# Machine Learning for Better Medicine

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NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

10/9/2022

Northwestern University

# Lack of evidence in medical practice

- Only 11 percent of sampled American College of Cardiology and American Heart Association guidelines used evidence from RCTs or meta-analyses

JAMA Network

JAMA

Original Contribution

February 25, 2009

## Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD; Joseph M. Allen, MA; Judith M. Kramer, MD, MS; et al

Author Affiliations | Article Information

*JAMA.* 2009;301(8):831-841. doi:10.1001/jama.2009.205

# Lack of evidence in medical practice

- Of more than 4000 recommendations for infectious diseases, 14 percent were based on RCTs

JAMA Network

JAMA Internal Medicine

**Original Investigation**

January 10, 2011

## Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines

Dong Heun Lee, MD; Ole Vielemeyer, MD

» Author Affiliations | Article Information

*Arch Intern Med.* 2011;171(1):18-22. doi:10.1001/archinternmed.2010.482

# Lack of evidence in medical practice

- 88 publications of CPGs involving 3119 recommendations
- 9% based on PRCTs and percentage decreased over time

*Intensive Care Med* (2018) 44:1189–1191
https://doi.org/10.1007/s00134-018-5142-8

LETTER

CrossMark

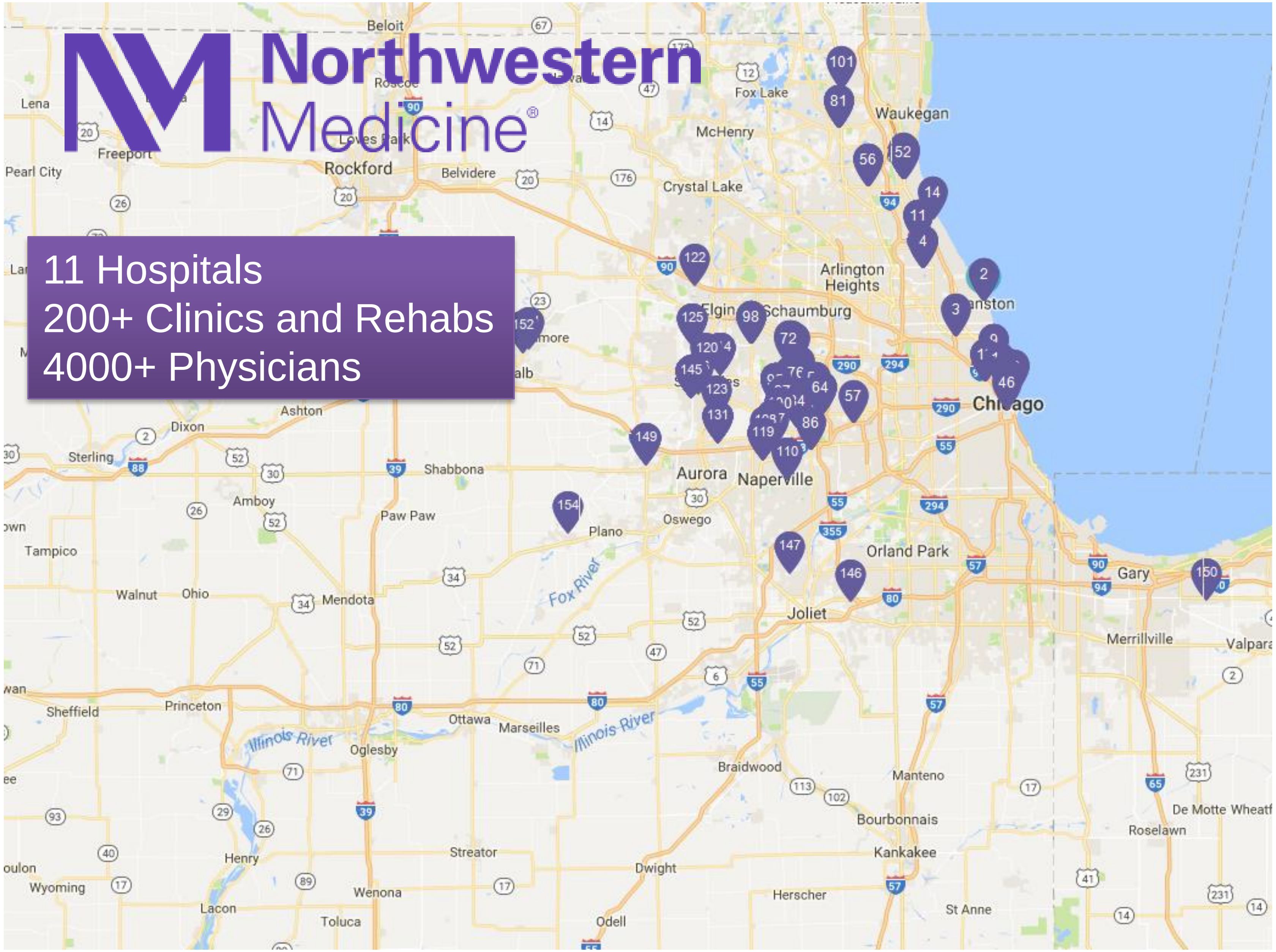
## Scientific evidence underlying the recommendations of critical care clinical practice guidelines: a lack of high level evidence

Zhongheng Zhang*, Yucai Hong and Ning Liu

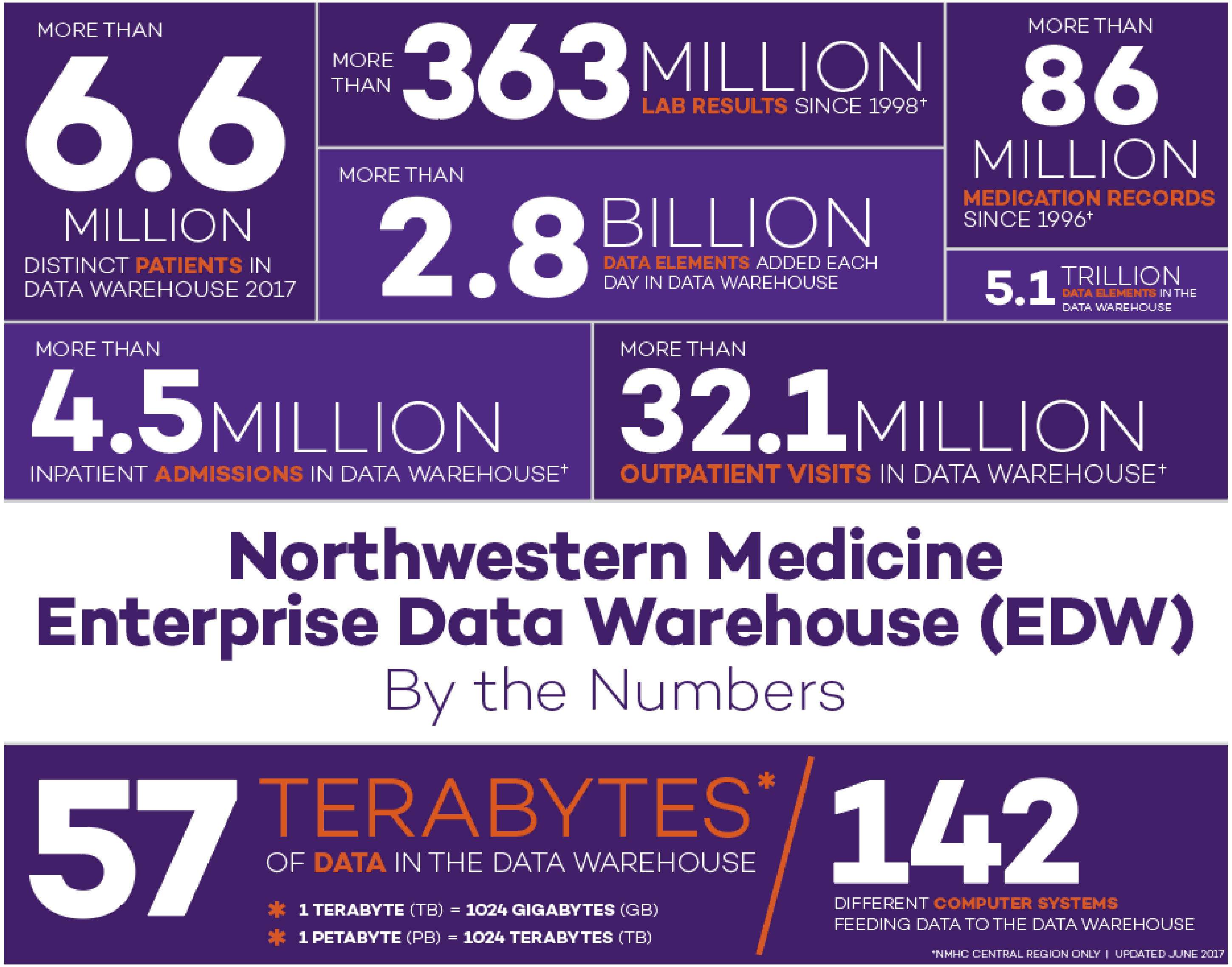
# Evidence-based medicine or expert opinion

Northwestern Medicine®

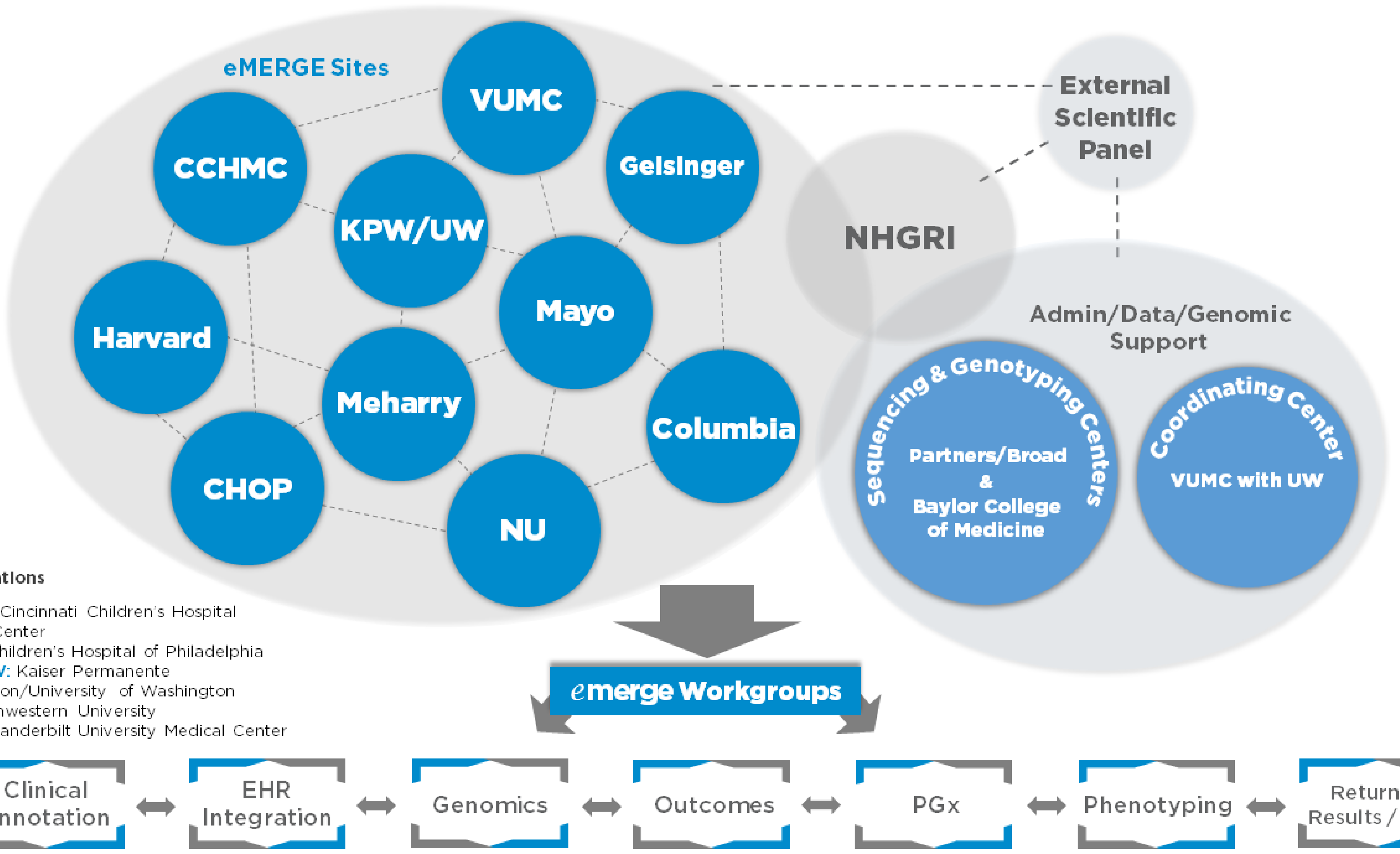
11 Hospitals
200+ Clinics and Rehabs
4000+ Physicians



# Northwestern Medicine Enterprise Data Warehouse



# Electronic Medical Records and Genomics (eMERGE) Network




abbreviations

CCHMC: Cincinnati Children's Hospital Medical Center
CHOP: Children's Hospital of Philadelphia
KPW/UW: Kaiser Permanente Washington/University of Washington
NU: Northwestern University
VUMC: Vanderbilt University Medical Center

# Machine learning to integrate multi-modal healthcare data

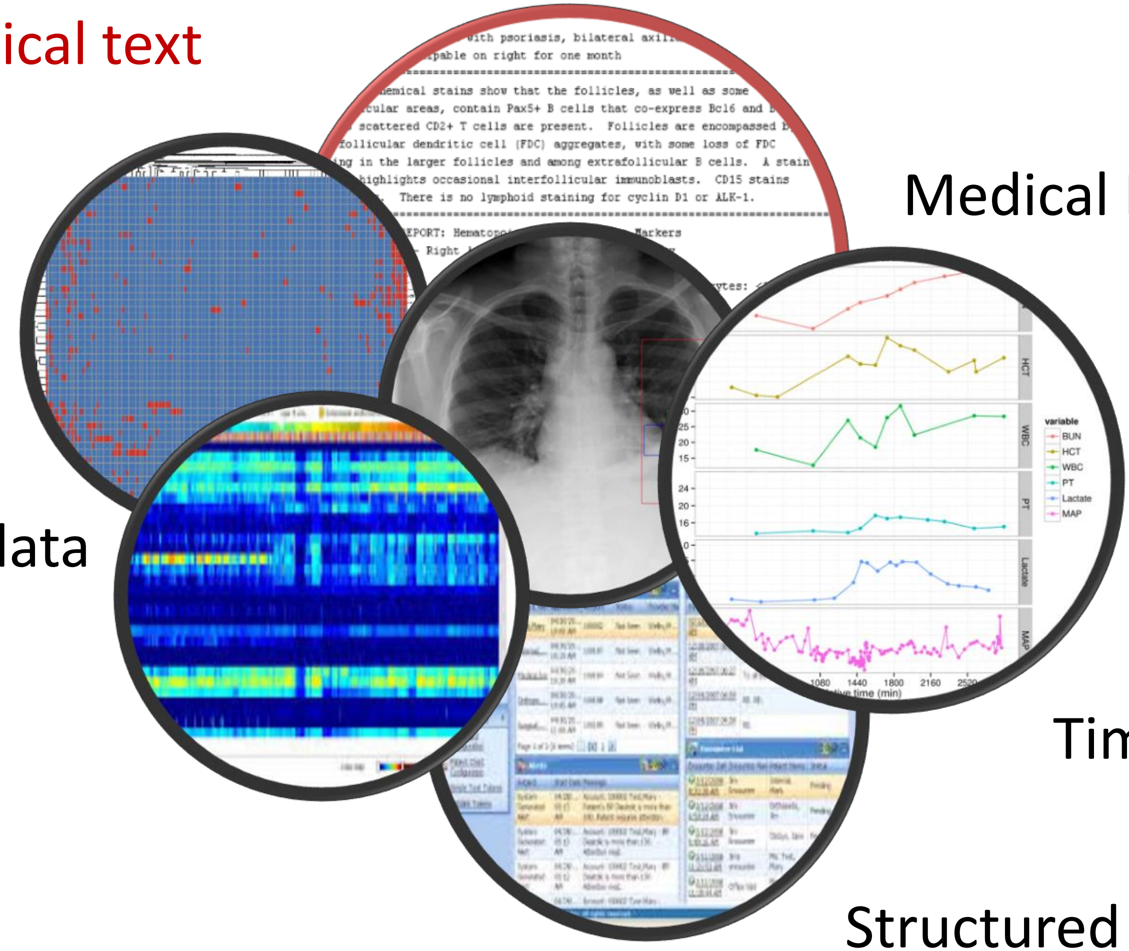
Biomedical text

Medical Imaging

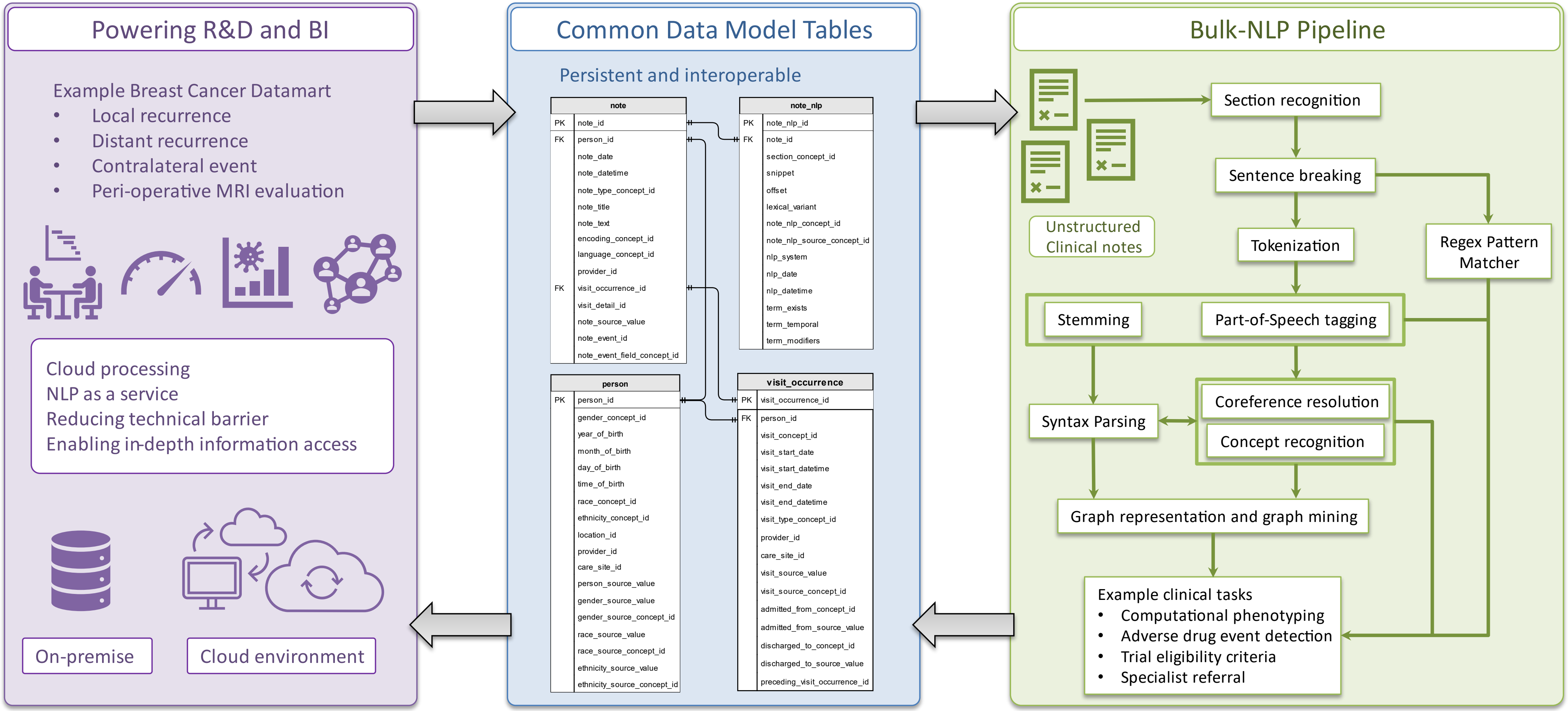
Omics data

Time series

Structured data



# Bulk NLP to power R&D and BI




NUCATS Clinical and Translational Sciences Institute · Northwestern · Northwestern Medicine · Ann & Robert H. Lurie Children's Hospital of Chicago · Northwestern Medicine Feinberg School of Medicine · Shirley Ryan Abilitylab

# Computational phenotyping to ascertain breast cancer recurrence

## After 48 Years, NCI Aims to Track Breast Cancer Recurrences

**Change to SEER Eventually Planned**

Nick Mulcahy
January 08, 2021

1 Read Comment ADD TO EMAIL ALERTS


The problem we tried to solve: Cancer Recurrence data are hard to come by

# Computational phenotyping to ascertain breast cancer recurrence

- Progress notes and pathology report contain rich information on BC local, distant recurrences and contralateral events


Springer Link

Research Article | Published: 08 April 2019

**Identifying Breast Cancer Distant Recurrences from Electronic Health Records Using Machine Learning**

Zexian Zeng, Liang Yao, Ankita Roy, Xiaoyu Li, Sasa Espino, Susan E Clare, Seema A Khan & Yuan Luo

*Journal of Healthcare Informatics Research* **3**, 283–299(2019) | Cite this article

AMIA Annual Symposium Proceedings Archive

AMIA Annu Symp Proc. 2017; 2017: 1885–1892. PMCID: PMC5977664

Published online 2018 Apr 16. PMID: 29854260

**Contralateral Breast Cancer Event Detection Using Nature Language Processing**

Zexian Zeng,[1] Xiaoyu Li,[2] Sasa Espino,[3] Ankita Roy,[3] Kristen Kitsch,[3] Susan Clare,[3] Seema Khan,[3] and Yuan Luo[1,*]

Zeng *et al. BMC Bioinformatics* 2018, **19**(Suppl 17):498
https://doi.org/10.1186/s12859-018-2466-x

BMC Bioinformatics

RESEARCH Open Access

**Using natural language processing and machine learning to identify breast cancer local recurrence**

Zexian Zeng[1], Sasa Espino[2], Ankita Roy[2], Xiaoyu Li[3], Seema A. Khan[2], Susan E. Clare[2], Xia Jiang[4], Richard Neapolitan[1] and Yuan Luo[1*]

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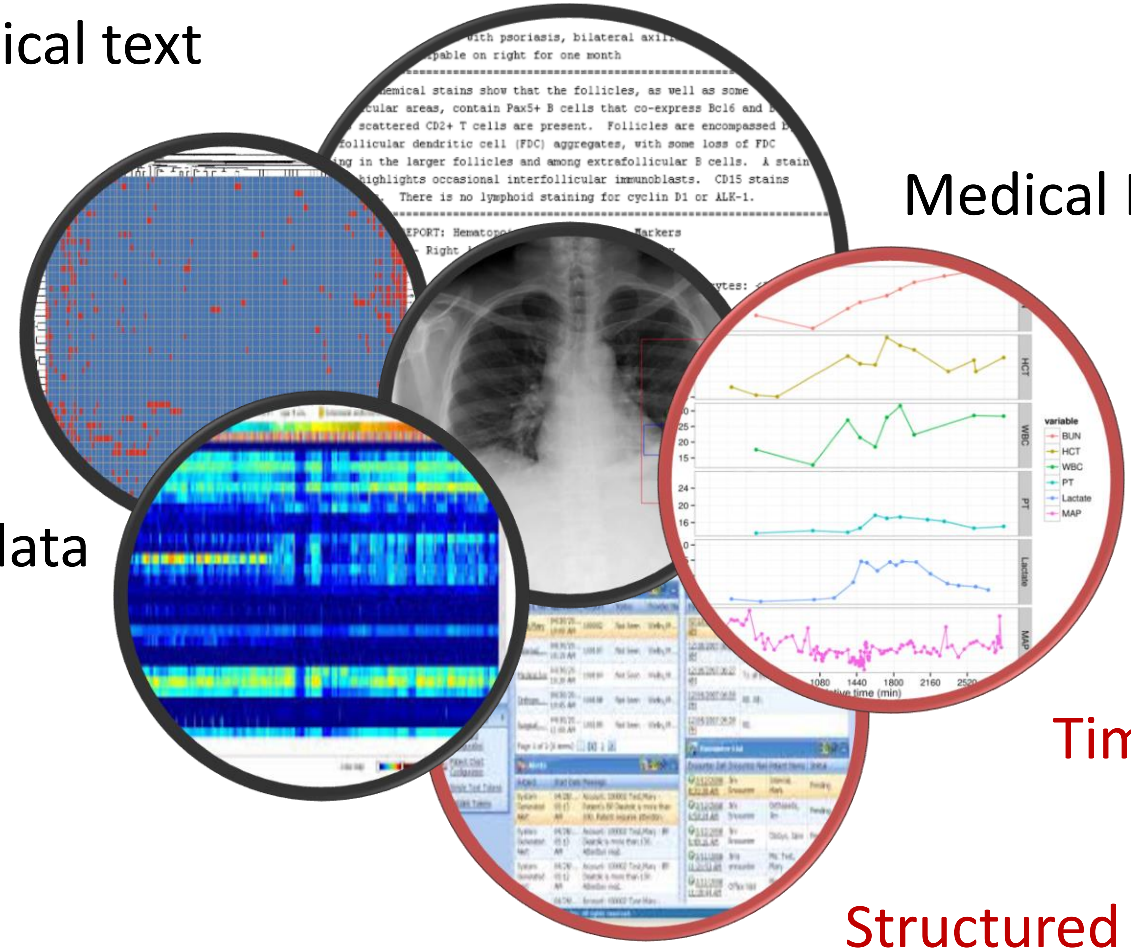



Time series

Structured data

# Simulation of Ventilator Allocation in Critically Ill Patients with COVID-19

American Journal of Respiratory and Critical Care Medicine

Home > American Journal of Respiratory and Critical Care Medicine > List of Issues > Just Accepted

Article Tools

## Simulation of Ventilator Allocation in Critically Ill Patients with COVID-19

Previous Article Next Article

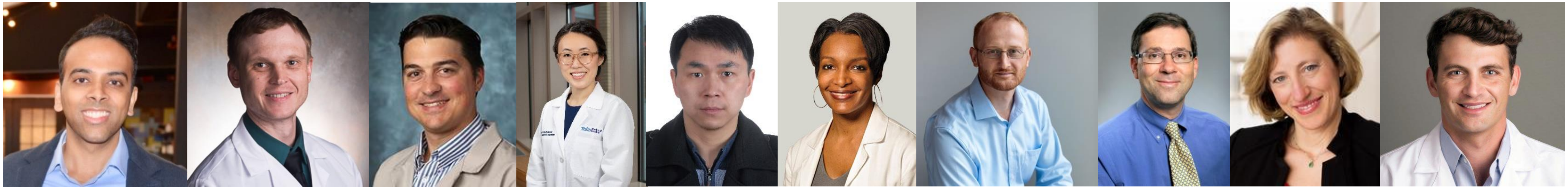
**Sivasubramanium V Bhavani** * **Yuan Luo** * **William D. Miller** , **Lazaro N. Sanchez-Pinto** ; **Xuan Han** , **Chengsheng Mao** , **Burhaneddin Sandikci** , **Monica E. Peek** , **Craig M. Coopersmith** , **Kelly N. Michelson** , and **William F Parker**

+ Author Information



https://doi.org/10.1164/rccm.202106-1453LE **PubMed:** 34499587

Received: June 17, 2021 Accepted: September 07, 2021

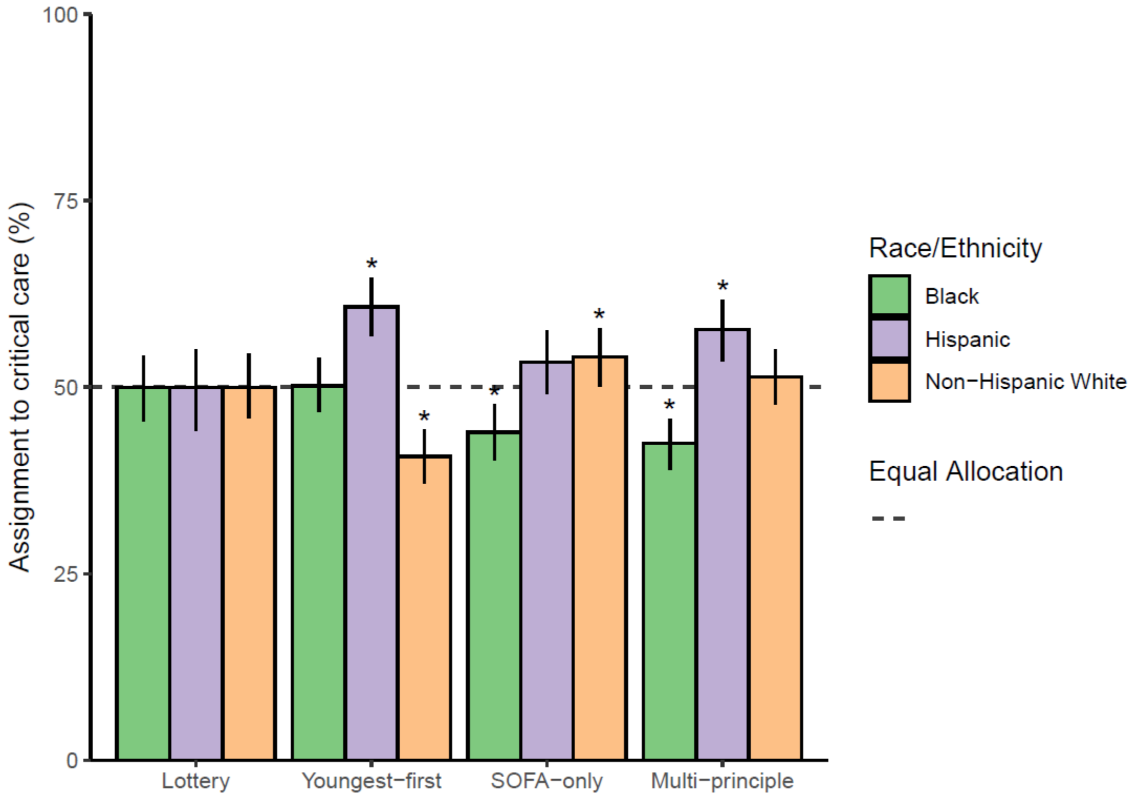


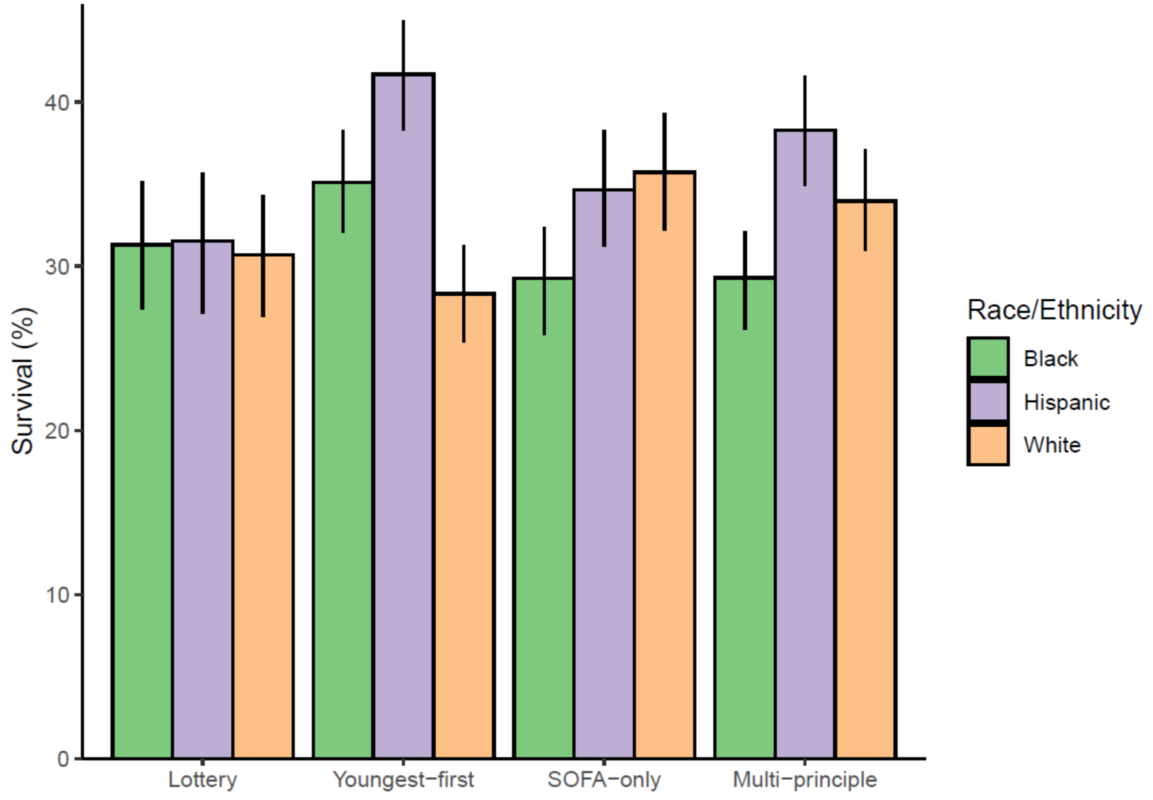
| | Total | Tertiary care hospital A | Tertiary care hospital B | Community hospital network |
|---|---|---|---|---|
| N | 2,363 | 643 | 687 | 1,033 |
| Age, years | 64 (52-75) | 63 (50-73) | 64 (51-74) | 65 (53-76) |
| Sex, male | 1,398 (59.2) | 364 (56.6) | 407 (59.2) | 627 (60.7) |
| Race/Ethnicity | | | | |
| Non-Hispanic Black | 760 (32.2) | 489 (76.0) | 204 (29.7) | 67 (6.5) |
| Non-Hispanic White | 828 (35.0) | 55 (8.6) | 209 (30.4) | 564 (54.6) |
| Hispanic | 582 (24.6) | 65 (10.1) | 202 (29.4) | 315 (30.5) |
| Other | 193 (8.2) | 34 (5.3) | 72 (10.5) | 87 (8.4) |
| Insurance | | | | |
| Medicare | 1,227 (51.9) | 341 (53) | 342 (49.8) | 544 (52.7) |
| Medicaid | 480 (20.3) | 188 (29.2) | 121 (17.6) | 171 (16.6) |
| Private | 613 (25.9) | 112 (17.4) | 211 (30.7) | 290 (28.1) |
| Unknown | 43 (1.8) | 2 (0.3) | 13 (1.9) | 28 (2.7) |
| SOFA score | 5 (3-8) | 6 (4-8) | 5 (3-8) | 5 (3-7) |
| Chronic Disease | | | | |
| Non-major (Score<16) | 1,730 (73.2) | 331 (51.5) | 480 (69.9) | 919 (89) |
| Major (16 ≥ score < 28) | 387 (16.4) | 187 (29.1) | 116 (16.9) | 84 (8.1) |
| Severe (score ≥ 28) | 246 (10.4) | 125 (19.4) | 91 (13.2) | 30 (2.9) |
| Critical care resources | | | | |
| Hemodialysis | 388 (16.4) | 171 (26.6) | 112 (16.3) | 105 (10.2) |
| Vasopressor use | 843 (35.7) | 259 (40.3) | 294 (42.8) | 290 (28.1) |
| High flow nasal cannula | 1,313 (55.6) | 293 (45.6) | 415 (60.4) | 605 (58.6) |
| Non-invasive ventilation | 621 (26.3) | 89 (13.8) | 186 (27.1) | 346 (33.5) |
| Mechanical ventilation | 998 (42.2) | 247 (38.4) | 353 (51.4) | 398 (38.5) |
| Outcomes | | | | |
| LOS, d | 11.7 (6.0-21.1) | 10.8 (6.3-18.4) | 15.1 (7.4-27.3) | 10.2 (4.9-18.7) |
| Mortality rate | 475 (20.1) | 162 (25.2) | 111 (16.2) | 202 (19.6) |

# Ventilator allocation protocols

| Protocol | Ethical Principles | Rules | Countries and US States with Similar Protocols | Lives saved (%) |
|---|---|---|---|---|
| Lottery | Treating people equally | Random assignment | None | 31.1 (29.7-32.6) |
| Youngest-first | Save life-years<br><br>Prudential Lifespan Equity | Rank by age | Italy | 34.7 (33.5-35.8) |
| SOFA-only* | Save lives | Three SOFA tiers:<br>Red: ≤ 7<br>Yellow: 8-11<br>Blue: >11<br><br>Lottery tiebreaker | Arizona, California, Indiana, Iowa, Kansas, Louisiana, Michigan, Nevada, New Mexico,<br>New York,<br>South Carolina, Tennessee, Vermont, Washington | 32.9 (31.6-34.1) |
| Multi-principle† | Save lives<br><br>Save life-years | SOFA category points:<br>1. ≤8<br>2. 9-11<br>3. 12-14<br>4. >14<br><br>Chronic conditions:<br>+ 3 points if “severe”<br><br>Age tiebreaker‡ | Maryland, Massachusetts, Pennsylvania, Oklahoma | 33.5 (32.3-34.8) |

# Allocation and survival by race



## Unintended Disparities in Scarce Resource Allocation in Critically Ill Patients with COVID-19

- Black patients had higher SOFA scores and higher prevalence of comorbidities
- Leading to lower priority tiers and significantly less allocation of ventilators
- In turn leading to significantly lower survival
- White patients have increased vents in the SOFA-only protocol, but did not translate into higher survival

# International shared-task challenge for clinical missing data imputation

All admissions where each of the 13 tests was recorded at least once
- •47,862 unique admissions
- •696,673 time points
- •7,601,216 test results

Exclude time points with more than half of the 13 laboratory tests missing

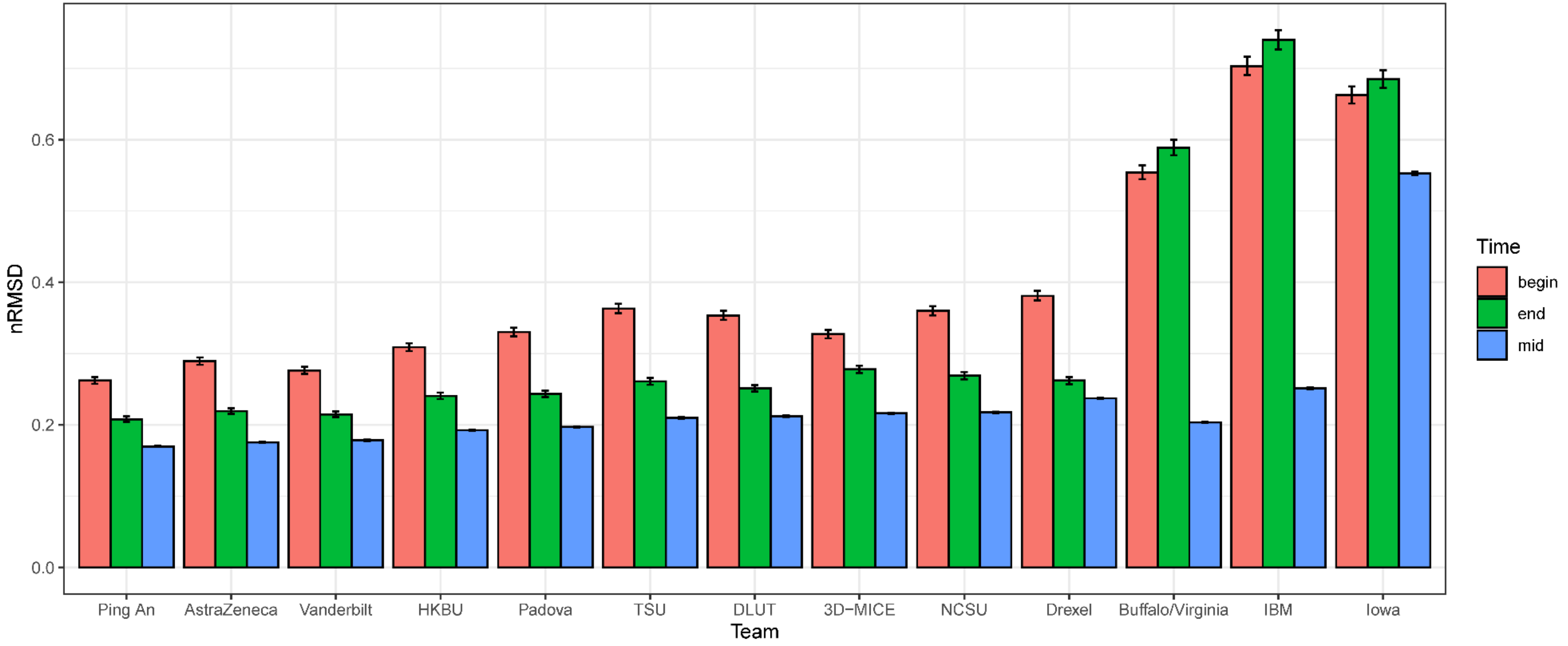
- •47,862 unique admissions
- •594,187 time points
- •7,143,122 test results

Exclude admissions without at least 10 remaining time points for each variable

- •16,537 unique admissions
- •396,668 time points
- •4,774,228 test results

Exclude admissions with a constant value across time points for a test

- •16,534 unique admissions
- •396,631 time points
- •4,773,769 test results




Luo Y, Evaluating the state-of-the-art in missing data imputation for clinical data, *Briefings in Bioinformatics* 2021 [https://doi.org/10.1093/bib/bbab489](https://doi.org/10.1093/bib/bbab489)

# Machine learning to integrate multi-modal healthcare data

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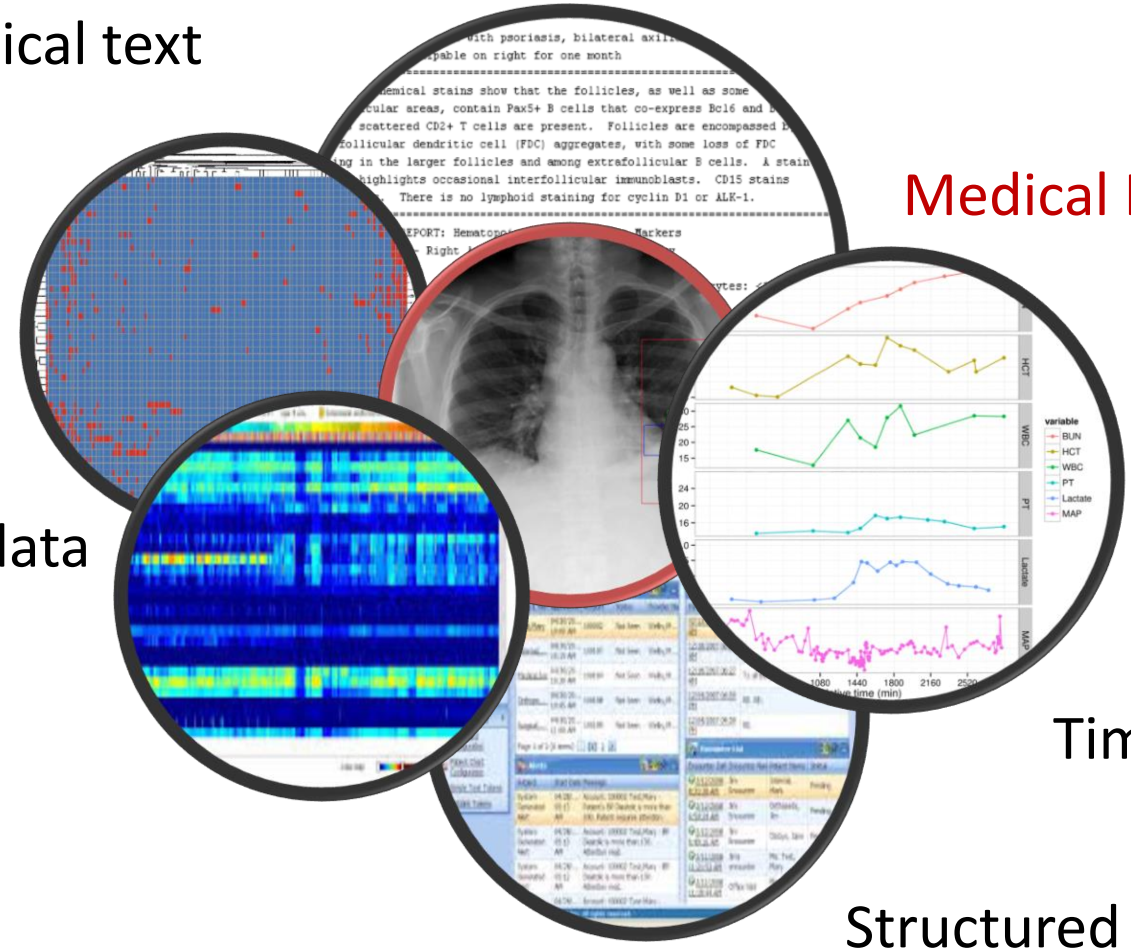
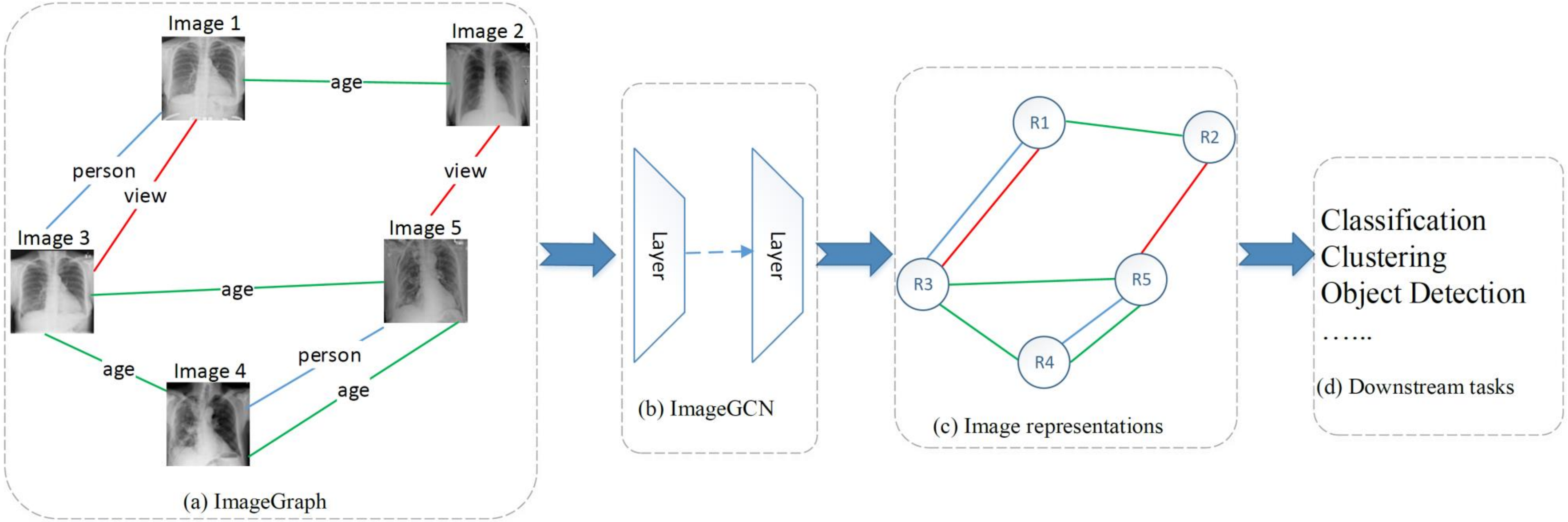



Time series

Structured data

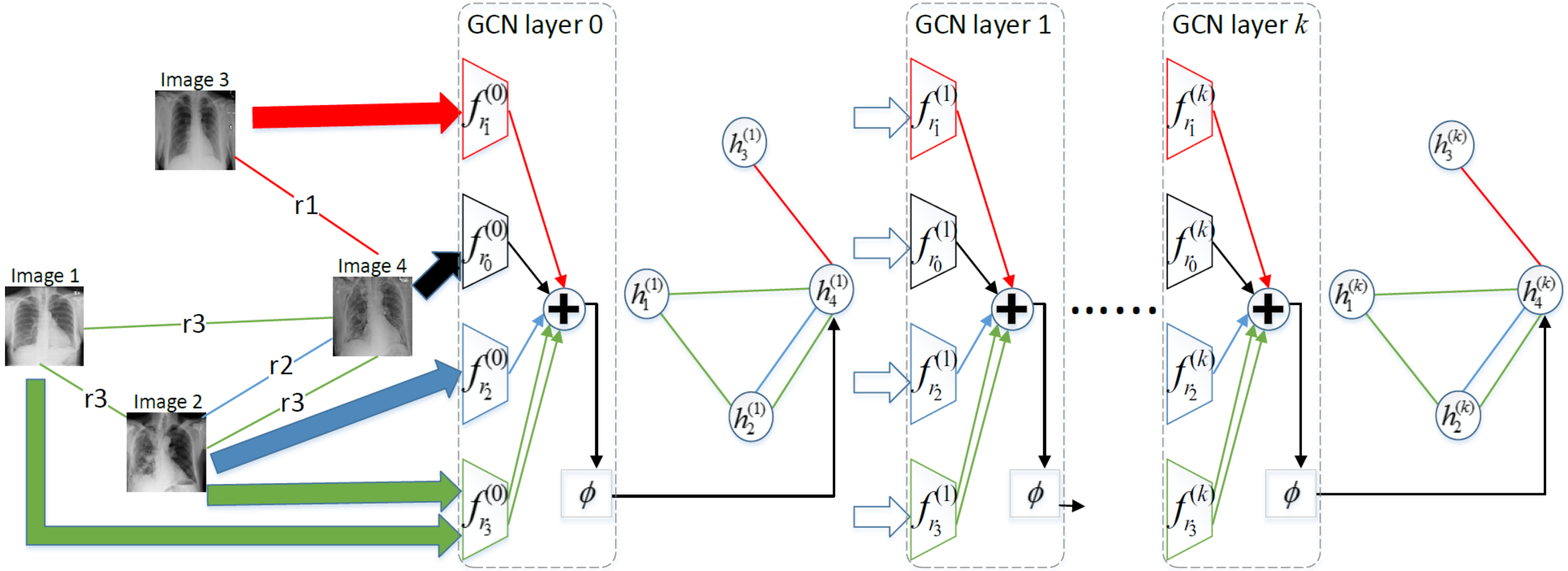
# ImageGCN: Graph Neural Networks to model relations between images




C Mao, L Yao, Y Luo, ImageGCN: Multi-Relational Image Graph Convolutional Networks for Disease Identification with Chest X-rays. *IEEE Transactions on Medical Imaging 2022 10.1109/TMI.2022.3153322*.

# ImageGCN: Graph Neural Networks to Model Relations Between Images

Multi-dimensional relations between medical images =>
deep graph neural networks =>
Better interpretability and better accuracy



# ImageGCN: Graph Neural Networks to Model Relations Between Images

| | Atel | Card | Effu | Infi | Mass | Nodu | Pneu1 | Pneu2 | Cons | Edem | Emph | Fibr | PT | Hern | mean | MR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A-GCN-PPS (ours) | 0.781 | 0.899 | 0.865 | 0.701 | 0.813 | 0.721 | 0.718 | 0.881 | 0.788 | 0.888 | 0.882 | 0.804 | 0.778 | 0.904 | 0.816 | 6.73 |
| A-GCN-APS | 0.739 | 0.876 | 0.815 | 0.671 | 0.799 | 0.704 | 0.679 | 0.857 | 0.762 | 0.846 | 0.863 | 0.792 | 0.765 | 0.910 | 0.791 | 13.73 |
| AlexNet | 0.782 | 0.895 | 0.863 | 0.705 | 0.781 | 0.714 | 0.716 | 0.869 | 0.790 | **0.889** | 0.876 | 0.799 | 0.773 | 0.899 | 0.811 | 7.93 |
| R-GCN-PPS (ours) | 0.785 | 0.890 | 0.868 | 0.699 | 0.824 | 0.739 | 0.723 | 0.895 | 0.790 | 0.887 | 0.911 | 0.819 | 0.786 | 0.941 | 0.826 | 4.47 |
| R-GCN-APS | 0.741 | 0.861 | 0.822 | 0.680 | 0.819 | 0.728 | 0.684 | 0.873 | 0.768 | 0.852 | 0.889 | 0.790 | 0.751 | 0.908 | 0.798 | 12.27 |
| ResNet50 | 0.789 | 0.889 | 0.863 | 0.698 | 0.807 | 0.723 | 0.714 | 0.876 | 0.791 | 0.888 | 0.899 | 0.799 | 0.772 | 0.933 | 0.817 | 6.93 |
| V-GCN-PPS (ours) | **0.802** | 0.894 | **0.874** | 0.702 | **0.843** | 0.768 | 0.715 | **0.900** | 0.796 | 0.883 | 0.915 | 0.825 | **0.791** | **0.943** | **0.832** | **2.60** |
| V-GCN-APS | 0.754 | 0.871 | 0.826 | 0.676 | 0.820 | 0.737 | 0.688 | 0.872 | 0.769 | 0.839 | 0.894 | 0.789 | 0.770 | 0.926 | 0.802 | 11.07 |
| VGGNet16BN | 0.796 | 0.893 | 0.872 | 0.700 | 0.831 | 0.756 | 0.717 | 0.882 | 0.794 | 0.878 | 0.909 | 0.799 | 0.785 | 0.923 | 0.824 | 4.60 |
| Wang et al. [8] | 0.716 | 0.807 | 0.784 | 0.609 | 0.706 | 0.671 | 0.633 | 0.806 | 0.708 | 0.835 | 0.815 | 0.769 | 0.708 | 0.767 | 0.738 | 17.33 |
| Yao et al. [11] | 0.772 | 0.904 | 0.859 | 0.695 | 0.792 | 0.717 | 0.713 | 0.841 | 0.788 | 0.882 | 0.829 | 0.767 | 0.765 | 0.914 | 0.803 | 10.80 |
| Li et al. [44] | 0.800 | 0.870 | 0.870 | 0.700 | 0.830 | 0.750 | 0.670 | 0.870 | **0.800** | 0.880 | 0.910 | 0.780 | 0.760 | 0.770 | 0.804 | 8.40 |
| Kumar et al. [12] | 0.762 | **0.913** | 0.864 | 0.692 | 0.750 | 0.666 | 0.715 | 0.859 | 0.784 | 0.888 | 0.898 | 0.756 | 0.774 | 0.802 | 0.794 | 10.67 |
| Tang et al. [45] | 0.756 | 0.887 | 0.819 | 0.689 | 0.814 | 0.755 | 0.729 | 0.85 | 0.728 | 0.848 | 0.906 | 0.818 | 0.765 | 0.875 | 0.803 | 10.33 |
| Shen et al. [46] | 0.766 | 0.801 | 0.797 | **0.751** | 0.76 | 0.741 | **0.778** | 0.800 | 0.787 | 0.82 | 0.773 | 0.765 | 0.759 | 0.748 | 0.775 | 13.40 |
| Mao et al. [13] | 0.750 | 0.869 | 0.810 | 0.687 | 0.782 | 0.726 | 0.695 | 0.845 | 0.728 | 0.834 | 0.870 | 0.798 | 0.758 | 0.877 | 0.788 | 14.33 |
| Guan et al. [14] | 0.781 | 0.883 | 0.831 | 0.697 | 0.83 | 0.764 | 0.725 | 0.866 | 0.758 | 0.853 | 0.911 | 0.826 | 0.78 | 0.918 | 0.816 | 7.00 |
| Liu et al. [31] | 0.773 | 0.889 | 0.821 | 0.710 | 0.829 | **0.770** | 0.713 | 0.869 | 0.749 | 0.847 | **0.934** | **0.845** | 0.773 | 0.925 | 0.818 | 6.93 |
| p-val (RM-ANOVA) | *** | *** | *** | *** | * | * | *** | *** | *** | *** | *** | ** | ** | | *** | |
| PPS > APS | *** | *** | *** | *** | * | ** | *** | *** | *** | *** | *** | ** | ** | | *** | |
| PPS > base | | * | ** | | ** | ** | | *** | | | ** | * | ** | * | ** | |

Atel: Atelectasis; Card: Cardiomegaly; Effu: Effusion; Infi: Infiltration; Nodu: Nodule; Pneu1: Pneumonia; Pneu2:Pneumothorax; Cons: Consolidation; Edem: Edema; Emph: Emphysema; Fibr: Fibrosis; PT:Pleural Thickening; Hern: Hernia. MR=mean rank

https://github.com/mocherson/ImageGCN

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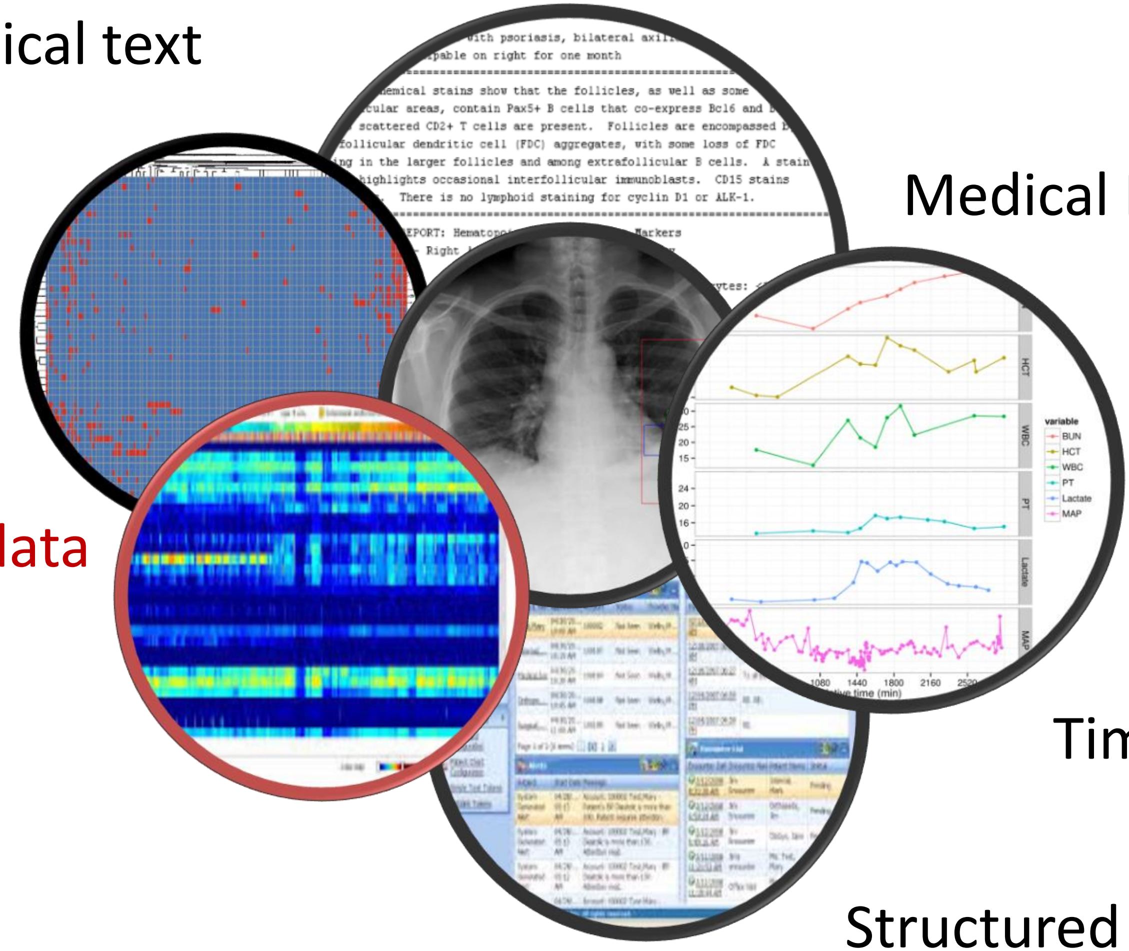
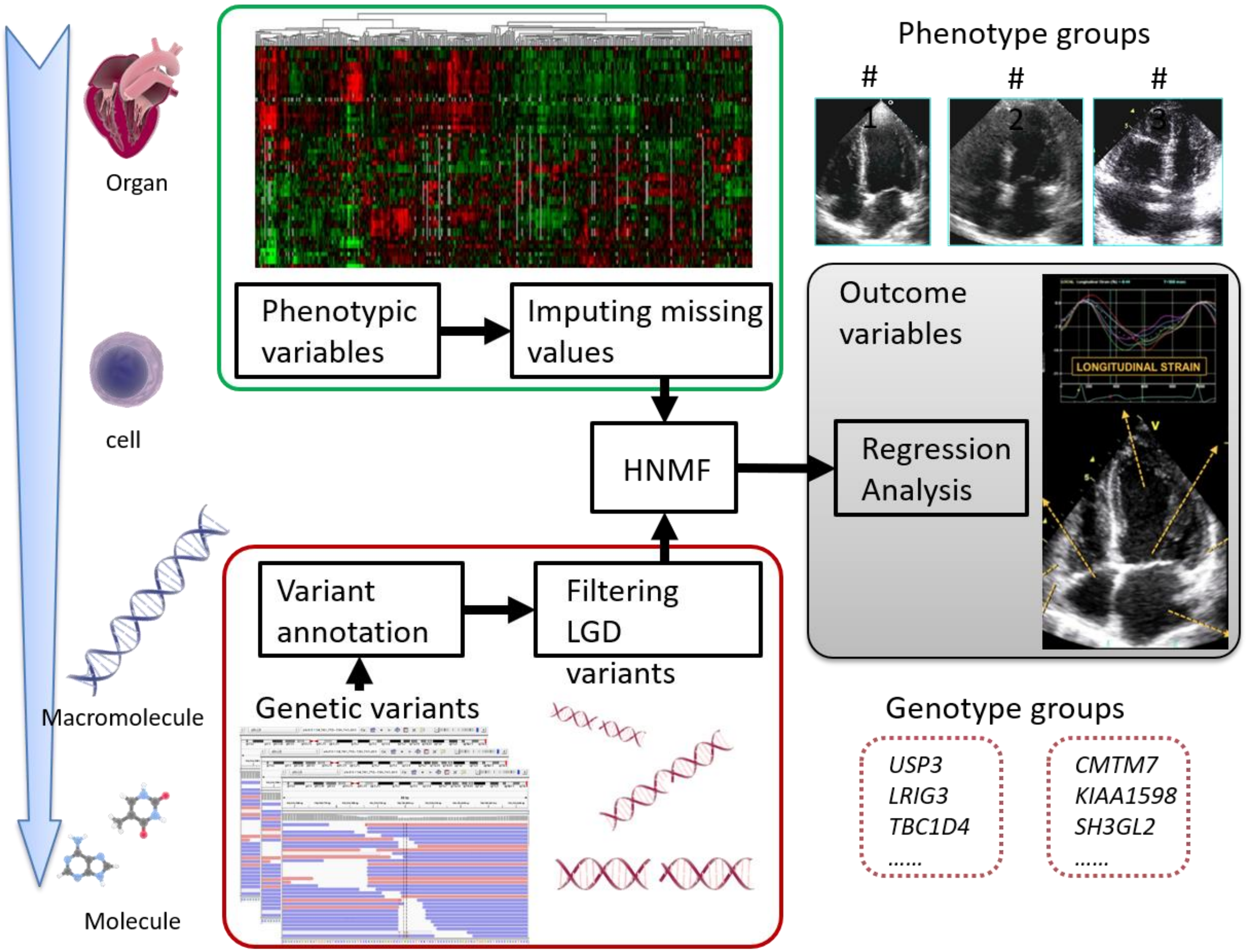


Time series

Structured data

# Integrative omics: CVD precision medicine




Integrating phenotype and genotype to better subtype heterogeneous patient cohort and inform targeted therapy

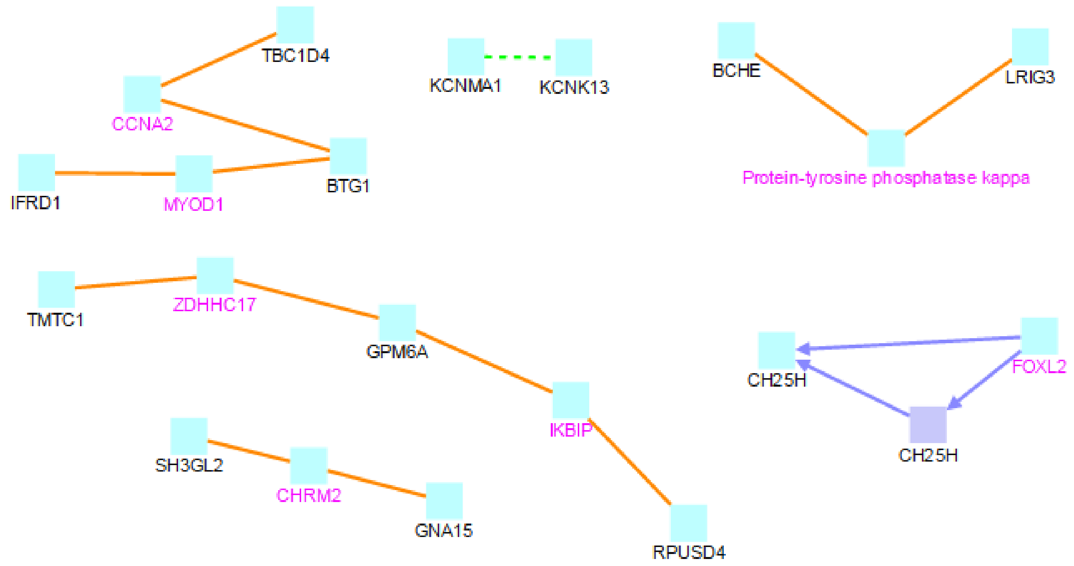
Y Luo, C Mao, Y Yang, F Wang, FS Ahmad, D Arnett, MR Irvin, SJ Shah. Integrating Hypertension Phenotype and Genotype with Hybrid Non-negative Matrix Factorization. *Bioinformatics 2018 PMID: 30239588*

# PANTHER: Pathway Augmented Nonnegative Tensor factorization for HighER-order feature learning in genetic medicine

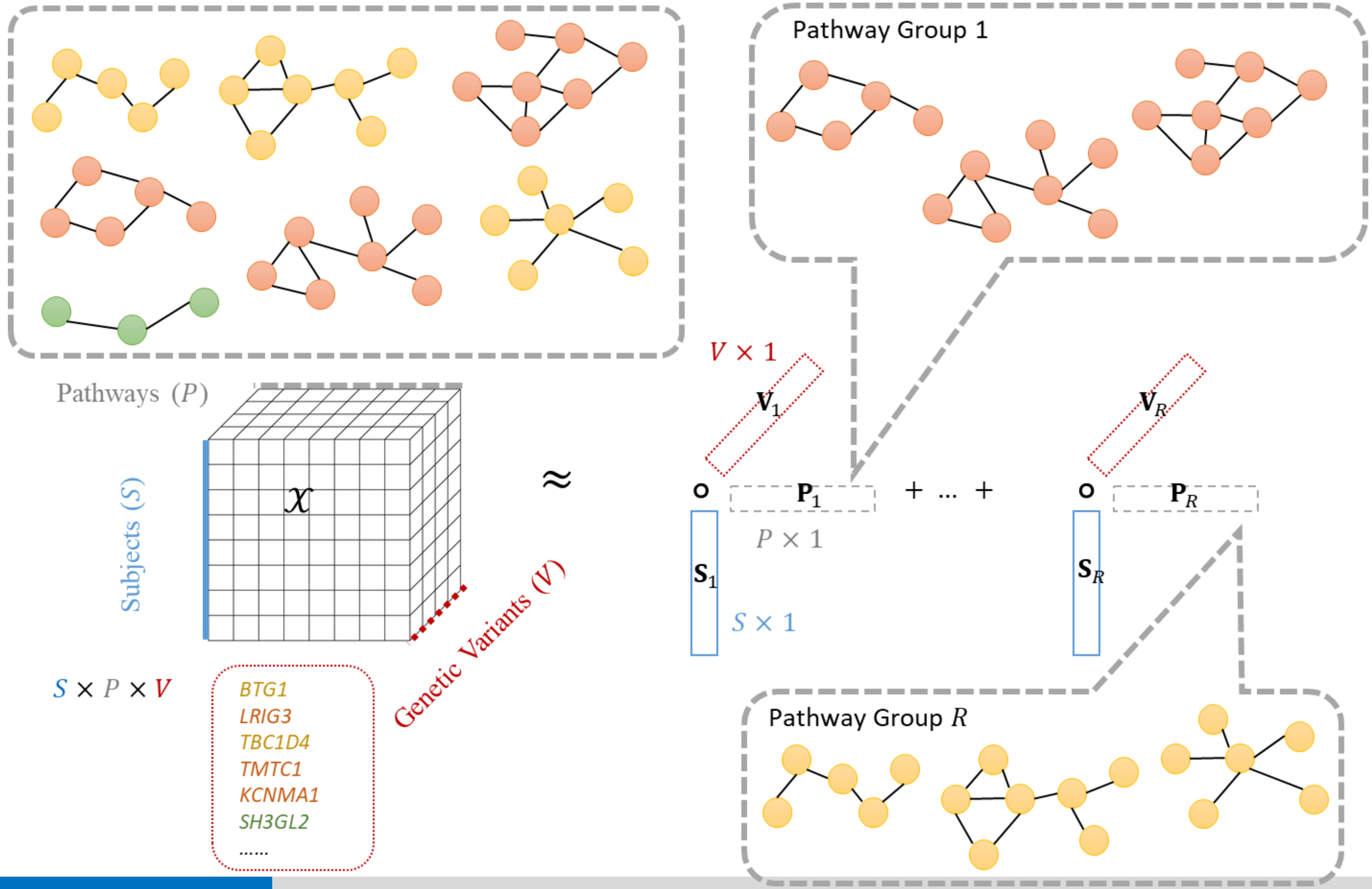
- Genetic pathways are important in understanding the molecular mechanisms
- Individual pathways are part of the entire biological system and interact with each other
- It is important to model co-functioning molecular mechanisms by grouping pathways together

*BTG1*
*LRIG3*
*TBC1D4*
*TMTC1*
*KCNMA1*
*SH3GL2*
……

v.s.

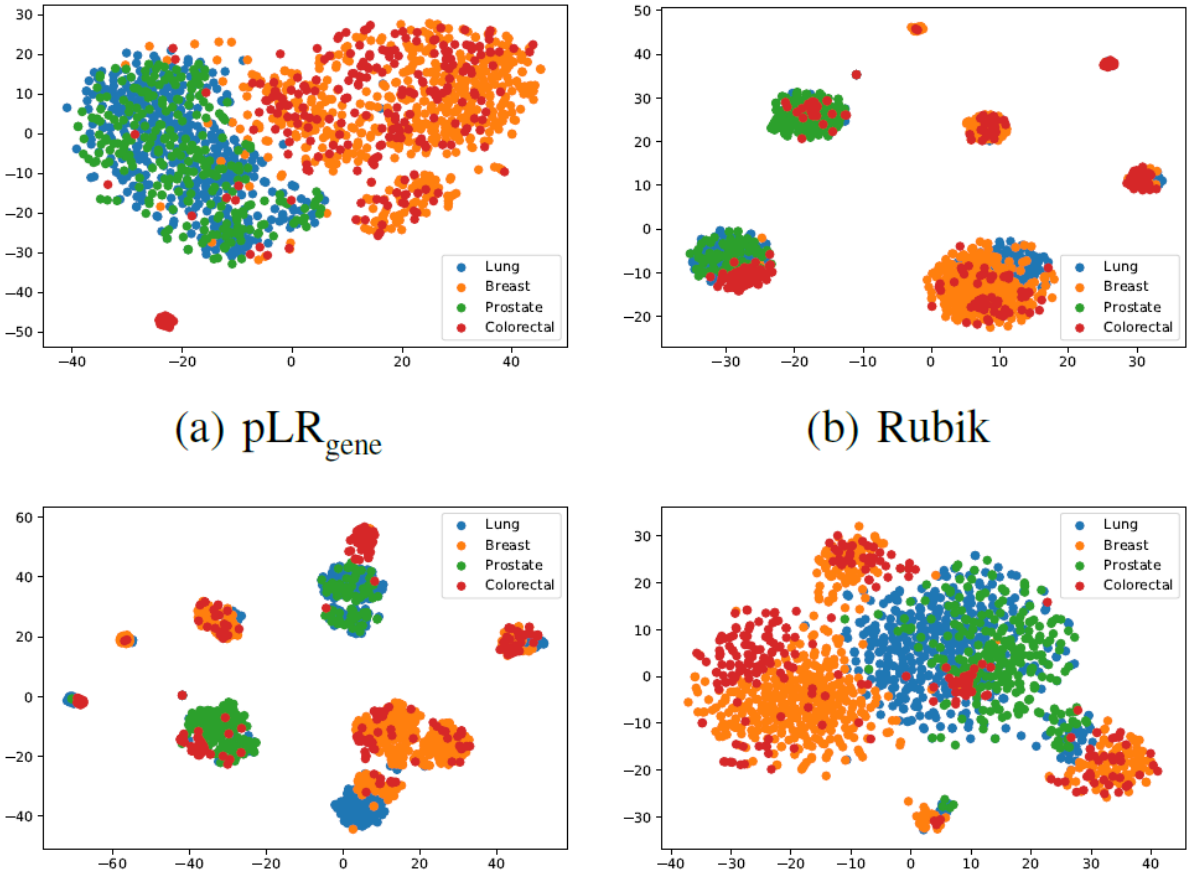


# PANTHER factorization scheme



# Results and t-SNE visualization of the learned train set subject features

| Model | $R$ | Test Accuracy |
|---|---|---|
| $\mathrm{pLR}_{\mathrm{gene}}$ | - | 0.8016 |
| $\mathrm{pLR}_{\mathrm{pathway}}$ | - | 0.7701 |
| $\mathrm{pLR}_{\mathrm{gene+pathway}}$ | - | 0.7682 |
| $\mathrm{brms}_{\mathrm{gene}}$ | - | 0.8016 |
| $\mathrm{brms}_{\mathrm{pathway}}$ | - | 0.7642 |
| $\mathrm{brms}_{\mathrm{gene+pathway}}$ | - | 0.8173 |
| $\mathrm{NMF}_{\mathrm{gene}}$ | 400 | 0.8173 |
| $\mathrm{NMF}_{\mathrm{pathway}}$ | 400 | 0.7819 |
| $\mathrm{NMF}_{\mathrm{gene+pathway}}$ | 100 | 0.7957 |
| $\mathrm{grpreg}_{\mathrm{gene}}$ | 66 | 0.6306 |
| $\mathrm{grpreg}_{\mathrm{pathway}}$ | 66 | 0.8153 |
| $\mathrm{grpreg}_{\mathrm{gene+pathway}}$ | 131 | 0.8016 |
| Rubik | 100 | 0.8035 |
| SUSTain | 450 | 0.7839 |
| SURF | 50 | 0.7466 |
| LogPar | 350 | 0.6031 |
| TASTE | 200 | 0.8369 |
| LOM | 100 | 0.7505 |
| PANTHER | 200 | **0.8644** |




(a) $\mathrm{pLR}_{\mathrm{gene}}$ (b) Rubik (c) TASTE (d) PANTHER

Y Luo, C Mao. PANTHER: Pathway Augmented Nonnegative Tensor factorization for HighER-order feature learning. *AAAI 2021*, *371-380*.

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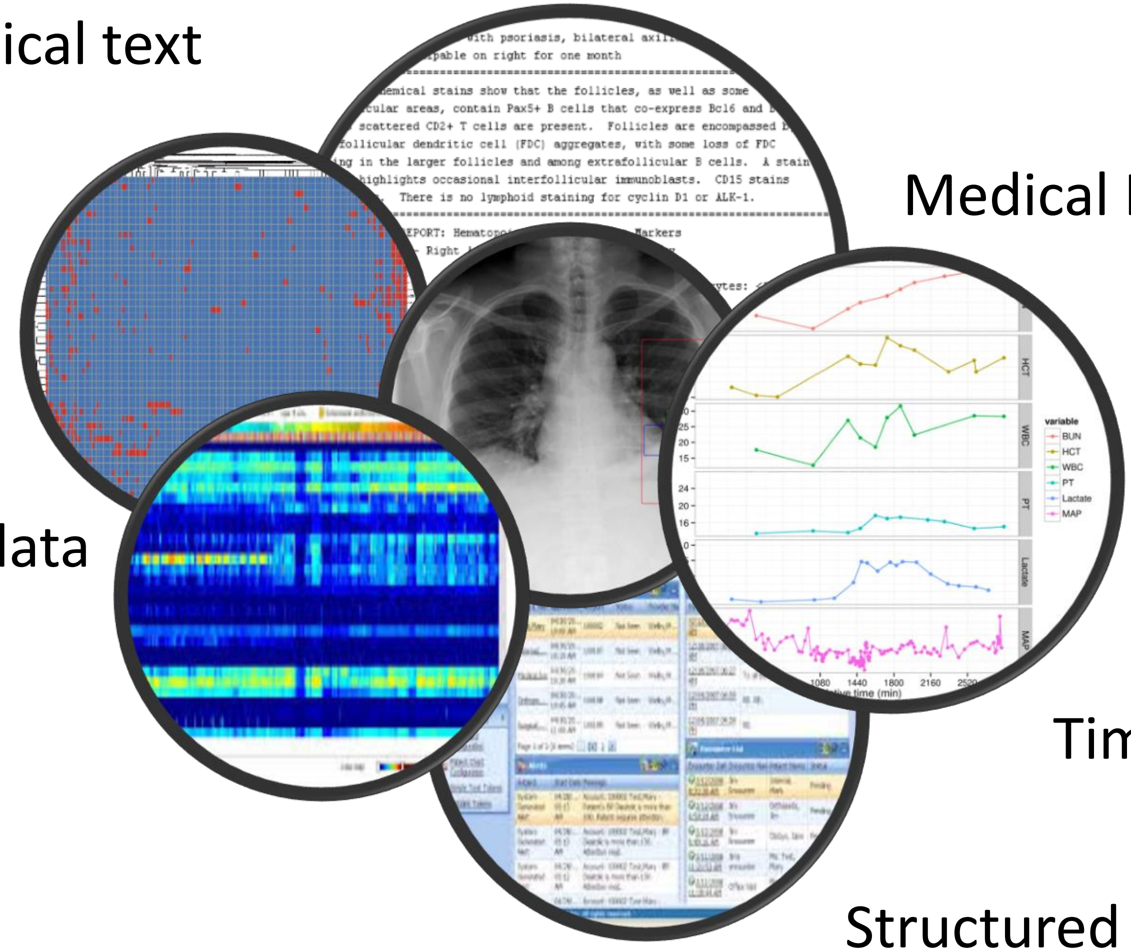



Time series

Structured data

nature medicine

BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-020-1007-0

Check for updates

# A multidimensional precision medicine approach identifies an autism subtype characterized by dyslipidemia

Yuan Luo[1,2,3,4,10], Alal Eran[5,6,7,10], Nathan Palmer[6], Paul Avillach[6], Ami Levy-Moonshine[8], Peter Szolovits[9] and Isaac S. Kohane[6] ✉






# Autism Spectrum Disorder (ASD)

- Common neurodevelopmental disorder
- Prevalence ~1%, male centric, early onset in childhood
- A strong genetic component
- Early molecular diagnosis is a promising path
- Unknown specific genetic cause in most cases

Photo credit: The Kobal Collection

# Identification of 33 neurodevelopmentally co-regulated, sex-differentially expressed exon clusters with ASD segregating deleterious variation

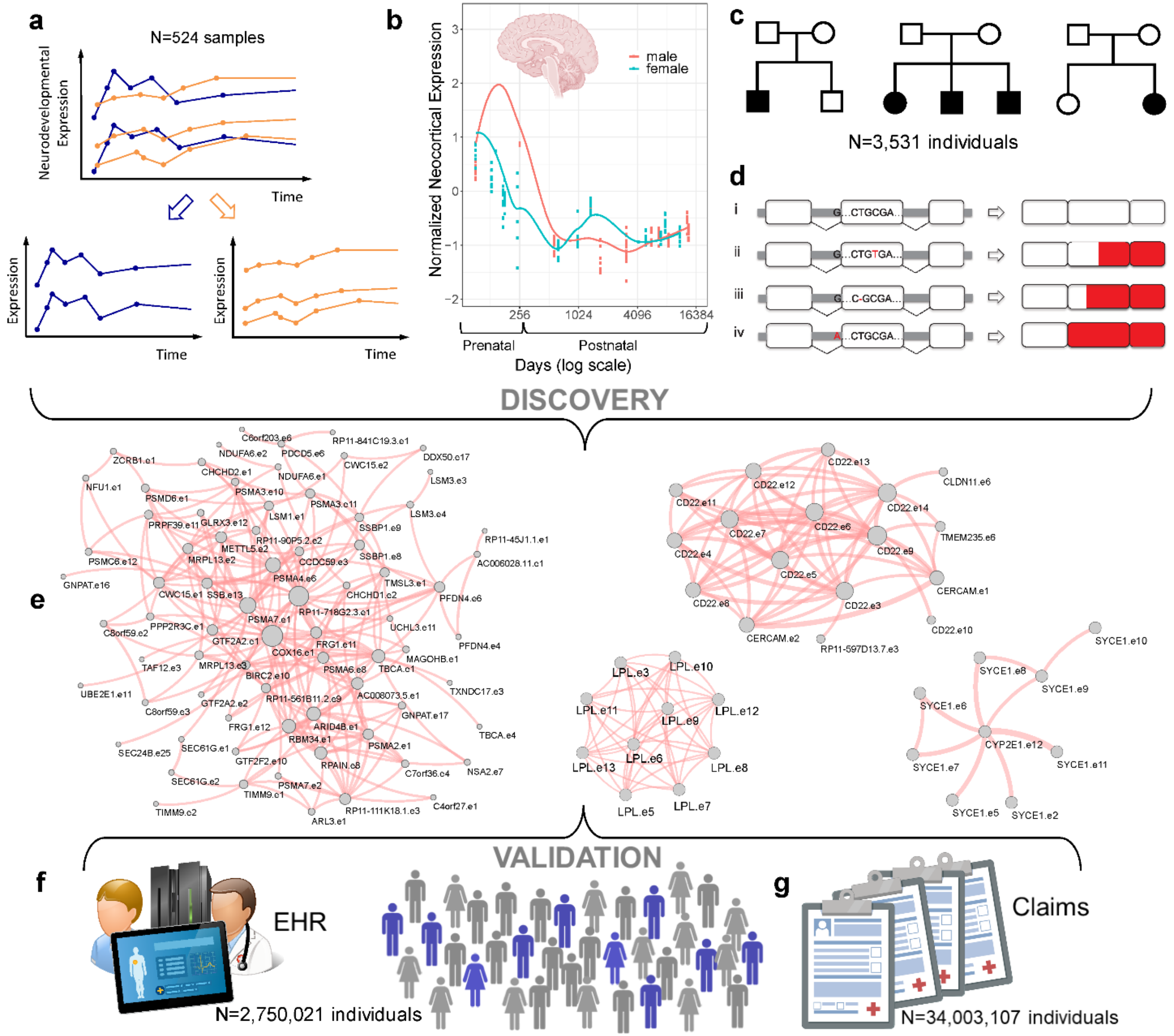



Figure.1

# One large cluster (84 genes) associated with lipid regulation functions

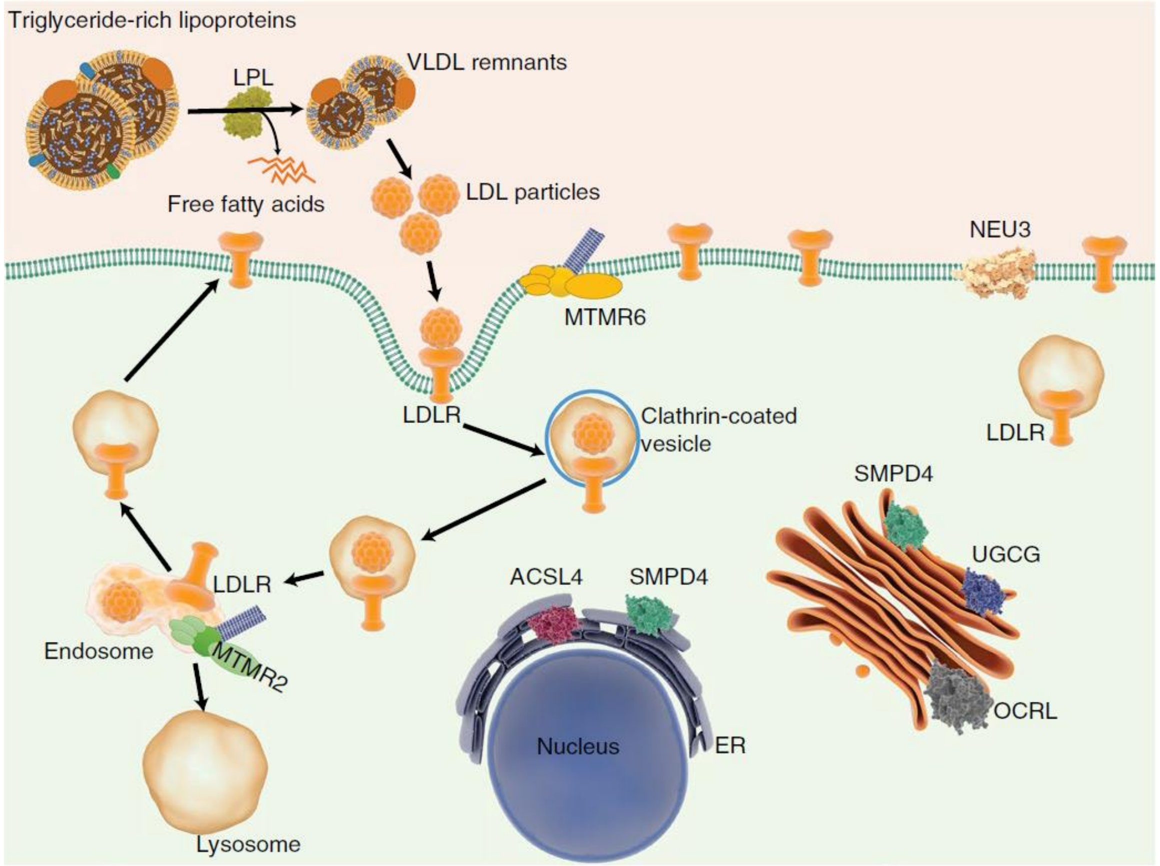



Figure.2c

| Cluster ID | Functional enrichment |
|---|---|
| 5965 | Reactome metabolism of lipids and lipoproteins |

# One large cluster (84 genes) associated with lipid regulation functions

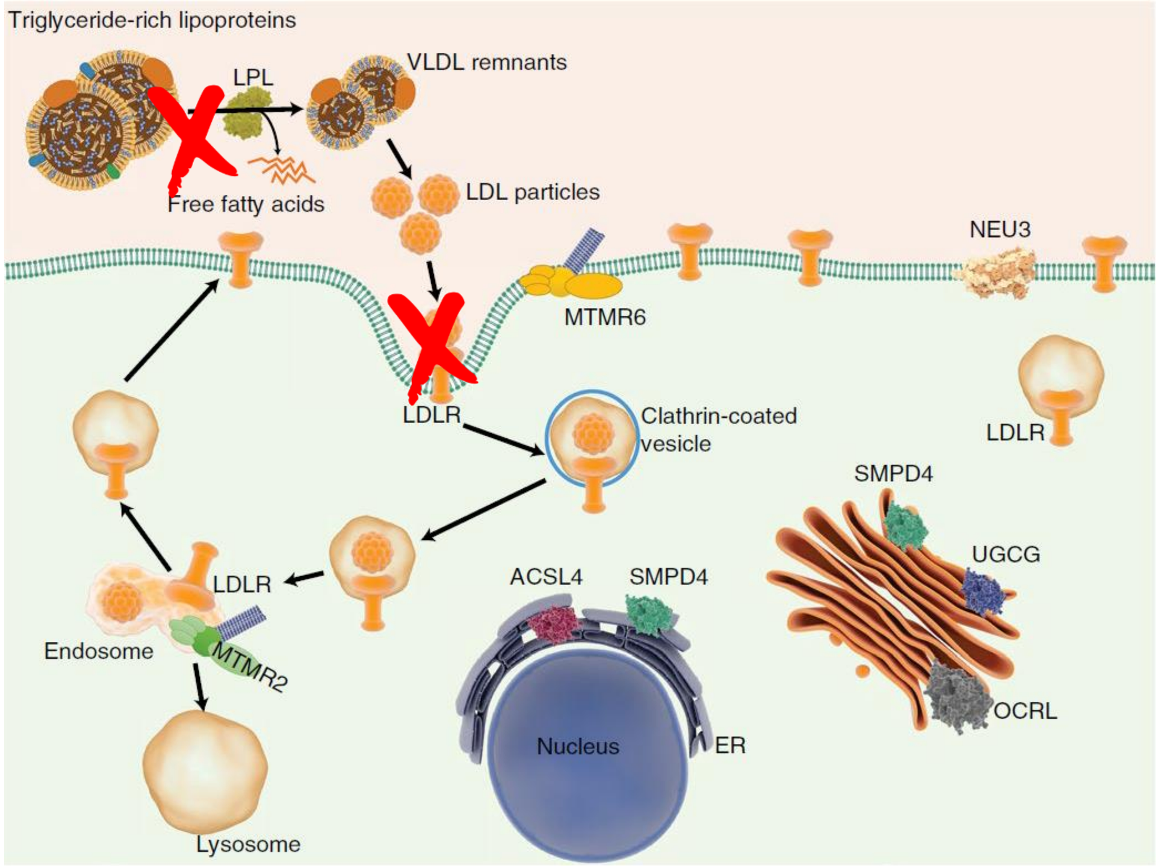



Figure.2c

| Cluster ID | Functional enrichment |
|---|---|
| 5965 | Reactome metabolism of lipids and lipoproteins |

# ASD have blood lipid profiles that are outside the normal range – Boston Children's Hospital (BCH)

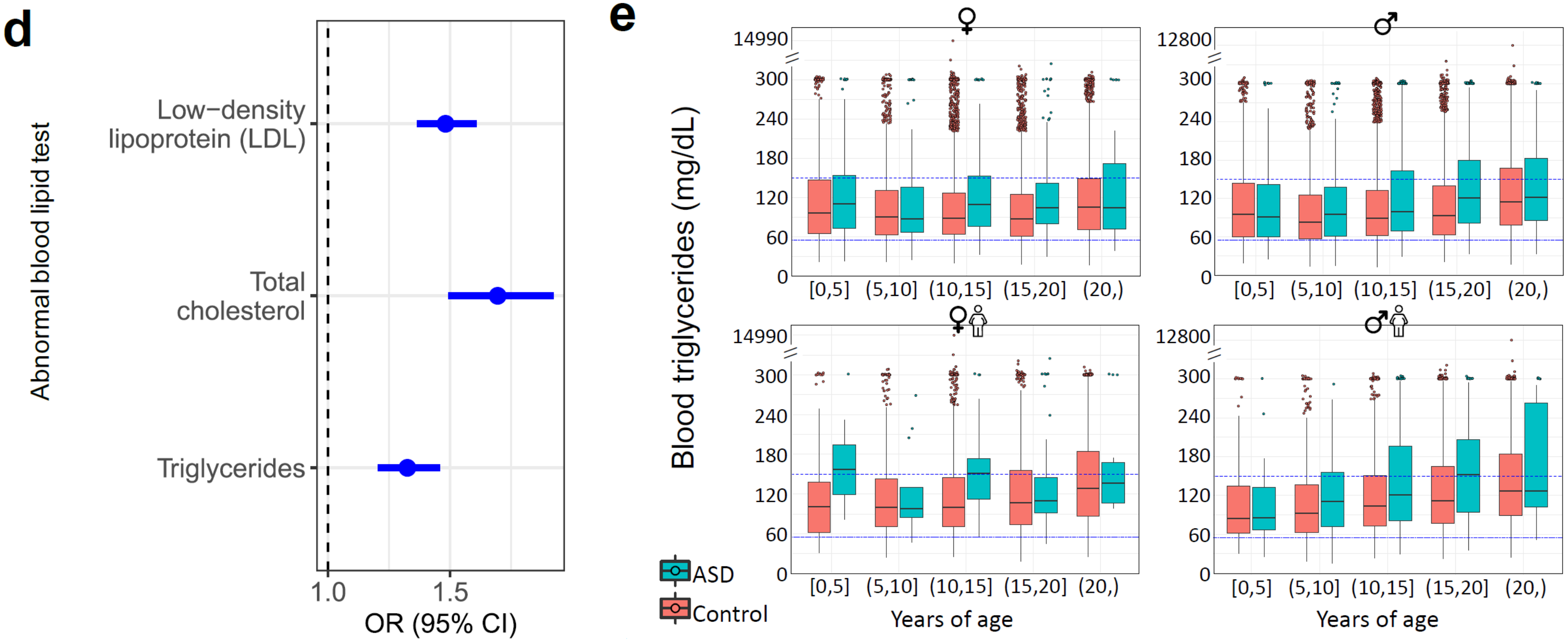



Figure 2e: Results from individuals with metabolic dysregulation, including obesity, diabetes and metabolic syndrome X, are shown at the bottom.

Figure 2d and 2e

# Enrichment of dyslipidemia diagnoses in individuals with ASD – Aetna healthcare claims

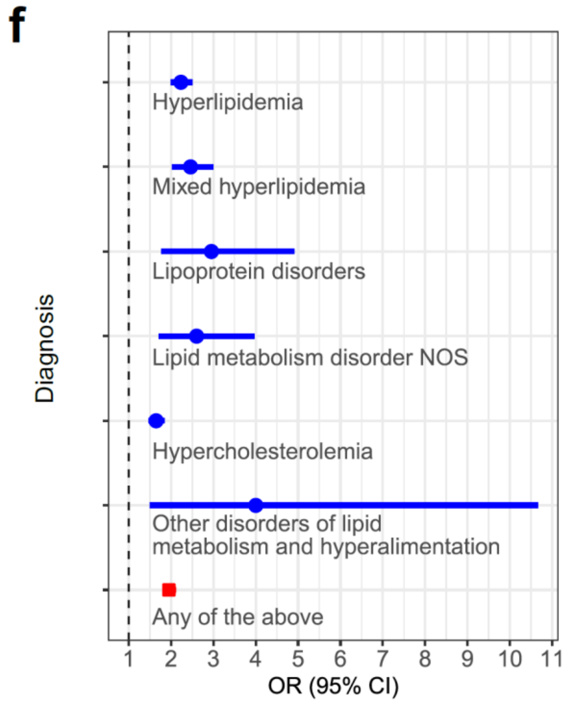
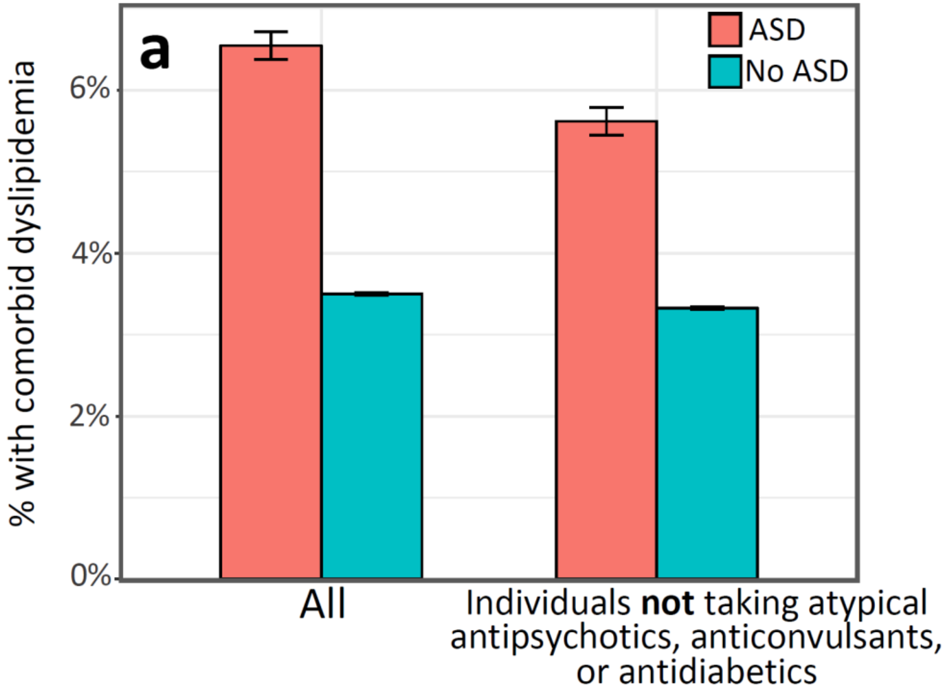
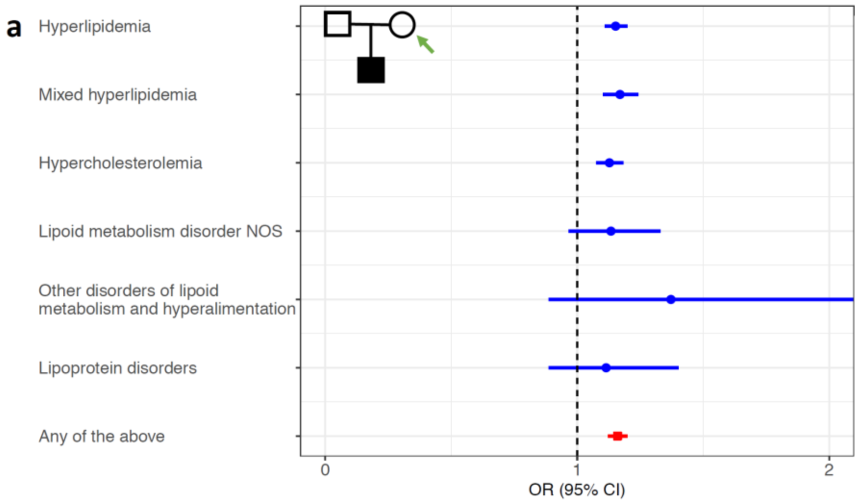


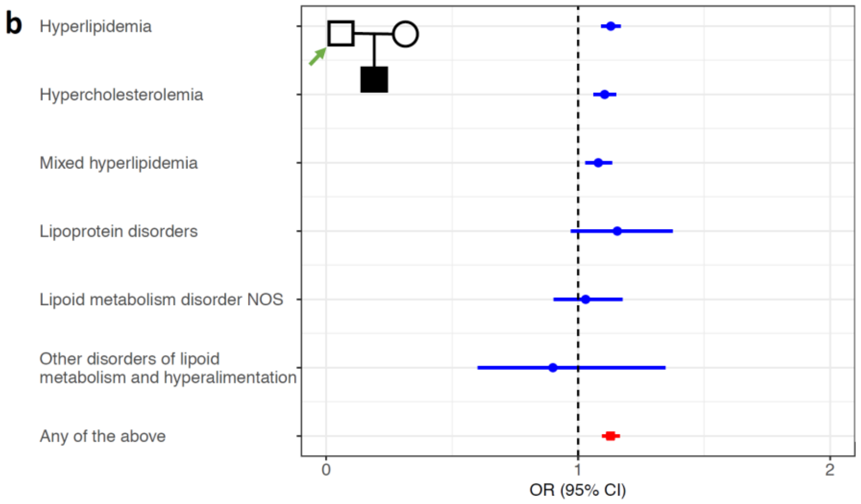

Figure 2f




Extended figure 2a

# Enrichment of dyslipidemia diagnoses in parents of children with ASD – Aetna healthcare claims

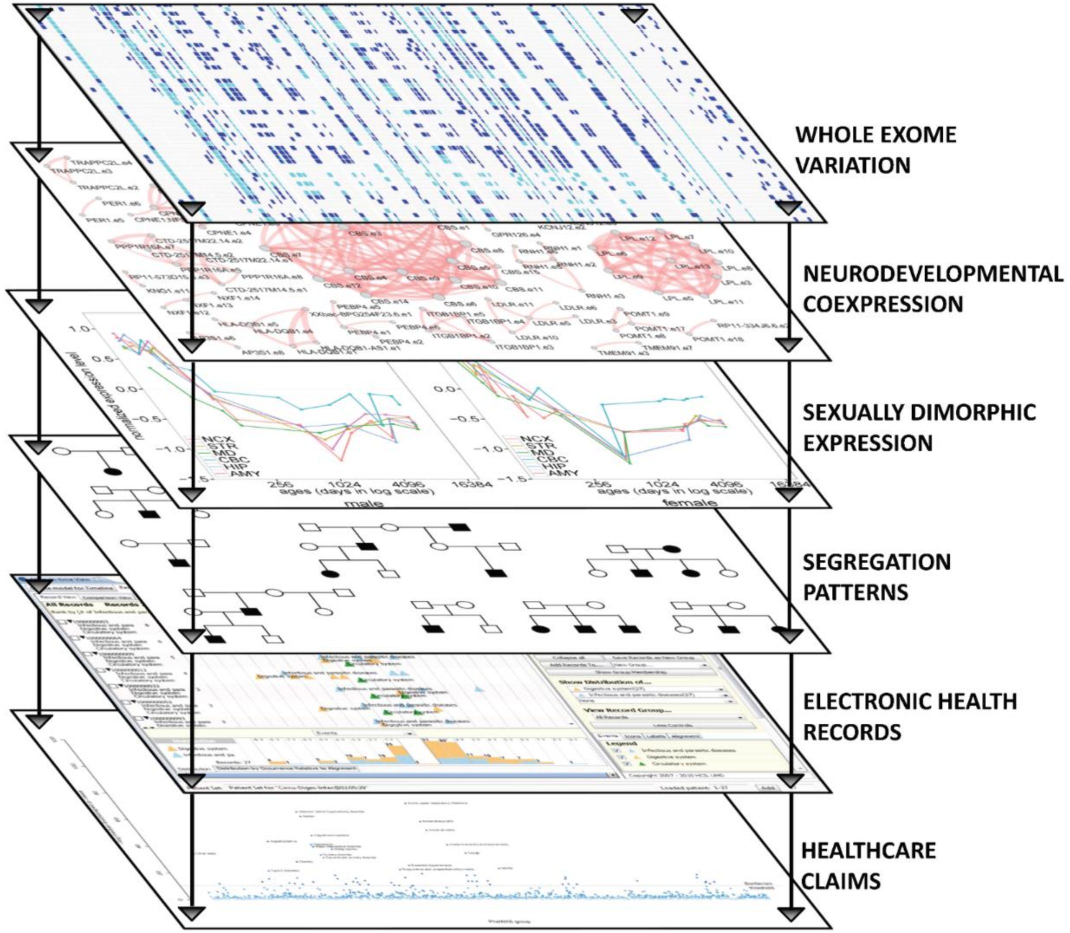



Extended figure 3

# ASD study conclusion

- New AI-driven precision medicine method to make sense out of massive genomic, transcriptomic, EHR and claims data etc.
- Identified a previously unrecognized risk factor for ASD which was verified in large clinical cohorts
- Opens avenue for early detection, intervention, and better outcomes for individuals with ASD and their family members




**Source code**: https://github.com/luoyuanlab/autism_precision_medicine

# The pandemic as a stress test for machine learning in healthcare

REVIEW ARTICLE | FOCUS

nature medicine

https://doi.org/10.1038/s41591-018-0300-7

**High-performance medicine: the convergence of human and artificial intelligence**

Eric J. Topol

nature machine intelligence

ANALYSIS

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

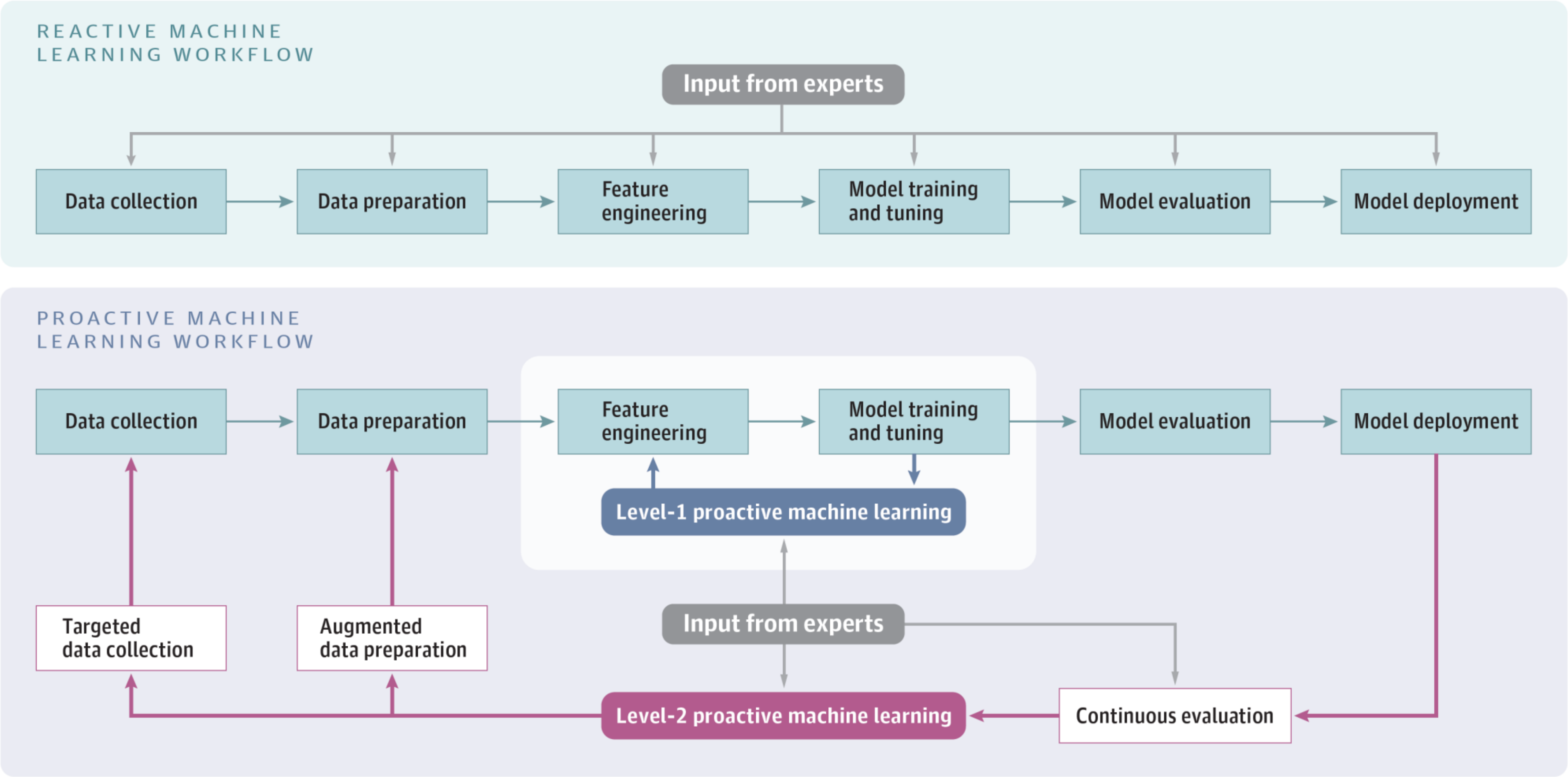
Check for updates

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]

# Moving from reactive to proactive multi-modal machine learning




Luo Y, Wunderink RG, Lloyd-Jones D. Proactive vs Reactive Machine Learning in Health Care: Lessons From the COVID-19 Pandemic. *JAMA. 2022*.

# Let us work together and bring it to a whole new level

- Collaboration welcome
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- @yuanhypnosluo
- We are hiring, multiple postdoc positions available
- https://labs.feinberg.northwestern.edu/luolab/
- Main funding support acknowledgement
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  - U54HL160273
  - R01LM013337
  - R01GM105688
  - R21LM012618
  - UL1TR001422
  - U01HG011169

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