Lecture 11: AI and COVID-19

Announcements

- A3 released, due Tue Nov 15
- Midterm: In class, Mon Nov 7
  - 80 minutes
  - 1 page 8.5” x 11” of notes allowed (back and front)
  - No calculators allowed or needed
  - Covers material through “Genomics: Introduction”
  - Practice midterm released on Ed
- Looking ahead:
  - Project milestone due Fri Nov 18
  - Just final project presentations / reports after this!

Today

- Applications of AI in Healthcare through the lens of a real-world case study: COVID-19

First application area: AI interpretation of chest radiology images

Bernheim et al.: COVID-19 hallmarks on chest CTs based on radiologist review

Key Results

- The hallmark CT manifestations of coronavirus disease 2019 (COVID-19) include bilateral and peripheral ground-glass and consolidative pulmonary opacities, sometimes with a rounded morphology and peripheral lung distribution.
- As the time between onset of symptoms and initial chest CT increases, some CT findings are observed with increasing frequency, including consolidation, bilateral and peripheral lung disease, greater total lung involvement, linear opacities, and the appearance of a crazy-paving pattern and reverse halo sign.
- Certain chest CT findings, including pleural effusions, lymphadenopathy, pulmonary nodules, and lung cavitation, are characteristically absent, and more than half of patients imaged quickly after symptom onset have a normal CT scan.

Bernheim et al. Chest CT Findings in Coronavirus Disease 2019 (COVID-19): Relationship to Duration of Infection, 2020.

Bernheim et al.: COVID-19 hallmarks on chest CTs based on radiologist review

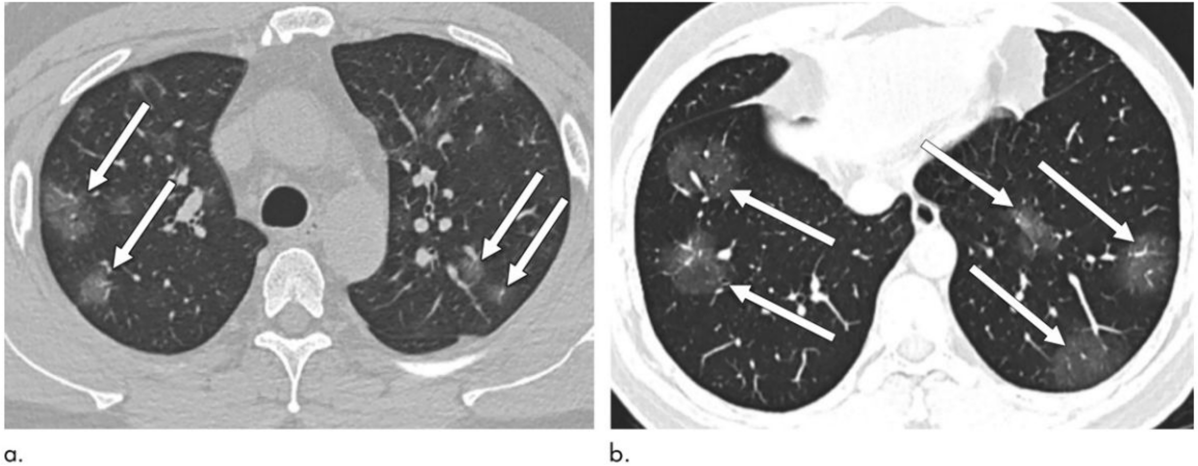
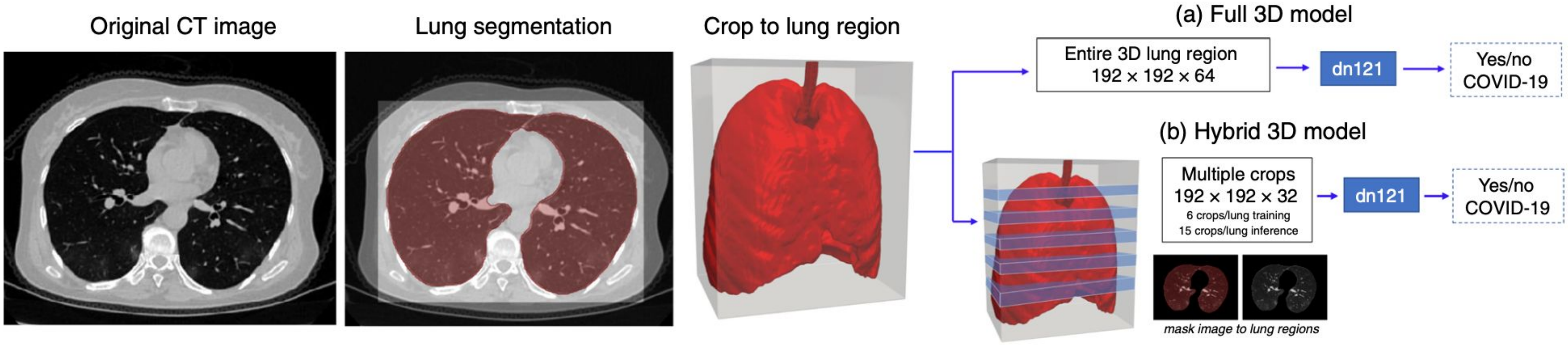


Figure 1: **(a)** Axial CT image obtained without intravenous contrast material in a 36-year-old man shows bilateral ground-glass opacities in upper lobes with a rounded morphology (arrows). **(b)** Axial CT image obtained in a 44-year-old man shows larger ground-glass opacities in the bilateral lower lobes with a rounded morphology (arrows). **(c)** Axial CT image obtained in a 65-year-old woman shows bilateral ground-glass and consolidative opacities with a striking peripheral distribution (arrows).

Bernheim et al. Chest CT Findings in Coronavirus Disease 2019 (COVID-19): Relationship to Duration of Infection, 2020.

Harmon et al.

- Detection of COVID-19 from CT images
- 2 stage process: lung segmentation followed by classification of COVID-19 or not
- Multinational dataset of 2724 scans from 2617 patients, with 1029 scans (922) patients confirmed positive for COVID-19



Harmon et al. Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets, 2020.

Harmon et al.

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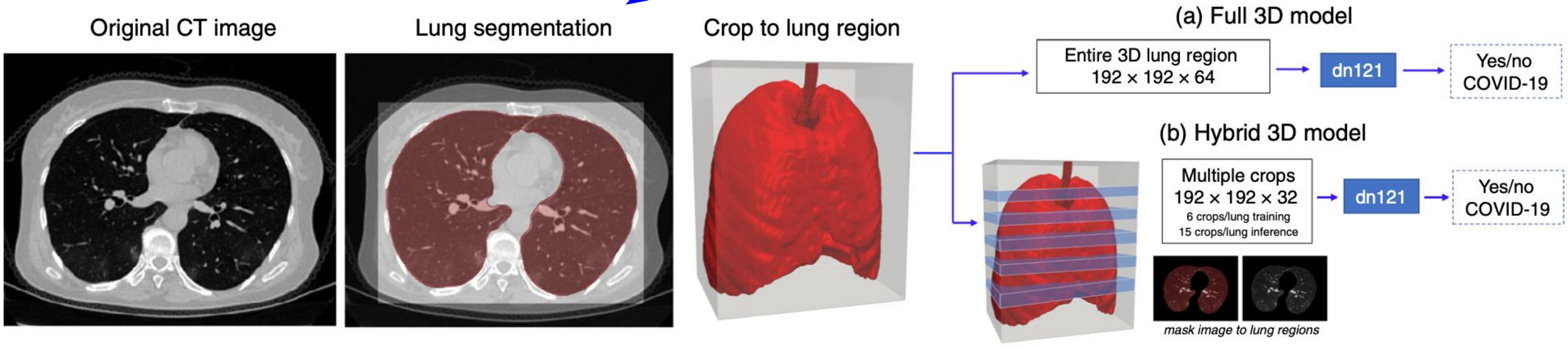
First stage: segmentation



Harmon et al. Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets, 2020.

Harmon et al.

- Detection of COVID-19 from CT images
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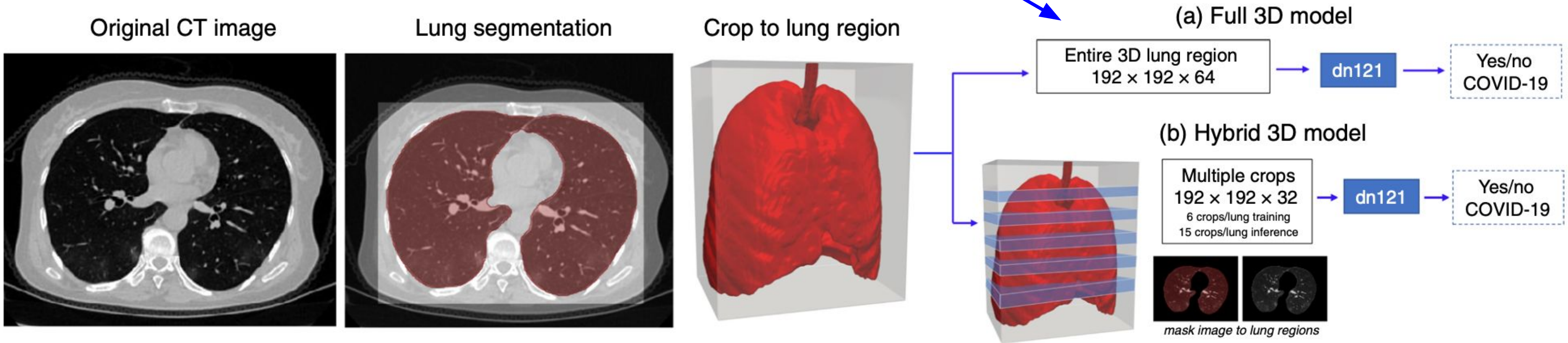
Second stage: classification based on whole lung region vs. combination of cropped regions



Harmon et al. Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets, 2020.

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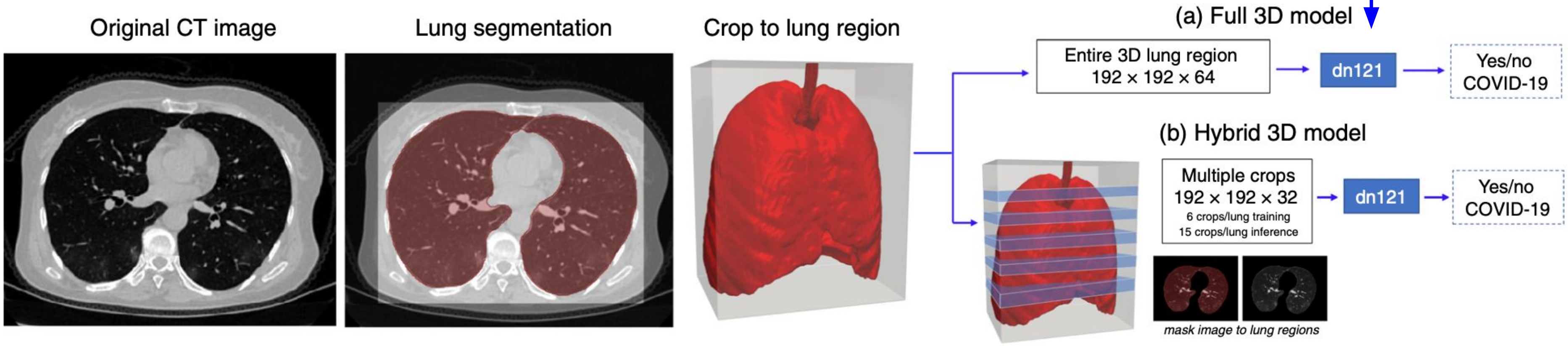
“DenseNet” convolutional neural network architecture



Harmon et al. Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets, 2020.

Harmon et al.

Multinational patient dataset

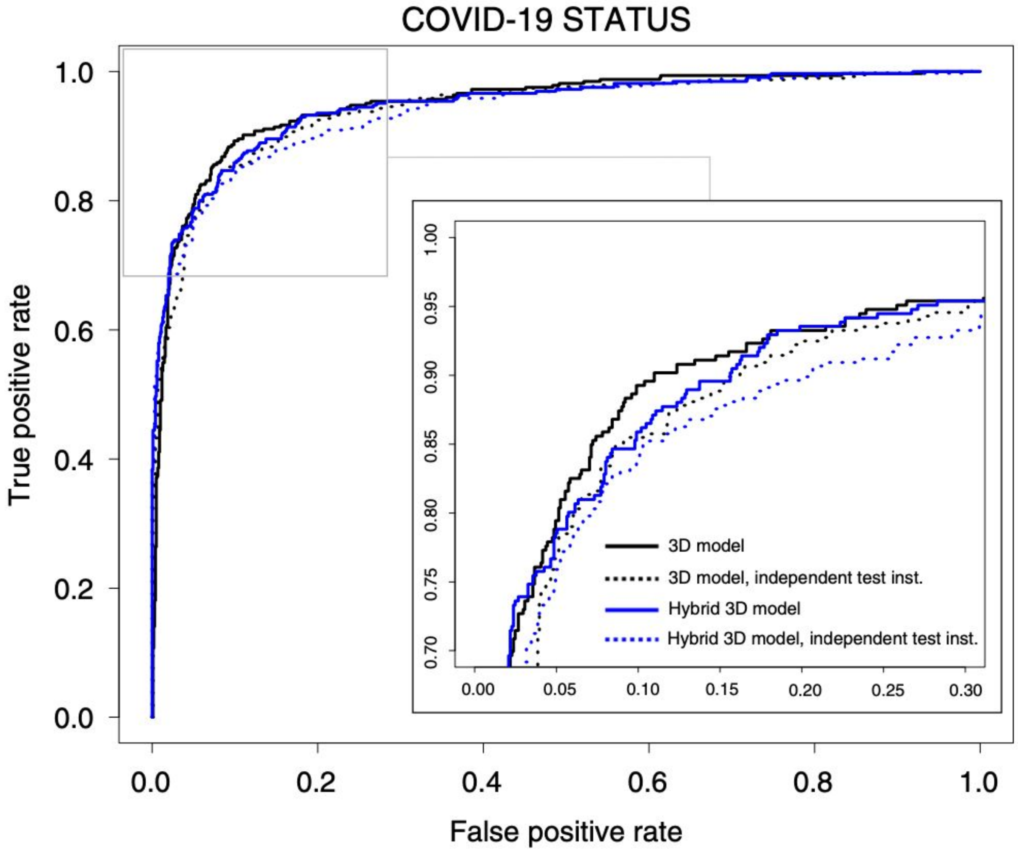
Disease cohort	Center	Demographics	Training	Validation	Testing
COVID-19	Hubei, China	363 Male, 353 female Median 49 (18[a]–92)	369 Scans *354 Patients*	122 Scans *113 Patients*	207 Scans *207 Patients*
	Milan, Italy	220 Male, 90 female Median 60 (18–96)	57 Scans *52 Patients*	24 Scans *17 Patients*	54 Scans *54 Patients*
	Tokyo, Japan	91 Male, 60 female Median 60 (4–87)	100 Scans *45 Patients*	31 Scans *15 Patients*	49 Scans *49 Patients*
	Milan, Italy	10 Male, 5 female Median 55 (31–85)	-	-	15 Scans *15 Patients*
	Syracuse, NY, USA	[b]See footnote	-	-	1 Scan *1 Patient*
Any clinical indication	Syracuse, NY, USA	437 Male, 534 female Median 65 (19–100)	356 Scans *356 Patients*	93 Scans *93 Patients*	500 Scans *500 Patients*
Cancer diagnosis and/or staging	LIDC[23]	N/A	149 Scans *149 Patients*	50 Scans *50 Patients*	271 Scans *271 Patients*
	NIH, USA	100 Male Median 69 (30–89)	-	-	100 Scans *100 Patients*
Pneumonia	Syracuse, NY, USA	73 Male, 42 female Median 66 (13–101)	-	-	140 Scans *140 Patients*
	NIH, USA	28 Male, 8 female Median 21 (4–71)	28 Scans *28 Patients*	8 Scans *8 Patients*	-
Total			*1059 Scans* *984 Patients*	*328 Scans* *296 Patients*	*1337 Scans* *1337 Patients*

[a]Age was not readily available for all Hubei, China patients.
[b]Demographics for COVID-19 diagnosis from SUNY is included in all-comer/any clinical indication grouping.

Harmon et al. Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets, 2020.

Harmon et al.

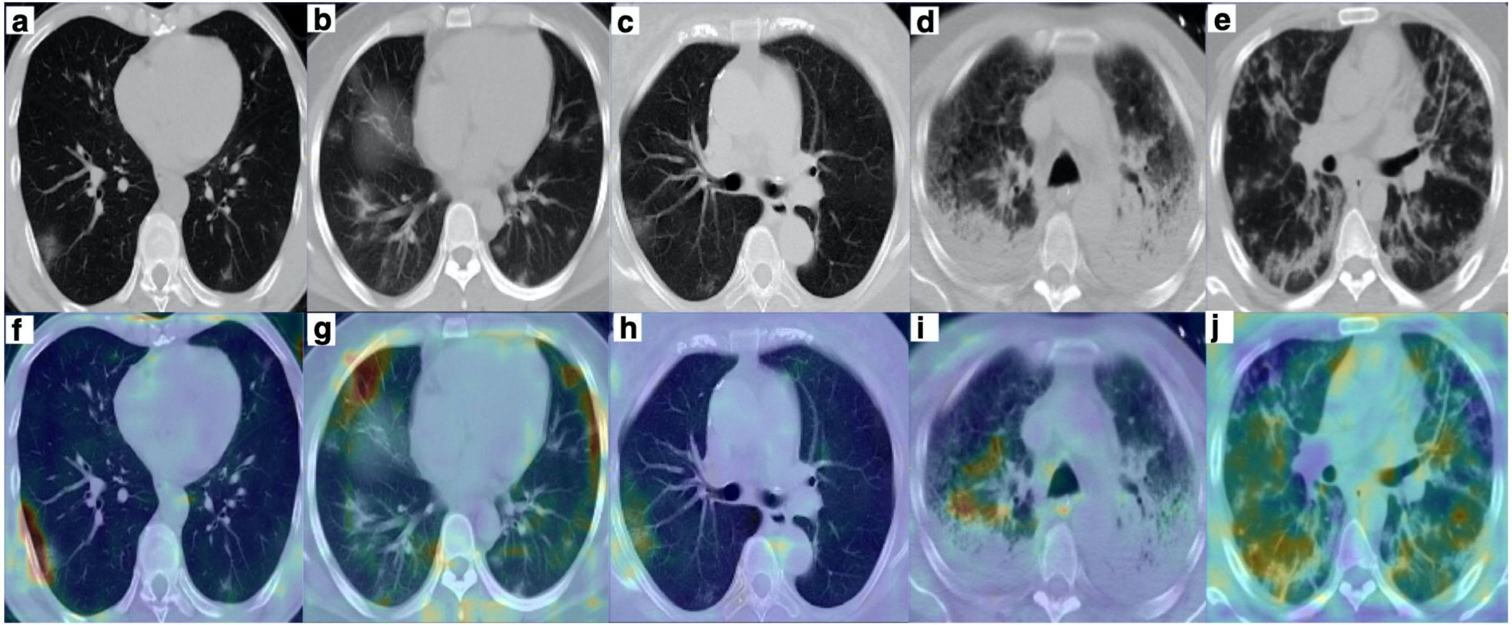
Model achieved 90.8% accuracy (84% sensitivity, 93% specificity)



Harmon et al. Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets, 2020.

Harmon et al.

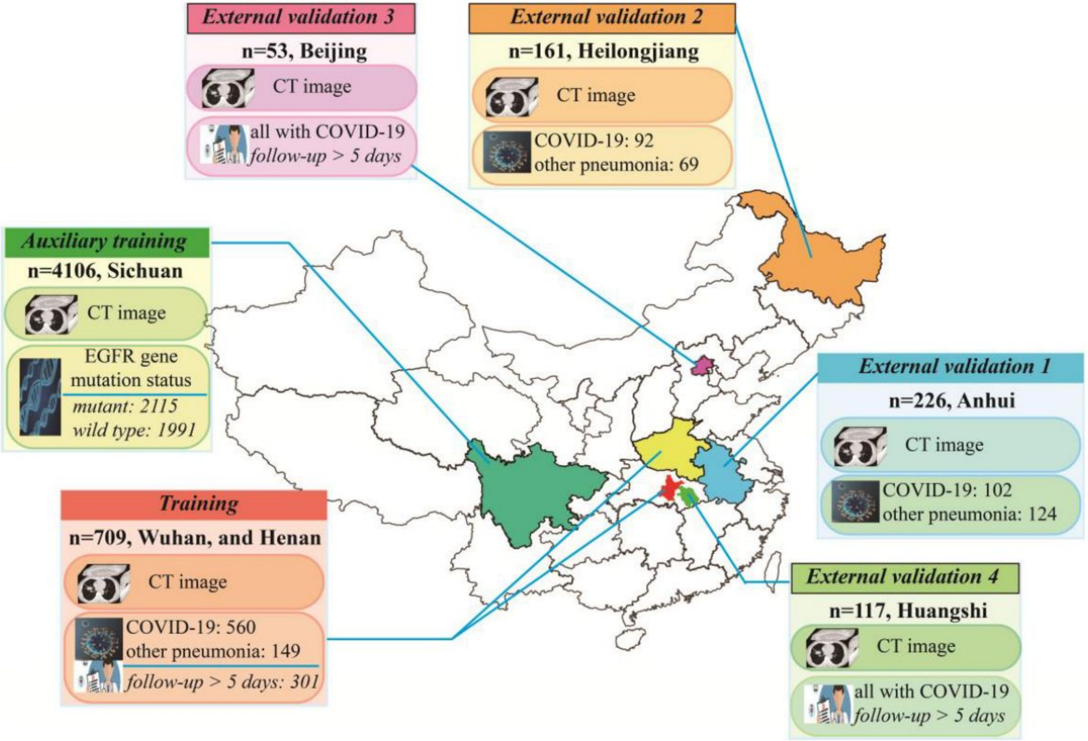
Grad-CAM saliency maps showing regions contributing most to model prediction (will discuss more in upcoming lecture)



Harmon et al. Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets, 2020.

Wang S. et al.

- Also detection of COVID-19 from CT images, based on 1266 patients (924 with COVID-19) from 7 Chinese cities or provinces
- Addressed lack of available data due to ongoing pandemic, through pre-training using a different dataset of 4106 lung cancer patients (that was trained to predict accompanying epidermal growth factor receptor (EGFR) gene mutation)

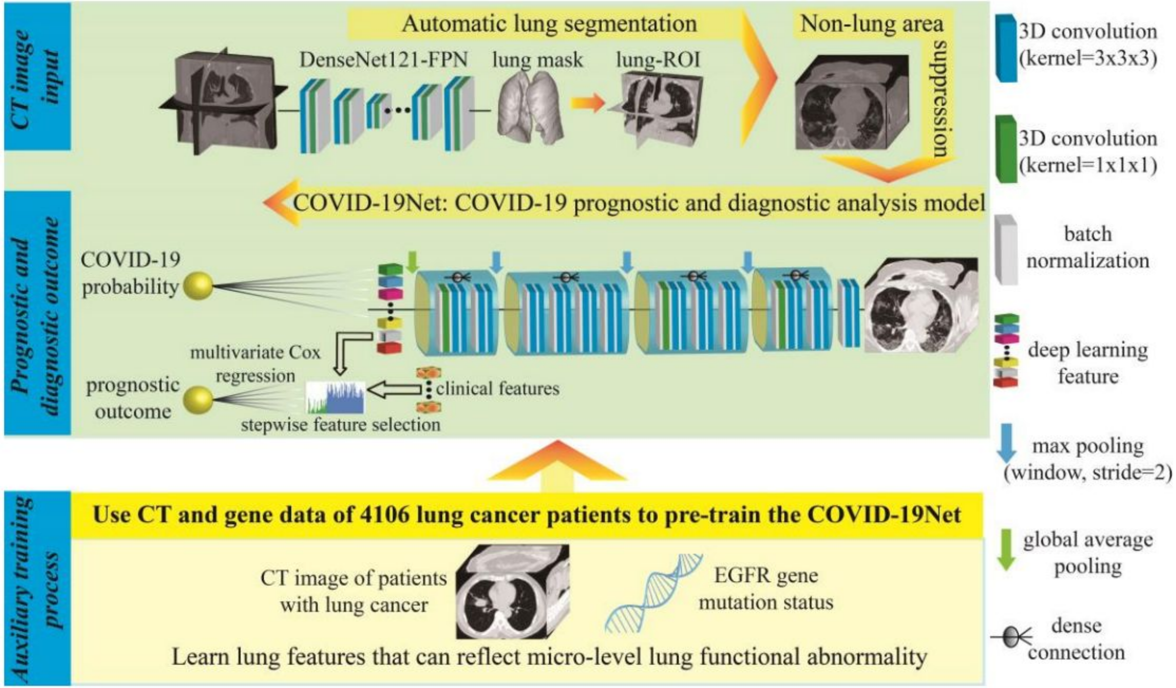


Wang S et al. A Fully Automatic Deep Learning System for COVID-19 Diagnostic and Prognostic Analysis, 2020.

Wang S. et al.

- Deep learning architecture is similar to a DenseNet (stacked modules, with dense connections between them)

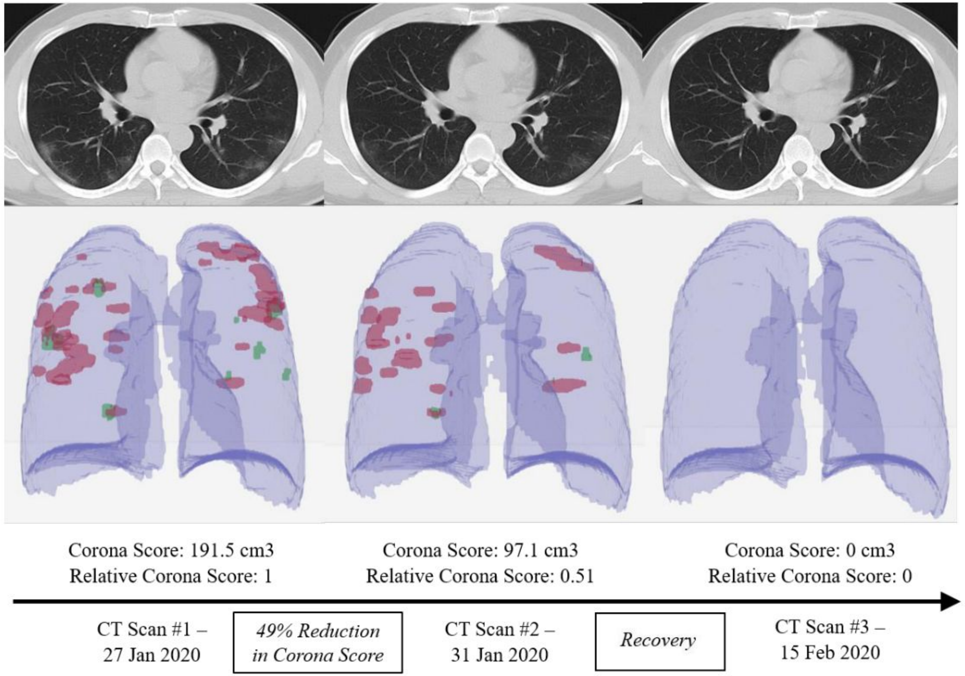
- Also extracted 64-dimensional visual features from the classification model, and combined it with clinical features to train a model for prognosis (higher-risk vs. lower-risk patients)



Wang S et al. A Fully Automatic Deep Learning System for COVID-19 Diagnostic and Prognostic Analysis, 2020.

Gozes et al.

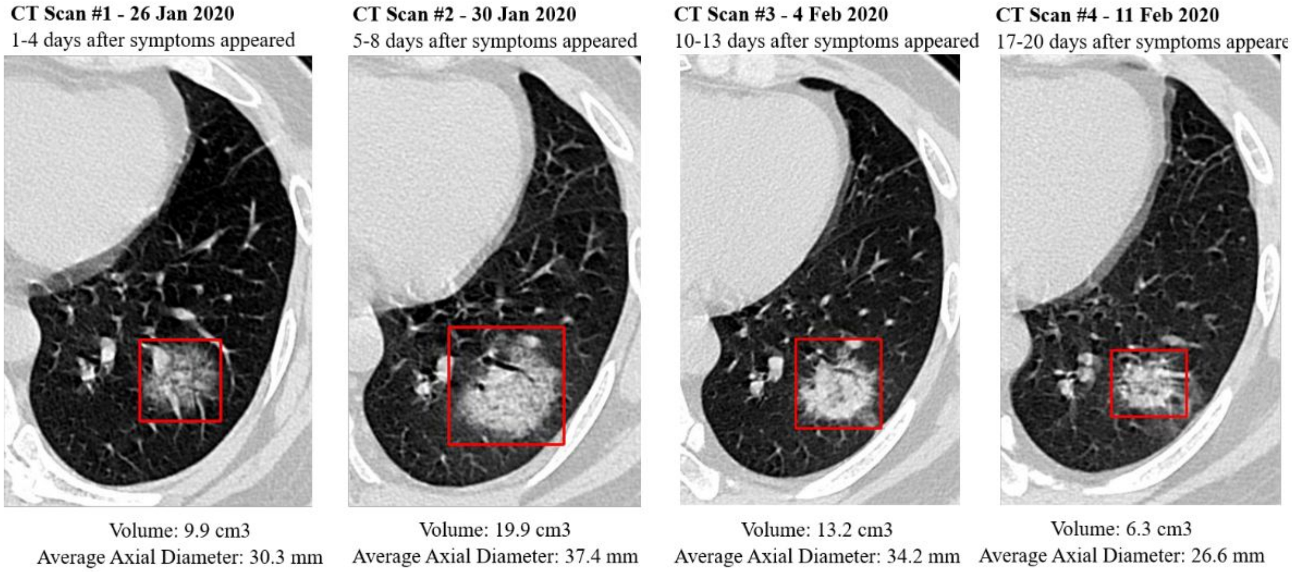
- Beyond COVID-19 classification on CTs, also outputs a “Corona score” to measure progression of the disease over time
- The score is a volumetric measurement of the opacities burden, and is based on a volumetric summation of network-activation maps and localized nodule detections
- A “relative Corona score” can perform patient-specific monitoring by normalizing the score by the score computed at the first time point.



Gozes et al. Rapid AI Development Cycle for the Coronavirus (COVID-19) Pandemic: Initial Results for Automated Detection & Patient Monitoring using Deep Learning CT Image Analysis, 2020.

Gozes et al.

- Multi-time point tracking of patient disease progression



Gozes et al. Rapid AI Development Cycle for the Coronavirus (COVID-19) Pandemic: Initial Results for Automated Detection & Patient Monitoring using Deep Learning CT Image Analysis, 2020.

Wang L. et al.

- This work takes a different approach and tries to detect COVID-19 from chest x-rays instead of CTs, since x-rays are fast, more accessible (especially in developing countries), and portable (can be performed e.g., within an isolation room)
- Trained a deep learning model to predict no infection, non-COVID-19 infection, COVID-19 infection

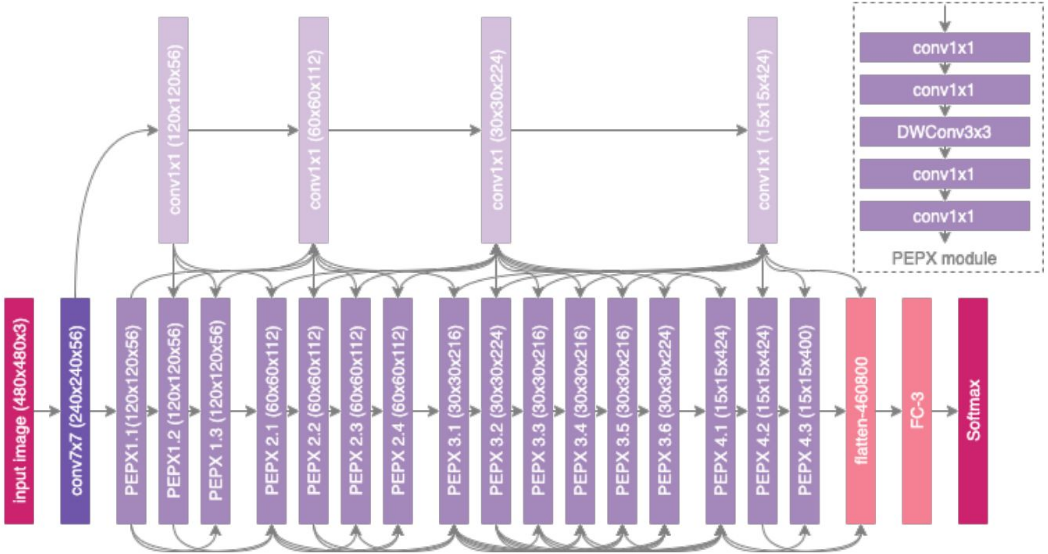
No infection

COVID-19 infection

Wang et al. COVID-Net: A Tailored Deep Convolutional Neural Network Design for Detection of COVID-19 Cases from Chest X-Ray Images, 2020.

Wang S. et al.

- Model architecture was selected based on a “network generation” approach to design a high-performing network for the task. But still based on familiar components!



Sensitivity (%)			
Architecture	**Normal**	**Non-COVID19**	**COVID-19**
VGG-19	**98.0**	90.0	58.7
ResNet-50	97.0	92.0	83.0
COVID-Net	95.0	**94.0**	**91.0**

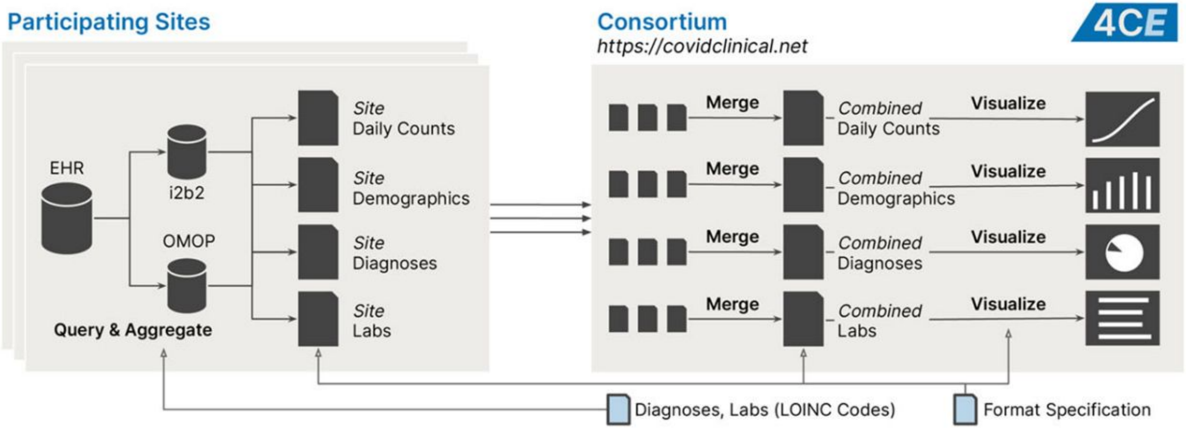
Positive Predictive Value (%)			
Architecture	**Normal**	**Non-COVID19**	**COVID-19**
VGG-19	83.1	75.0	98.4
ResNet-50	88.2	86.8	98.8
COVID-Net	**90.5**	**91.3**	**98.9**

Wang et al. COVID-Net: A Tailored Deep Convolutional Neural Network Design for Detection of COVID-19 Cases from Chest X-Ray Images, 2020.

Second application area: Modeling patient outcomes using EHR data

Aggregating data across many hospitals: the 4CE consortium

- Consortium for Clinical Characterization of COVID-19 by EHR (4CE): international consortium of 96 hospitals across five countries
- Used platforms such as OMOP to map all EHR to a common data model
- Total data covers 27,584 COVID-19 cases with 187,802 laboratory tests
- Initially includes 14 laboratory markers of cardiac, renal, hepatic, and immune dysfunction that have been associated with poor outcome in COVID-19 patients



Brat et ak, International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium, 2020.

Remember: OMOP Common Data Model

- Observational Medical Outcomes Partnership (OMOP)
- Created from public-private partnership involving FDA, pharmaceutical companies, and healthcare providers
- Standardized format and vocabulary
- Allows conversion of patient data from different sources into a common structure for analysis
- Intended to support data analysis

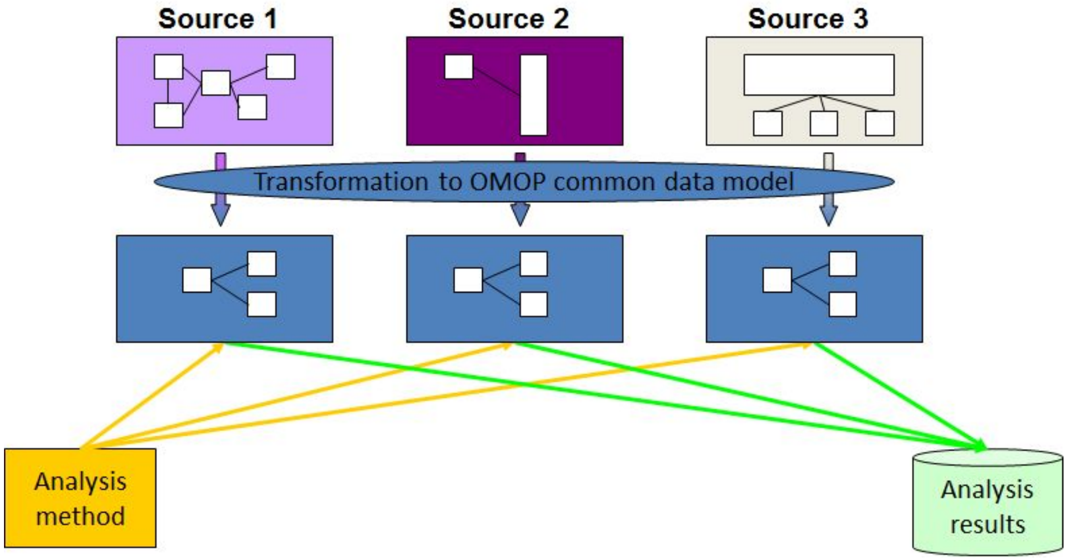


Figure credit: https://www.ohdsi.org/wp-content/uploads/2014/07/Why-CDM.png

Remember: OMOP Common Data Model

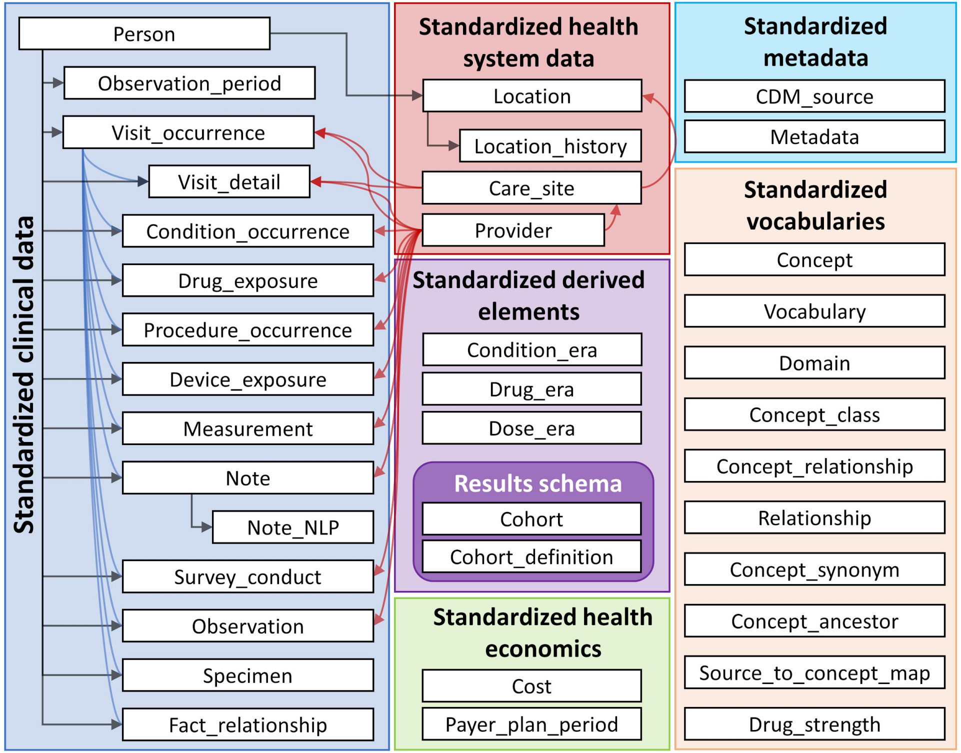


Figure credit: https://ohdsi.github.io/TheBookOfOhdsi/images/CommonDataModel/cdmDiagram.png

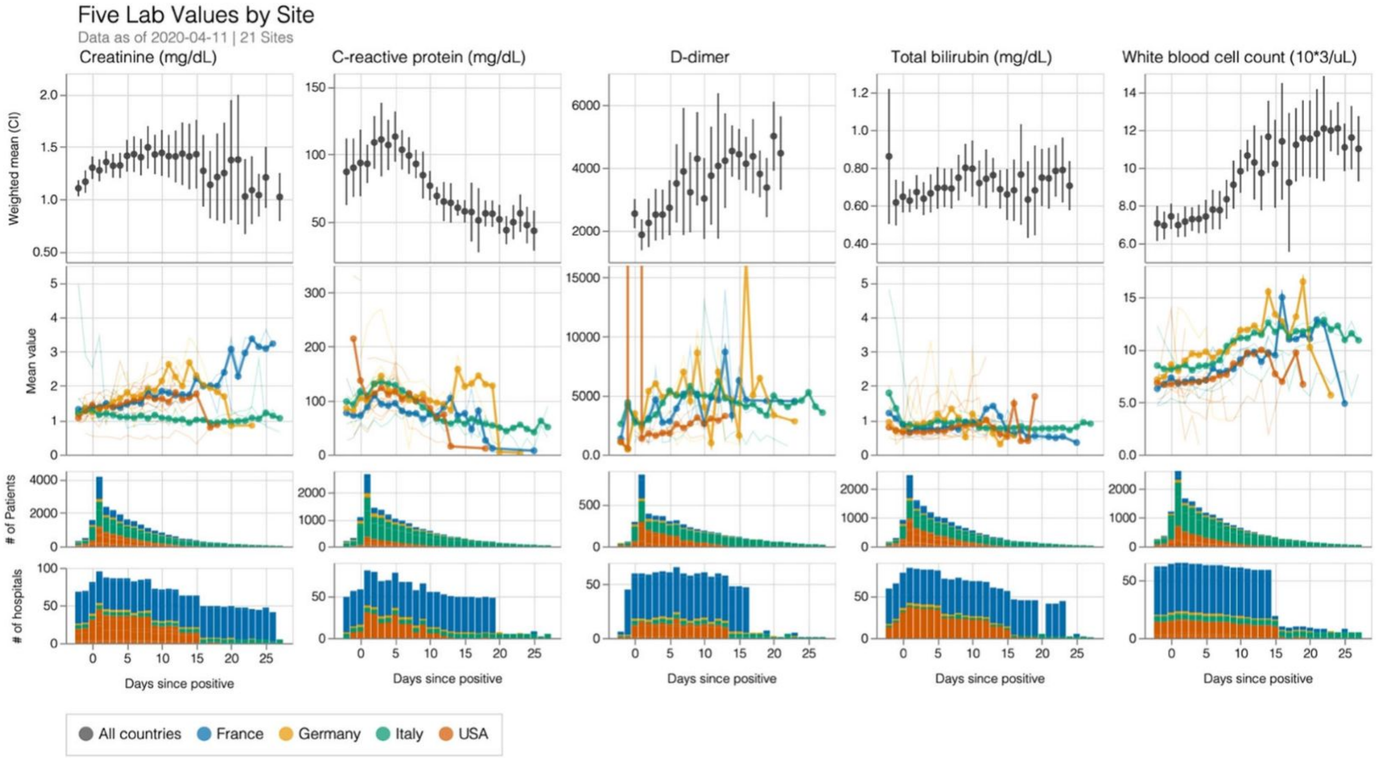
Aggregating data across many hospitals: the 4CE consortium

Table 1. Sites contributing data to the consortium.

Healthcare system	Acronym	City	Country	Population	Hospitals	Beds	Inpatient discharges/year
Assistance Publique—Hôpitaux de Paris	APHP	Paris	France	Adult & Pediatric	39	20,098	1,375,538
Bordeaux University Hospital	FRBDX	Bordeaux	France	Adult & Pediatric	3	2,676	130,033
Erlangen University Hospital	UKER	Erlangen	Germany	Adult & Pediatric	1	1,400	65,000
Medical Center, University of Freiburg	UKFR	Freiburg	Germany	Adult & Pediatric	1	1,660	71,500
University Medicine Mannheim	UMM	Mannheim	Germany	Adult & Pediatric	1	1,352	50,748
ICSM Pavia Hospital	ICSM1	Pavia	Italy	Adult	1	426	8616
ICSM Lumezzane/Brescia Hospitals	ICSM5	Lumezzane/Brescia	Italy	Adult	1	149	1296
ICSM Milano Hospital	ICSM20	Milan	Italy	Adult	1	200	2432
Policlinico di Milano	POLIMI	Milan	Italy	Adult & Pediatric	1	900	40,000
ASST Papa Giovanni XXIII Bergamo	HPG23	Bergamo	Italy	Adult & Pediatric	1	1080	45,000
National University Hospital	NUH	Singapore	Singapore	Adult & Pediatric	1	1556	100,977
Boston Children's Hospital	BCH	Boston, MA	USA	Pediatric	1	404	28,000
Beth Israel Deaconess Medical Center	BIDMC	Boston, MA	USA	Adult	1	673	40,752
Children's Hospital of Philadelphia	CHOP	Philadelphia, PA	USA	Pediatric	1	564	25,406
University of Kansas Medical Center	KUMC	Kansas City, KS	USA	Adult & Pediatric	1	794	54,659
Mayo Clinic	MAYOC	Rochester, MN	USA	Adult & Pediatric	1	2059	100,000
Mass General Brigham (Partners Healthcare)	MGB	Boston, MA	USA	Adult & Pediatric	10	3418	163,521
Medical University of South Carolina	MUSC	Charleston, SC	USA	Adult & Pediatric	8	1600	55,664
University of Pennsylvania	UPenn	Philadelphia, PA	USA	Adult	5	2469	118,188
University of California, LA	UCLA	Los Angeles, CA	USA	Adult & Pediatric	2	786	40,526
University of Michigan	UMICH	Ann Arbor, MI	USA	Adult & Pediatric	3	1000	49,008
University of North Carolina at Chapel Hill	UNC	Chapel Hill, NC	USA	Adult & Pediatric	11	3095	52000
UT Southwestern Medical Center	UTSW	Dallas, TX	USA	Adult	1	608	26,905
				Total	96	45,352	2,444,792

Brat et ak, International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium, 2020.

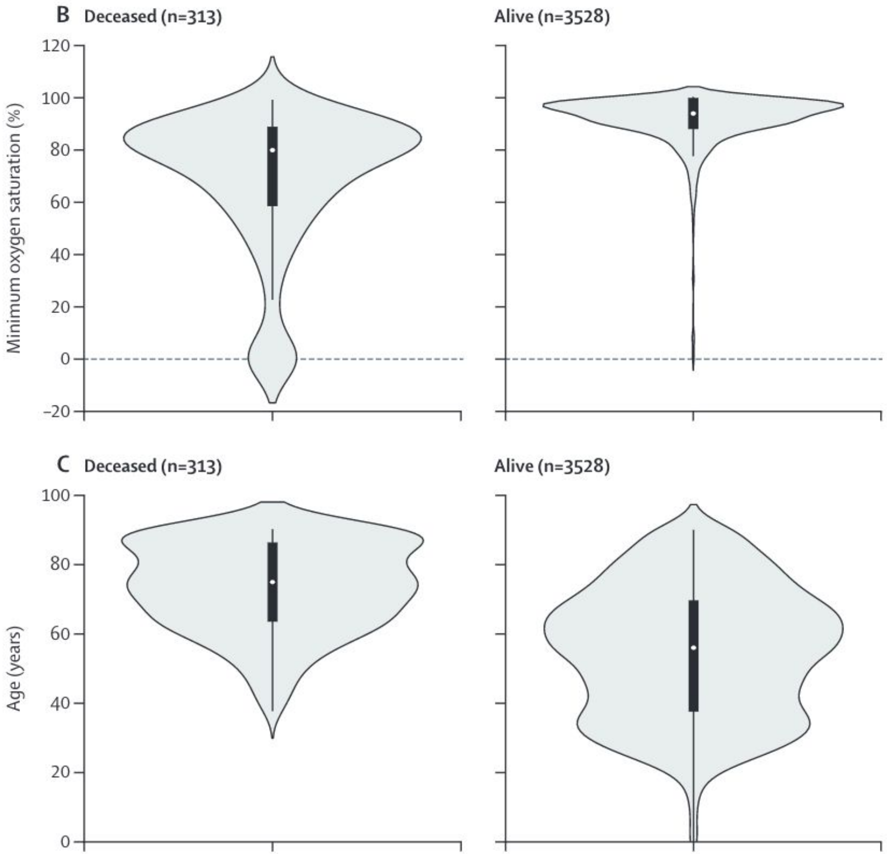
Aggregating data across many hospitals: the 4CE consortium



Brat et ak, International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium, 2020.

Yadaw et al.

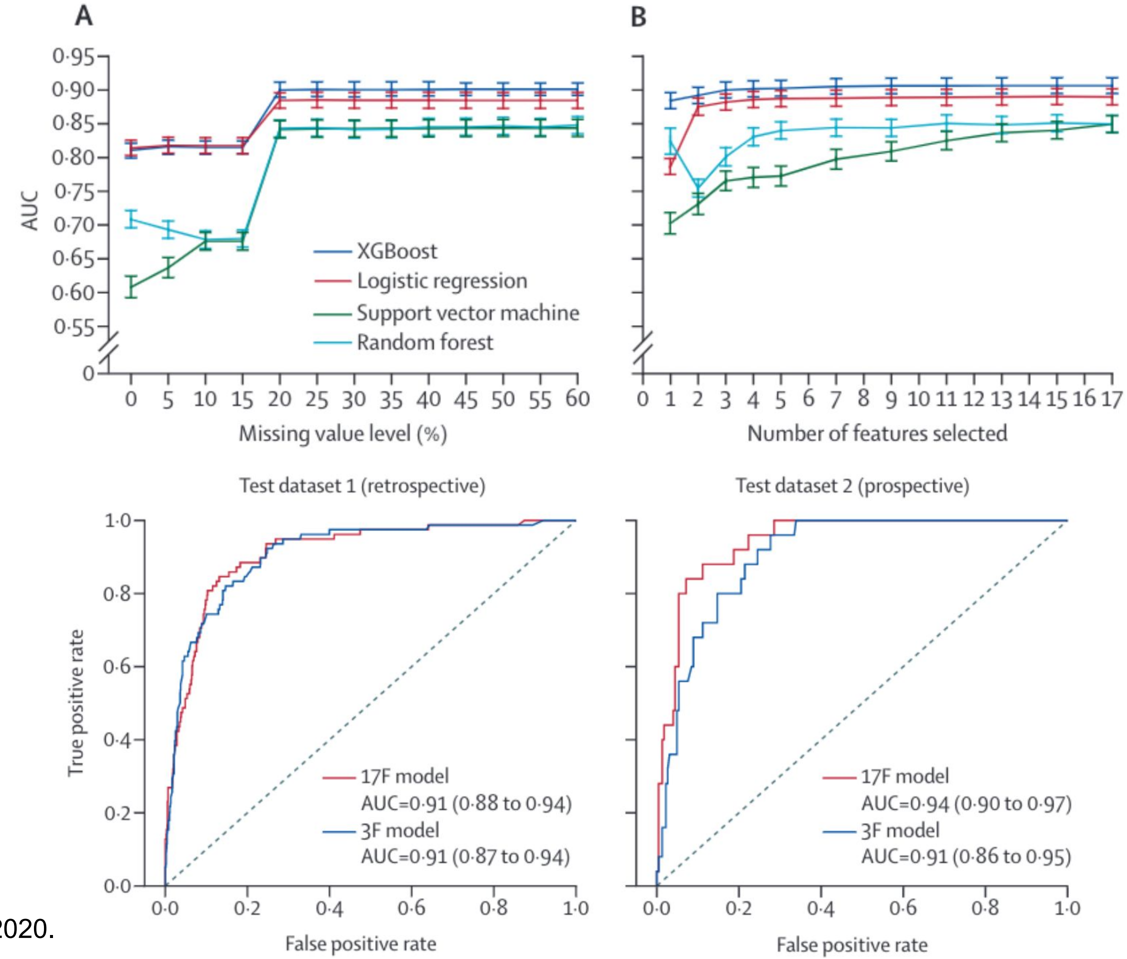
- Prediction of COVID-19 patient mortality from patient clinical variable data
- Trained on 3841 patients from the Mount Sinai Health System in NYC. Tested on 961 retrospective and 249 prospective patients.
- Needed to perform missing value imputation (remember from Lecture 6)



Yadaw et al. Clinical features of COVID-19 mortality: development and validation of a clinical prediction model, 2020.

Yadaw et al.

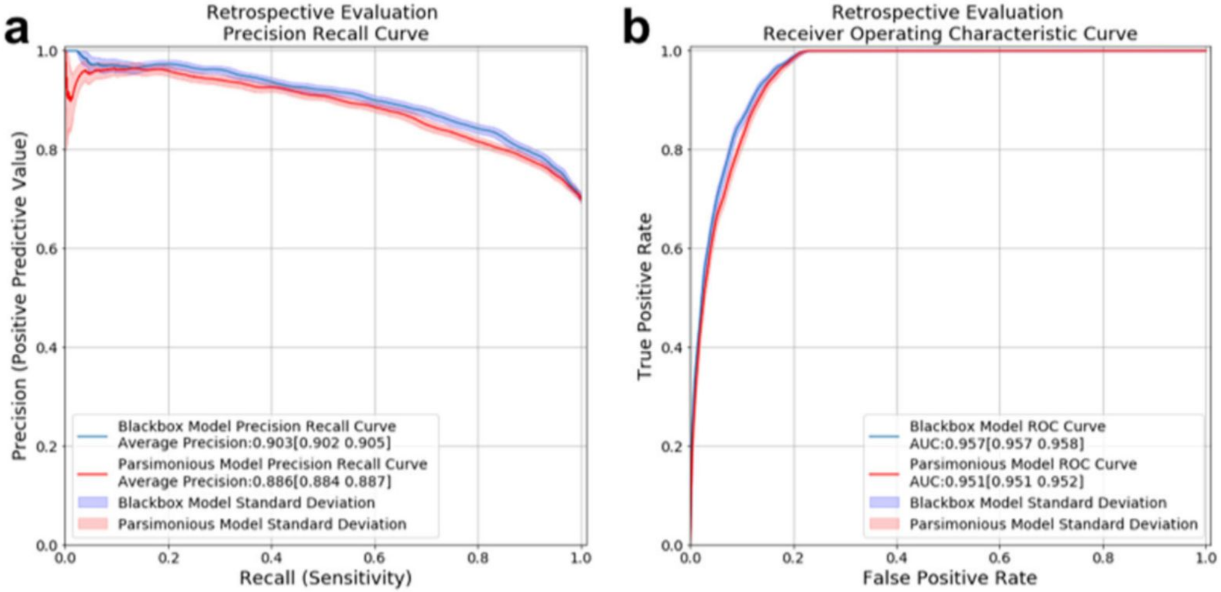
Evaluation of multiple types of machine learning models



Yadaw et al. Clinical features of COVID-19 mortality: development and validation of a clinical prediction model, 2020.

Razavian et al.

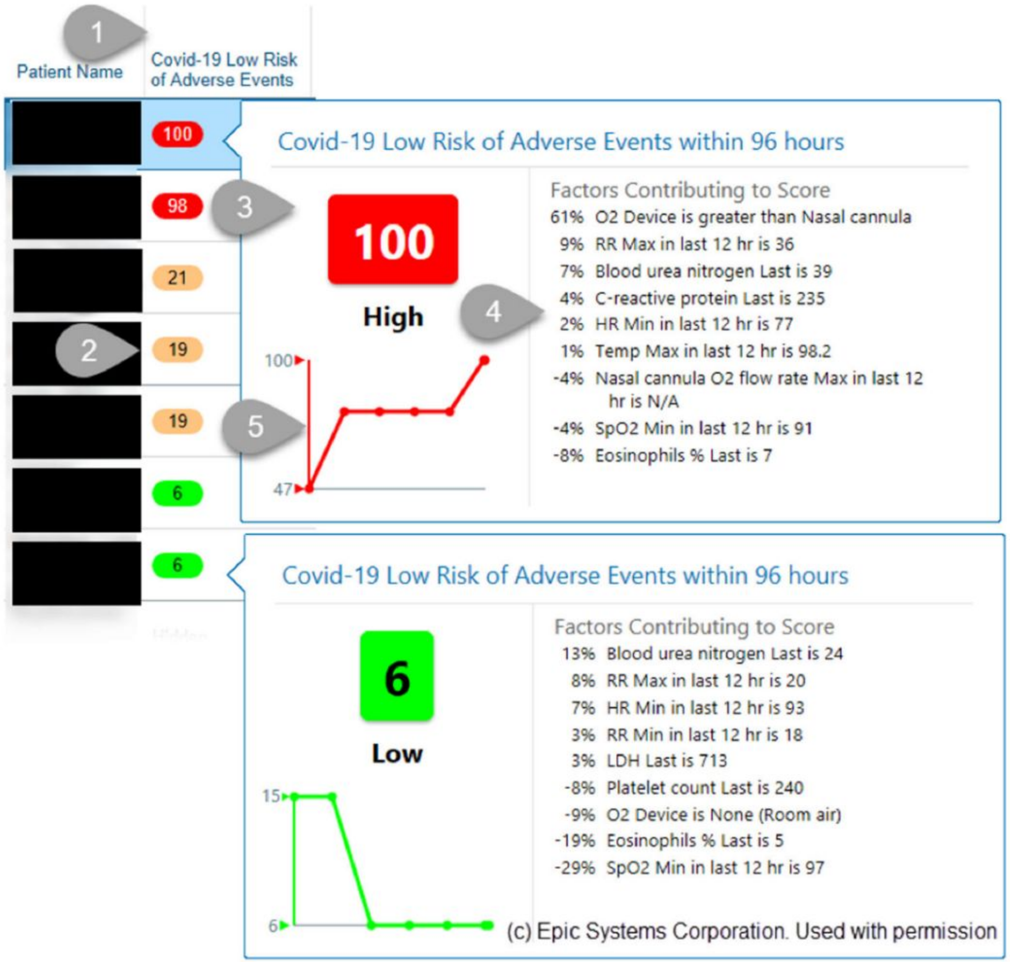
- Instead of mortality, predict favorable outcomes (may be more meaningful when ICUs are already saturated!)
- Trained multiple types of machine learning models on 3345 and 474 prospective hospitalizations, using clinical variable data.



Razavian et al. A validated, real-time prediction model for favorable outcomes in hospitalized COVID-19 patients, 2020.

Razavian et al.

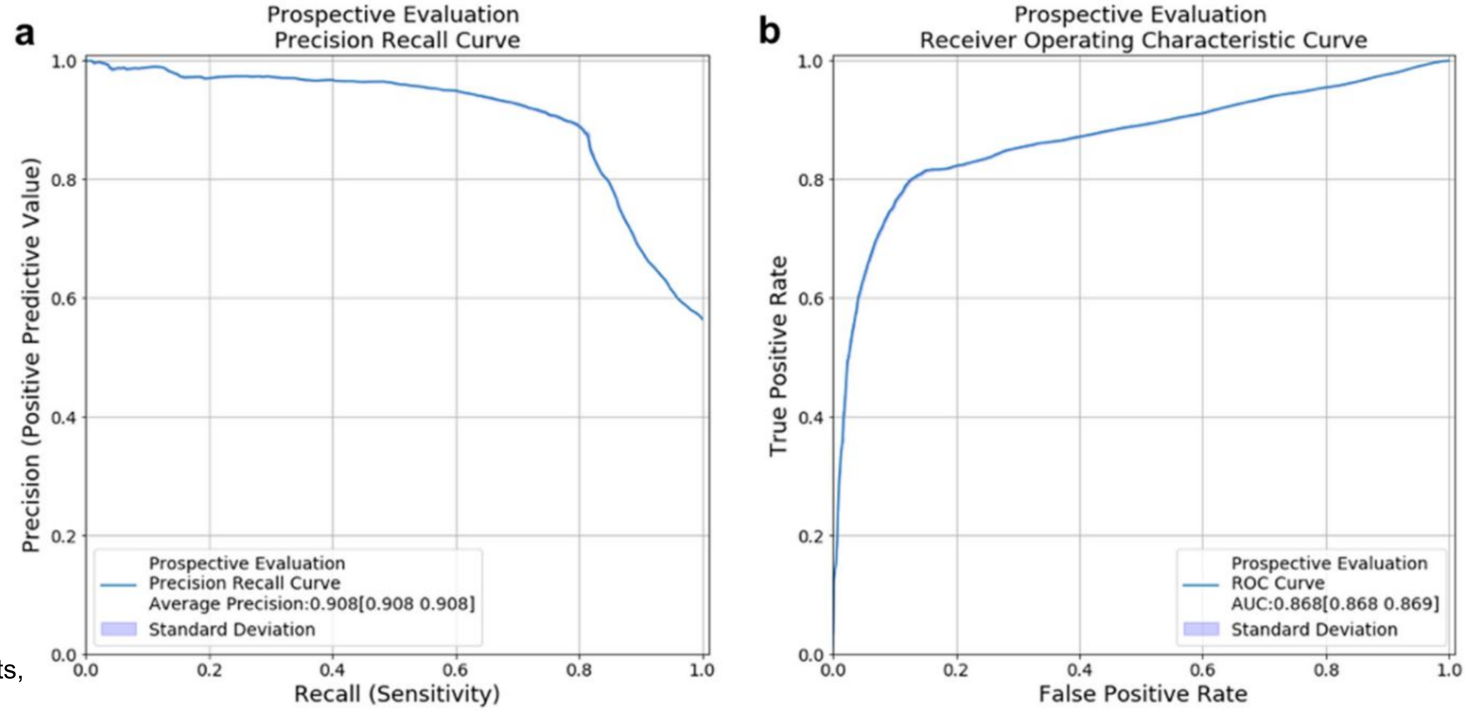
Integrated and deployed in NYU hospitals EHR system



Razavian et al. A validated, real-time prediction model for favorable outcomes in hospitalized COVID-19 patients, 2020.

Razavian et al.

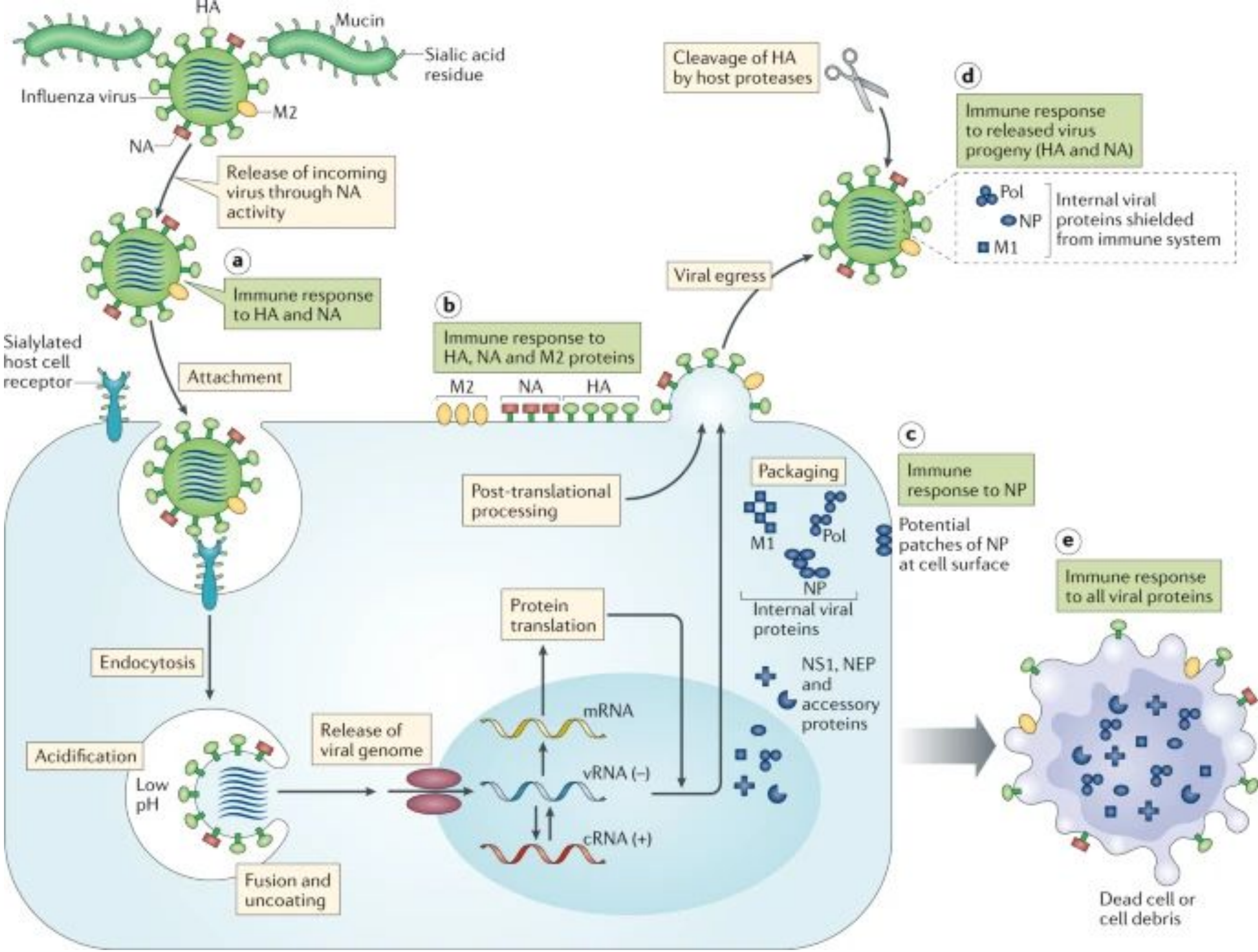
Prospective model performance



Razavian et al. A validated, real-time prediction model for favorable outcomes in hospitalized COVID-19 patients, 2020.

Third application area: Finding treatments for the disease

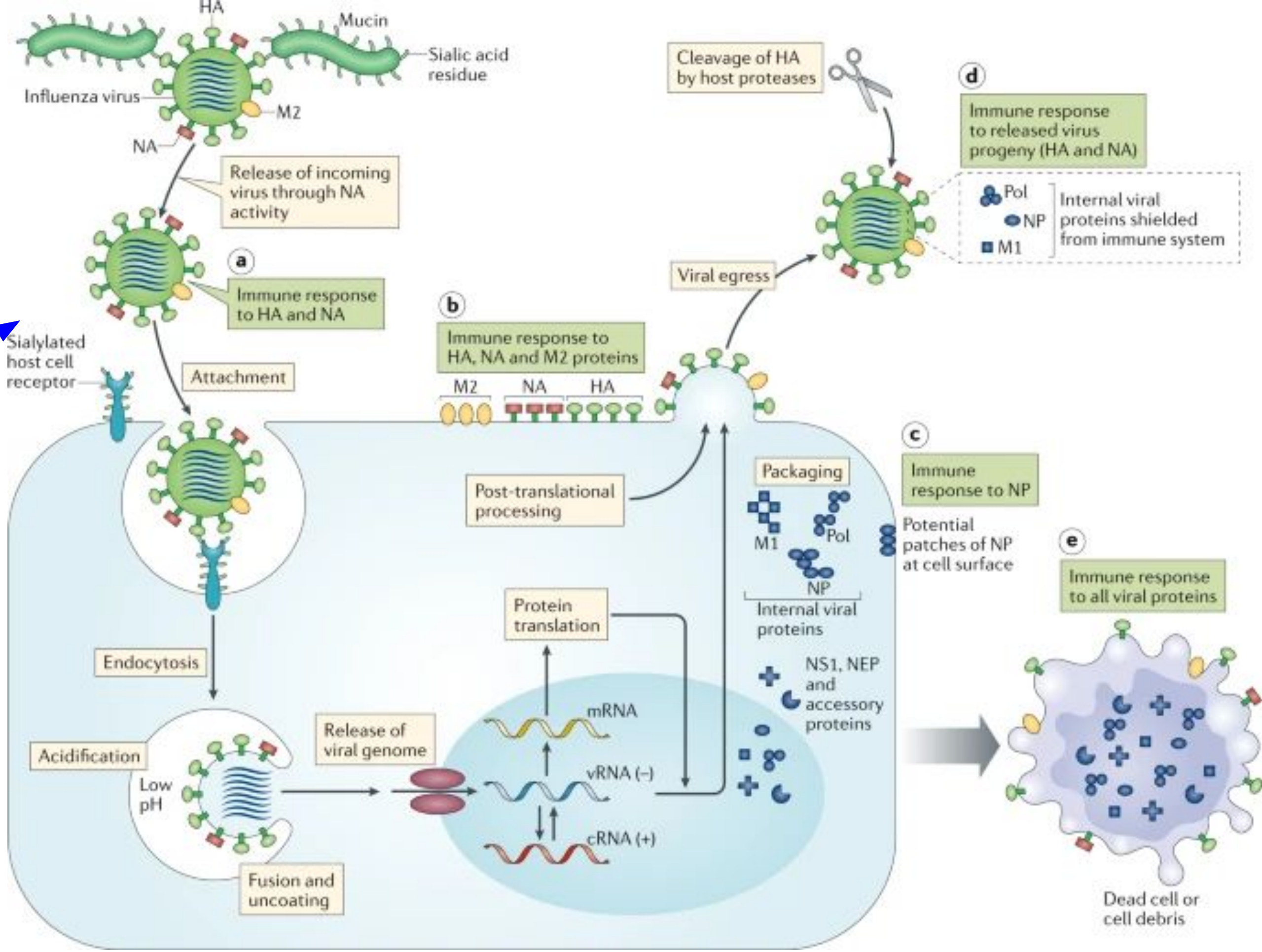
How does virus infection work?



Krammer. The human antibody response to influenza A virus infection and vaccination, 2020.

How does virus infection work?

Virus surface proteins are used to bind onto host cell receptor



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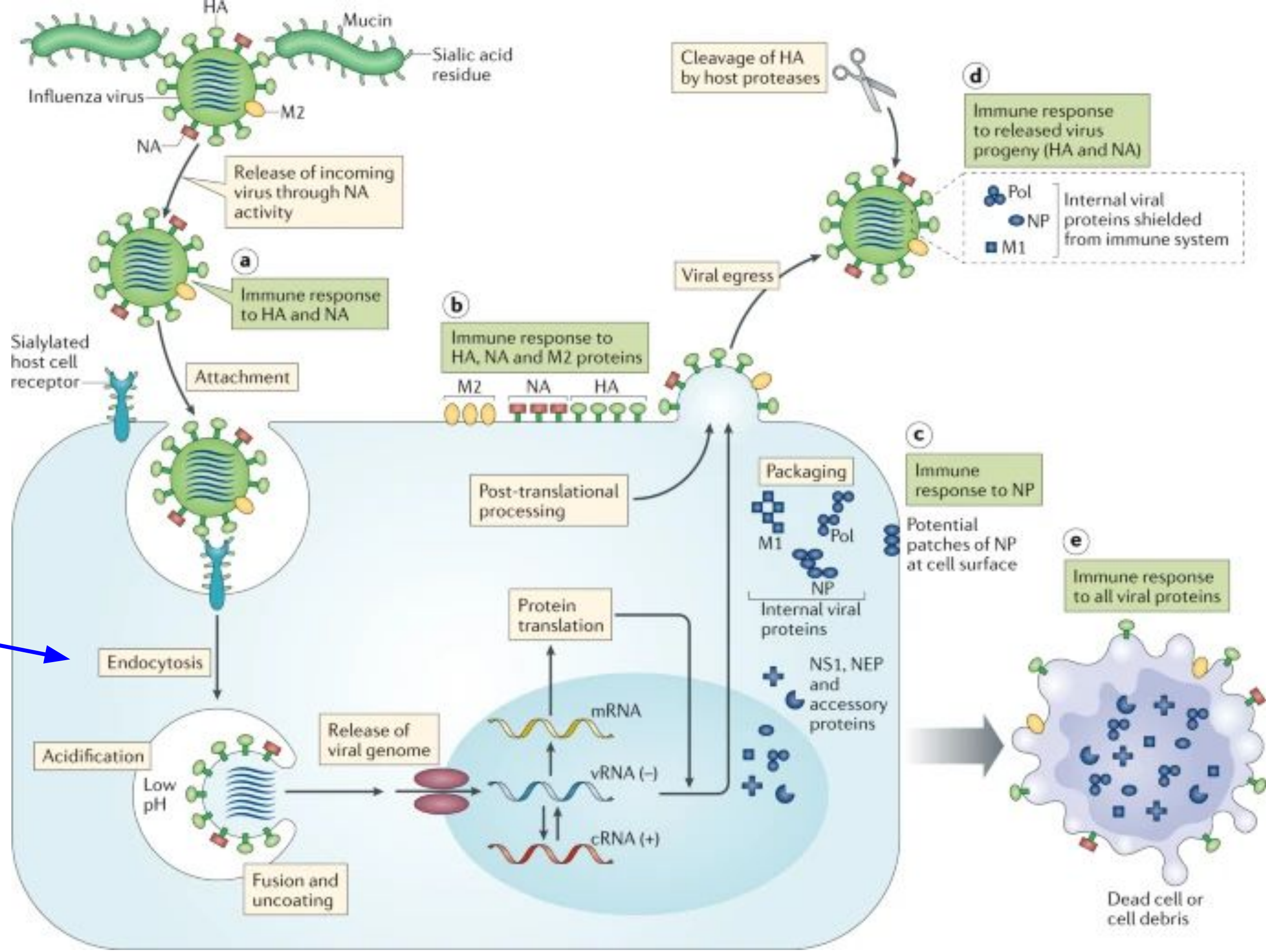
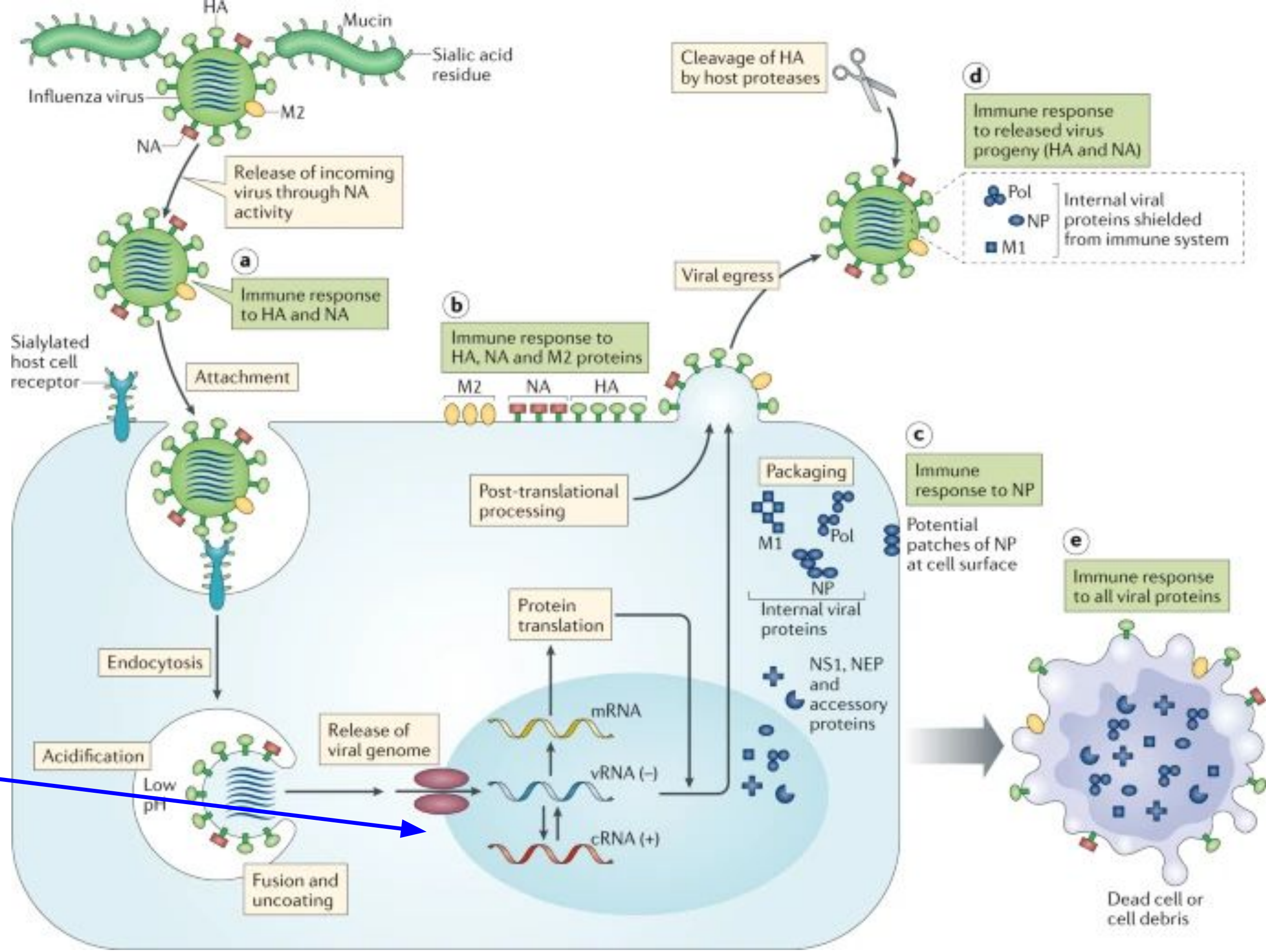


Virus enters cell through endocytosis

Krammer. The human antibody response to influenza A virus infection and vaccination, 2020.

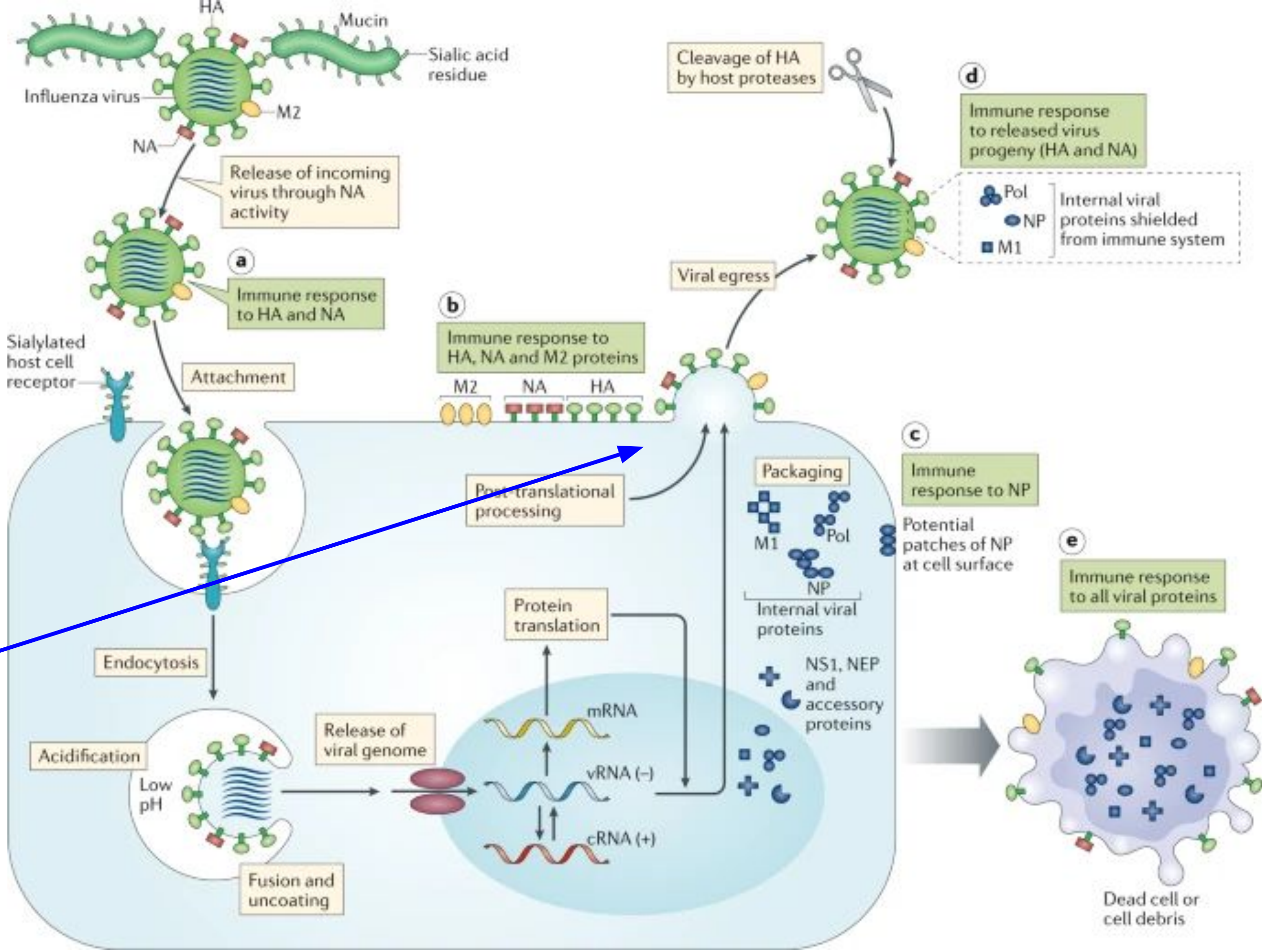
How does virus infection work?



Viral contents are released and viral RNA is reproduced, with the help of host components

Krammer. The human antibody response to influenza A virus infection and vaccination, 2020.

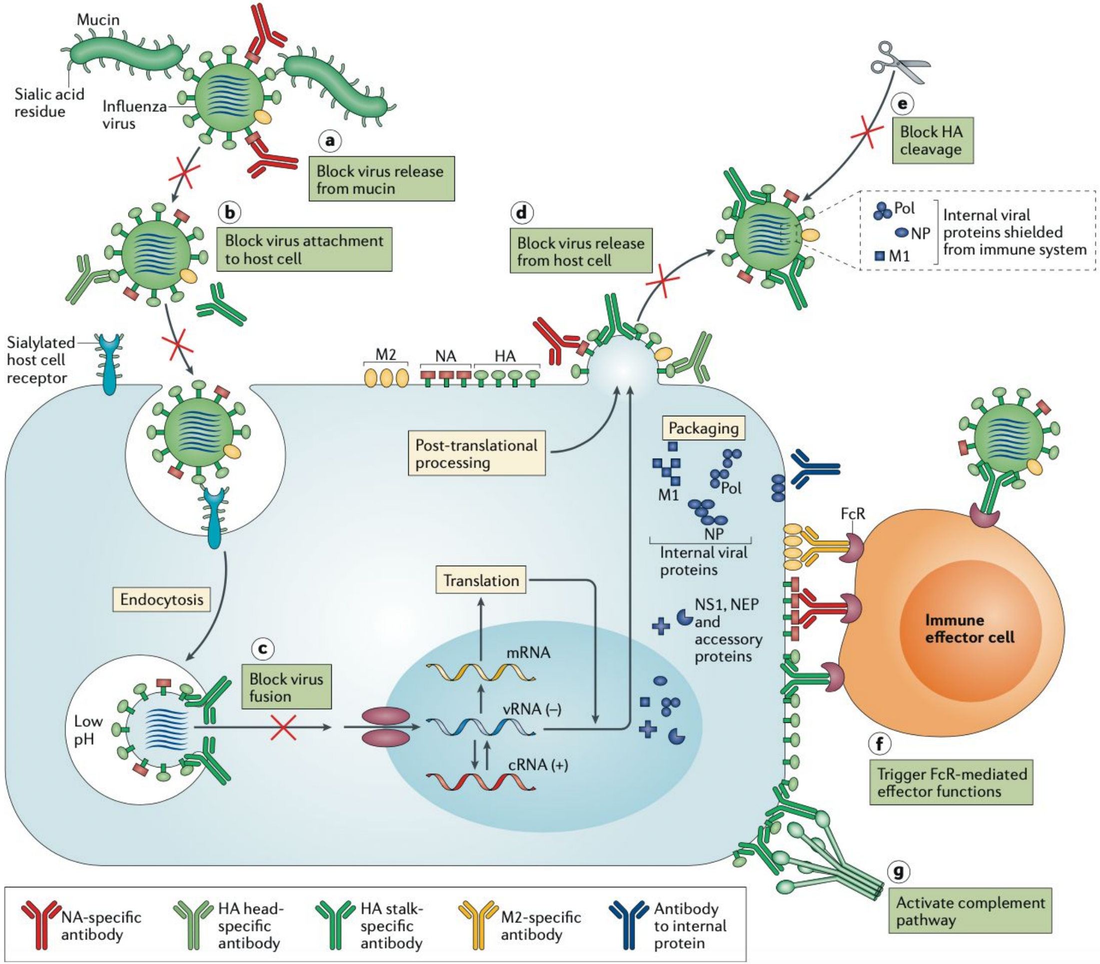
How does virus infection work?



New viruses are assembled and leave the cell through viral egress

Krammer. The human antibody response to influenza A virus infection and vaccination, 2020.

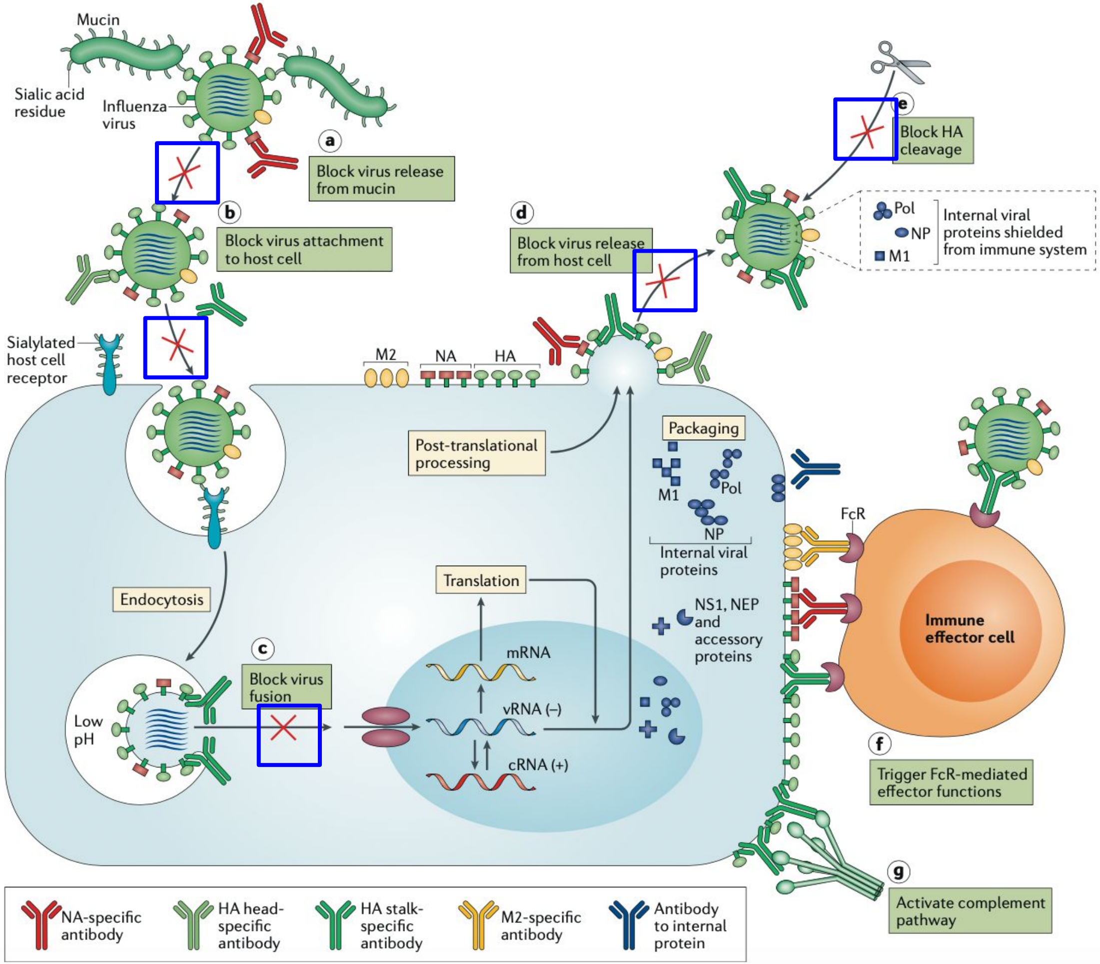
How does virus infection work?



Krammer. The human antibody response to influenza A virus infection and vaccination, 2020.

How does virus infection work?

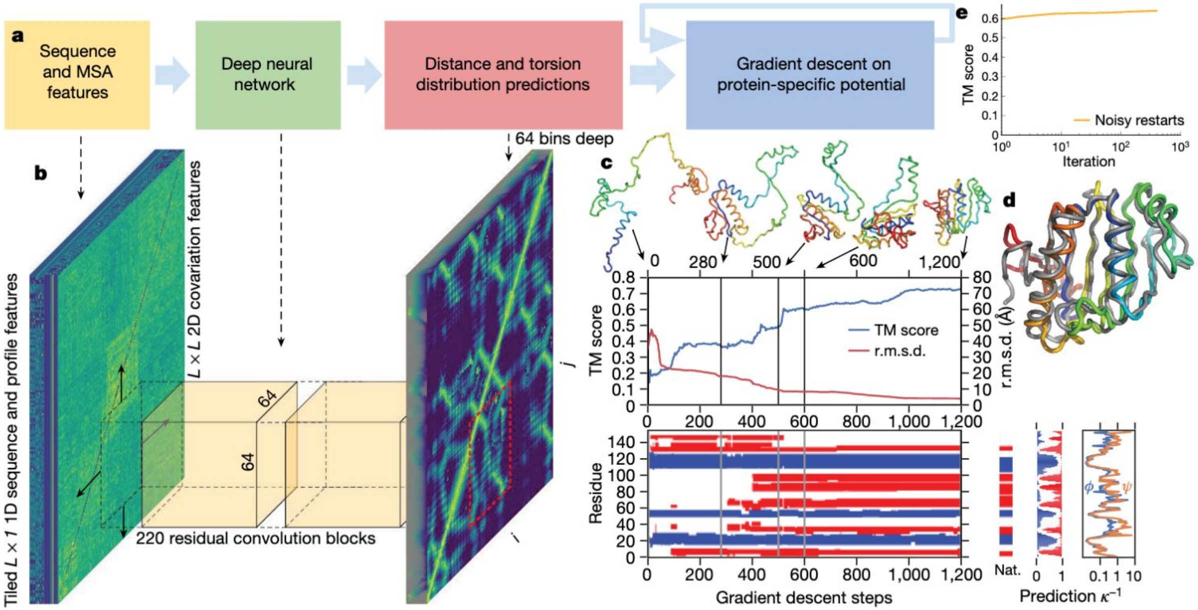
Mechanisms for viral treatments include antibody binding to viral proteins that block / disrupt steps in the viral replication process



Krammer. The human antibody response to influenza A virus infection and vaccination, 2020.

AlphaFold

- Protein structure prediction: determining the 3D shape of a protein from its amino acid sequence
- Based on neural network that predicts distances between pairs of residues, then energy minimization to determine most likely 3D shape



Senior et al. Improved protein structure prediction using potentials from deep learning, 2020.

Jumper et al. Highly accurate protein structure prediction with AlphaFold. Nature, 2021.

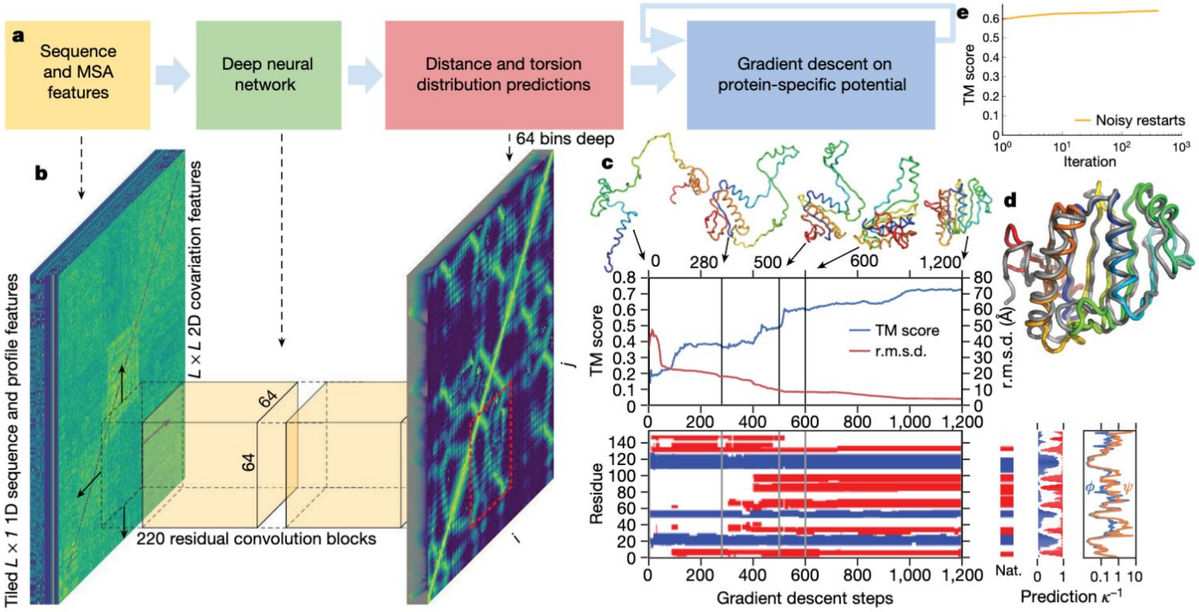
AlphaFold

- Protein structure prediction: determining the 3D shape of a protein from its amino acid sequence
- Based on neural network that predicts distances between pairs of residues, then energy minimization to determine most likely 3D shape

Used approach to release structure predictions for proteins associated with SARS-CoV-2

Senior et al. Improved protein structure prediction using potentials from deep learning, 2020.

Jumper et al. Highly accurate protein structure prediction with AlphaFold. Nature, 2021.



Beck et al.

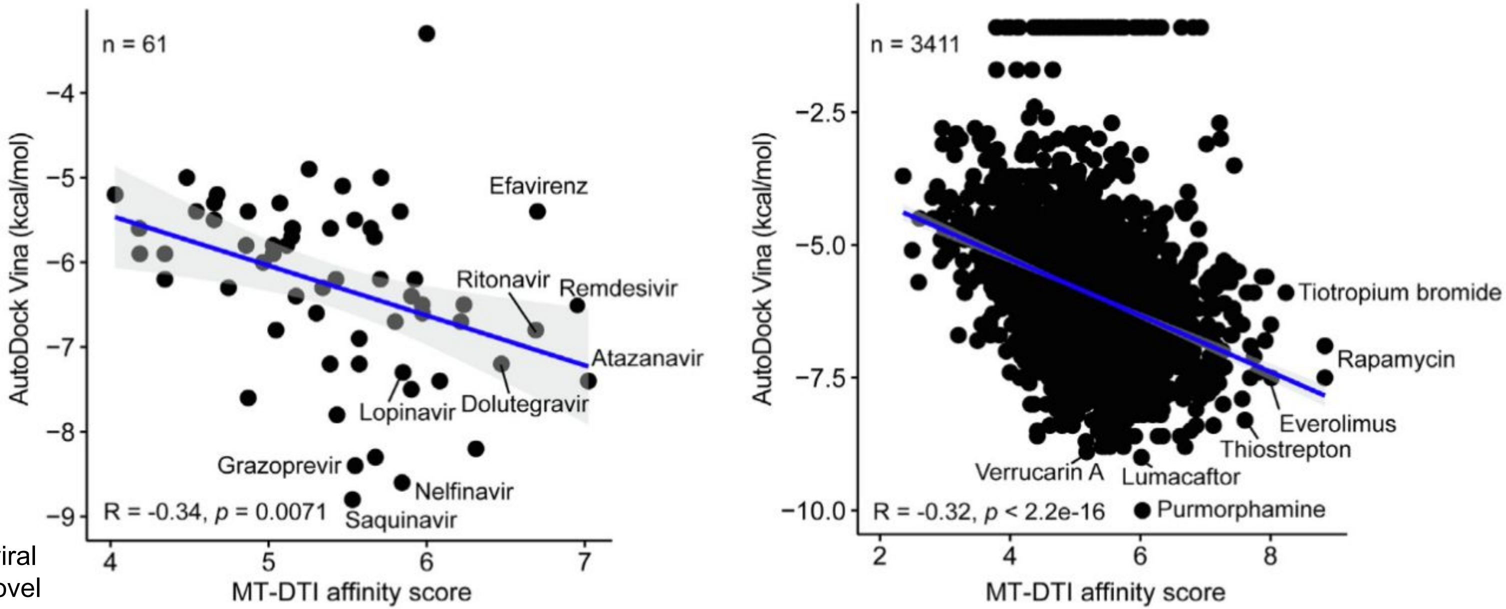
- Deep learning-based drug-target interaction model that predicts whether commercially available drugs can act on viral protein of SARS-CoV-2 (drug repurposing)
- Extracted amino acid sequences of proteins from the SARS-CoV-2 replication complex
- Can use sequence models from NLP to model the data!

Atazanavir	COC(=O)NC(C(=O)NC(Cc1ccccc1)C(O)CN(Cc1ccc(−c2ccccn2)cc1)NC(=O)C(NC(=O)OC)C(C)(C)C)C(C)(C)C
Remdesivir*	CCC(CC)COC(=O)[C@H](C)N[P@](=O)(OC[C@@H]1[C@H]([C@H]([C@](O1)(C#N)C2 = CC = C3N2N = CN = C3N)O)O) OC4 = CC = CC = C4
Efavirenz*	O = C1Nc2ccc(Cl)cc2[C@@](C#CC2CC2)(C(F)(F)F)O1
Ritonavir	CC(C)c1nc(CN(C)C(=O)NC(C(=O)NC(Cc2ccccc2)CC(O)C(Cc2ccccc2)NC(=O)OCc2cncs2)C(C)C)cs1
Dolutegravir	CC1CCOC2Cn3cc(C(=O)NCc4ccc(F)cc4F)c(=O)c(O)c3C(=O)N12
Asunaprevir	C = CC1CC1(NC(=O)C1CC(Oc2ncc(OC)c3ccc(Cl)cc23)CN1C(=O)C(NC(=O)OC(C)(C)C)C(C)(C)C)C(=O)NS(=O)(=O)C1CC1
Ritonavir*	CC(C)c1nc(CN(C)C(=O)N[C@H](C(=O)N[C@@H](Cc2ccccc2)C[C@H](O)[C@H](Cc2ccccc2)NC(=O)OCc2cncs2)C(C)C)cs1
Simeprevir*	COc1ccc2c(O[C@H]3CC4C(=O)N(C)CCCC/C = C\[C@H]5C[C@@]5(C(=O)NS(=O)(=O)C5CC5)NC(=O)[C@@H]4C3)cc(−c3nc(C (C)C)cs3)nc2c1C

Beck et al. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model, 2020.

Beck et al.

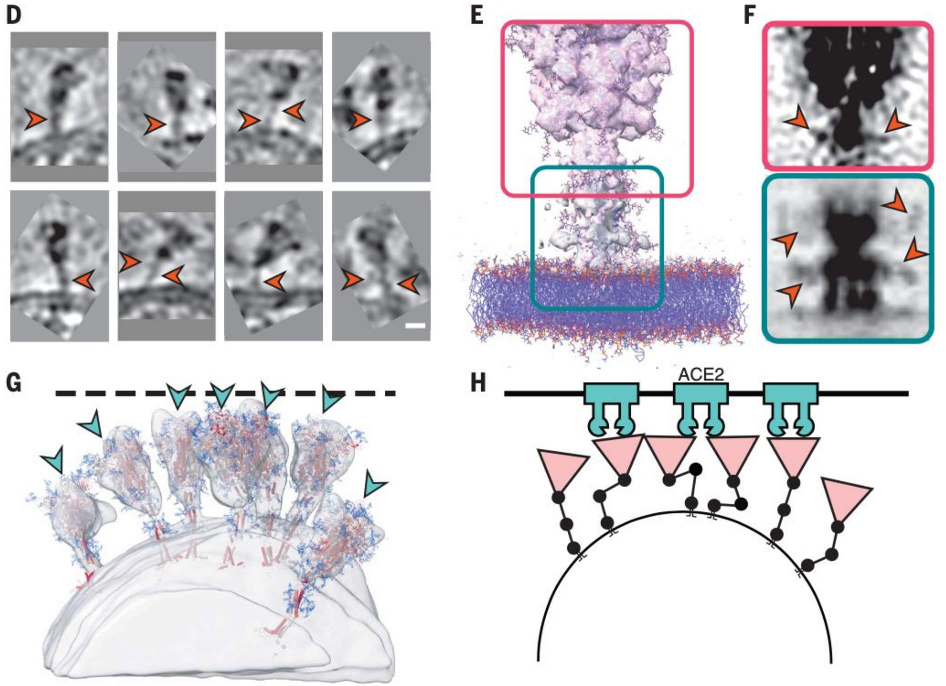
Identified promising drugs such as atazanavir, remdesivir, and others



Beck et al. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model, 2020.

CryoET high resolution imaging of virus spike structure

- CryoET (cryogenic electron tomography) imaging can provide high-resolution visualization of virus particles
- Analysis of virus spike (surface protein) structure, organization and variability can provide insight into how it binds to host cell receptors

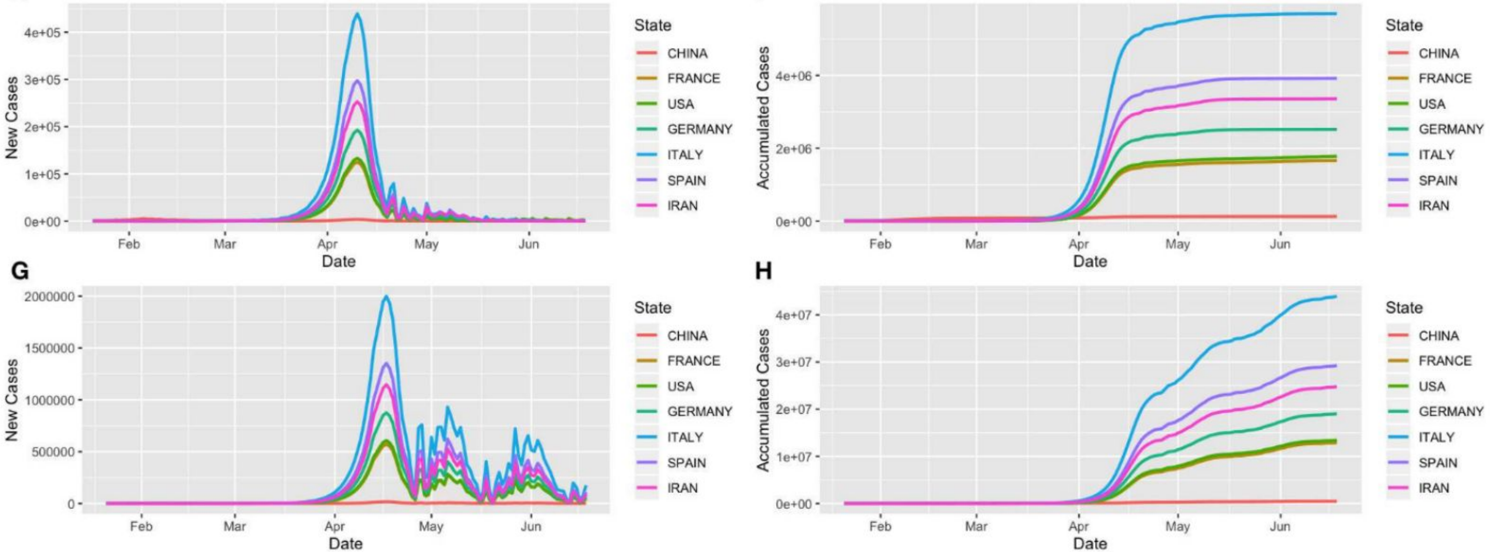


Turonova et al. In situ structural analysis of SARS-CoV-2 spike reveals flexibility mediated by three hinges, 2020.

Additional application areas

Epidemiology and disease forecasting

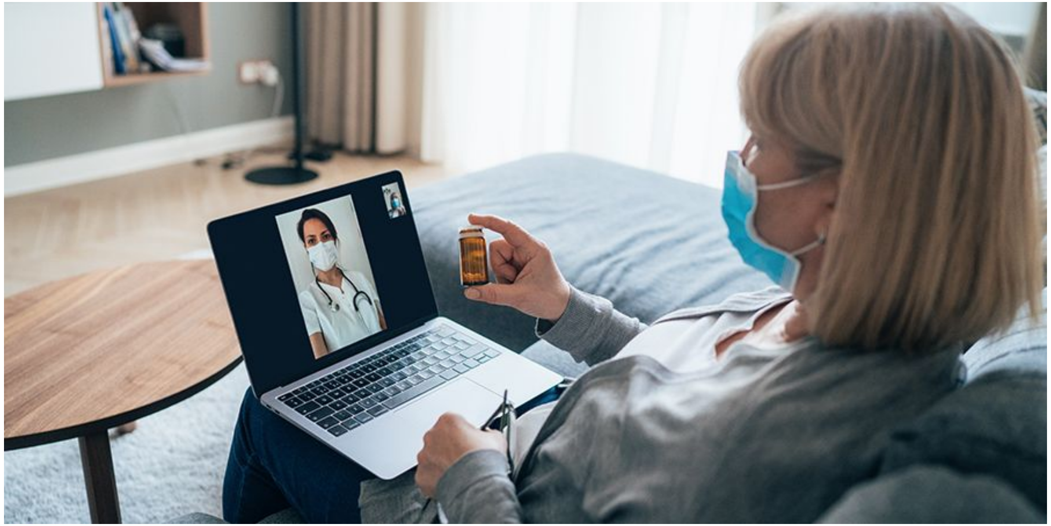
- Epidemiological models e.g., SIR, SEIR, based on numbers of susceptible, exposed, infected, recovered individuals help with anticipating and preparing for upcoming challenges
- Also efforts at deep learning-based forecasting of future cases



Hu et al. Forecasting and Evaluating Multiple Interventions for COVID-19 Worldwide, 2020.
Shinde et al. Forecasting Models for Coronavirus Disease (COVID-19): A Survey of the State-of-the-Art, 2020.

Telehealth

- Demand for virtual visits are up more than 1000x in some care settings[1]
- Digital setting offers opportunity for AI algorithms
- Already many AI applications and even products popping up around use cases such as triaging, vitals measurement, and even cough analysis



[1]https://www.aarp.org/health/conditions-treatments/info-2020/telehealth-surges-during-coronavirus-outbreak.html
Figure credit: https://www.healthwise.org/blog/patient-ed-telehealth-amid-covid-19.aspx

Some cautionary tales -- has AI lived up to its potential?

nature machine intelligence

ANALYSIS

https://doi.org/10.1038/s42256-021-00307-0

Check for updates

OPEN

Common pitfalls and recommendations for using machine learning to detect and prognosticate for COVID-19 using chest radiographs and CT scans

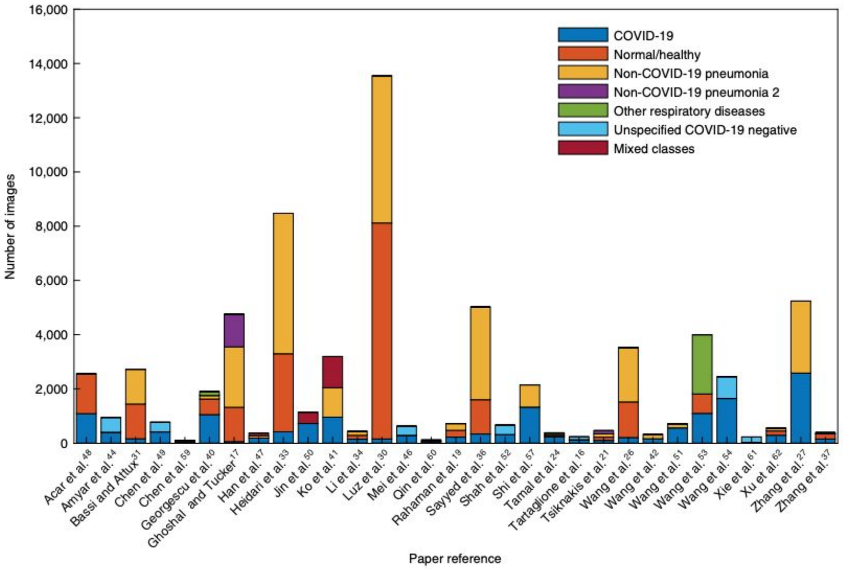
Michael Roberts[1,2], Derek Driggs[1], Matthew Thorpe[3], Julian Gilbey[1], Michael Yeung[4], Stephan Ursprung[4,5], Angelica I. Aviles-Rivero[1], Christian Etmann[1], Cathal McCague[4,5], Lucian Beer[4], Jonathan R. Weir-McCall[4,6], Zhongzhao Teng[4], Effrossyni Gkrania-Klotsas[7], AIX-COVNET*, James H. F. Rudd[8,36], Evis Sala[4,5,36] and Carola-Bibiane Schönlieb[1,36]

Why has there been limited ability to translate into utilization in clinical practice?

- Common issues
  - “Frankenstein” datasets assembled from many sources, unrealized duplication issues
  - Many machine learning researchers used a publicly available dataset of non-COVID cases as negatives, without realizing they were pediatric patients
  - Lack of reproducibility of method
  - Lack of reporting about demographics
  - Insufficient generalization evaluation
  - Unable to assess performance in comparison to RT-PCR
  - High risk of bias

Roberts et al. Common pitfalls and recommendations for using machine learning to detect and prognosticate for COVID-19 using chest radiographs and CT scans. Nature Machine Intelligence, 2021.

One takeaway: larger collaborative efforts could have helped



Roberts et al. Common pitfalls and recommendations for using machine learning to detect and prognosticate for COVID-19 using chest radiographs and CT scans. Nature Machine Intelligence, 2021.

Summary

Today we covered:

- Applications of AI in Healthcare through the lens of COVID-19
  - AI interpretation of chest radiology images
  - Modeling patient outcomes using EHR data
  - Finding treatments for the disease
  - Additional application areas
  - Has AI lived up to the potential?

Next time:

- Unsupervised Learning and Reinforcement Learning