



Webinar Tuberculosis Day  
Perhimpunan Dokter Paru Indonesia Cabang Jakarta  
Minggu, 11 April 2021

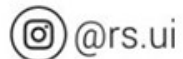


# Artificial Intelligence Era of Pulmonology and Respiratory Medicine: **Updates in Tuberculosis Biomolecular and *In-silico* Diagnostic Tools**

**dr. Irandi Putra Pratomo, Ph.D., Sp.P(K), FAPSR**

- Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia
- COVID-19 Task Force – Pulmonology Unit, Universitas Indonesia University Hospital
- *Bioinformatics Core Facilities – Infectious Disease and Immunology Research Center – Human Cancer Research Center, IMERI FKUI*
- Indonesian Society of Respirology/Perhimpunan Dokter Paru Indonesia

Jl. Prof Bahder Djohan, Kampus UI, Depok



# dr. Irandi Putra Pratomo, Ph.D., Sp.P(K), FAPSR

**Status:** PUI, Dosen Tetap Non-PNS

**NIP:** xxxxxxxx20190930001

**NIDN:** 0018058306

**SCOPUS:** 57192904477

**SINTA:** 6664786

**GARUDA:** 346519

## Pekerjaan:

- Ketua KSM Paru RSUI (2021 – sekarang)
- Ketua Satgas COVID-19 RSUI (2020 – sekarang)
- SpP RS Mayapada Kuningan (2020 – sekarang)
- SpP RSUI (2019 – sekarang)
- SpP RSUD Tarakan Jakarta (2019 – sekarang)
- Dosen FKUI (2019 – sekarang)
- Anggota peneliti IMERI FKUI (2017 – sekarang)

**Kompetensi/peminatan:** pulmonologi dan kedokteran respirasi, website, mahadata, kecerdasan buatan, kedokteran genomik

## Pendidikan:

- SpP(K), Kolegium Pulmonologi dan Kedokteran Respirasi Indonesia (2020)
- SpP FKUI (2018)
- Ph.D Hiroshima University (2017)
- S1 & Profesi FKUI (2008)
- SMAN 4 Jakarta (2001)

## Aktivitas akademis saat ini:

### **Pembimbing tesis/disertasi:**

- 1 mahasiswa doktor biomedis FKUI
- 1 mahasiswa pascasarjana IPB

### **Penelitian:**

- Berbagai topik COVID-19 dengan berbagai institusi kesehatan, pendidikan, dan pemerintahan
- *Indoor Air Pollution*, FKUI – Kementerian PUPR – Hiroshima University





# Presentation Outline

- The End TB Strategy Challenges
- TB Diagnostic Challenges
- Molecular Diagnostics
- *In-silico* Investigations: Gene & Drugs Discovery
- Artificial Intelligence-aided Decision Making: CAD4TB
- Take Home Message and Conclusions





# The End TB Strategy Challenges



- Vision: A **world free of TB**. Zero deaths, disease and suffering due to TB
- Goal: **End the global TB epidemic**
- Indicators:
  - **95% reduction by 2035 in TB deaths compared with 2015**
  - **90% reduction by 2035 in TB incidence rate compared with 2015**
  - **Zero TB-affected families facing catastrophic costs due to TB by 2035**

<https://www.who.int/tb/strategy/end-tb/en/>



# The End TB Strategy Challenges



- Top 10 causes of death in the world, including the **2<sup>nd</sup> top infectious disease after HIV/AIDS**
- 95% occur in low-income people and **responsible in 98% of deaths in low-to-middle income countries**
- Global public health problem due to increasing numbers of **drug-resistant cases**
- Emergence of drug-resistance strains and deaths from TB **can be prevented** if TB adequately detected & managed

<https://www.who.int/tb/strategy/end-tb/en/>  
<https://doi.org/10.1007/s11033-020-05413-7>



# The End TB Strategy Challenges



## PROGRESS



**43 million lives saved**  
between 2000 and 2014 through effective TB diagnosis and treatment



**47% decline in TB mortality rate**  
and 42% decline in TB prevalence rate since 1990



**HIV-related TB deaths down**  
by 32% in the last decade



**Fragile progress in MDR-TB**  
Treatment for MDR-TB has increased with almost all cases detected in 2014 started treatment

<https://www.who.int/tb/strategy/end-tb/en/>



# The End TB Strategy Challenges



## CHALLENGES



**US\$ 1.4 billion funding gap** per year for implementation of existing TB interventions. An additional gap of US\$ 1.3 billion exists for research



**3.6 million people with TB are missed** by health systems every year and therefore may not get adequate care they need

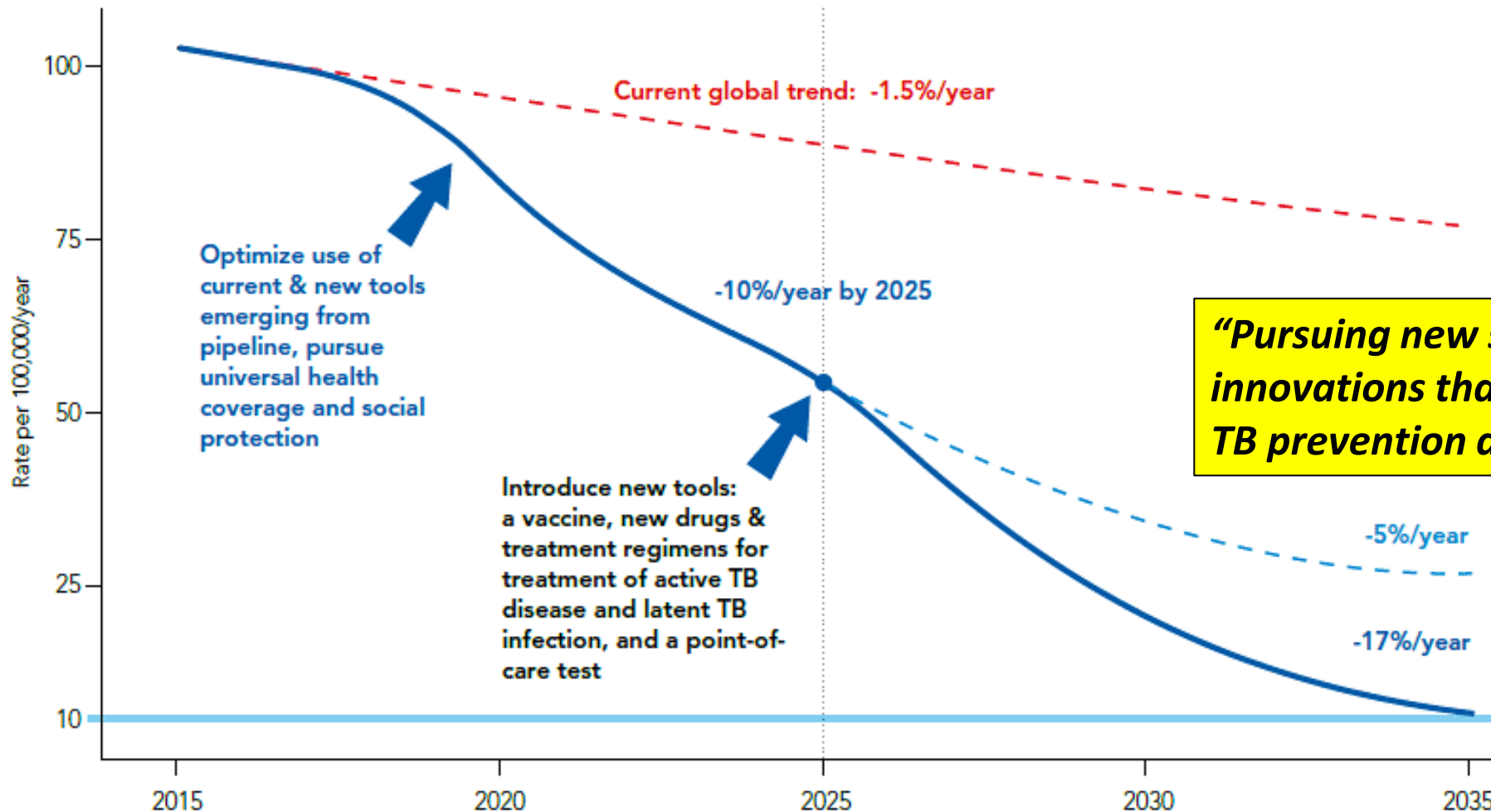


**TB/HIV response needs acceleration**  
Antiretroviral treatment, treatment of latent TB infection and other key interventions still need further scale-up



**MDR-TB remains a public health crisis**  
Only one in four MDR-TB cases detected and one in two cases cured

<https://www.who.int/tb/strategy/end-tb/en/>



***“Pursuing new scientific knowledge and innovations that can dramatically change TB prevention and care”***

<https://www.who.int/tb/strategy/end-tb/en/>



## Digital health for the End TB Strategy: progress since 2015 and future perspectives

### PILLARS AND COMPONENTS

#### 1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION

- A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
- B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support
- C. Collaborative tuberculosis/HIV activities, and management of co-morbidities
- D. Preventive treatment of persons at high risk, and vaccination against tuberculosis

#### 2. BOLD POLICIES AND SUPPORTIVE SYSTEMS

- A. Political commitment with adequate resources for tuberculosis care and prevention
- B. Engagement of communities, civil society organizations, and public and private care providers
- C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
- D. Social protection, poverty alleviation and actions on other determinants of tuberculosis

#### 3. INTENSIFIED RESEARCH AND INNOVATION

- A. Discovery, development and rapid uptake of new tools, interventions and strategies
- B. Research to optimize implementation and impact, and promote innovations

Electronic tools to help stock management and procurement

SMS communication

Electronic notification of TB cases

Mobile phone credit as enabler

Automated laboratory results

VOT

eLearning for staff

eLearning for patients

Digital unique identifier

Add-on hardware to smartphones to permit clinical measurement

Mobile devices as resources for data collection

<https://www.who.int/tb/publications/digitalhealth-meetingreport2017/en/>




KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

# SITT

Online versi 10.04

Sistem Informasi Tuberculosis Terpadu



KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

YOKYAKUD  
**KNCV INDONESIA**  
untuk Indonesia Bebas TB



## SITRUST

Sistem Informasi Tracking untuk Spesimen Transport

Welcome to e-TB Manager

### e-TB Manager

TB Management Information System


Enter your User Name and Password to login

User Name:


Password:

Remember me

User not logged in. Please log in first



USAID FROM THE AMERICAN PEOPLE



SPS Strengthening Pharmaceutical Systems

International Version

Language

English

Forgot your password? [Click here](#)

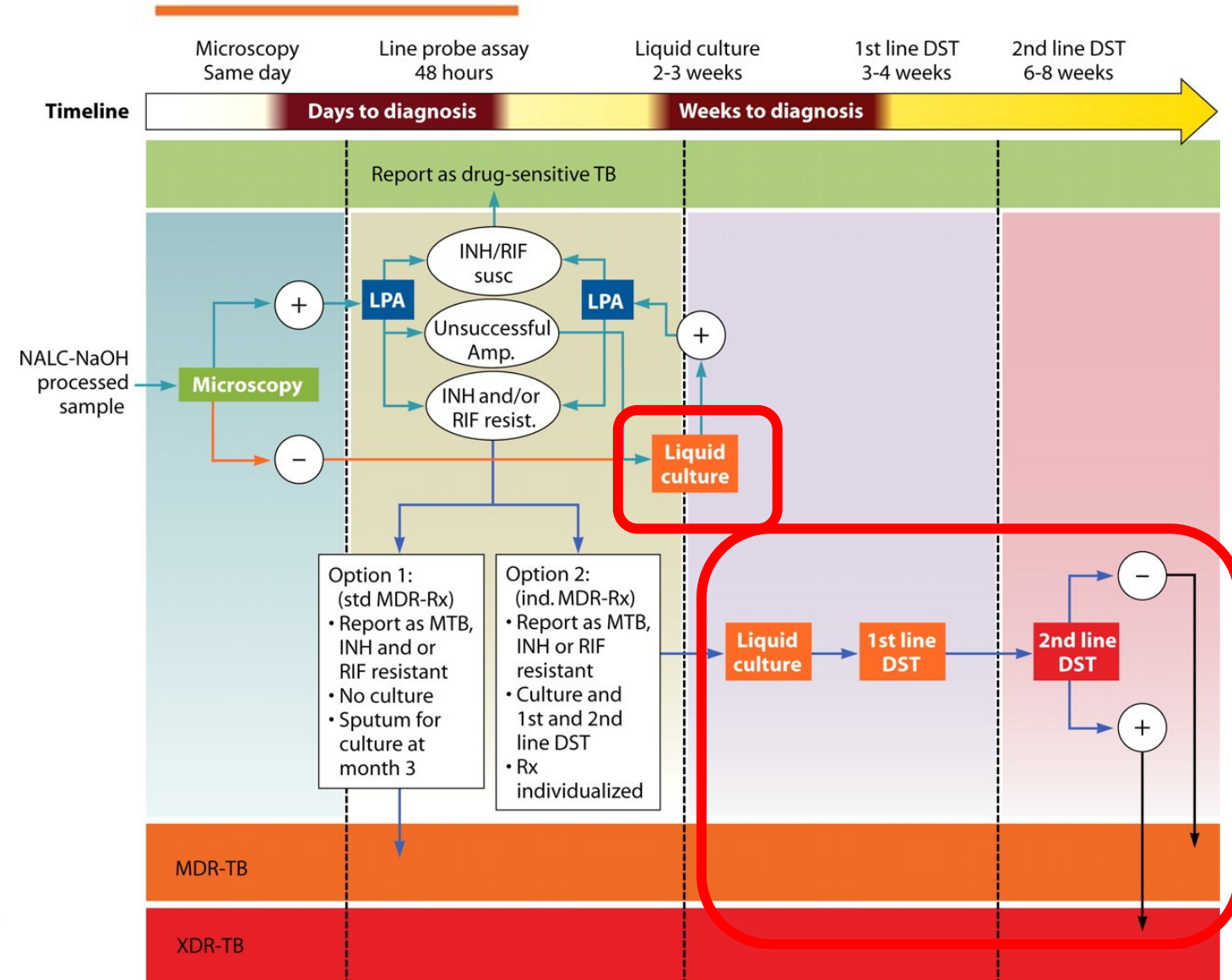
e-TB Manager version 2.0-b1029  
Copyright © 2005 Management Sciences for Health, Inc. All rights reserved.

<https://www.kncv.or.id/pendekatan-ctb.html>



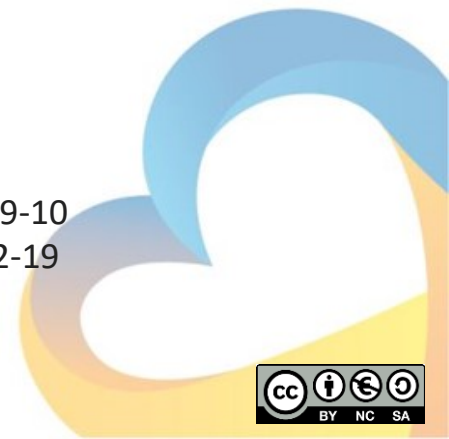


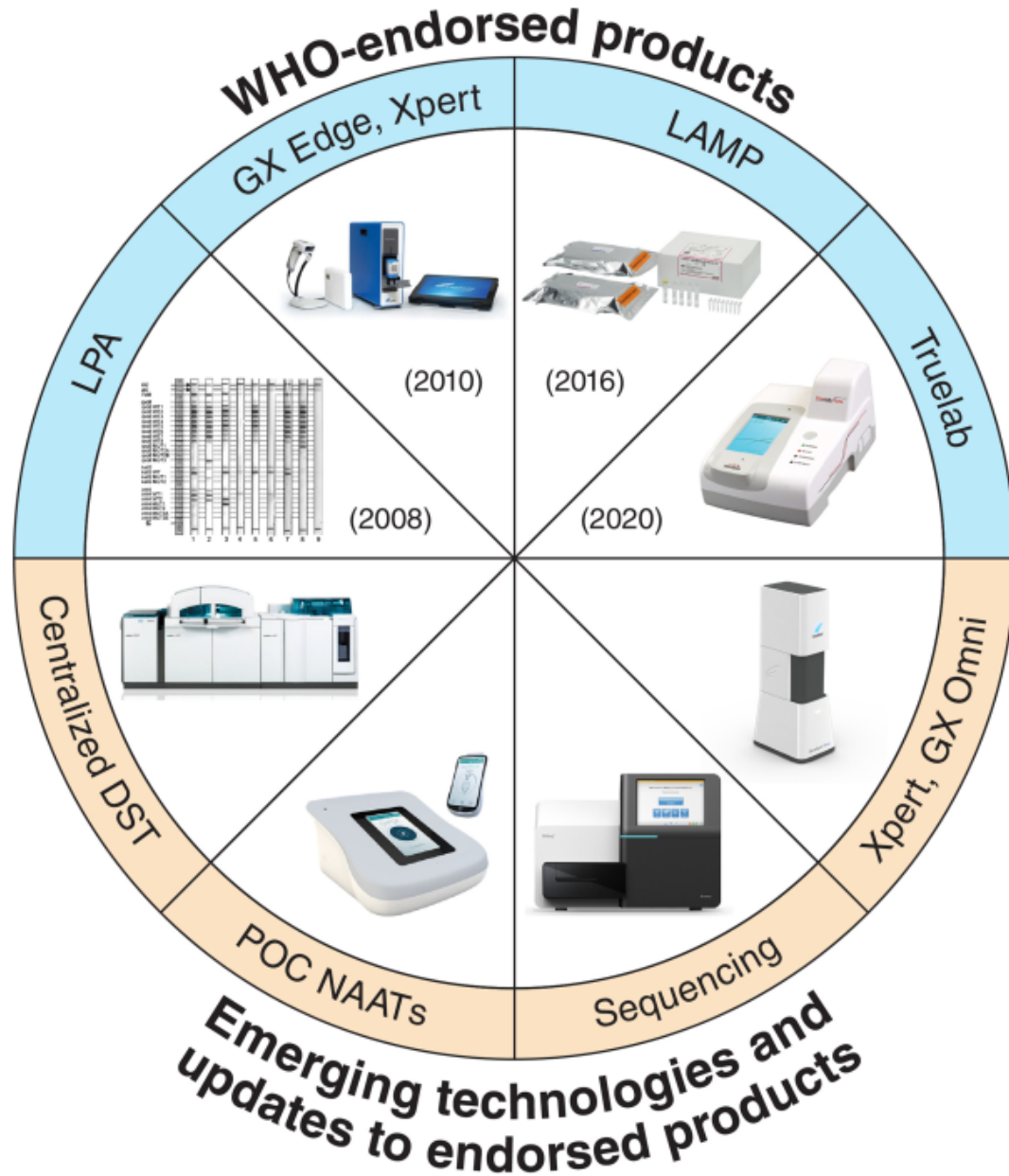
# TB Diagnostics Challenges



The availability of **practical, affordable and efficient** diagnostic solutions in this environment remains one of the **greatest challenges** for ending the global TB epidemic.

<https://doi.org/10.1128/CMR.00059-10>  
<https://doi.org/10.1128/JCM.01582-19>



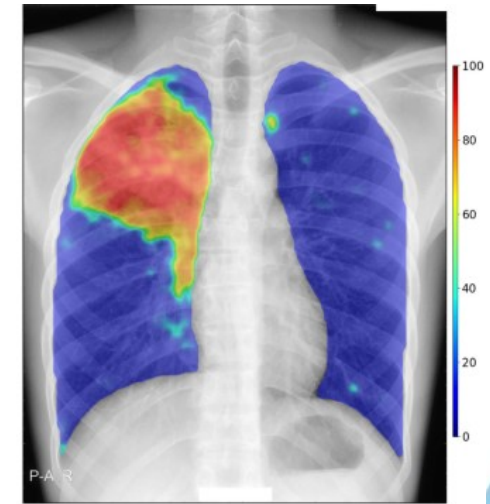


### Other Investigations:

Artificial intelligence-aided decision making, based on radiographical findings



a



b

<https://doi.org/10.1128/JCM.01582-19>

<https://doi.org/10.1038/s41598-020-62148-y>



# Molecular Diagnostics

**TABLE 1** WHO-endorsed molecular tests for pulmonary TB detection and drug susceptibility testing<sup>a</sup>

Technology	Year endorsed	Method principle	Intended use	Sensitivity (%) <sup>b</sup>	Specificity (%) <sup>b</sup>	Target setting of use	Turnaround time (h)	Amenable to rapid test-and-treat?	Reference for policy guidance
Xpert MTB/RIF	2010	qPCR	MTB diagnosis and RIF resistance detection	85 (pooled), 96 (RIF resistance)	99 (MTB detection), 98 (RIF resistance)	District or subdistrict laboratory	<2	Yes, especially on Omni platform	WHO 2020 (21), WHO 2016 (84)
Xpert MTB/RIF ultra	2017	qPCR/melting temperature analysis (RIF resistance)	MTB diagnosis and RIF resistance detection	90 (pooled), 94 (RIF resistance)	96 (MTB detection), 98 (RIF resistance)	District or subdistrict laboratory	<2	Yes, especially on Omni platform	WHO 2020 (21)
First-line probe assays (e.g., GenoType MTBDRplus and NIPRO)	2008	PCR, hybridization	Diagnosis of RIF and INH resistance	98 (RIF resistance), 84 (INH resistance)	99 (RIF resistance), >99 (INH resistance)	Reference laboratory	5	No	WHO 2008 (14)
Second-line probe assays (e.g., GenoType MTBDRsl)	2016	PCR, hybridization	Diagnosis of FLQ and SLID resistance	86 (FLQ resistance), 87 (SLID resistance)	99 (FLQ resistance), 99 (SLID resistance)	Reference laboratory	5	No	WHO 2016 (15)
Loopamp MTBC assay	2016	Loop-mediated isothermal amplification	MTB diagnosis	78 (pooled)	98 (MTB detection)	Peripheral laboratory	<2	Yes	WHO 2016 (16)
Truenat MTB plus	2020	Micro RT-PCR	MTB diagnosis	80 (pooled)	96 (MTB detection)	Peripheral laboratory	<2	Yes, on Truelab platform	WHO 2020 (21)
Truenat MTB-RIF Dx	2020	Micro RT-PCR	Diagnosis of RIF resistance	84 (RIF resistance)	97 (RIF resistance)	Peripheral laboratory	<2	Yes, on Truelab platform	WHO 2020 (21)

<sup>a</sup>FLQ, fluoroquinolone; INH, isoniazid; LAMP, loop-mediated isothermal amplification; NAAT, nucleic acid amplification tests; RIF, rifampin; RT-PCR, reverse transcriptase PCR; SLID, second-line injectable drugs; SSM+/C-, sputum smear microscopy positive/culture positive; SSM-/C+, sputum smear microscopy negative/culture positive; WHO, World Health Organization.

<sup>b</sup>Performance estimates have been retrieved from different studies and are not the result of head-to-head comparisons. Therefore, comparing performances between tests must be made with caution. All reported values are from the policy guidance document cited.



Xpert MTB/RIF assay



GeneXpert system



5	20	80	Samples per shift	500-1000
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<https://doi.org/10.1183/09031936.00157212>





# Genoscholar kit (Line probe assay)

## Feature

### Speedy

Genoscholar kits can get drug resistance information in one day.

Conventional method (1month)

Genoscholar kit (1 day)

### Multiple

Genoscholar kits can detect 1<sup>st</sup> line TB drug resistance (Rifampicin, Isoniazid and Pyrazinamide) and 2<sup>nd</sup> line TB drug resistance (Fluoroquinolone and Kanamycin) simultaneously.

TB positive

Rifampicin

Isoniazid

Pyrazinamide

Fluoroquinolone

Kanamycin

### Detection of NTM

It is possible to interpret not only *M.tuberculosis* but also non tuberculosis mycobacterium (NTM) in one test.

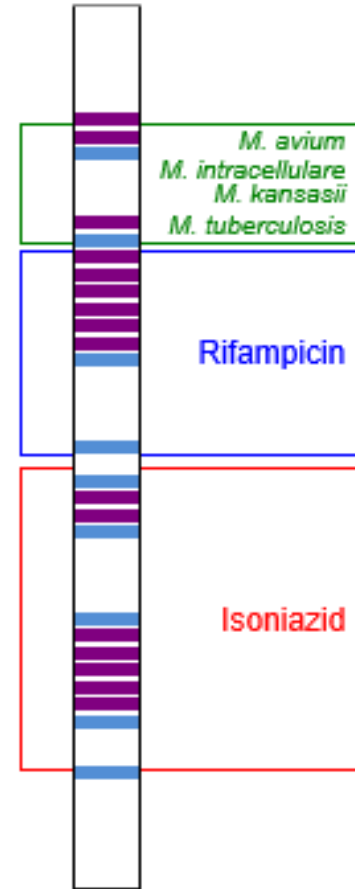




# Genoscholar™ NTM+MDR TB II

- Detect Rifampicin and Isoniazid resistance in 1 day by 1 single test.
- Identify not only *M. tuberculosis* but also *M. avium*, *M. intracellulare* and *M. kansasii*.
- Make test results available from direct samples or cultured materials.
- Easy visual interpretation.
- Highly sensitive and specific detection.

WHO endorsed



RFP※1	LPA profile	
	Mutation	Wild Type
Susceptibility (n)		
RFP-resistant (172)	159	13
RFP-sensitive (202)	5	197

Sensitivity : 92.4% (159/172)

Specificity : 97.5% (197/202)

INH※1	LPA profile	
	Mutation	Wild Type
Susceptibility (n)		
INH-resistant (199)	179	20
INH-sensitive (177)	1	176

Sensitivity : 89.9% (179/199)

Specificity : 99.4% (176/177)



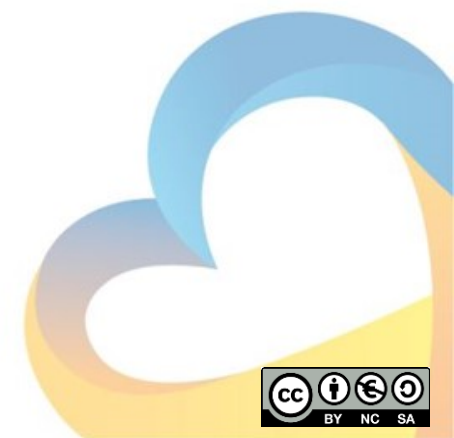
# Genoscholar™ PZA TB II

- Detect Pyrazinamide resistance in 1 day by 1 single test.
- Make test results available from direct samples or cultured materials.
- Easy visual interpretation.
- Highly sensitive and specific detection of Pyrazinamide resistance.

<b>PZA※1</b>	LPA profile	
Susceptibility (n)	Mutation	Wild Type
PZA-resistant (58)	52	6
PZA-sensitive (250)	10	240

Sensitivity : 89.7% (52/58)

Specificity : 96.0% (240/250)

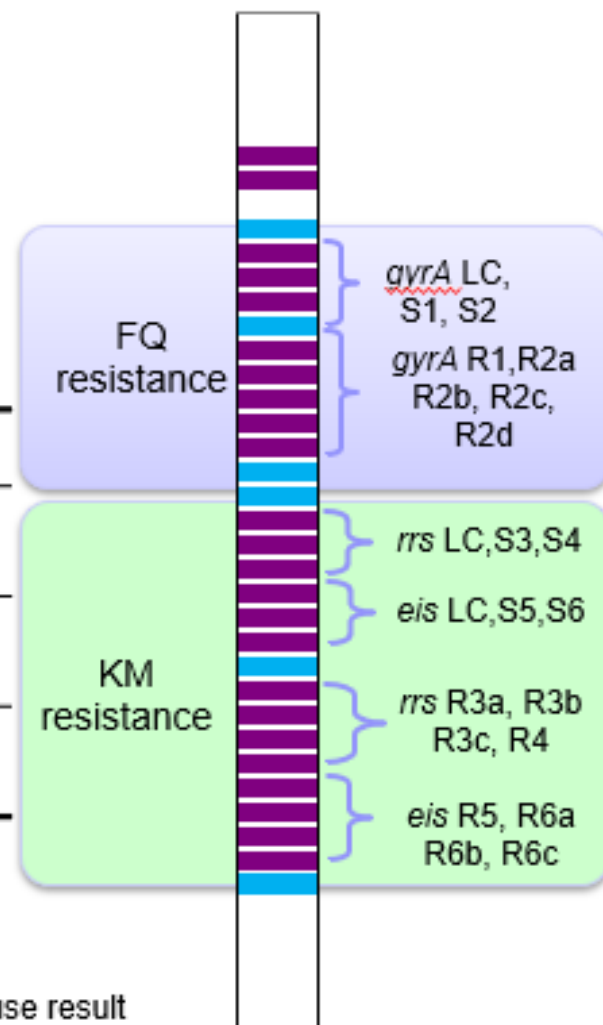




# Genoscholar™ FQ+KM-TB II

(RUO)

- Detect Fluoroquinolone and kanamycin resistance in 1 day with only 1 single test.
- It is possible to get result from direct sample or cultured material.
- Easy visual interpretation.
- Highly sensitive and specific detection of FQ/KM resistance.



<b>FQ</b> ※1			<b>KM</b> ※2		
LPA profile			LPA profile		
Susceptibility (n)	Mutation	Wild Type	Susceptibility (n)	Mutation	Wild Type
FQ-resistant (57)	53	4	KM-resistant (22)	22	0
FQ-sensitive (146)	0	146	KM-sensitive (62)	3	59

Sensitivity : 93.0% (53/57)

Sensitivity : 100 % (22/22)

Specificity : 100 % (146/146)

Specificity : 95.1% (59/62)

※1 S. Mitarai et al. : J. Clin. Microb. 50:884-890(2012)

※2 In-house result





SINCE 1828

GAMES

BROWSE THESAURUS

WORD OF THE DAY

WORDS AT PLAY


in silico


Dictionary

**Thesaurus**

# in silico

adverb or adjective

 Save Word

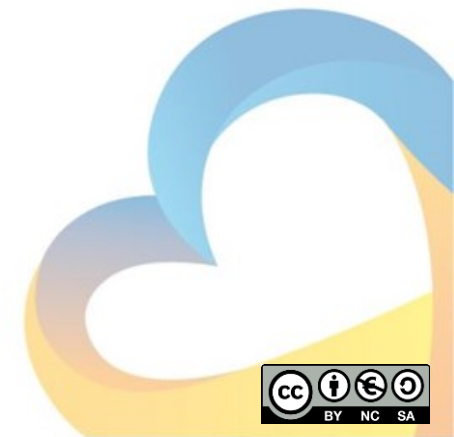
in sil·i·co | \ in-'si-li-,kō  \

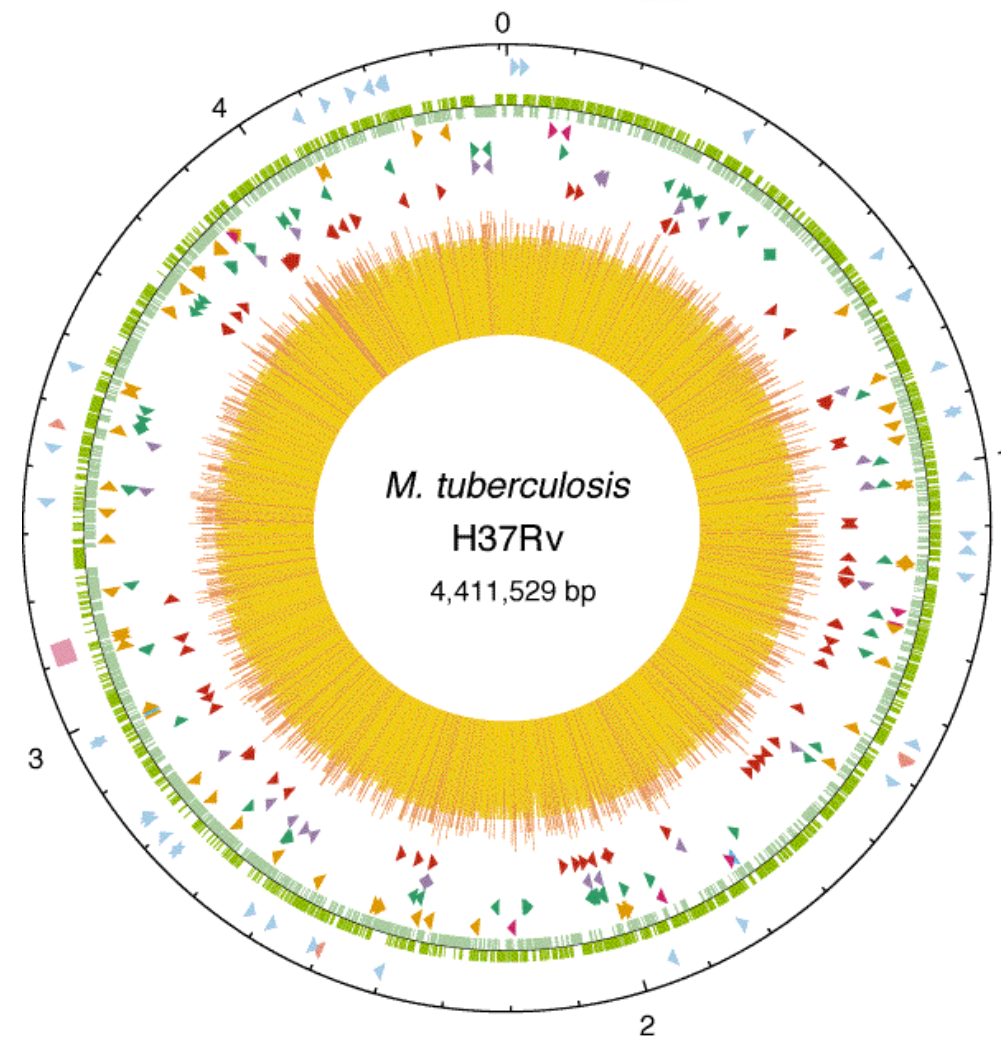
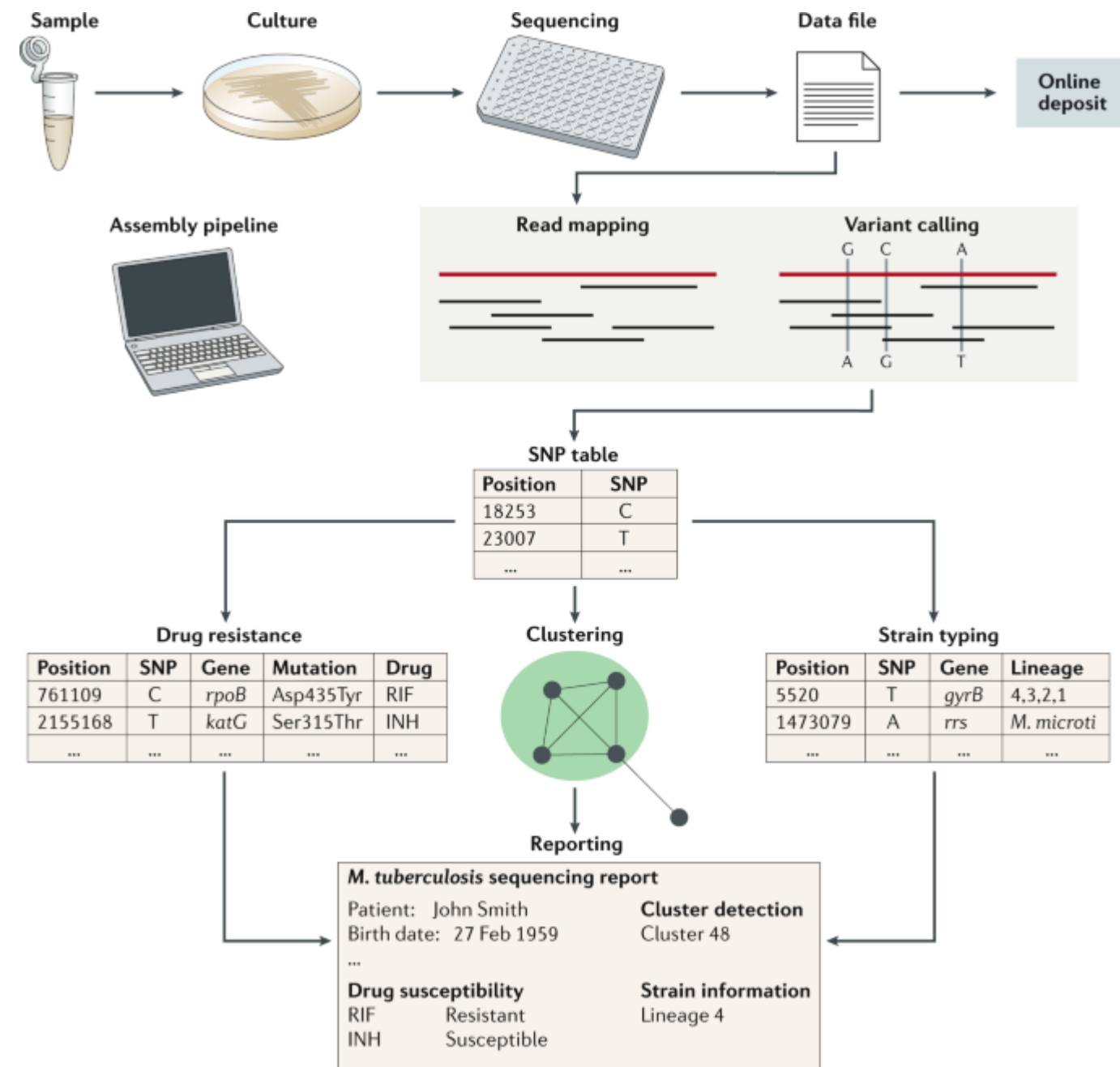
## Definition of *in silico*

: in or on a computer : done or produced by using computer software or **simulation**

// *in silico* predictions

// dissect a frog *in silico*

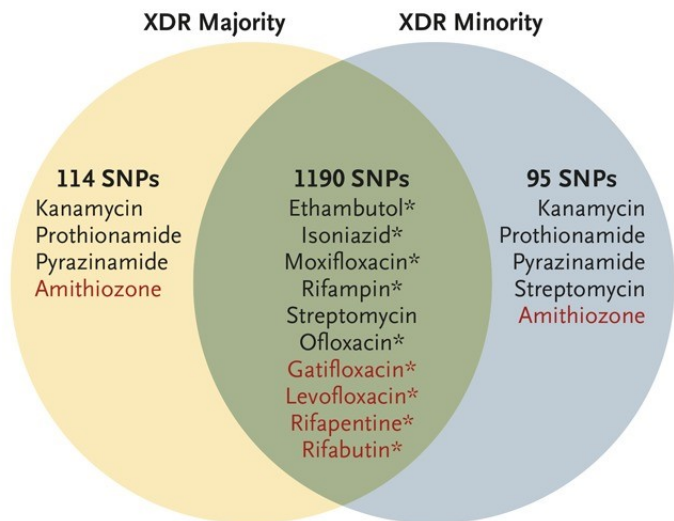




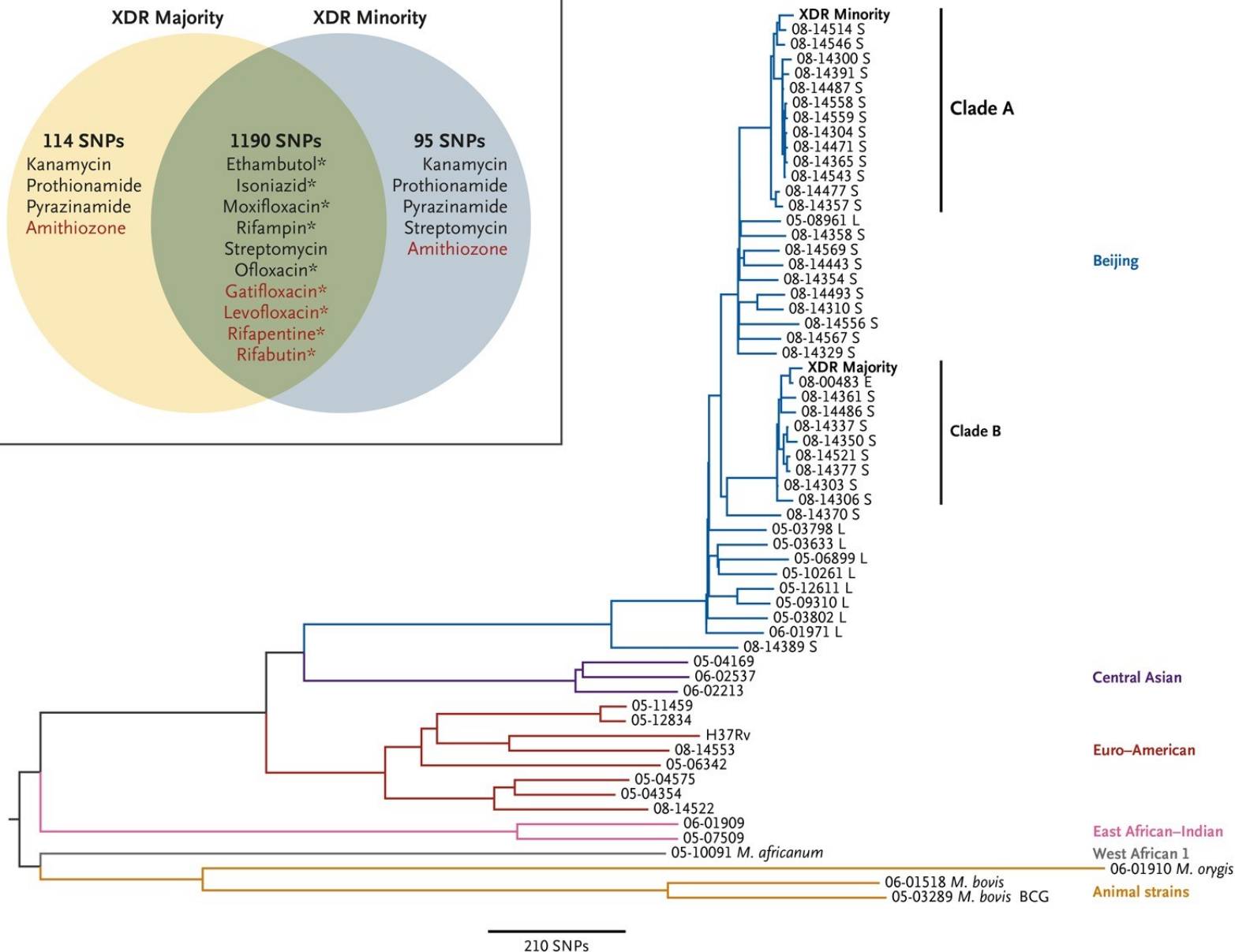
<https://doi.org/10.1038/s41579-019-0214-5>  
<https://doi.org/10.1038/31159>



**A Distribution of SNPs and Resistance Mutations**

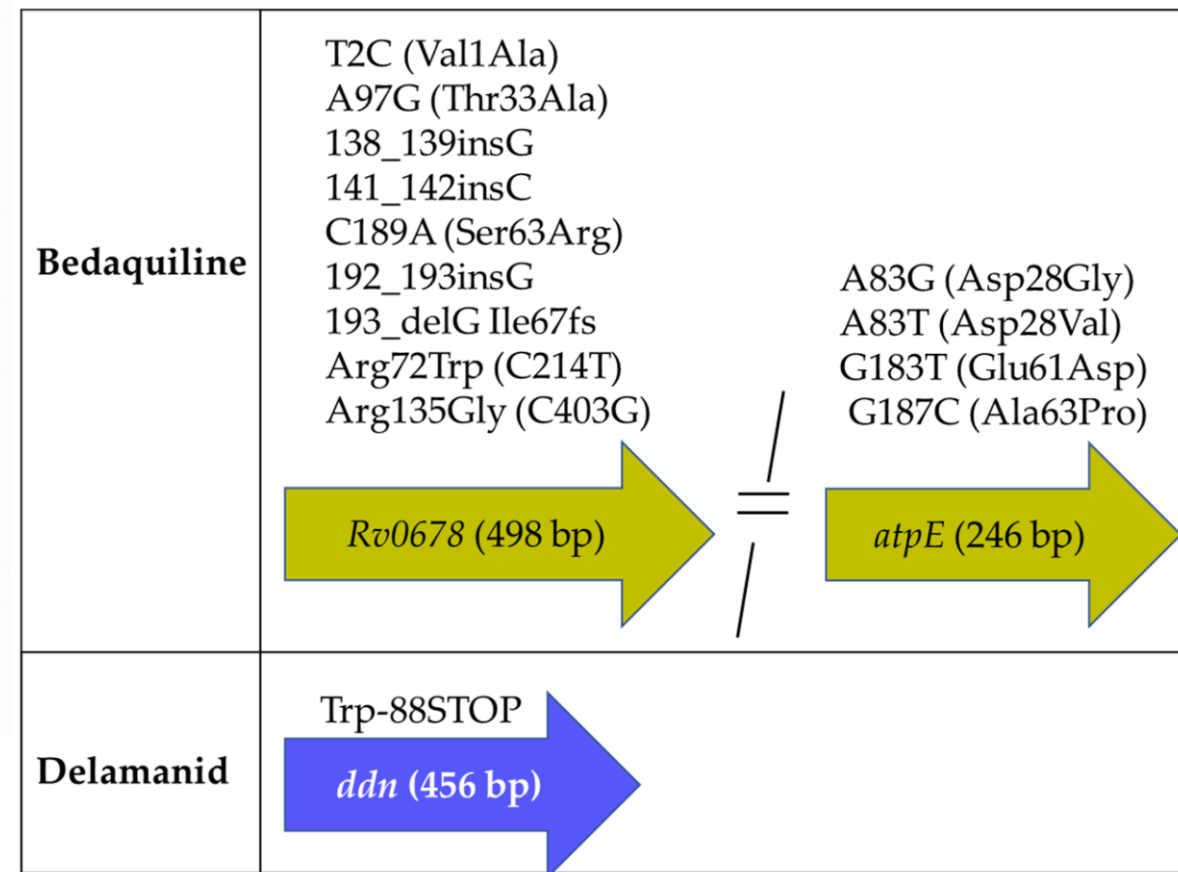
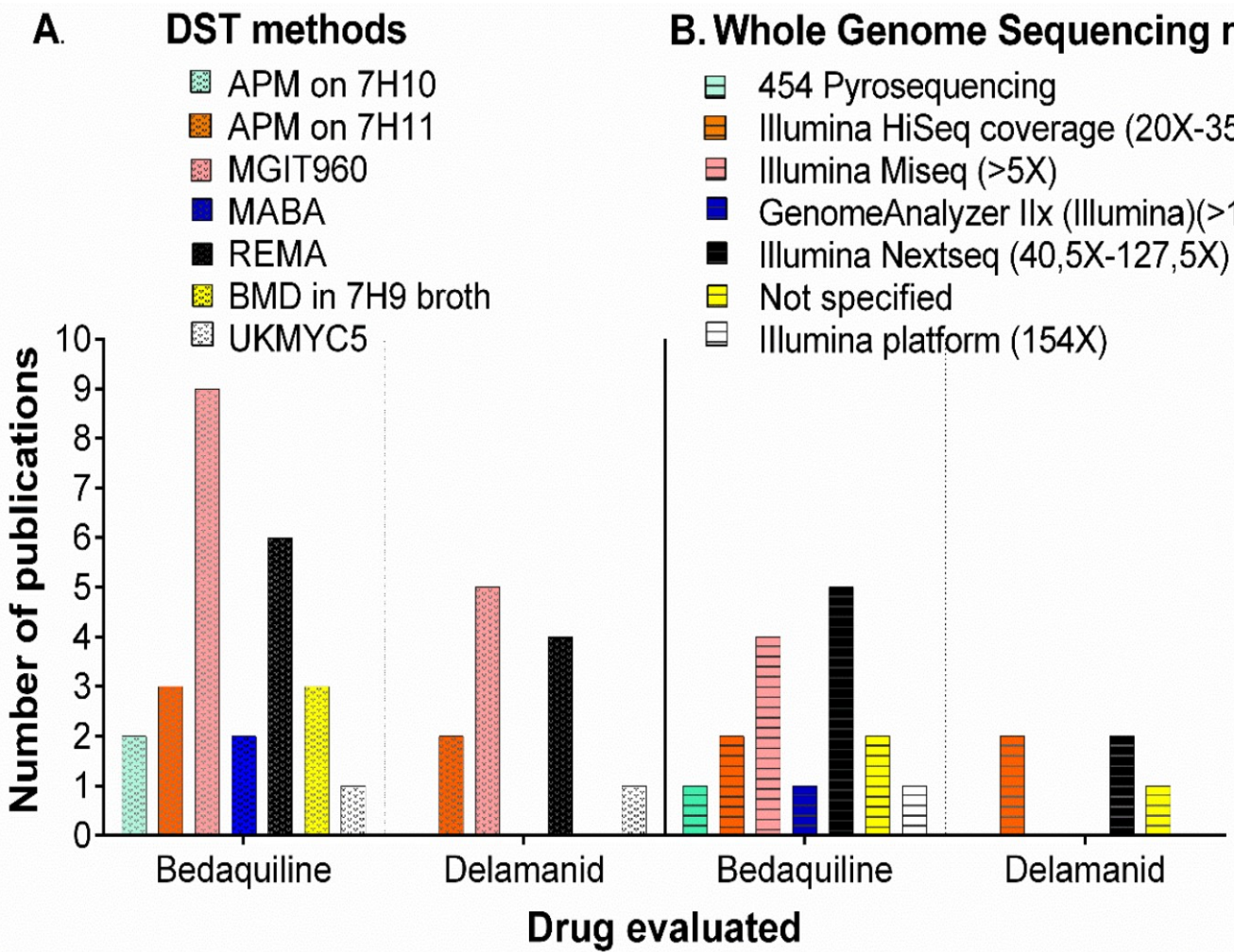


**B Phylogenetic Analysis**



<https://doi.org/10.1056/NEJMc1215305>

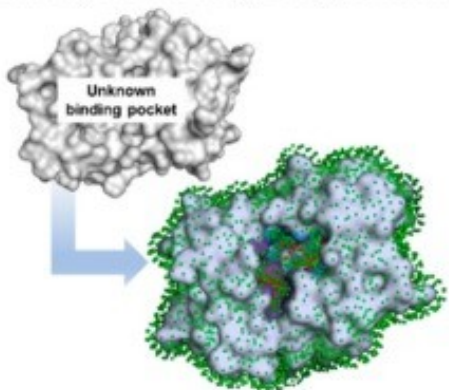




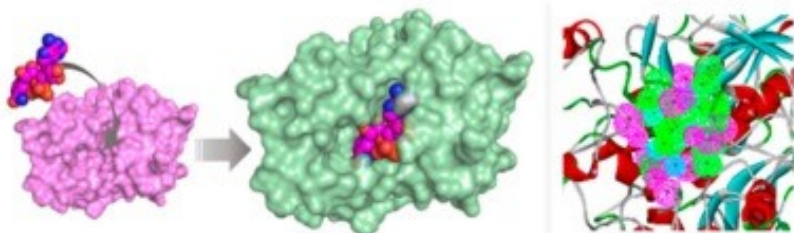


### Structure-based strategies

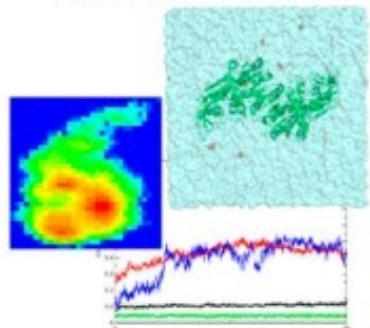
#### Binding site and druggability prediction



#### Binding mode and interaction prediction



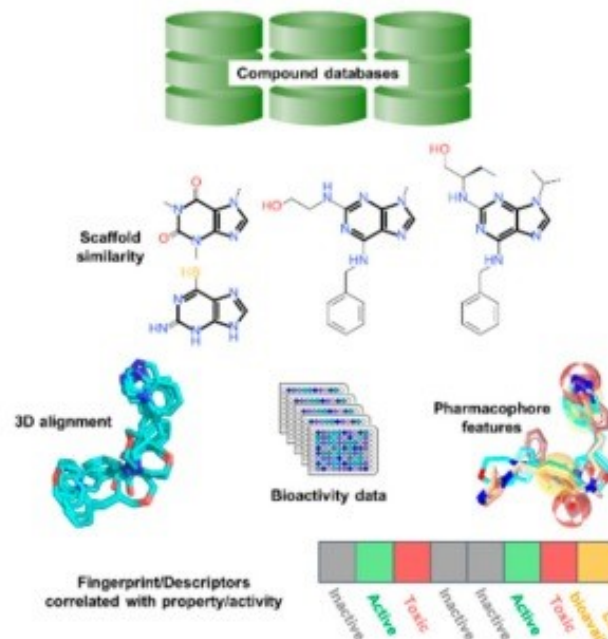
#### Refinement and incorporation of flexibility, solvation, and other energy terms



...and others  
(3D structure prediction, free energy calculations, etc.)

### Ligand-based strategies

#### Correlation of ligand structure and bioactivity or physicochemical properties



#### Property prediction of newly designed compounds

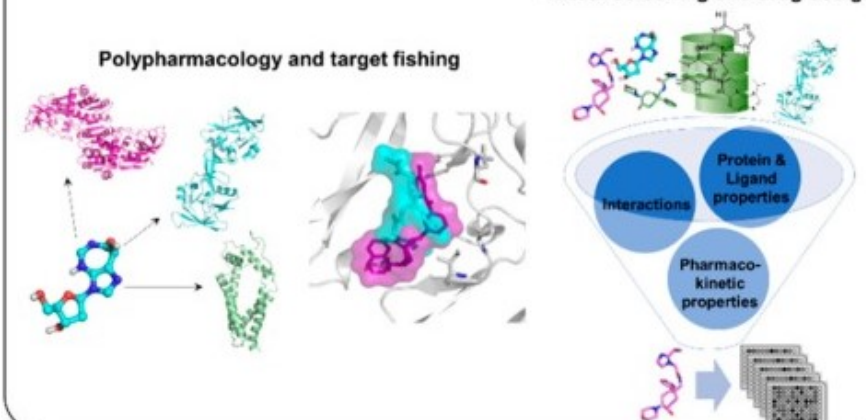
	1.00	34.56%	0.55
	0.98	10.47%	0.57
	0.88	90.00%	0.89
	0.56	0.00%	0.78

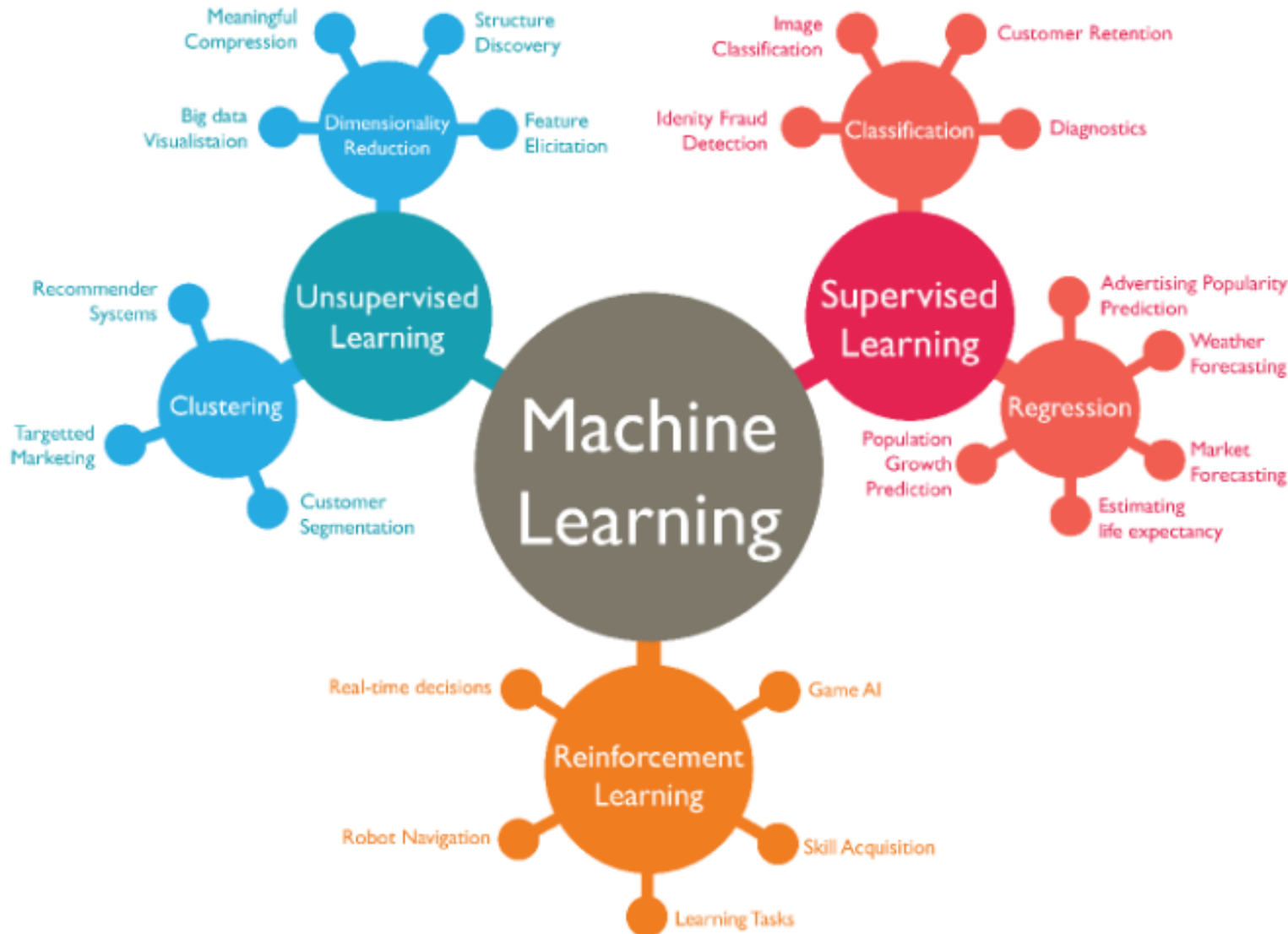
...and others  
(*in silico* ADME/Tox, scaffold hopping, activity cliffs, etc.)

### Integration of strategies

#### Virtual screening and drug design

#### Polypharmacology and target fishing





### ***Machine Learning (ML)***

Academic discipline and collection of techniques which allow computers to undertake complex tasks

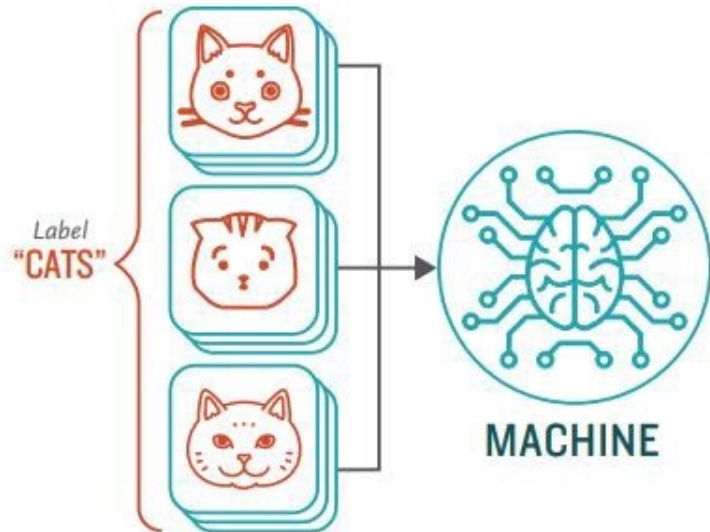
to drive the development of **'intelligent products'** with the ability to make accurate **predictions** using **diverse sources of data**



## How Supervised Machine Learning Works

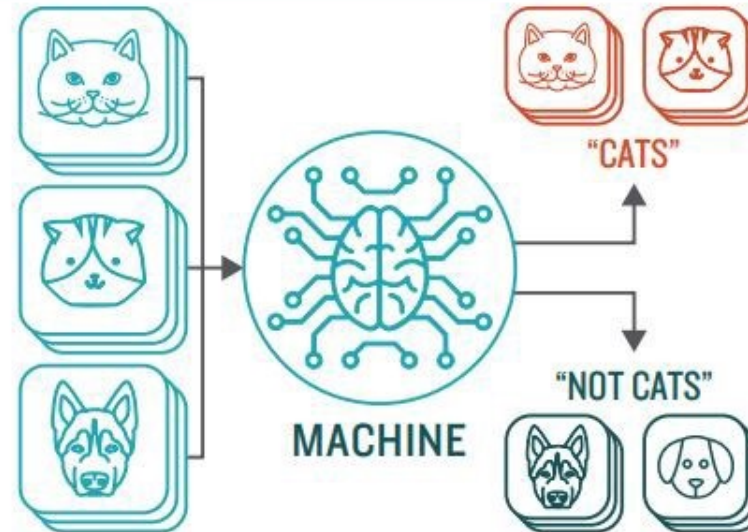
### STEP 1

Provide the machine learning algorithm categorized or "labeled" input and output data from to learn

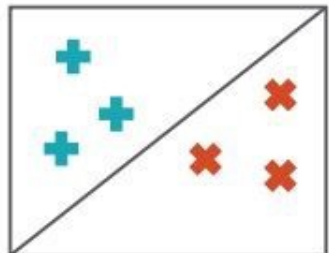


### STEP 2

Feed the machine new, unlabeled information to see if it tags new data appropriately. If not, continue refining the algorithm

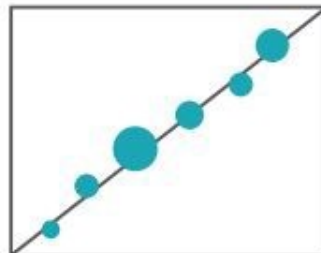


## TYPES OF PROBLEMS TO WHICH IT'S SUITED



### CLASSIFICATION

Sorting items into categories



### REGRESSION

Identifying real values (dollars, weight, etc.)

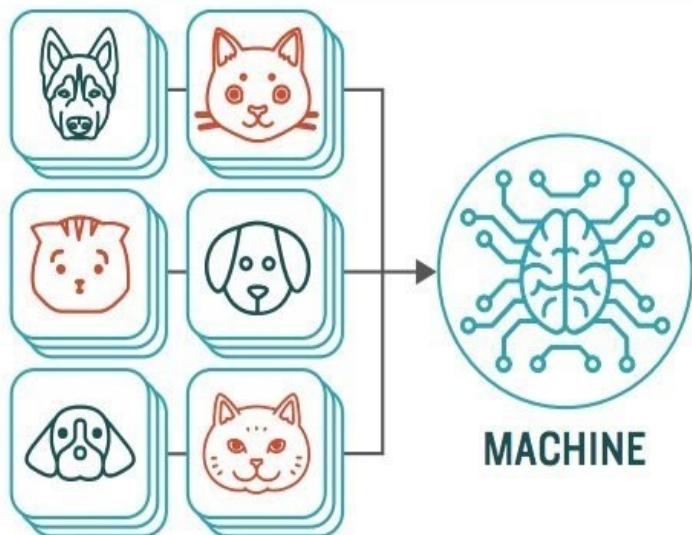
<https://dx.doi.org/10.1186/s12874-019-0681-4>  
<https://www.uc.ac.id/ict/perbedaan-supervised-learning-and-unsupervised-learning/>



## How **Unsupervised** Machine Learning Works

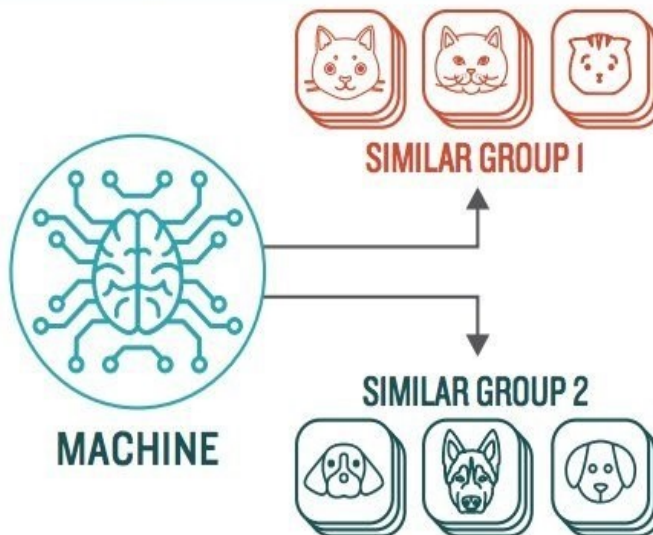
### STEP 1

Provide the machine learning algorithm uncategorized, unlabeled input data to see what patterns it finds

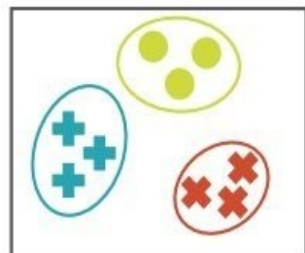


### STEP 2

Observe and learn from the patterns the machine identifies



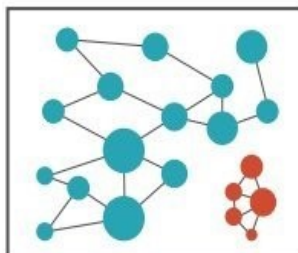
## TYPES OF PROBLEMS TO WHICH IT'S SUITED



### CLUSTERING

Identifying similarities in groups

For Example: Are there patterns in the data to indicate certain patients will respond better to this treatment than others?

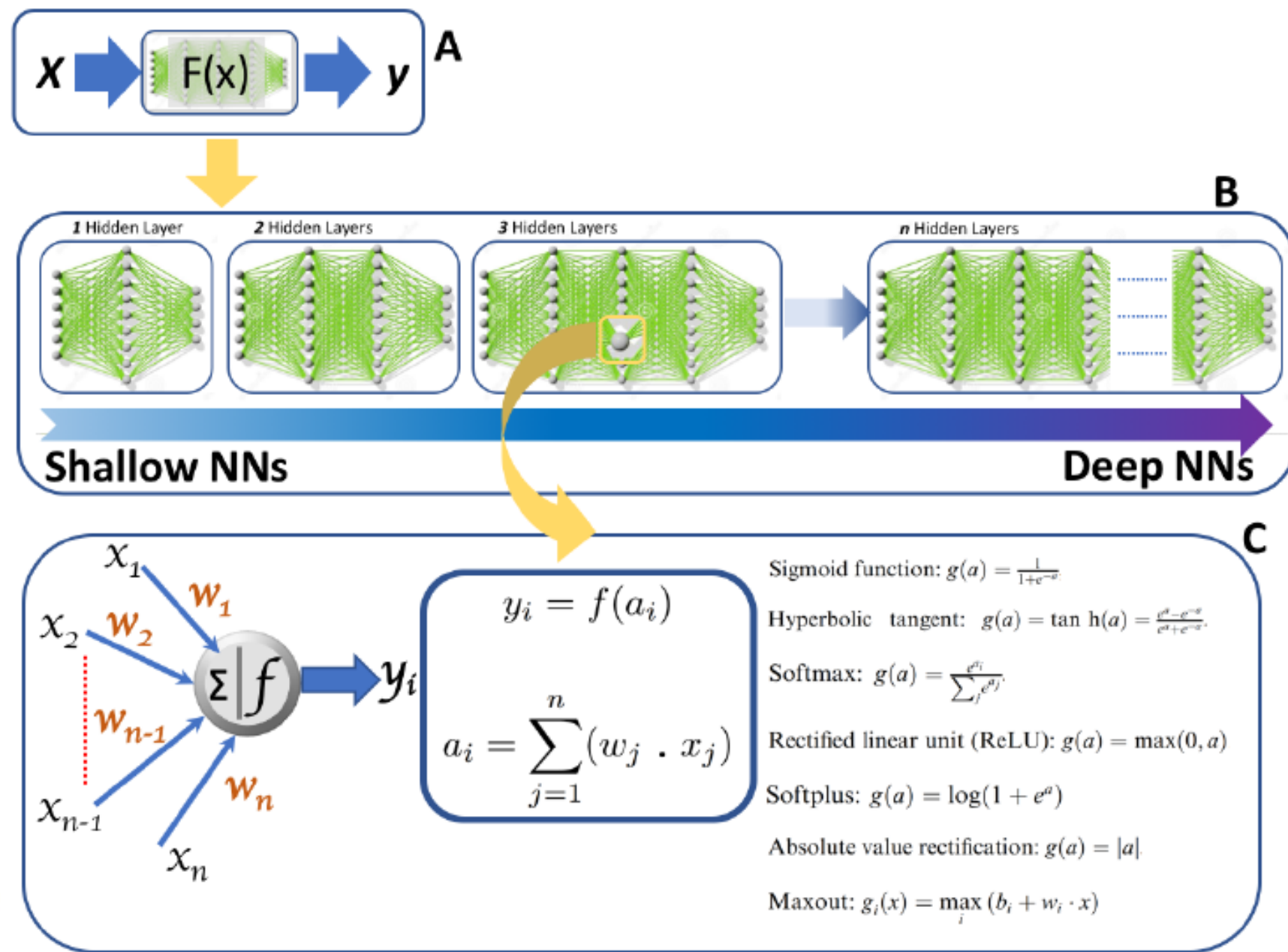


### ANOMALY DETECTION

Identifying abnormalities in data

For Example: Is a hacker intruding in our network?

<https://dx.doi.org/10.1186/s12874-019-0681-4>  
<https://www.uc.ac.id/ict/perbedaan-supervised-learning-and-unsupervised-learning/>



<https://dx.doi.org/10.3390/app9081526>





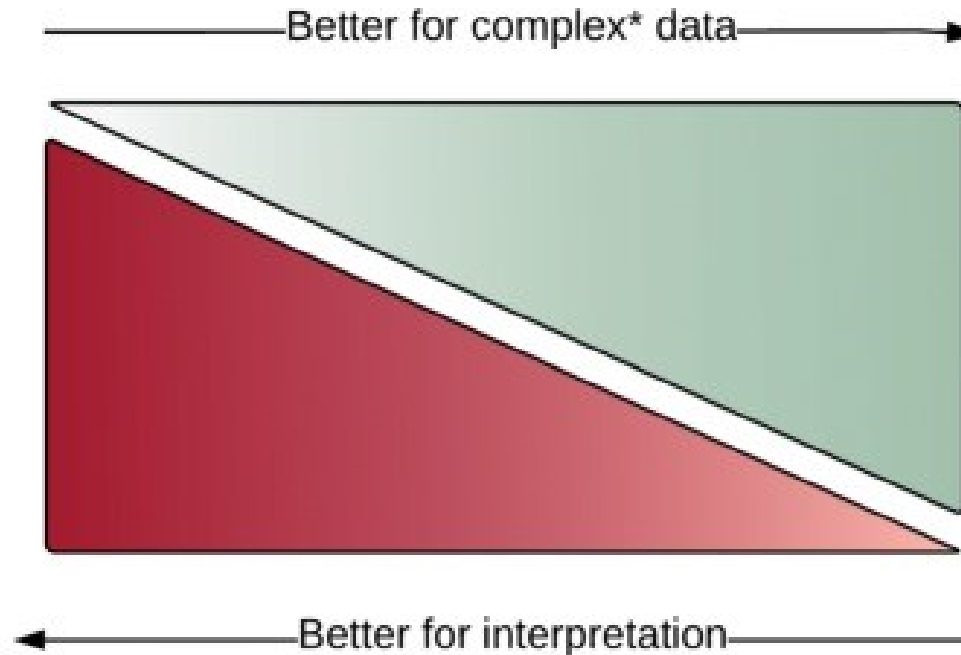
## Auditable Algorithms

Simpler models including multiple regression and decision trees.

Linear relationships between predictors and outcomes facilitate interpretation.

Many commonalities to statistical techniques.

Computationally 'cheap' can often be run on a consumer PC.



## Black Boxes

Complex models including neural networks and some Support Vector Machines.

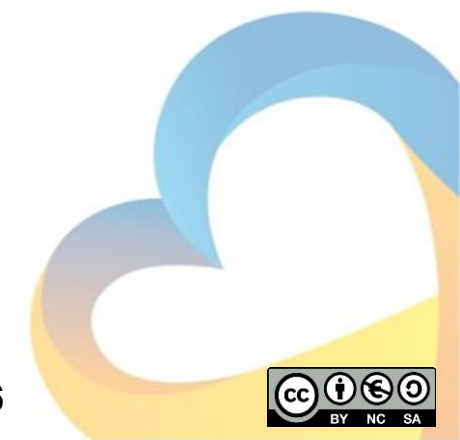
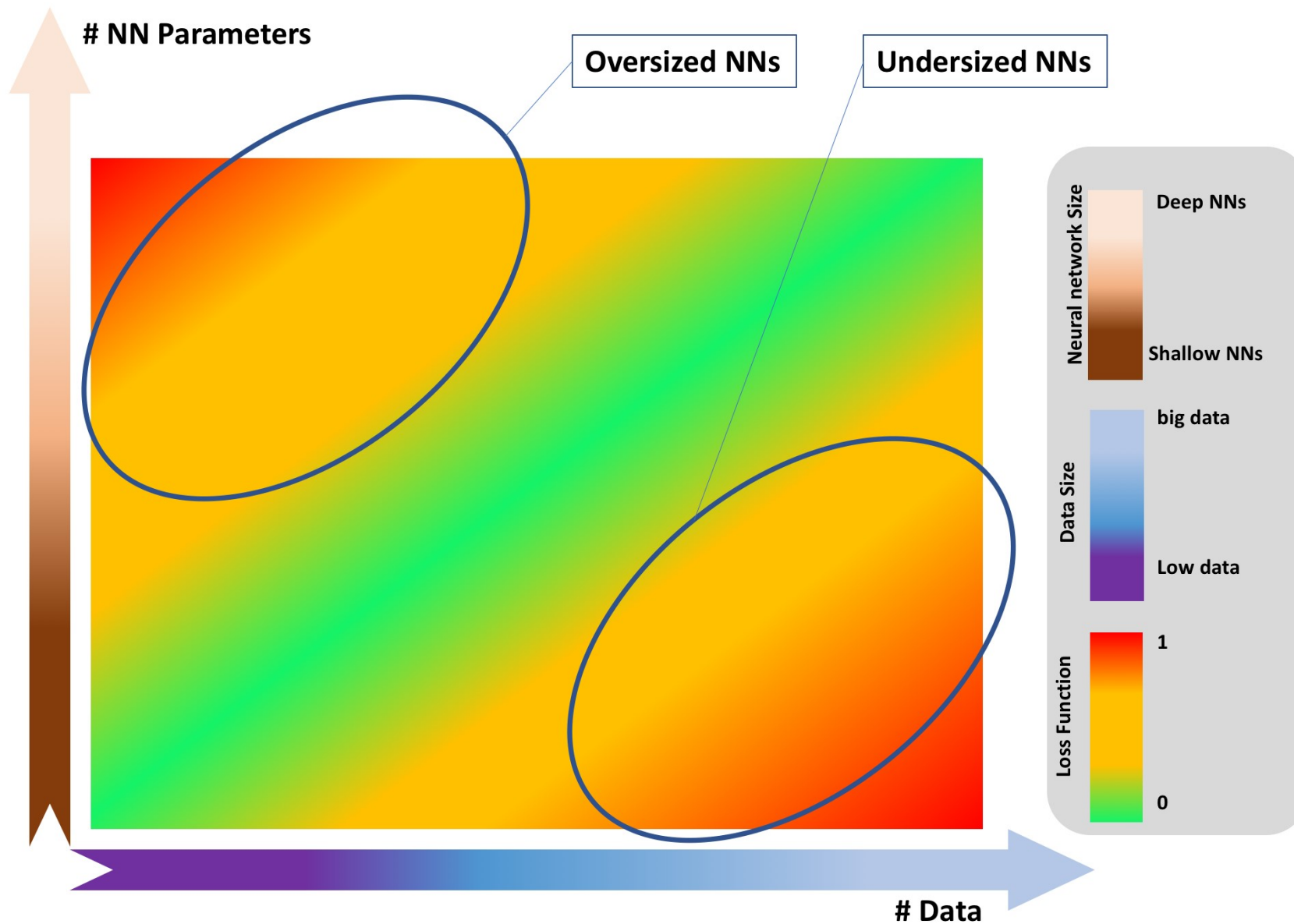
Non-linear relationships between predictors and outcomes make interpretation extremely difficult.

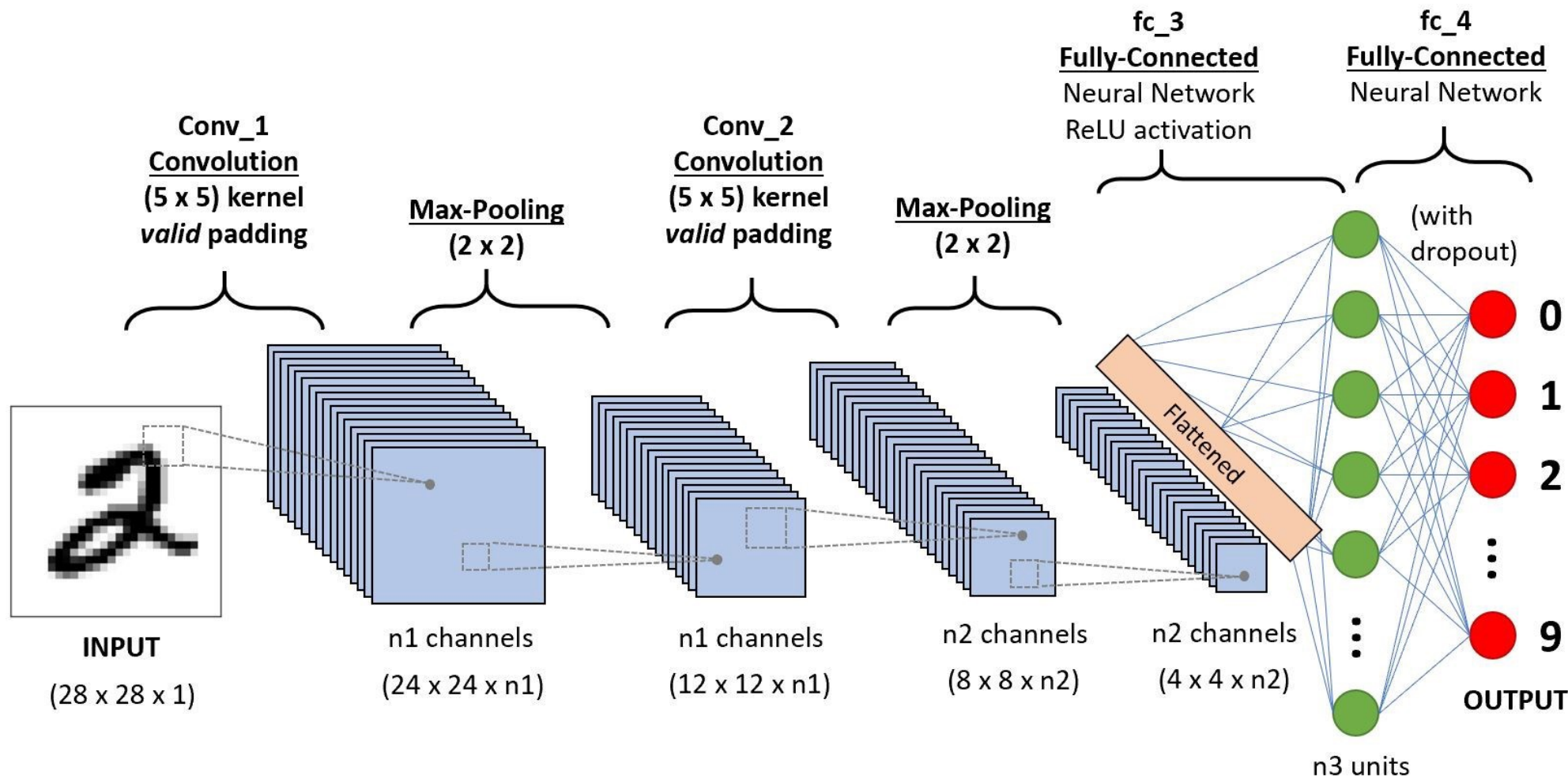
Share few commonalities to statistical techniques.

Computationally 'expensive', may require days of processor time to build models.

\* 'Complex' data could refer to data which do not have a linear relationship with the outcome, such as a pixel in an image, the frequency of a wave in a sound bite, or movement data captured by a smart phone.



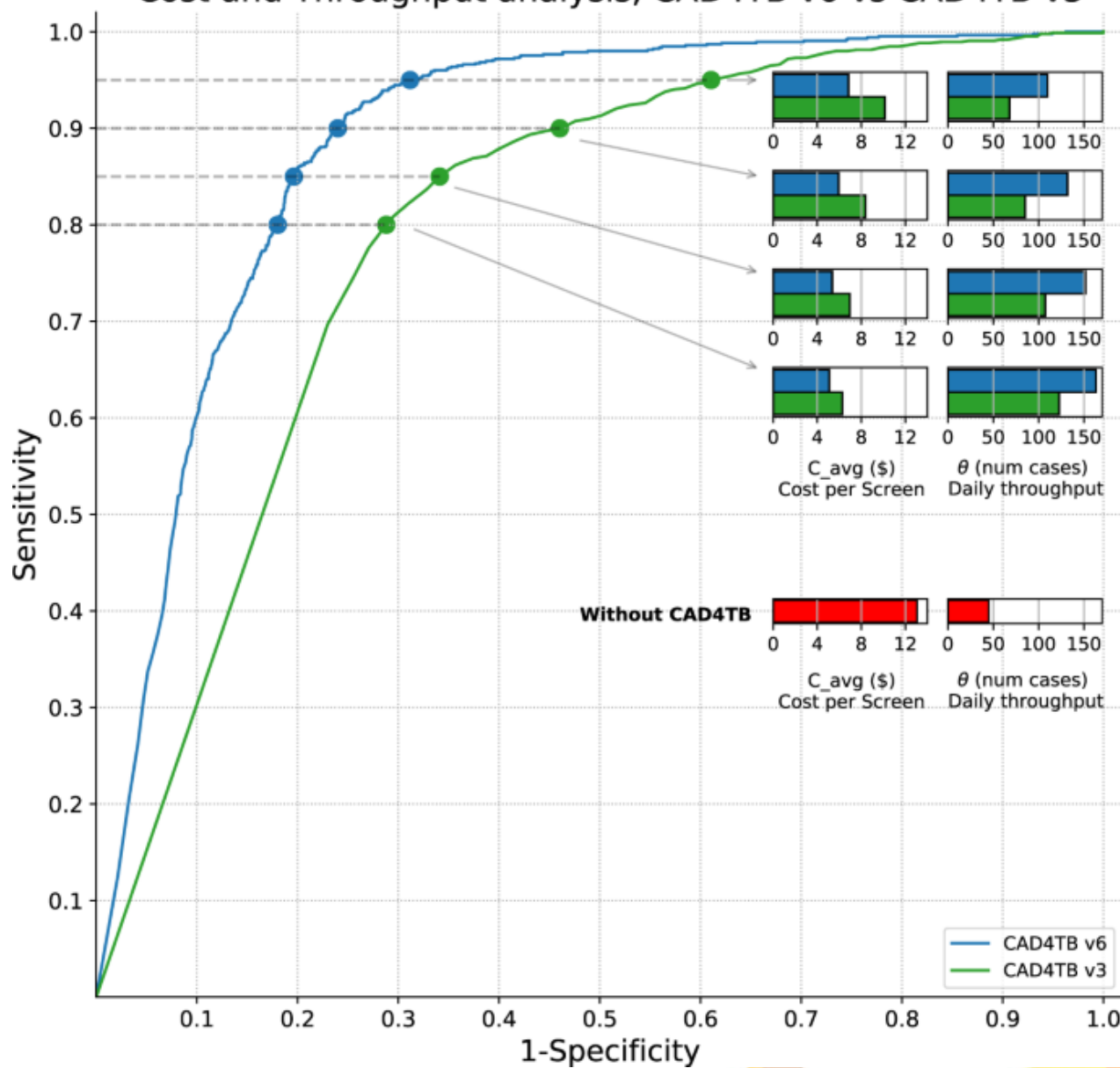
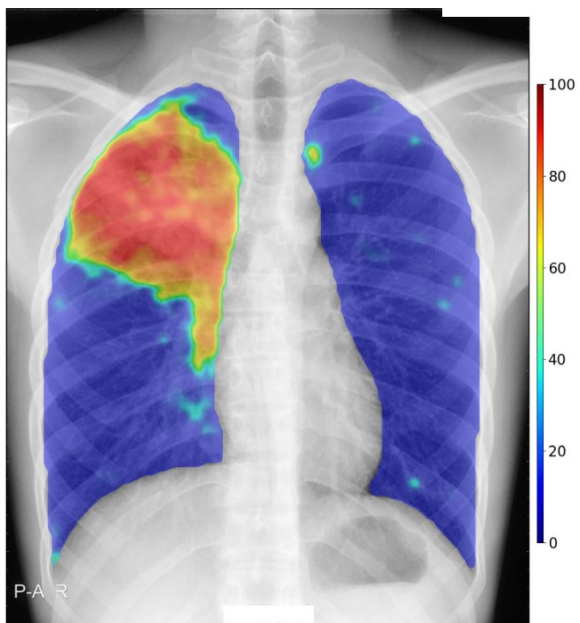




<https://towardsdatascience.com/a-comprehensive-guide-to-convolutional-neural-networks-the-eli5-way-3bd2b1164a53>

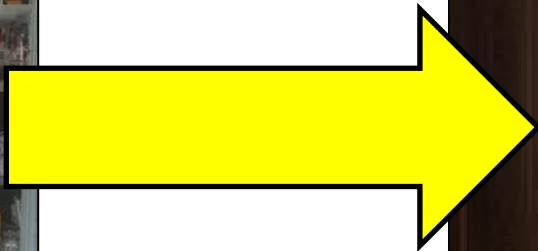
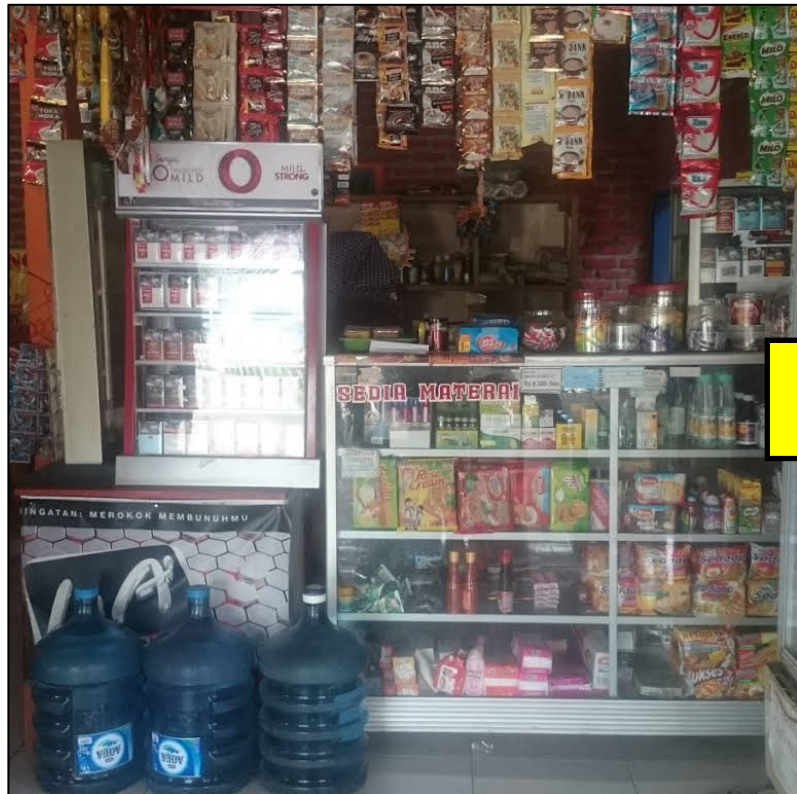


**Cost and Throughput analysis, CAD4TB v6 vs CAD4TB v3**



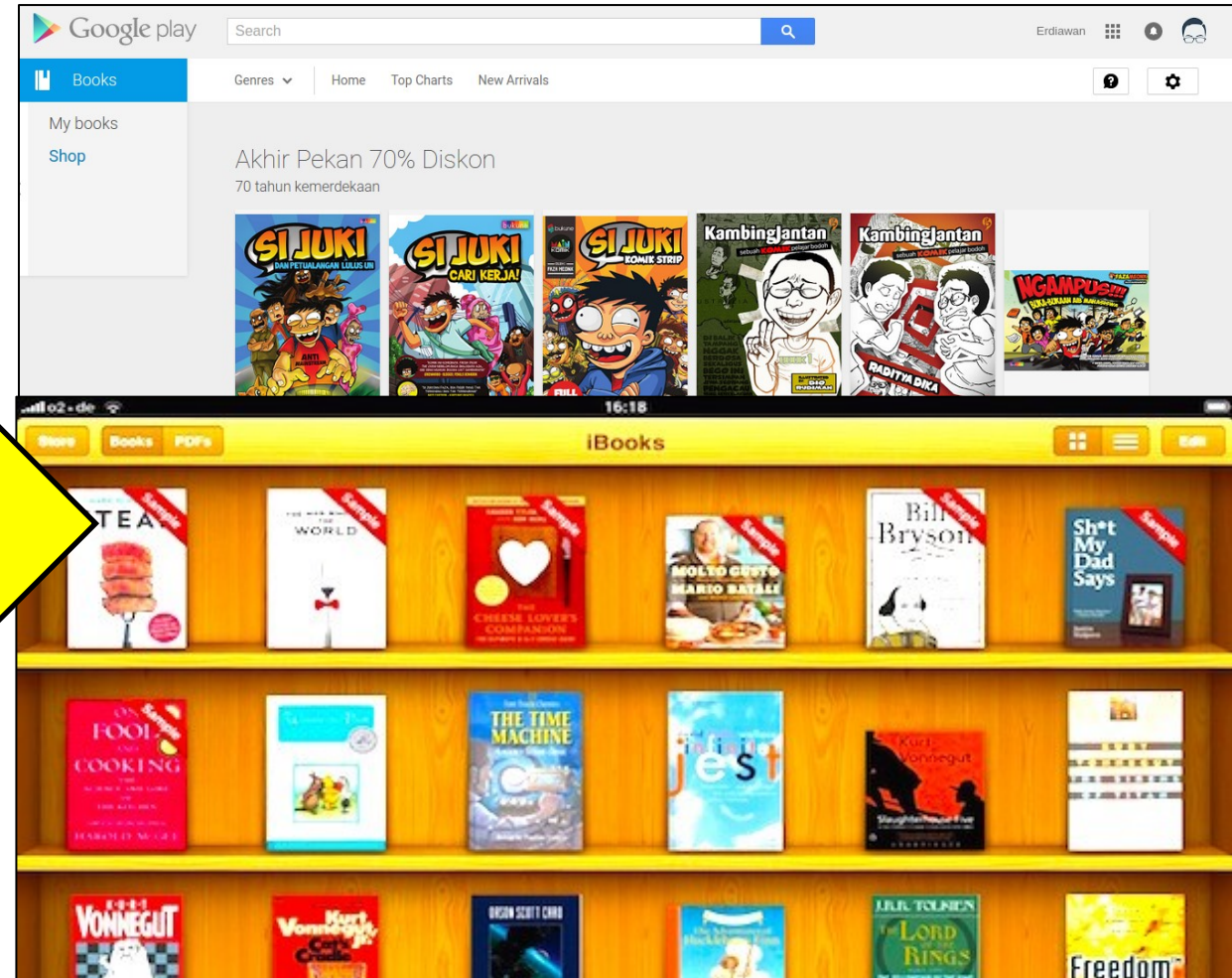
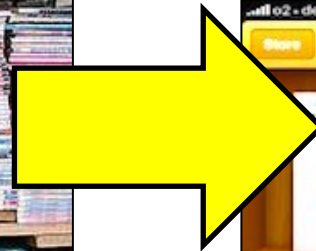


# #10yearschallenge










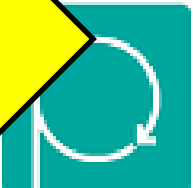




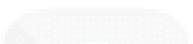




# #10yearschallenge





# #10yearschallenge



 <p>Shopee: No.1 Belanja Shopee</p> <p>★★★★★ GRATIS</p>	 <p>Bukalapak - Jual Beli PT Bukalapak.com</p> <p>★★★★★ GRATIS</p>	 <p>JD.id - Jual Beli On- JingDong Indonesia</p> <p>★★★★★ GRATIS</p>	 <p>Blibli.com Belanja C blibli.com</p> <p>★★★★★ GRATIS</p>	 <p>OLX - Jual Beli Onlin OLX Indonesia</p> <p>★★★★★ GRATIS</p>
 <p>Prelo - Jual Beli Bek Prelo</p> <p>★★★★★ GRATIS</p>	 <p>VIP Plaza: Fashion C VIP Plaza</p> <p>★★★★★ GRATIS</p>	 <p>Seller Tokopedia - J Tokopedia</p> <p>★★★★★ GRATIS</p>	 <p>Sale Stock Toko Bel Sale Stock</p> <p>★★★★★ GRATIS</p>	 <p>Sepulsa - Pulsa &amp; P Sepulsa Teknologi Indo</p> <p>★★★★★ GRATIS</p>
				



Adapt or perish, now as ever, is nature's  
inexorable imperative.

(H. G. Wells)



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