,64) The MICs predicted by the models correlated with the presence of known resistance genes and the overall accuracy of the system was between 92 and 95% within a two-fold dilution. However, in a similar article predicting ciprofloxacin MIC in *E. coli*, the accuracy was only 65% within a two-fold dilution.(65) *Mycobacterium*

tuberculosis antibiotic susceptibility testing was the aim of seven ML systems, using WGS(66,67) or protein structure data extrapolated from genomic data.(68,69) Gumbo *et al.* conducted a supervised classification and regression tree analysis with clinical outcome data from 58 patients to determine the optimal pyrazinamide MIC for *Mycobacterium tuberculosis* susceptibility breakpoint.(70)

Viral genomes evolve under complex patterns of genetic changes to shape the landscape of their fitness and resistance to their environment. Advances in metagenomic sequencing technologies producing multiple time-point WGS, in conjunction with ML technologies, provided a better understanding of viral evolution and viral interactions with their host and/or environment. For example, Shim *et al.*(71) used artificial neural networks (ANN) with time-sampled whole-genome echovirus sequences to observe substitutions arising under disinfectant pressure. Their results supported the role of the viral structure protein VP1 in adapting to the disinfectant.

Another team used ANN to identify amino-acid substitutions in the viral protease that predicted HIV resistance to lopinavir (a protease inhibitor).(72) The authors confirmed their findings in a validation dataset including thousands of HIV-positive clinical samples. This use of ML could help to find unexpected mutations associated to the evolution of viral sequences and thereby pave the way for new diagnostic markers.

Diagnosis, disease classification and clinical outcomes

Twenty-one ML systems used microbiological data to diagnose and classify infectious or non-infectious diseases and predict clinical outcomes. Microbiota data (obtained by targeted gene sequencing or shotgun metagenomic sequencing) has been coupled with ML to predict periodontitis,(73) dental caries(74) or bacterial vaginosis.(75) However, the pathogenicity of the microorganisms found with this method is still debated.(76) In a recent proof of concept study, Langelier *et al.* combined microbiological and host transcriptome data in tracheal aspirates to differentiate patients with proven LRTI (LRTIs, n=26) and patients with non-infectious acute respiratory failure (n=18) with a 100% sensitivity and 87% specificity.(45)

Among the 21 ML systems, 10 used microbiota data to diagnose non-infectious diseases such as irritable bowel syndrome,(77,78) inflammatory bowel disease,(79) colorectal cancer(80) or insomnia.(81)

Regarding clinical outcomes, Njage et al. used ML with data from WGS of shiga toxin-producing *E. coli* to predict the severity of the disease(82) and Staley *et al.* analysed the modification of gut microbiota to predict the recurrence of *C. difficile* infection following encapsulated faecal microbiota transplantation.(83) For viral respiratory infections, a ML system provided a 84-gene expression pattern that could discriminate between children with mild Respiratory Syncytial Virus (RSV) infection from those with severe RSV disease.(84) The identified signature was independently validated in other cohorts and could serve to develop prognostic tests for the management of RSV disease.

ML can also pave the way for the analysis of new and complex data that is not used yet for diagnosis in clinical practice. For example, three articles used ML to analyse the odour (volatile organic compounds) of various clinical samples in order to diagnose urinary tract infections,(85) acute chronic obstructive pulmonary disease exacerbations,(86) or active tuberculosis.(87)

DISCUSSION

ML for current and future data

We found ML systems analysing different sources of data including data currently used in clinical practice such as microscopic images of Gram stain or blood smears and data that is not yet used in routine such as microbiota data. ML systems using current data mainly aimed to develop the automation of repetitive tasks in the CM laboratory and to allow clinical microbiologists to take action at the end of the process for the validation of the results. By contrast, the development of ML systems analysing complex, high-dimensional and sparse data pave the way for leveraging new data that could become prominent in the CM laboratory. Microbiota data is currently not used in routine practice but we identified a number of ML systems that aimed at diagnosing diseases,(88) predicting clinical

outcomes(83) or identifying pathogens.(45) By providing the tools that will facilitate the analysis of microbiota, WGS or transcriptome data in the CM laboratory, ML could modify the way laboratories are commonly separated in hospitals. Classical borders are blurred with ML systems that use human transcriptomics data to predict the severity of infection(84,89) or ML applications that use microbiota data to diagnose inflammatory bowel diseases or colorectal cancer.(79,80,90)

The choice of the outcome is a critical point influencing the clinical relevance of a ML system. We identified ML systems with outcomes such as the classification of haemolysis on bacterial cultures(91) or the identification of *Leuconostoc*, *Fructobacillus* and *Lactococcus*.(92) While such systems can be technically worthwhile, they do not necessarily meet a clinical need. Regarding parasitology, most ML systems addressed easy tasks (e.g. the detection of intestinal helminths on microscopic images) but left difficult tasks aside (e.g. detection of amoeba). Moreover, the systems still required the most time-consuming step in the diagnosis which is the technical manipulation of the stools (fresh state, concentrations, preparations, colorations). In bacteriology, most ML systems targeted either bacteria identification or antibiotic susceptibility testing for a limited number of species (median 3, IQR 7-15) but optimal tools should be able to perform different tasks on a broad scope of species using the same data as has been done in some recent articles.(61,62)

Performance and interpretability of ML systems

All the ML systems reported a measure of performance such as sensitivity or specificity but few systems compared their performance with other methods. Ideally, ML systems performances and costs should be compared to reference methods used in routine. In some cases, ML systems yielded slightly lower performances than those obtained with an expert system.(55) Consequently, a comparison between ML systems and rule-based algorithms may sometimes be relevant. AI is best suited to augmenting human intelligence, bringing big-data into focus in order to support human decision-making. Therefore, developers should aim to study the interaction between clinicians and algorithms and to report comparisons

between humans alone and humans using ML systems. Indeed, the reporting of human-versus-algorithm comparison is not very relevant as ML systems and humans will not be competing on similar tasks but will perform different tasks.

Interpretability of ML systems is a major challenge as clinical microbiologists and other healthcare professionals are less prone to adopt ML systems whose intrinsic mechanisms they do not understand (the so-called 'black box'). Microbiologists must know why errors by ML systems might occur and what they should check before validating the results. For some ML systems, presenting the results in an interpretable way is relatively easy, for example by highlighting the part of the image that allows a diagnosis,(93) but for others, a special effort is needed to find appropriate visualization tools.(94) In our review, few articles detailed the interpretability of the ML system. Eck *et al.* assigned relevance values to each feature used by the ML algorithm so that clinical microbiologists can understand which features the algorithms used to discriminate between healthy subjects and patients with inflammatory bowel disease.(79) Drouin *et al.* used ML systems for genotype to phenotype prediction in *M. tuberculosis* and 11 bacteria species and presented the resulting classifiers as a hierarchical arrangement of rules.(61) Using the example of meropenem resistance in *K. pneumoniae*, they showed that their models confirmed existing knowledge such as the importance of *bla_{KPC-2}* but also identified new targets to understand resistance such as the *febB* gene, which encodes a periplasmic protein essential for virulence. A number of other tools for genotype-phenotype prediction presented the most relevant genes in their models, thereby easing the interpretation by a clinical microbiologist.(63,67,95)

Evaluation and implementation

From the clinical perspective, the evaluation of ML systems is still incomplete with 96 (99%) systems that presented performance data but only one tool that reported the use of the system in practice. This gap is a major challenge in the field of AI in healthcare and the pathway between development and routine use is long and fraught with obstacles, as emphasized by the non-adoption, abandonment, scale-up, spread and sustainability (NASS)

framework for digital technologies.(96) Besides, there is a lack of literature regarding the specificities of the implementation of the ML systems and the way forward to their adoption in routine work. In a recent review, we listed the challenges which are to be met to use ML systems in clinical practice.(6)

Among the systems that we identified, no article described their use in clinical practice nor reported clinical outcomes or impact on processes. Research on ML systems in real-world settings should aim to collect information on consequences both at the clinician and patient-levels and implementation outcomes such as appropriateness or fidelity may be key intermediate outcomes to study the success of strategies aiming to bring ML systems to the clinical practice.(97) Clinical microbiologists who are at the interface between physicians and diagnostics tools are crucial to bridge the gap between demand and supply of innovative systems.(98) In Figure 3, we summarized the different steps between the technical development of ML systems and their adoption in clinical practice.

Potential for diagnostics in LMICs

ML can trigger the development of innovative point of care diagnostic tools with the potential to be used in remote areas. Convolutional neural networks were used on smartphone photographs of thick blood smear to diagnose malaria or of stool samples to detect helminths.(99) Li *et al.* reports a mobile platform combining multimodal microscopy and ML systems to diagnose malaria in the field.(31) Another team described the early development of a diagnosis platform powered by solar energy and using ML to analyse changes in pH during DNA amplification for infectious diseases diagnosis.(100) These systems are particularly relevant in countries with lack of skilled laboratory staff to analyse easily obtained data (e.g. blood smears). However, much work is needed to ensure that these new technologies can be adopted in a sustainable way and the specificities of LMICs should be considered early in the development of the ML system.

As ML systems are constrained by available data, high-quality open access databases are paramount to the evolution of ML systems. CuratedMetagenomicData(101) for microbiota

analysis or PATRIC for WGS(102) were particularly important for a number of ML systems in CM.(67,69,88,103) Healthcare and clinical data repositories are increasingly important with the development of ML and a special effort should be made to integrate data from patients in LMICs. Indeed, the diversity of settings and populations included in training and validation datasets is essential to the development of unbiased and high-quality ML systems. ML systems are only as good as the data that they are provided with and a number of authors have described the risk of reproducing human bias and worsening inequalities with the use of ML.(104,105) The provision of public access to ML models(61,62) will be helpful and can be used to foster collaborations and to strengthen the education of clinical microbiologists about ML worldwide.

CONCLUSION

We found 97 ML systems in CM that used various sources of data with diverse practical applications. The existence of open-access databases of microbiota and WGS data is a strong asset for the development of ML systems and should be further encouraged. Despite systematic reporting of performance measures, the comparison of ML outputs with currently used reference methods was lacking. No article described the use of a ML system in clinical practice nor reported impact on processes or clinical outcomes. Future studies should aim to improve the interpretability of their ML systems and discuss their potential integration and implementation in real-world settings.

FIGURE LEGENDS

Figure 1: The three basic machine learning paradigms

*Most supervised machine learning systems wrongly classify data that was not included in the training dataset. Some algorithms can use Bayesian approaches to add an “unknown” class but this presents technical difficulties.

**Reinforcement learning involves the comparison of different policies that map a state (in the figure a polymicrobial clinical sample) to actions (in the figure, analyse or discard the sample). The comparison is done by studying the rewards (e.g. clinical outcomes) linked to one policy (e.g. discarding polymicrobial samples) as compared to another (e.g. analysing polymicrobial samples). Reinforcement learning is used when the best policy is not known.

Figure 2: Sankey diagram mapping the sources of data used by the 97 ML systems to their outcomes

Figure 3: The pathway towards implementation within routine clinical practice

Table 1: General characteristics of machine learning systems for clinical microbiology

ML systems		n=97 (%)
Microbiology specialty		
	Bacteriology*	69 (71)
	Mycobacteriology	13 (13)
	Parasitology	11 (11)
	Virology	9 (9)
	Mycology	3 (3)
Types of learning		
	Supervised	96 (99)
	Unsupervised	6 (6)
	Reinforcement	0
Machine learning techniques		
	Artificial Neural Network (including Convolutional Neural Network, Deep Neural Network, Spiking Neural Network, etc.)	46 (47)
	Support Vector Machine	34 (35)
	Random Forest	28 (29)
	Logistic Regression	11 (11)
	K-Nearest Neighbours	8 (8)
	Decision, Regression or Classification Trees	8 (8)
	(Extreme) Gradient Boosting	7 (7)
	Naïve Bayes	7 (7)
	Adaptive Boosting	6 (6)

	Others (LASSO, Genetic Algorithms, Elastic Net, Hierarchical Clustering, Linear Discriminant Analysis, L2-Regularization, etc.)	22 (23)
Evaluation**		
	Performance	96 (99)
	Implementation	1† (1)
	Impact	0
Geographical settings		
	High-income countries	71 (73)
	Low- and middle-income countries	36 (37)
Year published		
	2019	25 (26)
	2018	25 (26)
	2017	13 (13)
	2016 and before	34 (35)

*Including microbiota studies

**We separated studies that describe the performance (e.g. ROC curves) of the diagnostic system (performance), studies that describe the implementation and adoption of the system in routine clinical microbiology practice (implementation) and studies that describe the impact of the system on the microbiology laboratory processes or on patients' clinical outcomes (impact).

†One study reported the implementation of the system in routine practice but did not give any details on implementation or impact in the article(17)

Table 2: Input data and outcomes of the machine learning systems in clinical microbiology

ML systems		n=97 (%)
Type of input data		
	Whole genome sequencing	21 (22)
	Microbiota (16S RNA or DNA)	19 (20)
	Gut	12 (12)
	Lung	4 (4)
	Others (skin, oral cavity, maternal milk, vaginal)	3 (3)
	Microscopic images*	19 (20)
	Spectroscopy	17 (18)
	MALDI-TOF mass spectroscopy	7 (7)
	Fourier-transform infrared spectroscopy	4 (4)
	Others (Raman, quantitative phase, pyrolysis, etc.)	6 (6)
	Targeted gene sequencing	8 (8)
	Volatile organic compounds	6 (6)
	Bacterial colonies photographs	4 (4)
	Transcriptome	4 (4)
	Clinical data	3 (3)
	Protein structure	3 (3)
	Biochemical tests	1 (1)
Output of the machine learning systems		
	Micro-organisms detection, identification and quantification	40 (41)
	Cultures of bacteria	15 (15)
	Direct examination of bacteria	8 (8)
	<i>Mycobacterium tuberculosis</i>	4 (4)
	<i>Plasmodium spp.</i>	9 (9)
	Helminths	3 (3)
	<i>Candida spp.</i>	2 (2)
	Viruses	4 (4)

	Evaluation of antimicrobial susceptibility	36 (37)
	Enterobacterales	18 (19)
	Non-fermenting Gram-negative Bacilli	6 (6)
	<i>Mycobacterium tuberculosis</i>	7 (7)
	<i>Staphylococcus aureus</i>	8 (8)
	Viral resistance (HIV and echovirus)	2 (2)
	Other Gram-positive cocci (<i>Streptococcus</i> spp., <i>Enterococcus</i> spp.)	2 (2)
	Others (<i>Clostridioides difficile</i> and <i>Neisseria gonorrhoea</i>)	2 (2)
	Diagnosis, disease classification and clinical outcomes	21 (22)
	Diagnosis of non-infectious diseases**	8 (8)
	Diagnosis of lower respiratory tract infections	4 (4)
	Prediction of severity (Shiga-toxigenic <i>Escherichia coli</i> infection, Respiratory Syncytial Virus infection, irritable bowel syndrome, insomnia)	4 (4)
	Diagnosis and prediction of recurrence of <i>Clostridioides difficile</i> infection	2 (2)
	Diagnosis of dental infections	2 (2)
	Response to therapy (inflammatory bowel disease)	2 (2)
	Diagnosis of urinary tract infections	2 (2)
	Diagnosis of other infections (tuberculosis, Zika virus, bacterial vaginosis)	3 (3)

*One ML system analysed microscopic videos

**Insomnia, irritable bowel syndrome, inflammatory bowel disease, colorectal cancer, cirrhosis, type-2 diabetes, connective tissue disease.

SUPPLEMENTARY MATERIAL

1. List of the machine learning systems included in the review with their main characteristics

TRANSPARENCY DECLARATION

The authors have no relevant conflicts of interest to disclose.

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AUTHORS' CONTRIBUTIONS

Conceptualization and methodology: NPS, ER

Screening and selection of articles: NPS

Data analysis: NPS, SD, CR, GB, SF, ER

Writing original draft: NPS, ER

Writing – Review and Editing: SD, CR, GB, FXL, SF, ER

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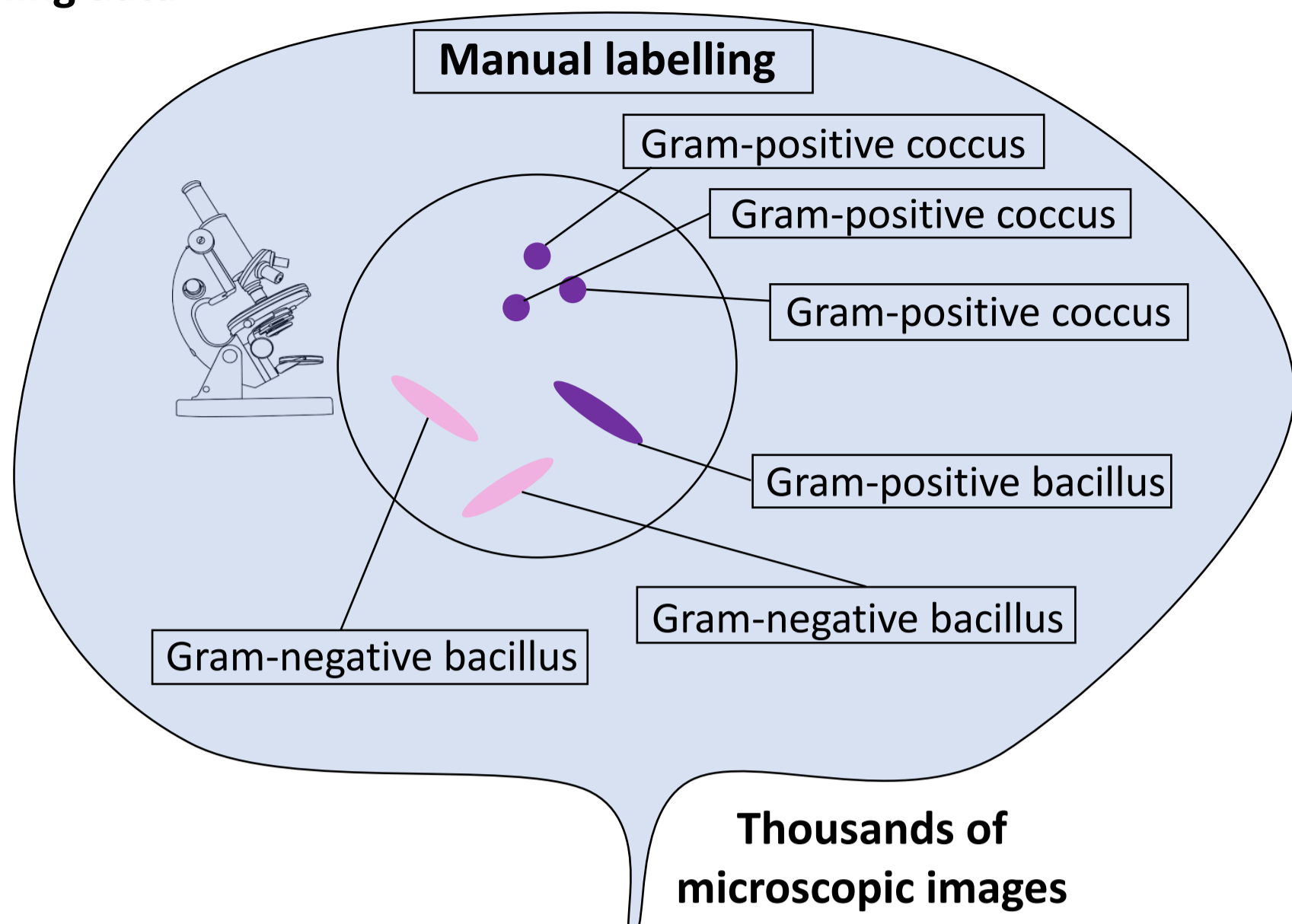
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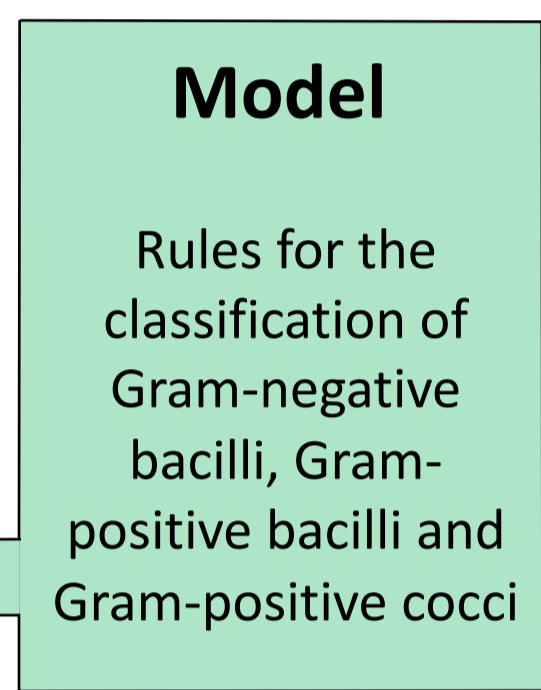
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Supervised learning

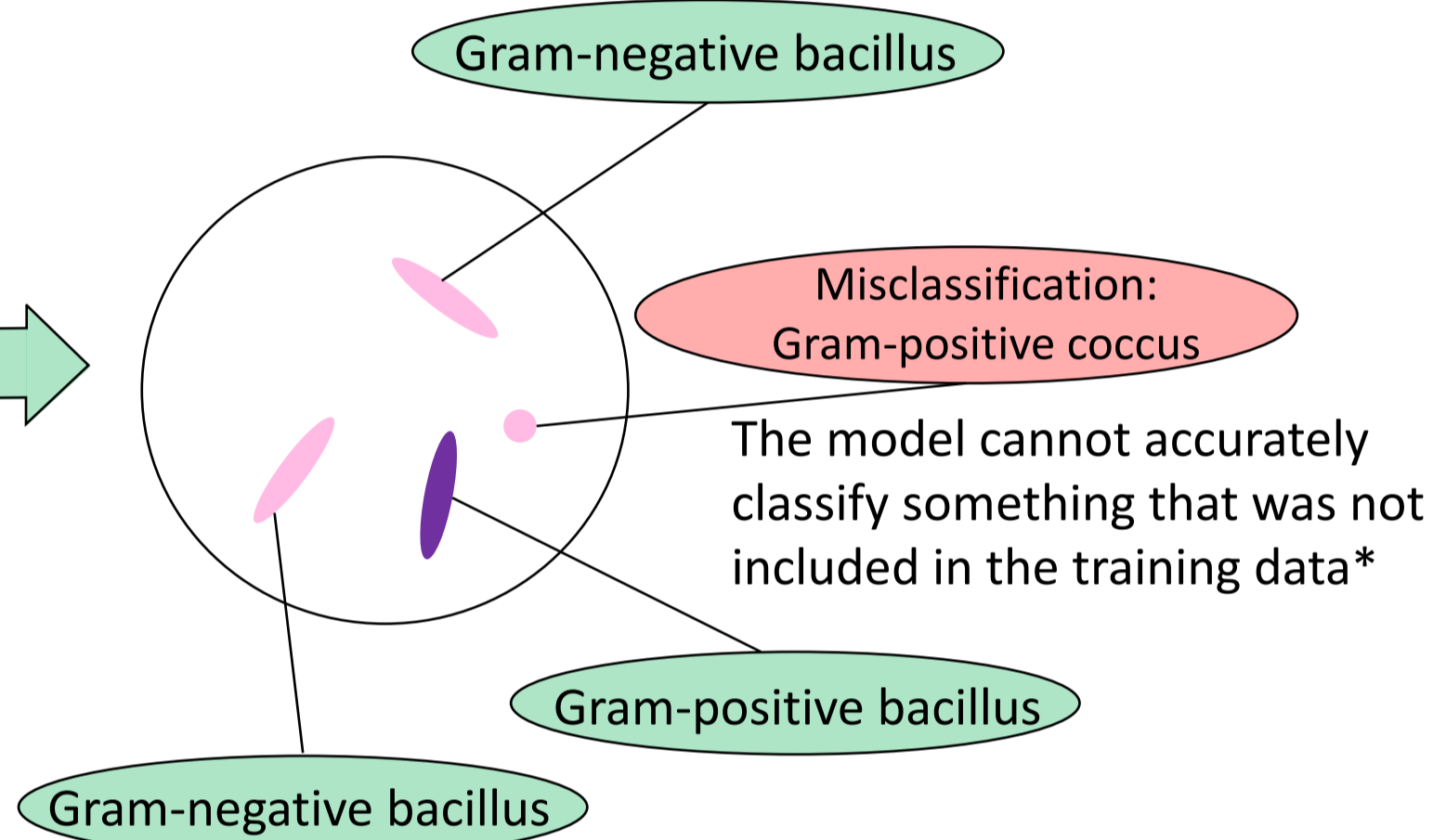
Training data



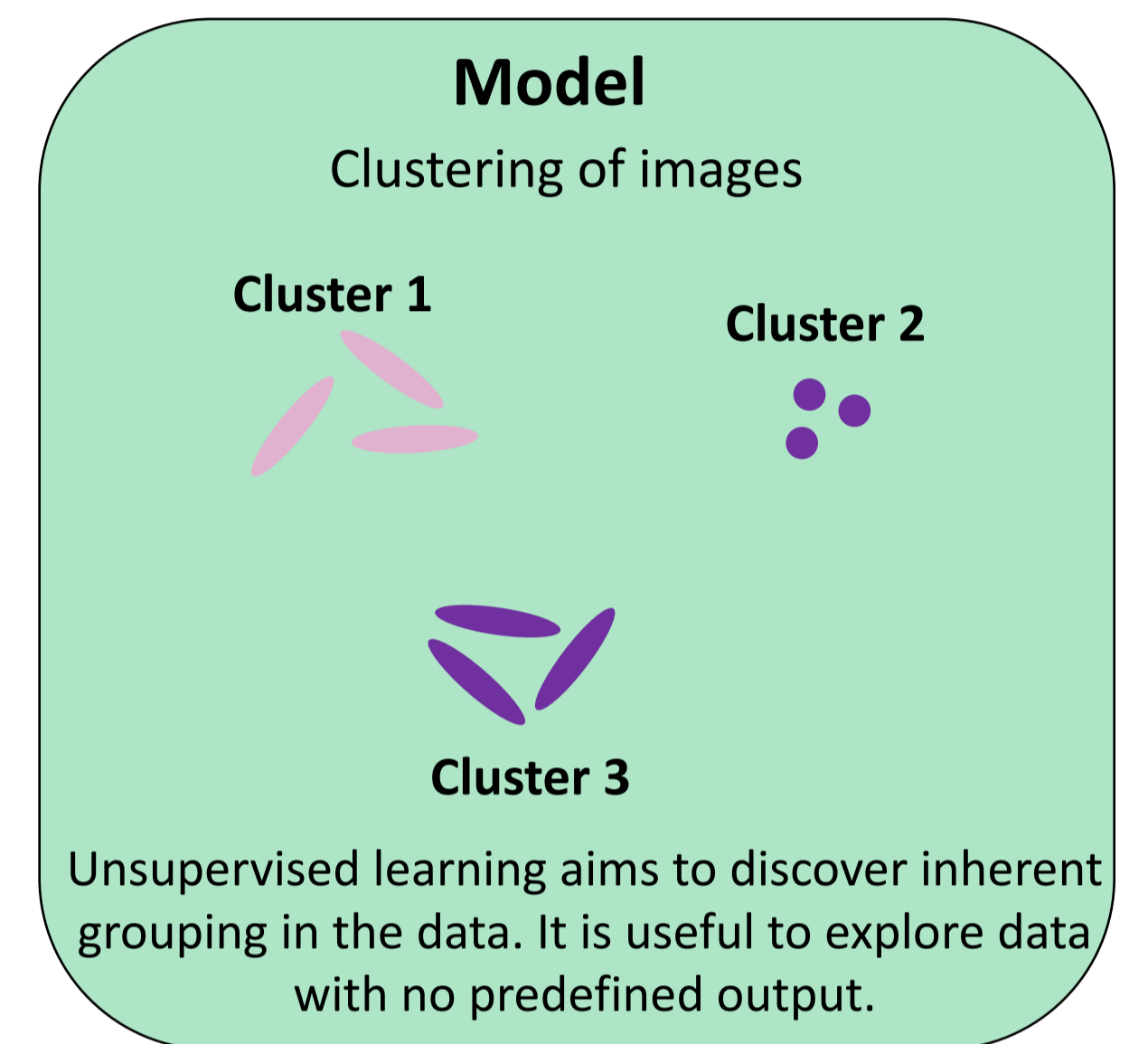
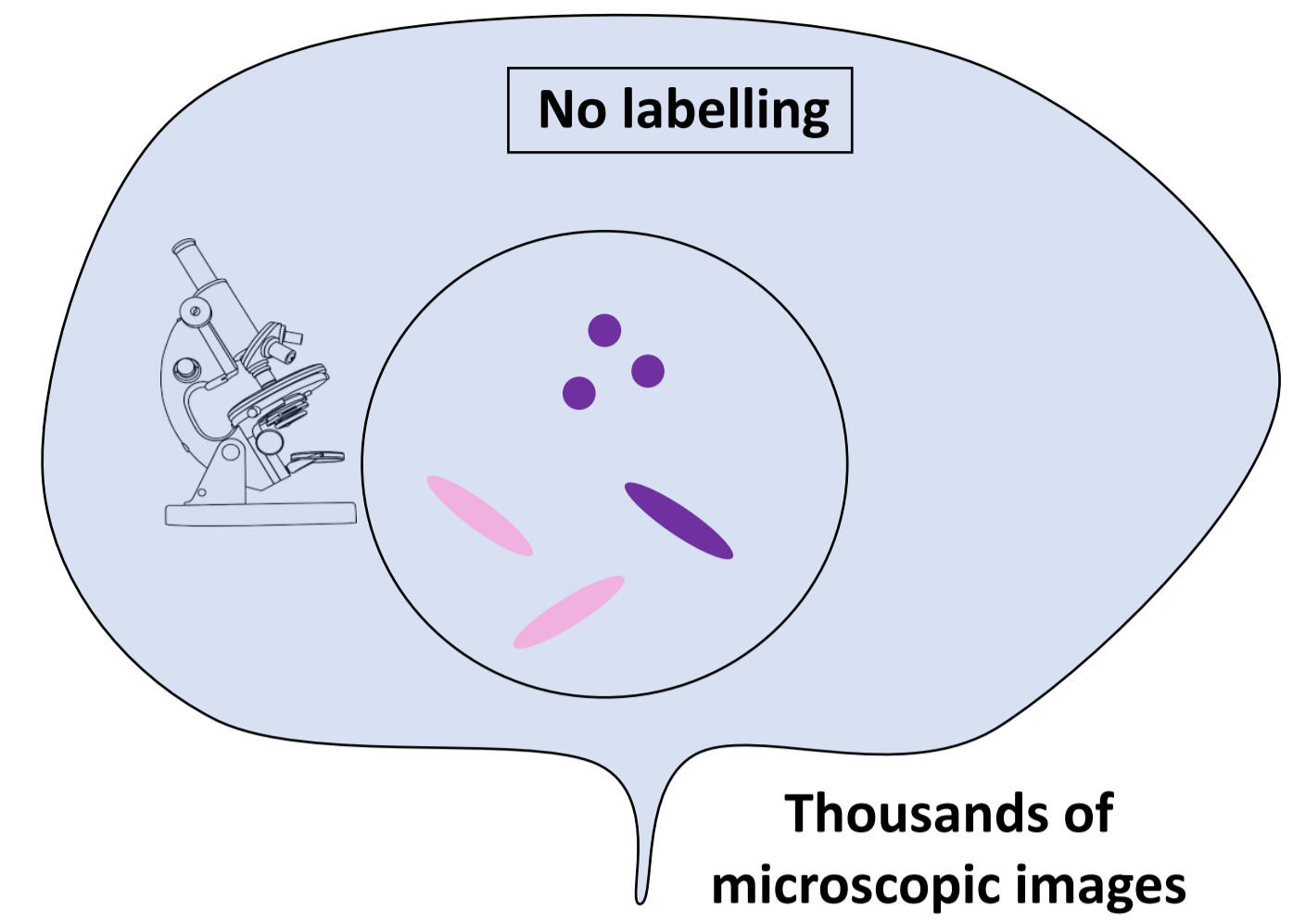
New data



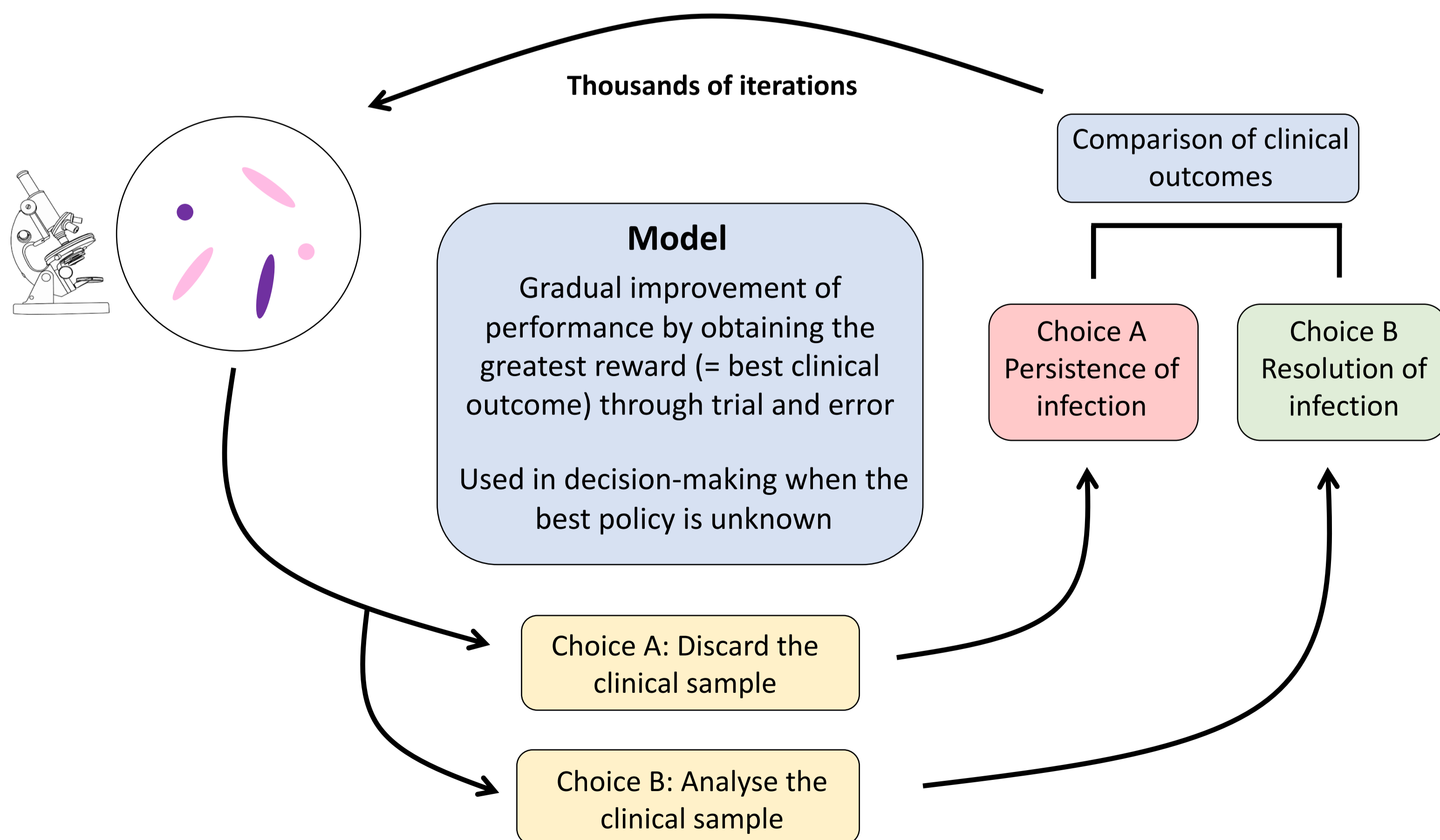
Prediction of the model

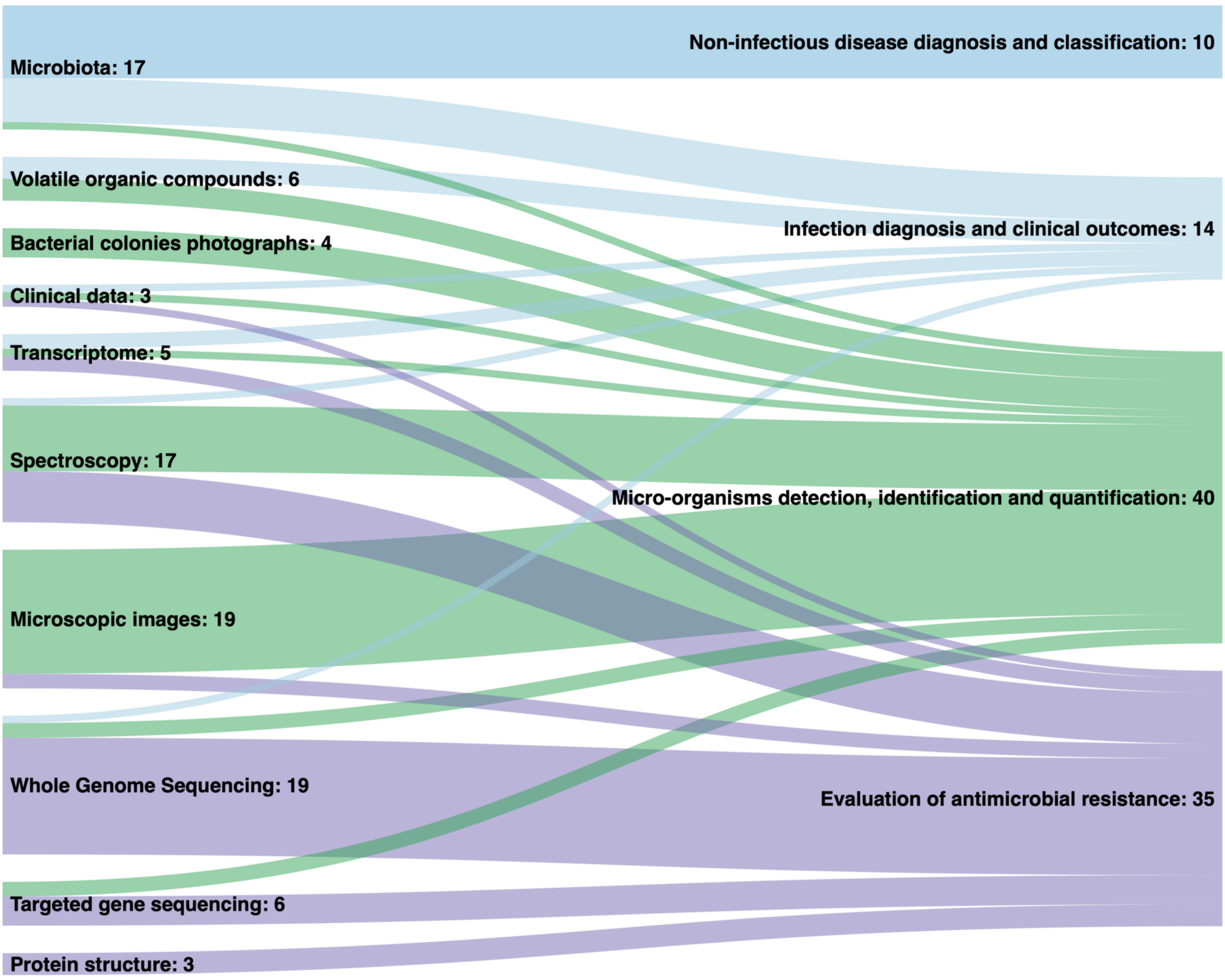


Unsupervised learning

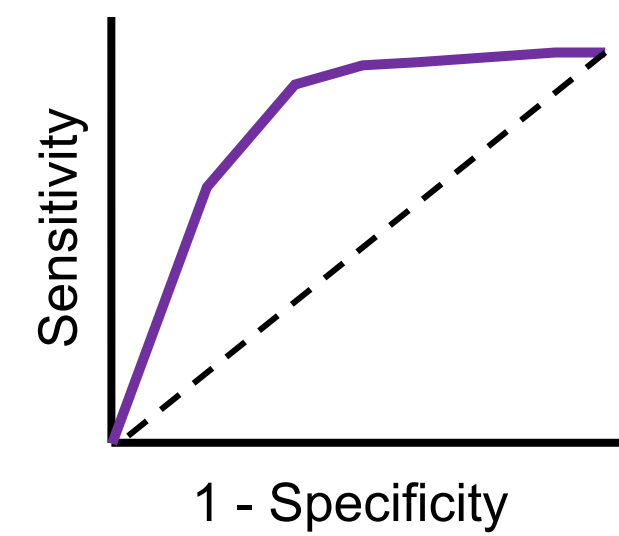
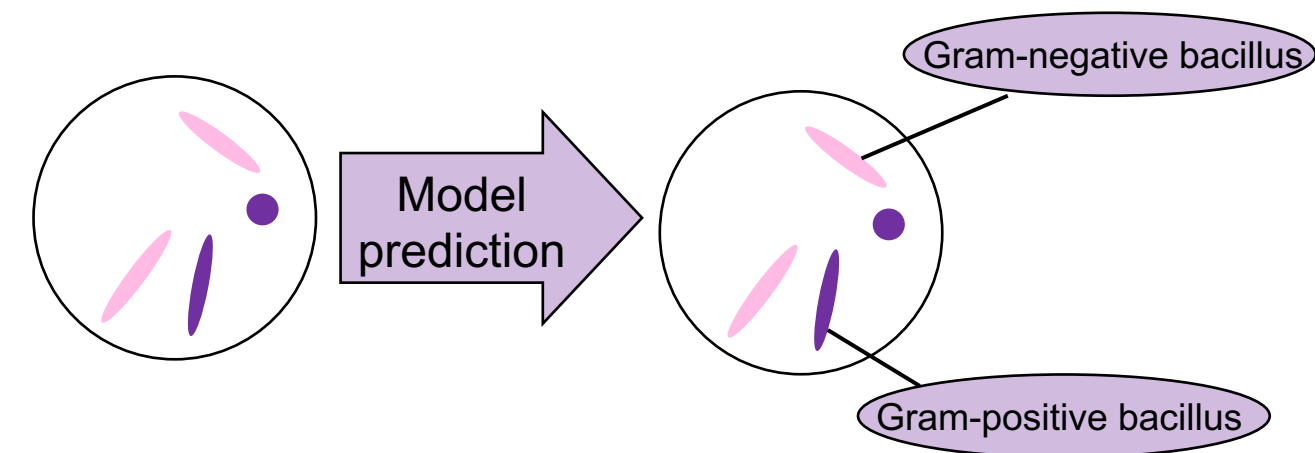


Reinforcement learning**



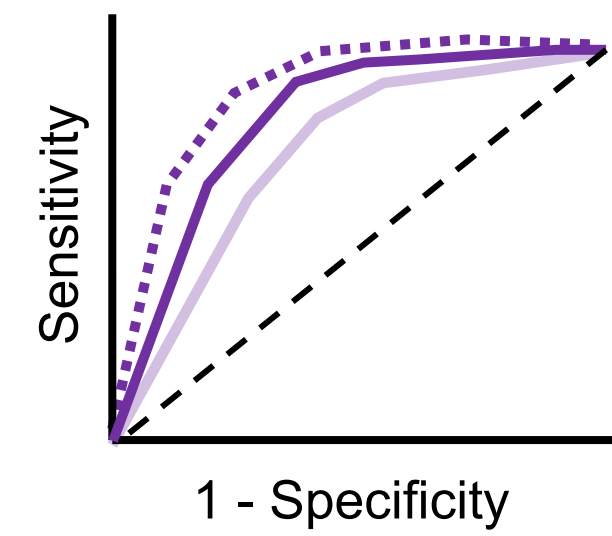
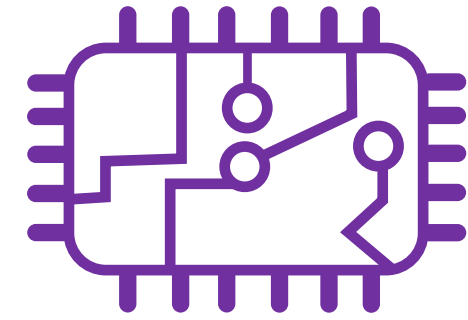


Development of a machine learning system



Evaluation of performance

Development of a platform for diagnostics

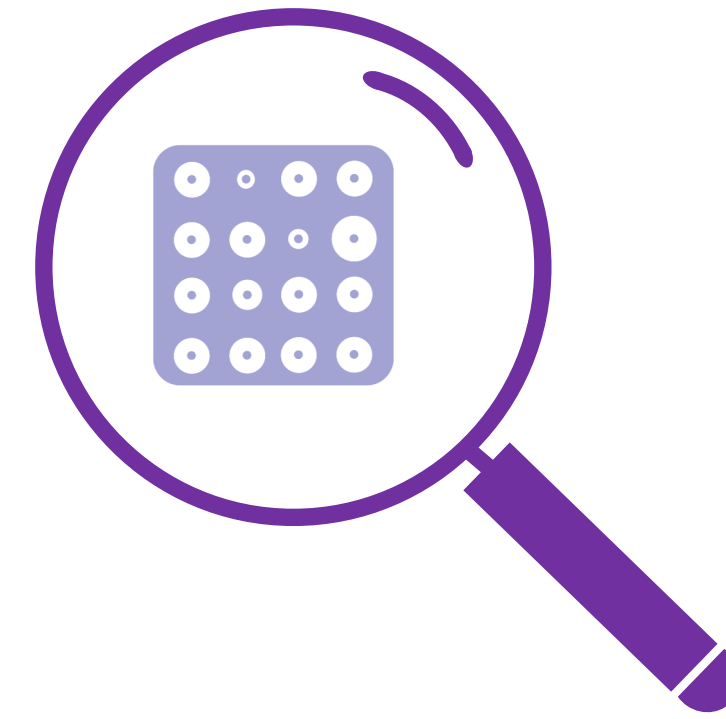


Comparison of performance with current systems

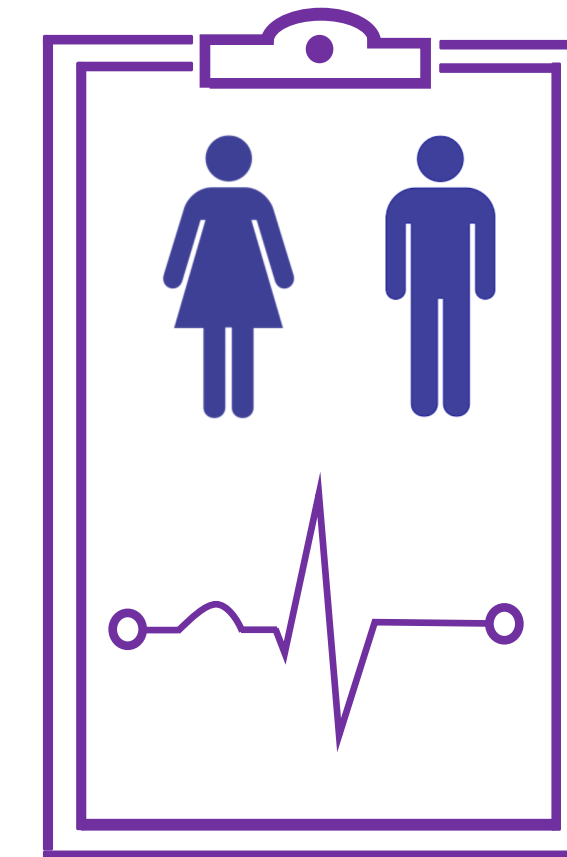


Usability

Clinical validation in real-world settings

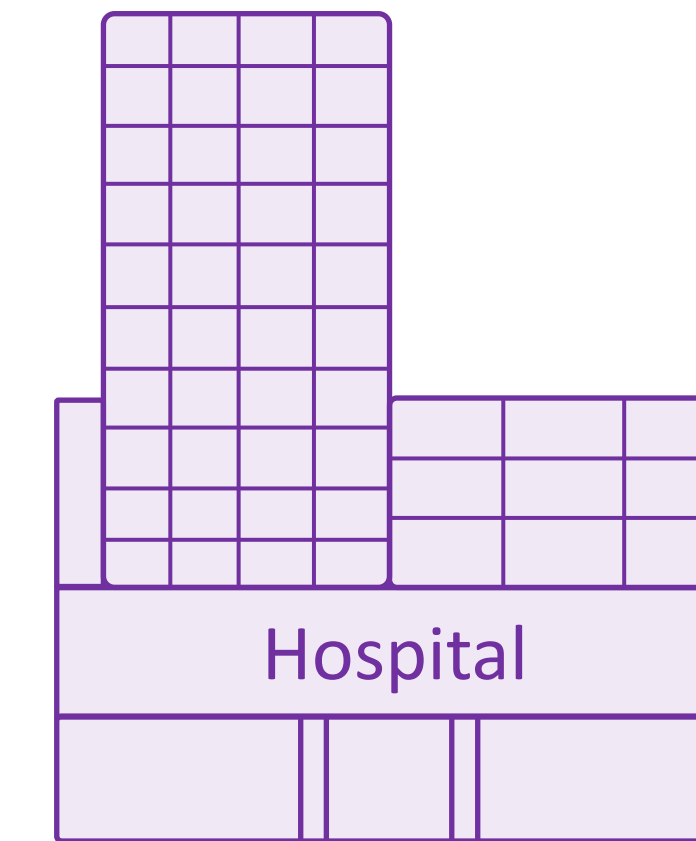


Process evaluation



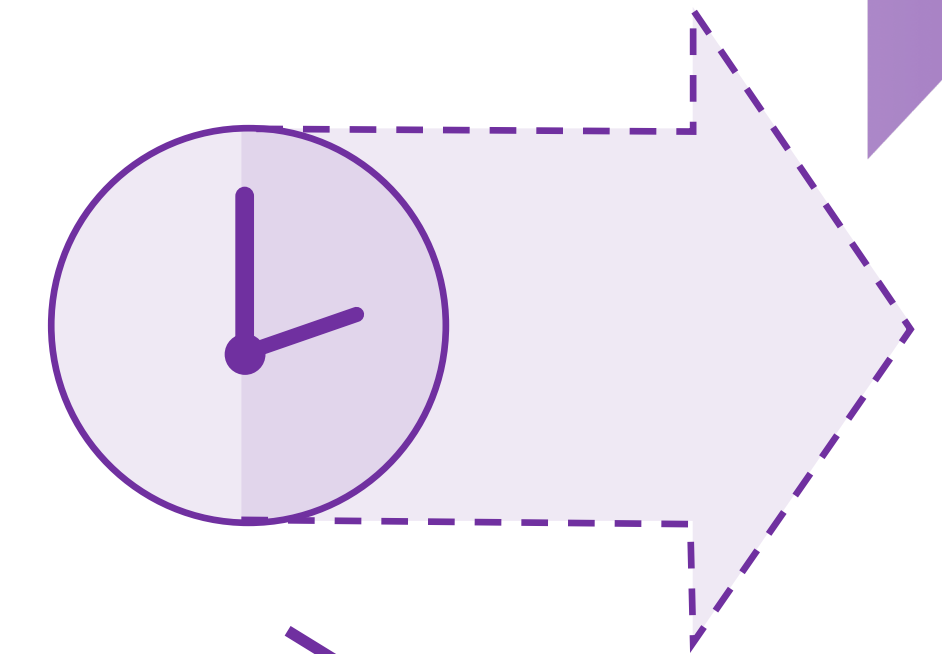
Clinical outcomes

Implementation into routine clinical practice

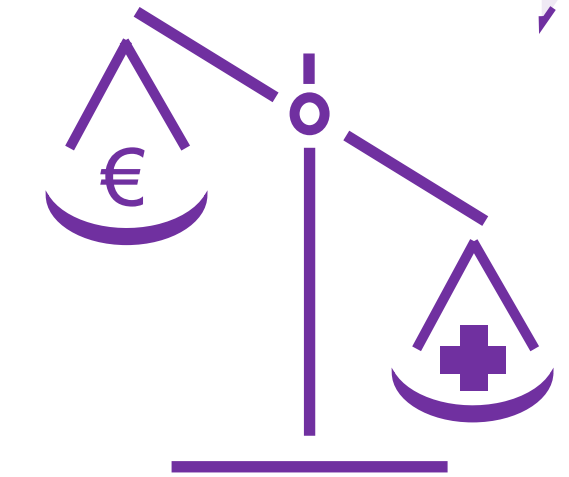


Implementation outcomes

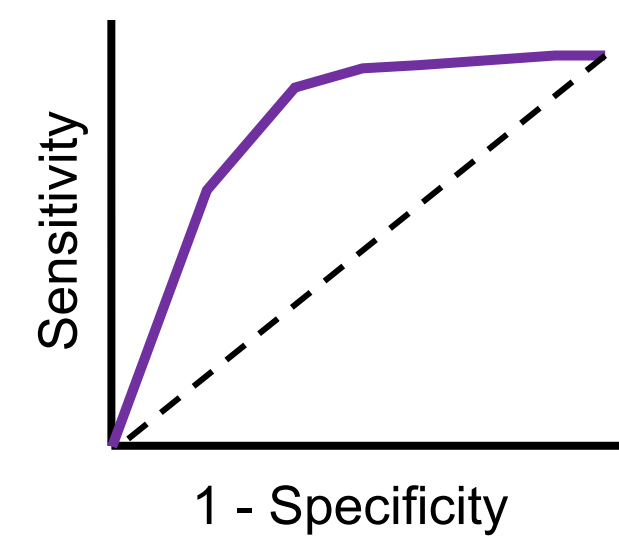
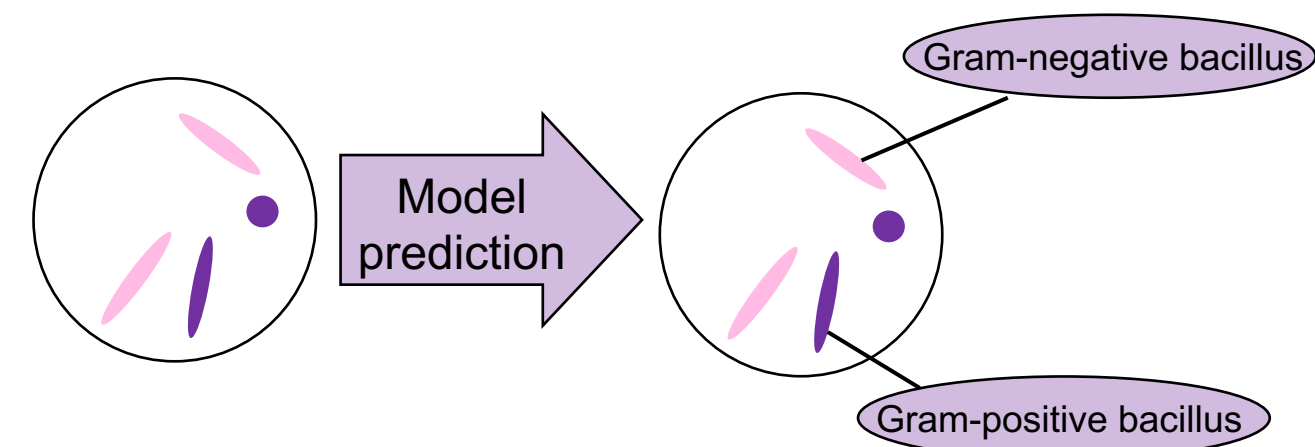
Sustainability



Long-term impact
Medico-economic studies

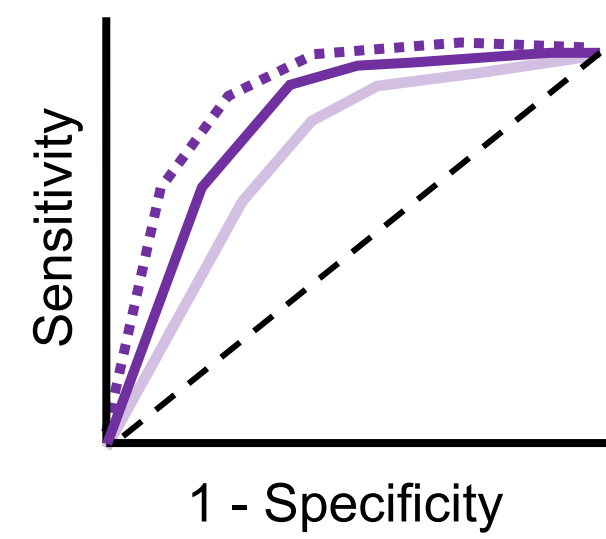
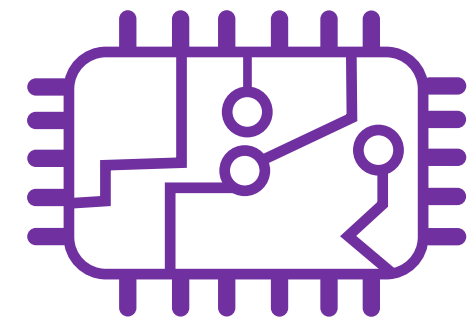


Development of a machine learning system



Evaluation of performance

Development of a platform for diagnostics

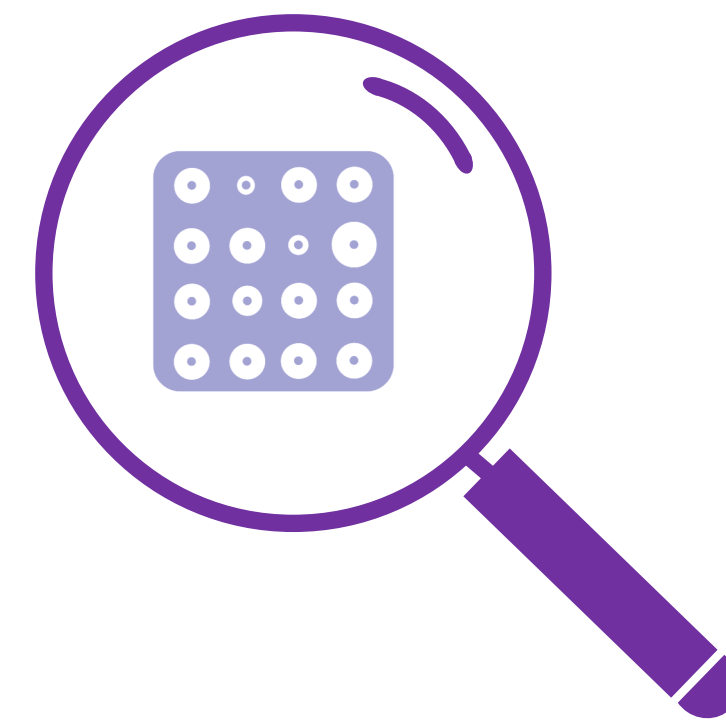


Comparison of performance with current systems

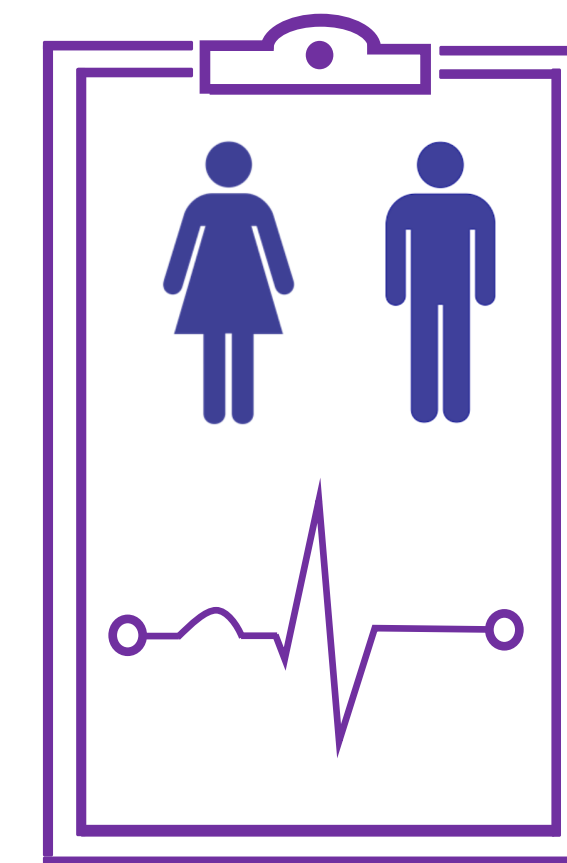


Usability

Clinical validation in real-world settings

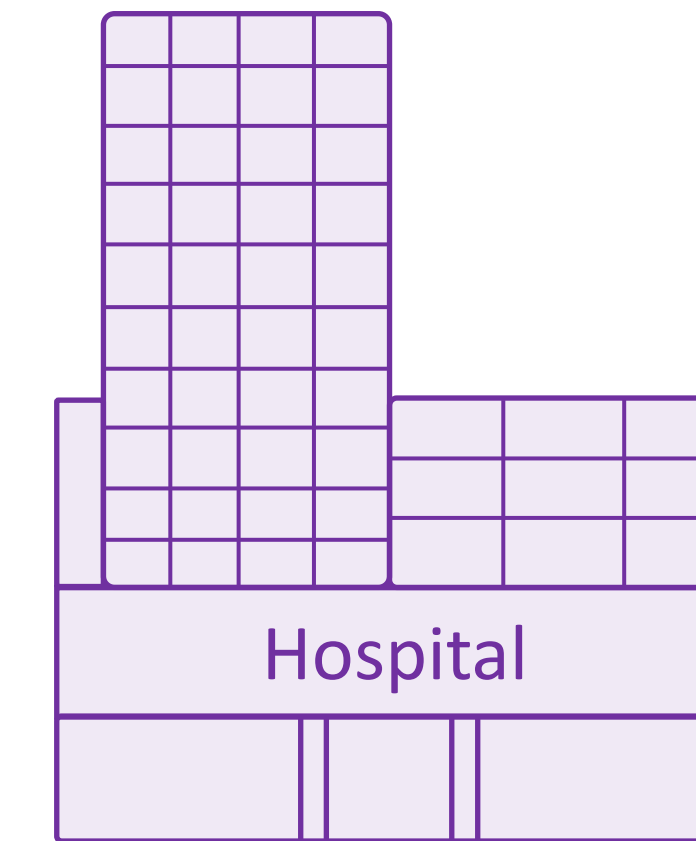


Process evaluation



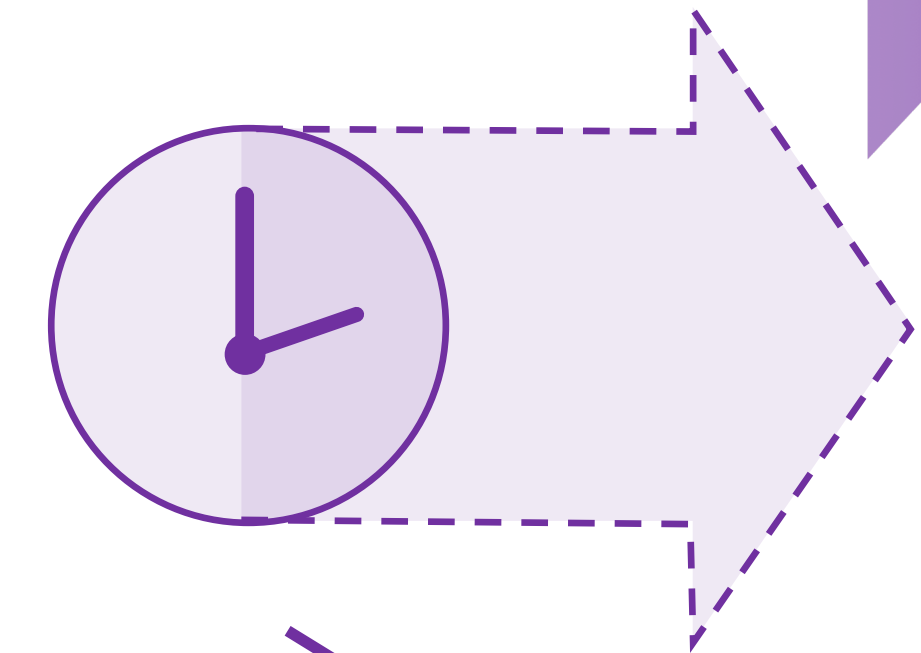
Clinical outcomes

Implementation into routine clinical practice



Implementation outcomes

Sustainability



Long-term impact
Medico-economic studies