
UC San Diego
Welcome to the 15th Anniversary
DBMI Symposium
We're excited to have you here!
Division of Biomedical Informatics | January 24, 2025

Transforming healthcare and biomedicine for a sustainable future

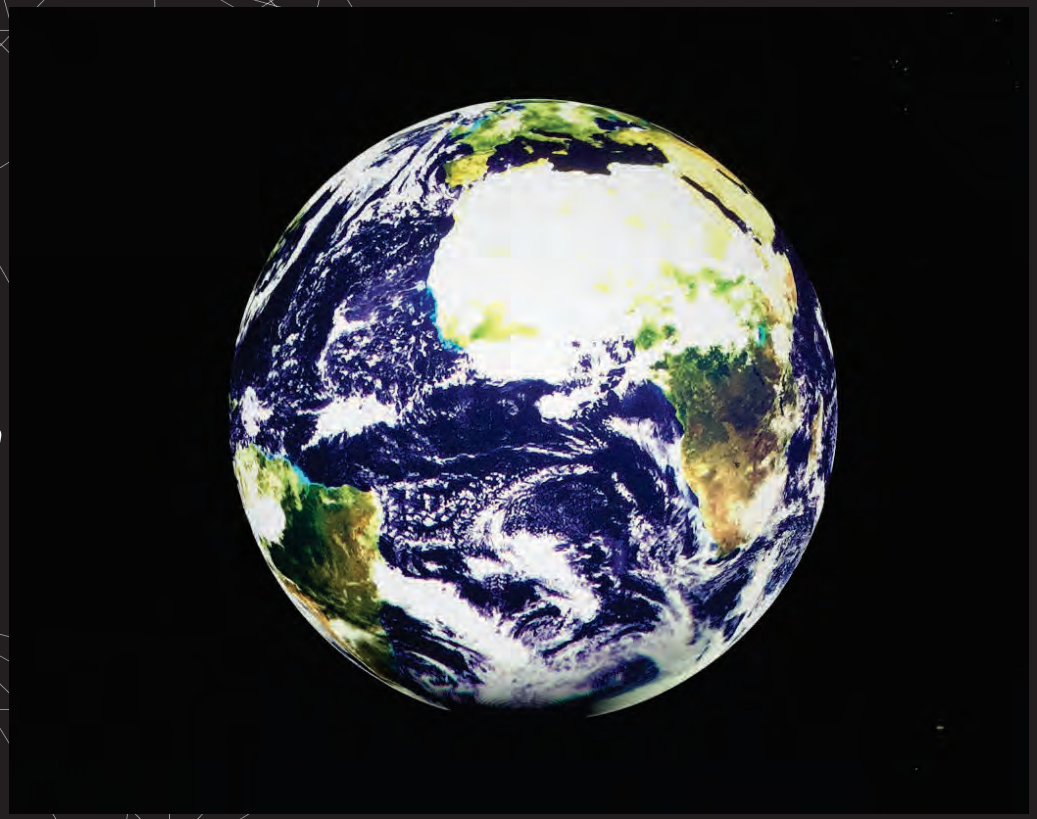
Welcome Biomedical Informatics 15th Anniversary

Amy M. Sitapati, MD
Chief and Chair of Biomedical Informatics
The Lawrence S. Friedman Professor of Population Health
UC San Diego School of Medicine
Pronouns: she/her/hers

Planet health

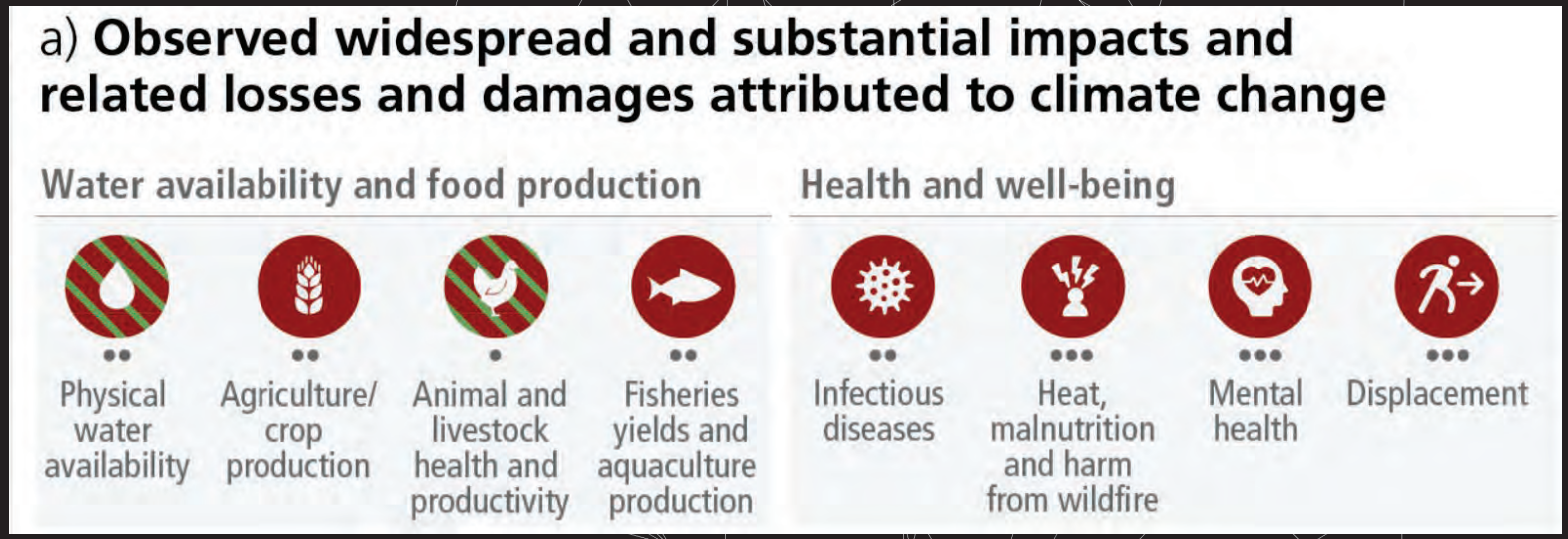
Facing impact of consumption by the estimated 8 billion human inhabitants:

- Water scarcity (*70% of Earth's available fresh water is used for irrigation*)
- Climate (*Increase 1.4 C since pre-industrial era*)
- Deforestation (*>40% of all land is for food production*)



Reference: Ten Billion by Stephen Emmott, 2013 and
Climate Change - NASA Science https://science.nasa.gov/climate-change/

Planet Earth & Human Health are Interconnected



Reference:
https://www.ipcc.ch/report/ar6/syr/downloads/figures/IPCC_AR6_SYR_SPM_Figure1.png

Asymmetry of Human Health Longevity

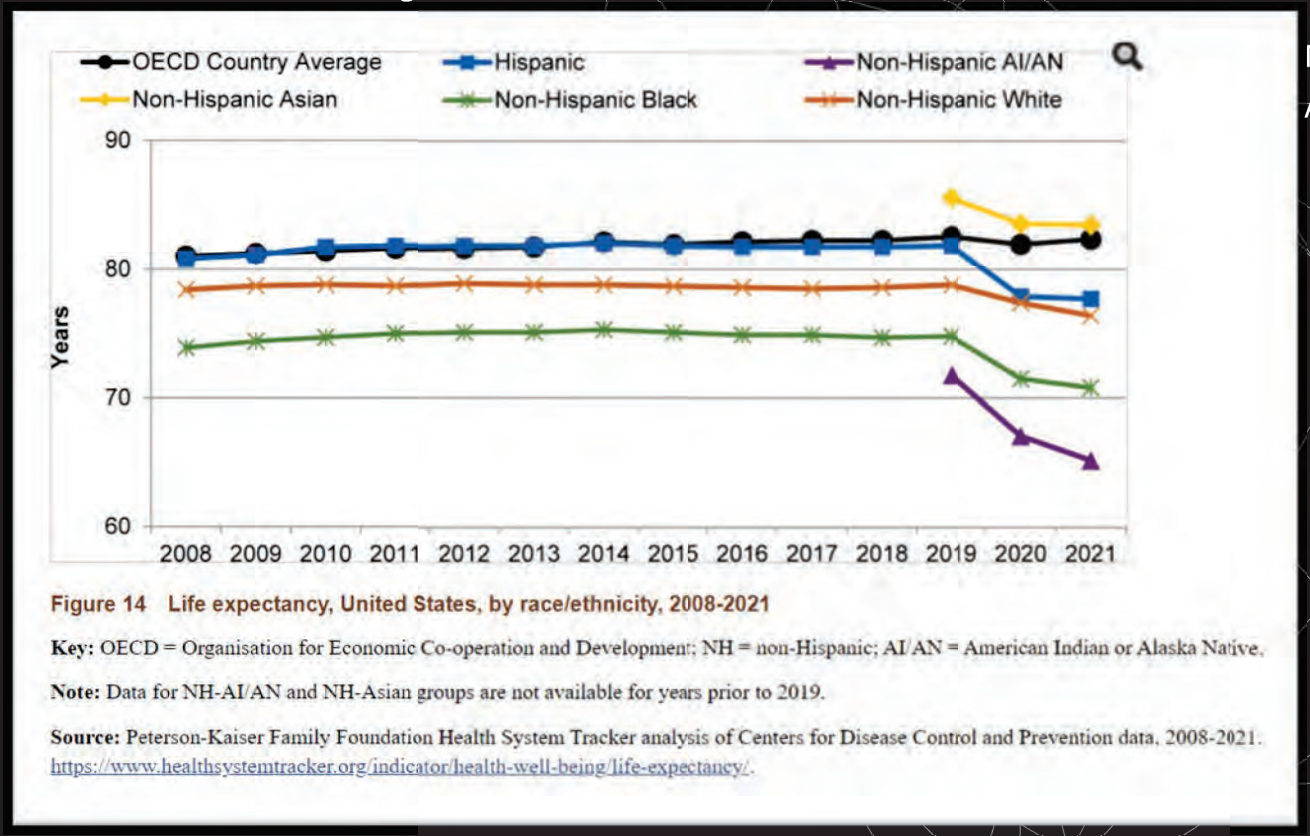


Figure 14 Life expectancy, United States, by race/ethnicity, 2008-2021

Key: OECD = Organisation for Economic Co-operation and Development; NH = non-Hispanic; AI/AN = American Indian or Alaska Native.

Note: Data for NH-AI/AN and NH-Asian groups are not available for years prior to 2019.

Source: Peterson-Kaiser Family Foundation Health System Tracker analysis of Centers for Disease Control and Prevention data, 2008-2021. https://www.healthsystemtracker.org/indicator/health-well-being/life-expectancy/.

NH = non-Hispanic;
AI/AN = American Indian or Alaska Native.

US Life expectancy (2021)

NH-Asian individuals (83.5 years)

Hispanic (77.7 years),

NH-White (76.4 years),

NH-Black (70.8 years),

NH-AI/AN (65.2 years)

Reference: 2023 National Healthcare Quality and Disparities Report. Rockville (MD): Agency for Healthcare Research and Quality (US); 2023 Dec. Portrait of American Healthcare. Available from: https://www.ncbi.nlm.nih.gov/books/NBK600454/

Root Causes (SDoH) Undermine Health Advancement

1 M children are **homeless** in the US

Housing prices since 2000 surged impacting median rent by a 192% (West Coast US)

Reference: Poverty by America, Matthew Desmond

Biomedical Informatics has served

to bridge translational efforts to deliver **technology-enabled** solutions to our patients that

Strengthen Engagement, Access And Prevention

Demonstrate Outcomes Impact

Support Justice, Equity, Inclusion

Build Reliable & Sustainable Capacity

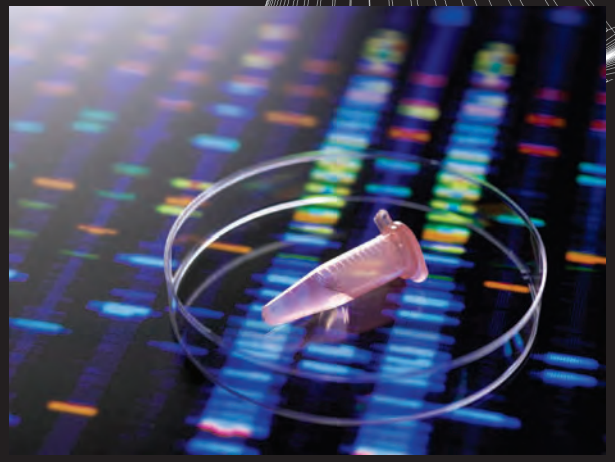
In the past 5 years, biomedical informatics

Developed and implemented health AI platforms and systems that..

- Standardize reliable high-quality care delivery
- Improve early identification of high-risk conditions
- Scale patient engagement
- Support diagnostic safety & efficiency by helping radiologists read medical images
- Accelerate discovery in genomic data interpretation & new therapeutic targets

Reference: Assisted by ChatGPT 40 mini for sources including Google DeepMind Alpha Fold,

What if our future Biomedical Informatics supported



SDoH: Access to drivers of health – food as medicine, clean water, housing, and care

Reliable care and Early Detection: Engagement in basic prevention, robust care pathways, and universal access to genomic sequencing

Discovery to Bedside: Acceleration of in precision medicine delivery to consumers that could extend life expectancy (20 years +)

Be a Spark!

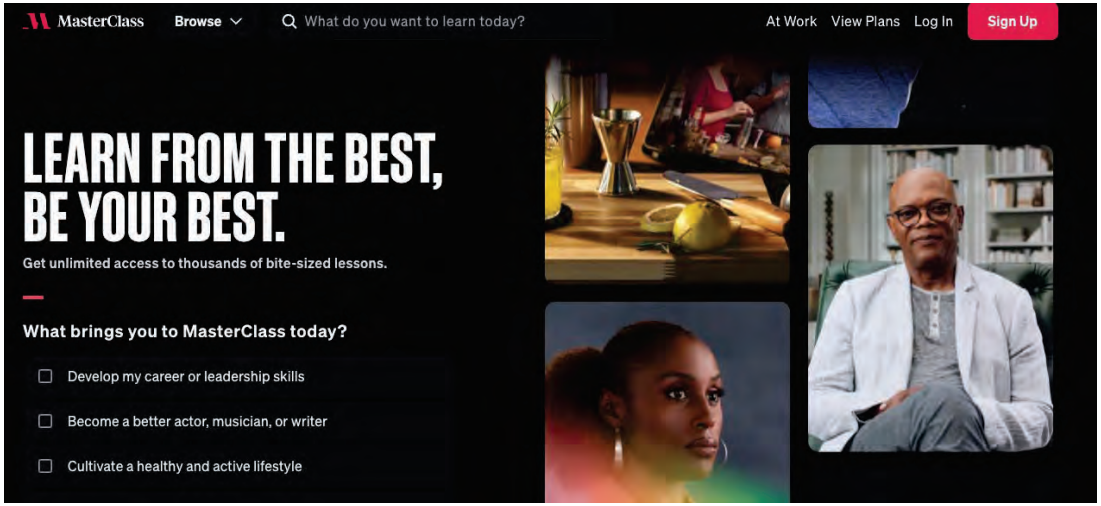
References & Reading

- Ten Billion by Stephen Emmott, 2013
- Intergovernmental Panel on Climate Change (IPCC) 2023
- NASA Science 2025
- 2023 National Healthcare Quality and Disparities Report
- Poverty by America, Matthew Desmond 2023

A Fireside Chat with Dr. Greenes and Dr. Jaffe

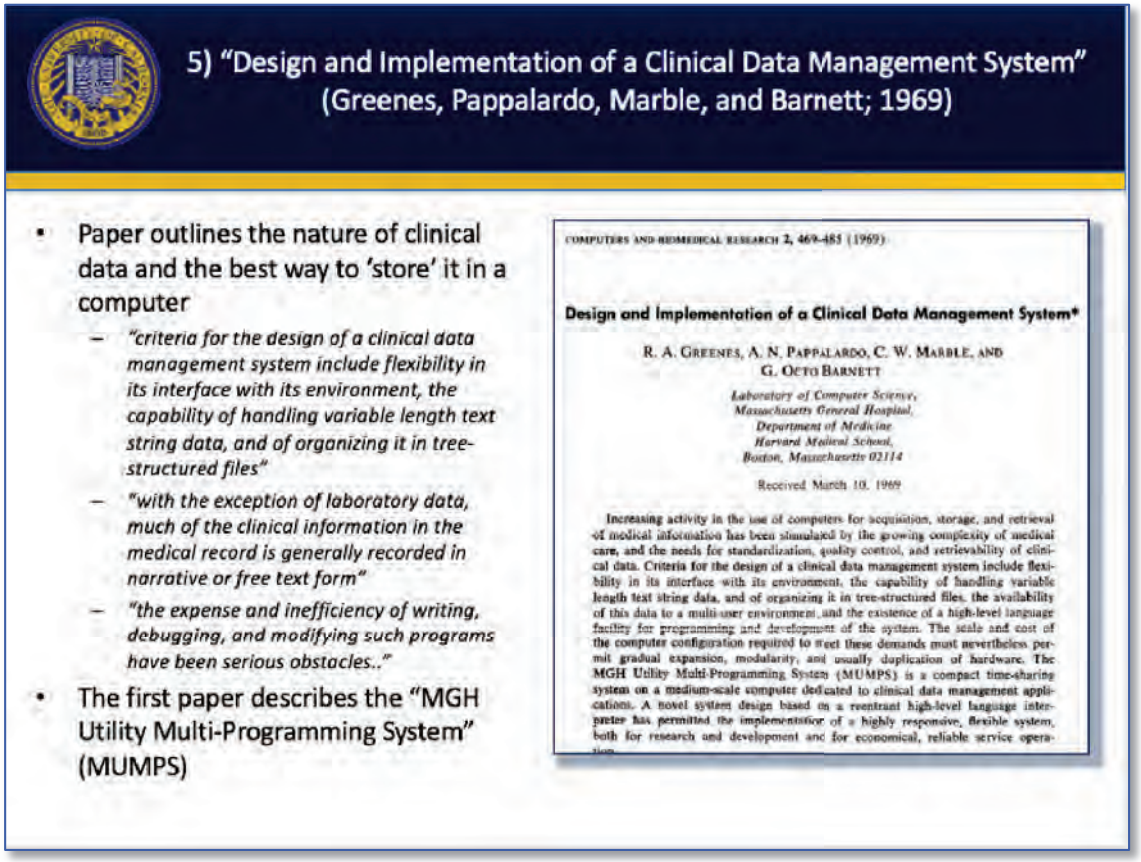
Michael Hogarth, MD, FACP, FACMI
Professor, Biomedical Informatics, Dept of Medicine

What is Masterclass?



Robert Greenes, MD, PhD

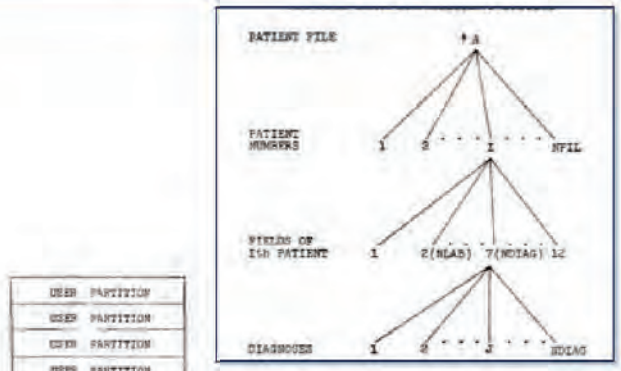
- MD – Harvard Medical School (1966)
- PhD – Applied Mathematics – focusing on computer science and the interactive capture of clinical progress notes using touchscreens.
- Radiology residency (MGH)
- Dept of Radiology, Brigham and Women's Hospital where he estalibshed the Decision Systems Group which he directed for 27 years
- Working with Dr. Octo Barnett at Mass General Hospital (MGH), he co-developed the Massachusetts General Hospital Utility Multi-Programming System (MUMPS)
- Morris Collen Award from ACMI in 2008



Innovations in MUMPS

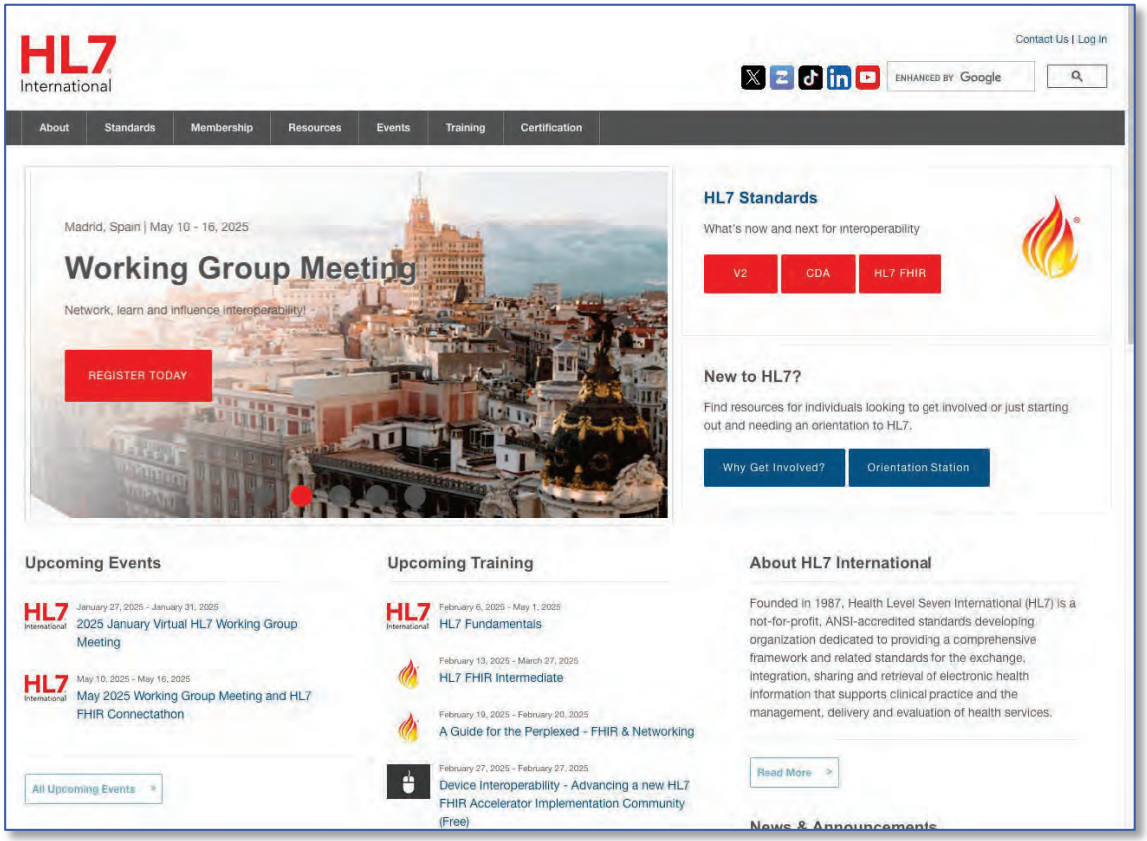
The importance of MUMPS

- An interpreted language (real-time interpreter)
  - Recognition that clinical data management environments do not require 'pure central processing'
  - Interpreters make it easier to have cross platform software systems
- Combining logic/computation and data storage in the same language
  - Provides significant speed and robustness
- Arrays as data storage – fast, simple
- Multi-user by design
  - multiple users executing different parts of the program at the same time using the same interpreter…
  - Uses a 're-entrant' interpreter
- Estimated that >70% of all health records in the US today are stored in a MUMPS-based system (Epic, VISTA, Meditech)



Chuck Jaffe, MD, PhD

- MD – Duke University (1972)
- PhD – Duke University (1972) in Experimental Pathology/Computer Science
- Post-doc – NIH (contemporary of Dr. Fauci)
- Faculty, Georgetown, Lombardi Cancer Center
- Dir of Medical Informatics, AstraZeneca
- PI for >200 clinical trials
- Championed the use of electronic data capture and data standards
- A leader in the use of clinical data sets and standards for data exchange
- Intel Senior Global Strategist
- HL7's 1st CEO: 2007 - present
- Instrumental in the adoption of HL7 FHIR



AI and the Spectrum of Clinical Decision Support

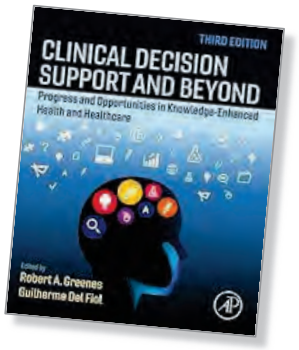
Reflections from a six-decade journey

Bob Greenes

My pitch:

- Purpose and scope of CDS have been evolving
  - From focus on diagnosis, treatment, and logic rules …
  - To broad-based support for cognitive processes and workflow
    - *Knowledge-Enhanced Health and Healthcare**

      ** See CDS & Beyond, 3rd Edition, Elsevier, 2022*



- AI is – and has been – part of that story

A Brief Chronology and Historical Context

When I got to HMS in 1962 ...

- The highest tech in medicine were the stethoscope, xray, and clinical lab analyzer
- I tried to find faculty working with computers
  - Found only two, including:
    - Octo Barnett – leading one of the first EHR projects

  - The technology of the time:

Meanwhile …

- @Cornell
  - Frank Rosenblatt  had already introduced the Perceptron in 1958
    - » First neural network

- Ledley & Lusted had published their Science paper (1959)
  - Warner et al (1964) and Lodwick (1965) were applying Bayes

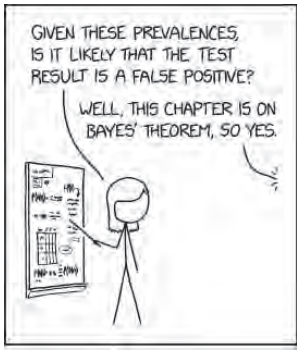
- AI was a hot topic @MIT
  - John McCarthy  introduced the term “artificial intelligence”
    - » Developed LISP
  - Marvin Minsky  created the vision for AI we have today
    - » Conceptual representation of cognitive processes

- While working on my PhD in late 1960s
  - Joe Weizenbaum*  created Eliza in 1966
    - » First ChatBot

**my thesis advisor*

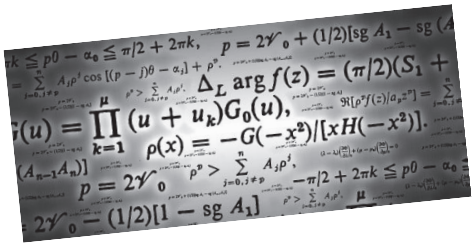
Chronology – 1960s

- Diagnosis
  - *Driven initially by academic interest*
  - Bayes

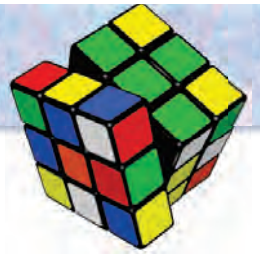


- First EHRs
  - As platform for CDS

- Algorithms for well defined problems



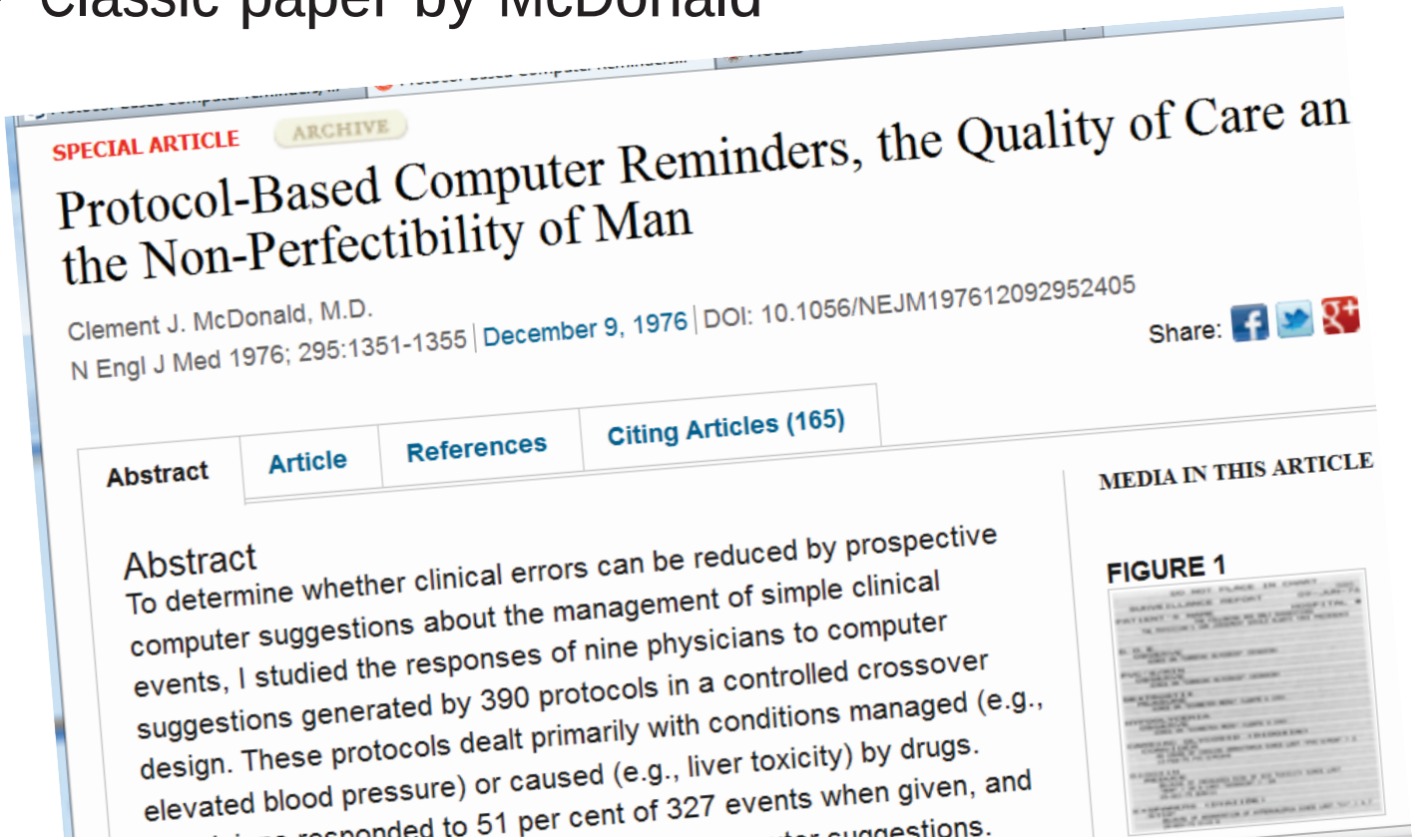
Chronology – 1970s



- Diagnosis & treatment
  - AI approaches
    - Heuristic reasoning
    - Expert systems
- Prognosis and prediction
  - From databases

Broader opportunities for CDS in EHR systems

- Classic paper by McDonald



SPECIAL ARTICLE ARCHIVE

Protocol-Based Computer Reminders, the Quality of Care an the Non-Perfectibility of Man

Clement J. McDonald, M.D.

N Engl J Med 1976; 295:1351-1355 | December 9, 1976 | DOI: 10.1056/NEJM197612092952405

Share:

Abstract | Article | References | Citing Articles (165)

Abstract

To determine whether clinical errors can be reduced by prospective computer suggestions about the management of simple clinical events, I studied the responses of nine physicians to computer suggestions generated by 390 protocols in a controlled crossover design. These protocols dealt primarily with conditions managed (e.g., elevated blood pressure) or caused (e.g., liver toxicity) by drugs. responded to 51 per cent of 327 events when given, and suggestions.

MEDIA IN THIS ARTICLE

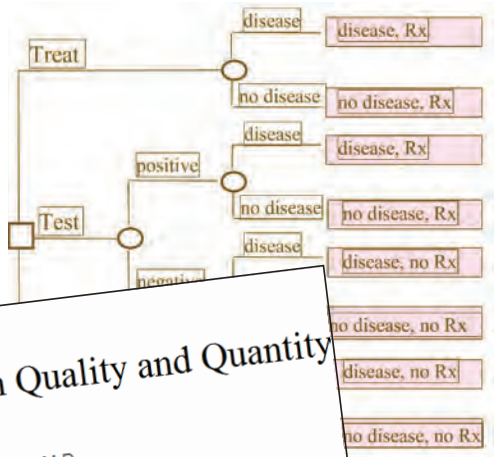
FIGURE 1

Monitoring activities and events

- Alerts
- Reminders
- Surveillance
  - Background statistics
- Feedback

Chronology – 1980s

- A focus on process
  - Early CPOE and interaction checks
  - Decision analysis
  - Shared decision making



SPECIAL ARTICLE ARCHIVE

Speech and Survival — Tradeoffs between Quality and Quantity of Life in Laryngeal Cancer

Barbara J. McNeil, M.D., Ph.D., Ralph Weichselbaum, M.D., and Stephen G. Pauker, M.D.

N Engl J Med 1981; 305:982-987 | October 22, 1981 | DOI: 10.1056/NEJM198110223051704

Share:

Abstract | Article | References | Citing Articles (192)

Abstract

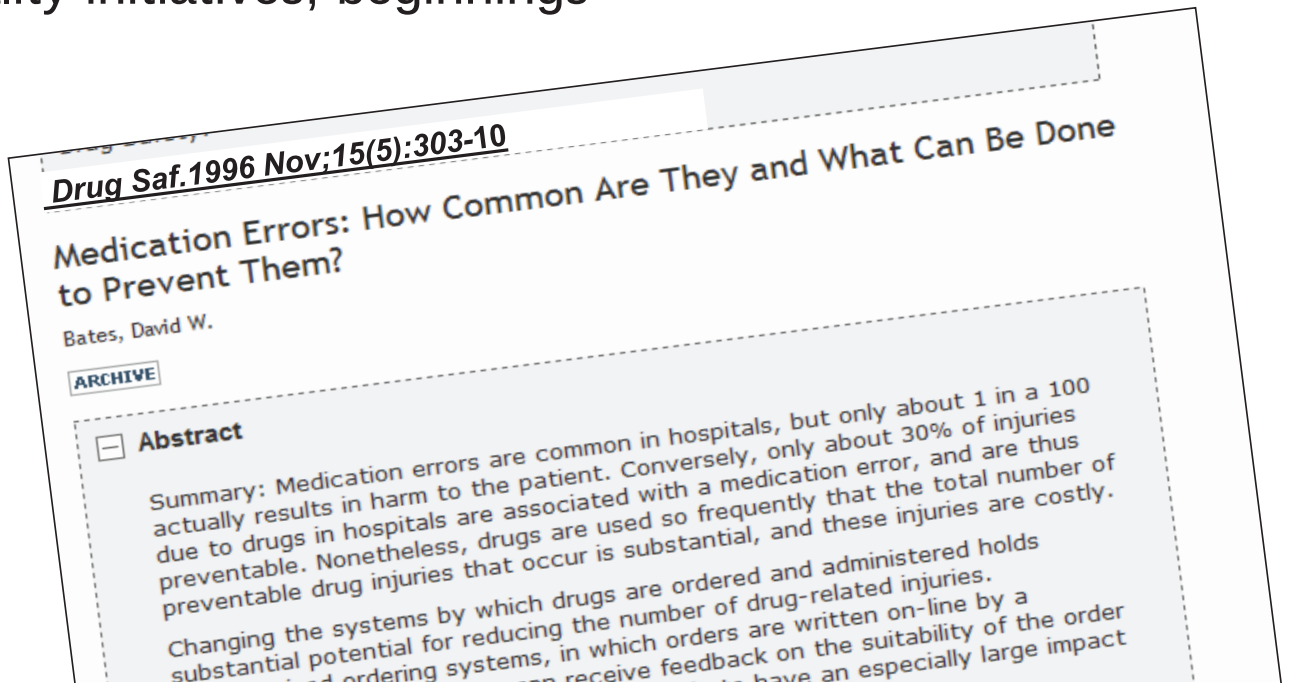
In Stage T3 carcinoma of the larynx (carcinoma restricted to the vocal cords, causing complete immobility of the cords but not extending to adjacent structures), laryngectomy leads to a three-year survival rate of approximately 60 per cent and the loss of normal speech. Radiation therapy, on the other hand, leads to a lower survival (30 to 40 per cent at three years) but preserves normal or nearly normal speech. We investigated attitudes toward the quantity and quality of life in 37 [illegible] interviewing 12 firefighters and 25 middle and

ARTICLE ACTIVITY

192 articles have cited this article »

Chronology – 1990s

- Arden Syntax as first standard for CDS
- Computer-interpretable guideline models
- Safety and quality initiatives, beginnings



Drug Saf.1996 Nov;15(5):303-10

Medication Errors: How Common Are They and What Can Be Done to Prevent Them?

Bates, David W.

ARCHIVE

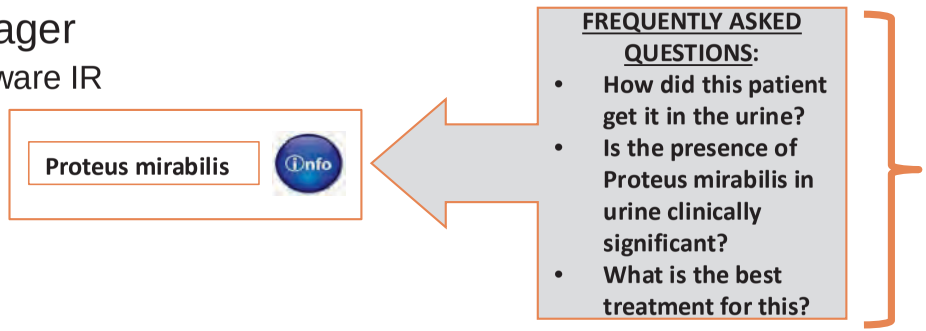
Abstract

Summary: Medication errors are common in hospitals, but only about 1 in a 100 actually results in harm to the patient. Conversely, only about 30% of injuries due to drugs in hospitals are associated with a medication error, and are thus preventable. Nonetheless, drugs are used so frequently that the total number of preventable drug injuries that occur is substantial, and these injuries are costly.

Changing the systems by which drugs are ordered and administered holds substantial potential for reducing the number of drug-related injuries. ordering systems, in which orders are written on-line by a receive feedback on the suitability of the order have an especially large impact

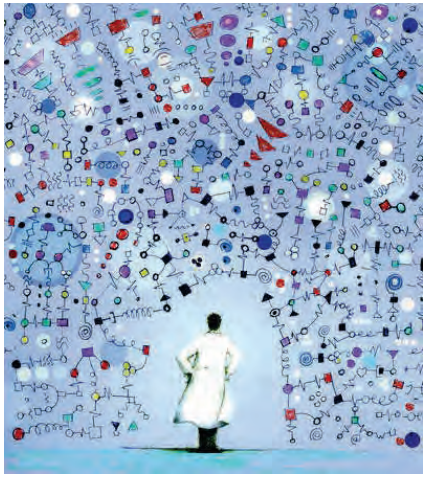
Chronology – 2000s

- Safety and quality as priorities
  - Landmark “Quality Chasm” IOM (NAM) reports
    - 1999, 2001, and others in series of 8 volumes
  - Other stakeholders
    - IHI, PROs, NCQA, AHRQ, …
- HITECH Act of 2009 to stimulate EHR use
- A focus on standards and interoperability
  - Introduction of infobutton manager
    - First attempt to provide context-aware IR



Chronology – 2010s

- EHR adoption stimuli
  - Meaningful Use criteria
- Wellness / health focus, patient-centeredness
  - Bundled payments, ACOs
- Connected patient
  - Data everywhere
  - Harnessing analytics
  - *Major focus of new DBMI!*



Cognitive process and workflow support

- Order sets
- Structured data forms
- Structured reports
- Dashboards
- Graphs, trends, ...

Chronology – 2020s and beyond

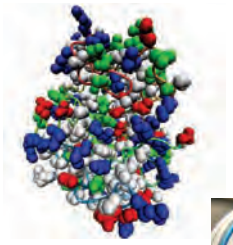
- Toward a holistic vision for the health system
  - -- The Quintuple Aim
  - -- The Learning Health System

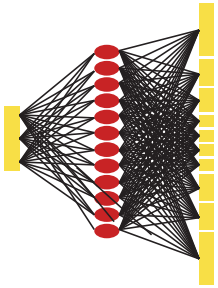
➔ *Knowledge-enhanced health and healthcare*

- The AI explosion
  - Very large databases
  - Machine learning, deep neural networks
  - LLMs, agents, and beyond – *just 2+ years ago!*

AI impact areas

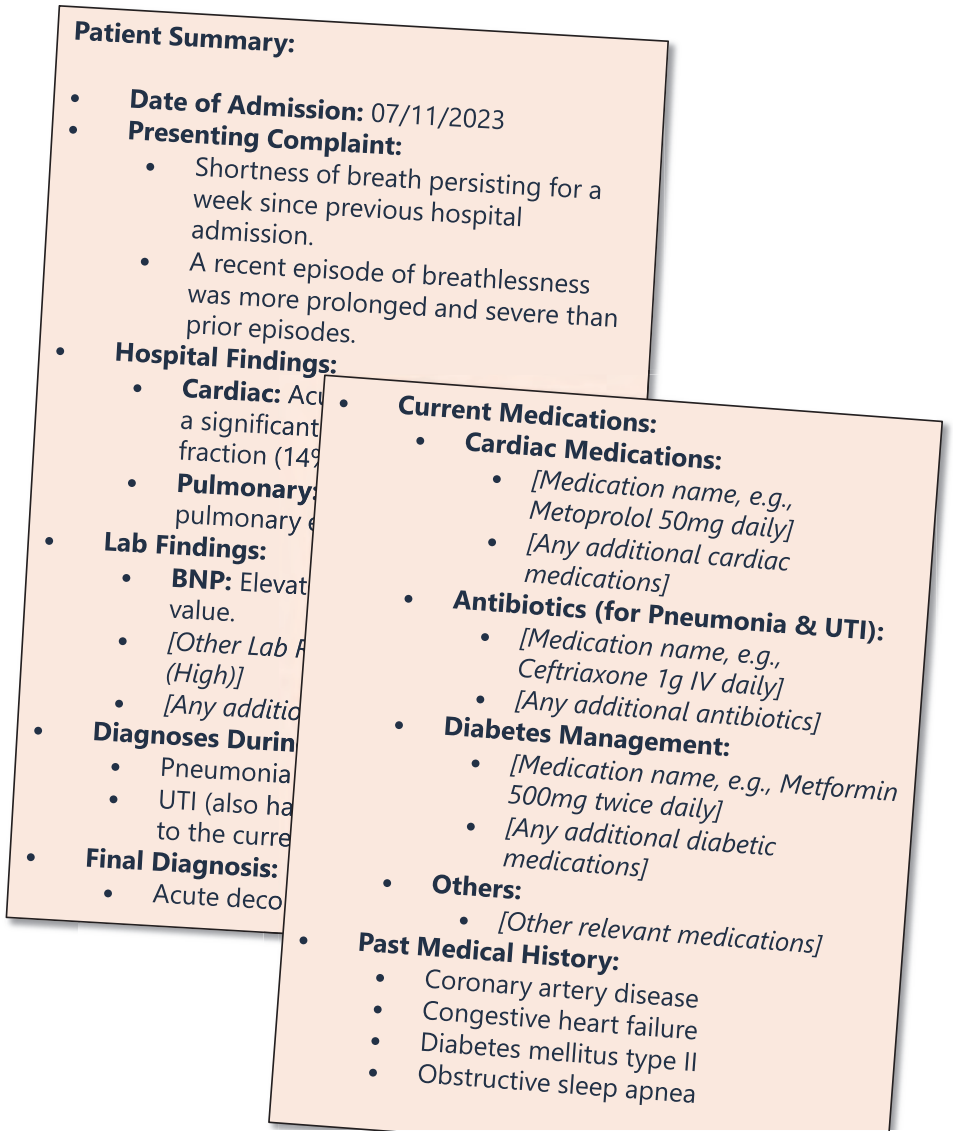
- Diagnosis, treatment, & prognosis
  - Genomics, precision medicine
  - Pharmacogenomics
  - Imaging
  - Predictive modeling





Care process

- Patient interaction
  - Facilitate triage process
  - Identify problems & concerns
- Patient education & training
- Encounter notes
  - Summarize past
  - Capture, transcribe, & organize
- Context-awareness
  - Relevant information
  - alerts/reminders



Personal monitoring

- Ubiquitous aid
- Context awareness
- Full access to current health data, environment, ambient conditions, activity
- Alerts and reminders
- Communication with provider, caregiver, others as needed

Agentic AI

1. Surgical robots

2. AI pharmacists

3. AI nurse

4. Therapist

Purposes for CDS – from an evolutionary perspective

1. Find needed information
2. Make decisions
3. Perform a computation
4. Monitor
5. Manage, optimize process & workflow
6. Organize or summarize information to facilitate decision making

- *Carry out or guide CDS processes as needed*
  - *AI as a Co-pilot, Collaborator, Co-Intelligence**

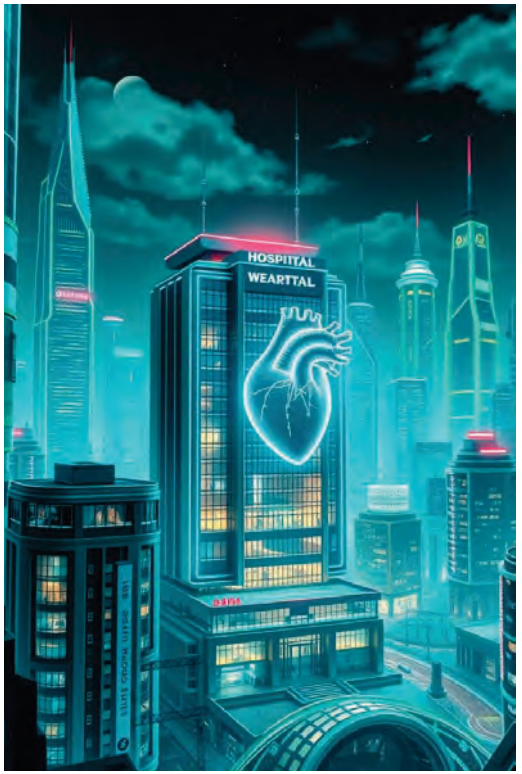
* Ethan Mollick, I, Porfolio, 2024

Purposes & Methods/Models

Purpose/ Dec Model	Find info	Make a decision	Do calc.	Monitor	Manage process	Organize or summ.	Collaborate
IR & search	X						X
Logic eval.	X	X	X	X		X	X
Prob. est.	X	X	X	X		X	X
Heuristic/Expert	X	X	X	X	X	X	X
Algorithmic	X	X	X	X	X	X	X
Grouping	X					X	X
Visualization	X				X	X	X
Data-trained AI	X	X	X	X	X	X	

What's coming soon...

- Agentic AI – federations of agents to carry out needed tasks and workflow processes
- Artificial General Intelligence (AGI) and shortly thereafter...
- Artificial Super Intelligence (ASI)*



**Klang E, et al. If machines exceed us: Health care at an inflection point. NEJM AI: 2024; 2 (10). DOI: 10.1056/AIp2400559*

Table 1. Advanced Potential AI Capabilities in Health Care, Highlighting Benchmarks Where AI May Significantly Enhance or Surpass Human Performance.*

Capability	Human Physician Drawback	ASI	Unique Impact of ASI
Ethical and emotional intelligence			
Adaptive ethics	Guidelines may lack context sensitivity	Ethical evolution with contextual understanding of cultural, emotional, and situational data	Resolves ethical dilemmas with nuanced decisions
Cognitive empathy	Influenced by personal biases and emotional states	Attuned to emotional makeup through behavioral data	Provides individualized emotional support adaptive to patient needs
Disparities mitigation	Susceptible to unconscious biases	Adaptive and holistic bias mitigation through continuous learning	Ensures fair and equitable treatment across diverse populations
Predictive altruism	Limited by current knowledge and personal experiences	Anticipatory altruism driven by analytics	Allocates resources to where they will help most
Analytical intelligence			
Cognition	Subject to fatigue, stress, and cognitive overload	Cognitive capacity limited only by computing capacity	Manages multiple crises simultaneously without performance drop
Cross-modal insight	Restricted to human sensory inputs	Integrates data sources	Establishes correlations across rich multimodal data
Self-optimization	Slower and dependent on sequential learning	Artificial neural networks enable parallel learning	Refines diagnostic and treatment processes
Human–machine neural symbiosis	Limited by individual cognitive capacity	Symbiotic integration with human cognition	Enhances decision-making through direct brain–computer interfaces, potentially leading to unprecedented levels of medical accuracy
Clinical and bioinformatical applications			
Holistic health view	Medical specialization can lead to fragmented care	Unified, system-wide health understanding	Develops all-encompassing understanding of the patient's journey
Temporal insight	Constrained by linear thinking and short-term focus	Nonlinear, intertemporal analysis	Predicts long-term health trajectories; simulates and optimizes across years, revolutionizes preventive medicine
Pharma simulation	Lengthy and costly research and development processes	Instant simulation of drug interactions	Accelerates drug discovery and targeted therapy
Patient tracking	Gaps in continuous monitoring and personalized guidance	Personalized health guidance at all times, tailored to individual learning, preferences, and needs	Improves patient engagement and adherence to treatment regimes
Molecular diagnostics	Limited by current diagnostic technology	Molecular-level analysis and coordinated nanomedical swarms	Early detection and targeted treatment combining molecular data analysis with intervention using nanomedical swarms
Existential safeguarding	Reactive rather than proactive in risk management	Utilizes global data to preemptively manage risks	Addresses pandemics and global health crises before they escalate
Universal translator	Language and cultural differences can impede	Instant translation and understanding of cultural nuance	Removes language barriers, enhancing global health communication

Challenges and Ethical Considerations

1	2	3	4
Errors and Fabrications	**Data Privacy and Security Concerns**	**Human-AI Interaction Complexity**	**Algorithm Bias and Transparency**
LLM hallucinations	Protecting data	Achieving balance	Awareness and amelioration

Conclusion

- This is actually **not** a conclusion but a beginning
- Based on what has happened just since in 2022, what can we expect in next 5 years???

"I think the promise is a little overhyped in the next two or three years, but in the next seven to nine years, it's going to completely change healthcare delivery. It's going to be the biggest thing since antibiotics, because it's going to lift every single doctor to be the best possible doctor and it's going to empower patients in ways they never have been before."

-- *Chris Longhurst, MD, CMO at UCSD Health, San Diego Magazine, 9/30/24*

UCSD DBMI 15th Anniversary

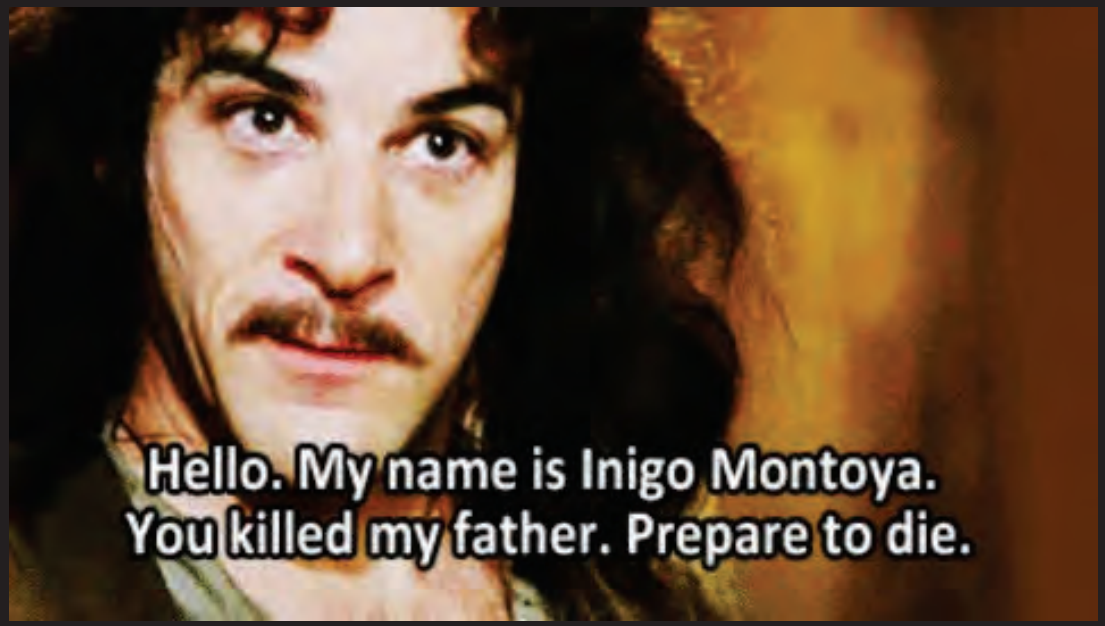
My Journey

Charles Jaffe, MD, PhD

Chief Executive Officer
Health Level 7 International

January 24, 2025

Rules for a Successful Introduction



1. Offer a polite greeting.
2. State your name.
3. Share a relevant personal link.
4. Manage expectations.

“If I had more time,

it would have been shorter.”

Mark Twain

Every story has a beginning.

This is mine.

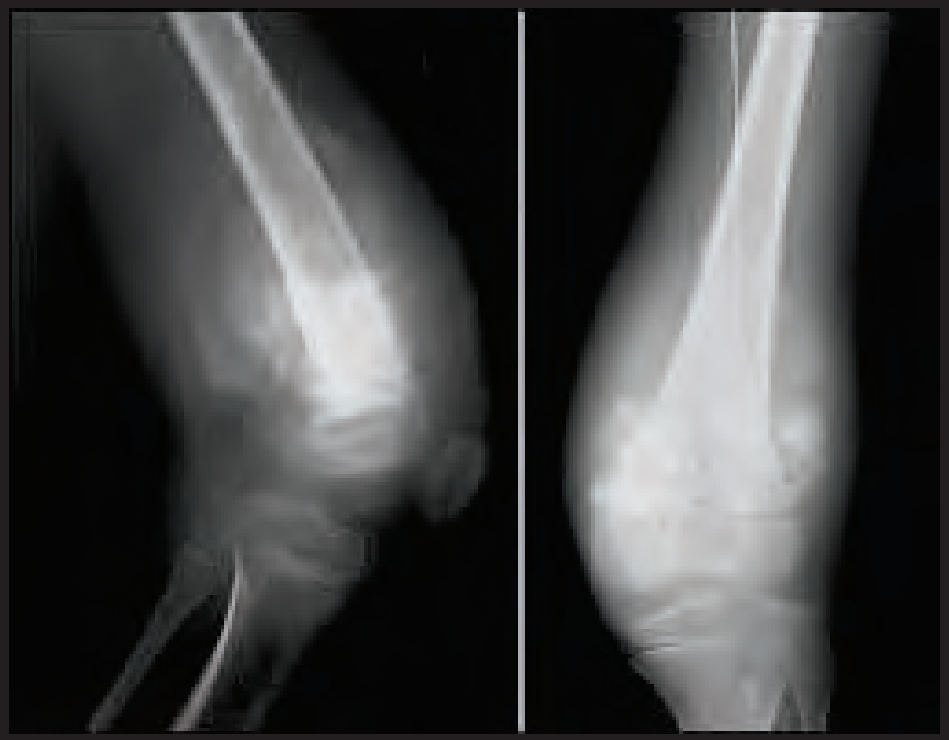
My journey in valuing health information began with Jack.

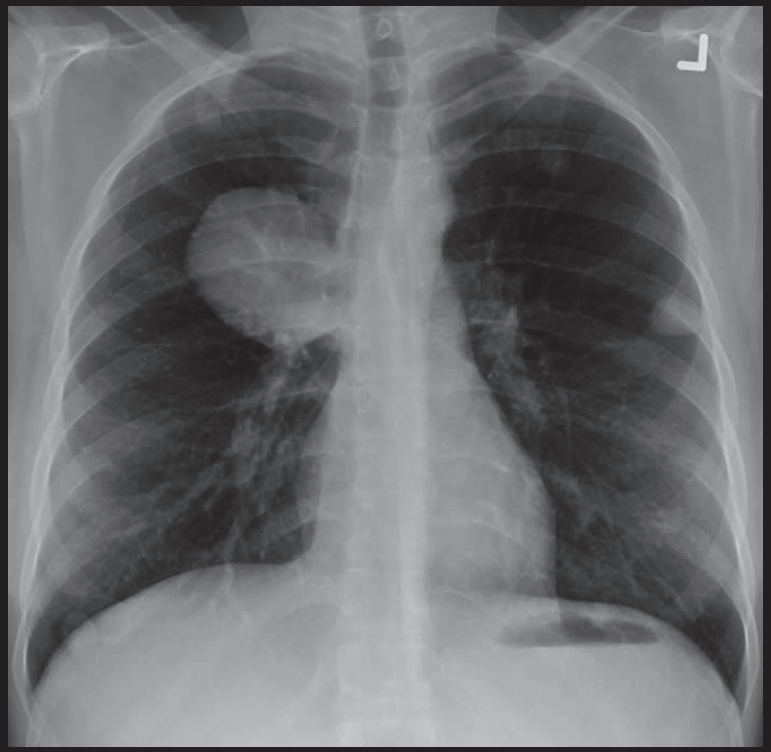
This is Jack

Honor student
Sports hero
University bound

Jack complained
to his Family Doctor
about knee pain.

This is what Jack’s knee looked like, but his doctor never saw the report.





This is Jack’s chest x-ray after I first saw him.

The Pathology Report read metastatic osteosarcoma.

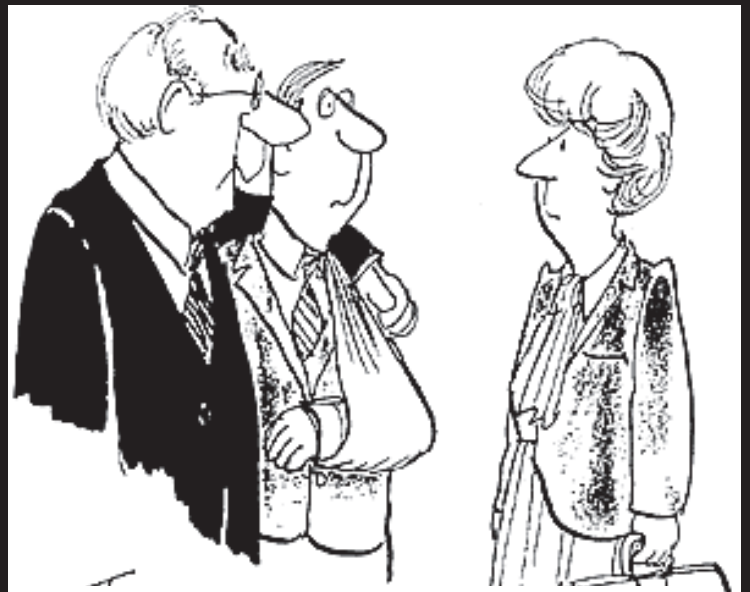
There should be
no more stories
like Jack’s.

There had to be
a better way to exchange
clinical information.

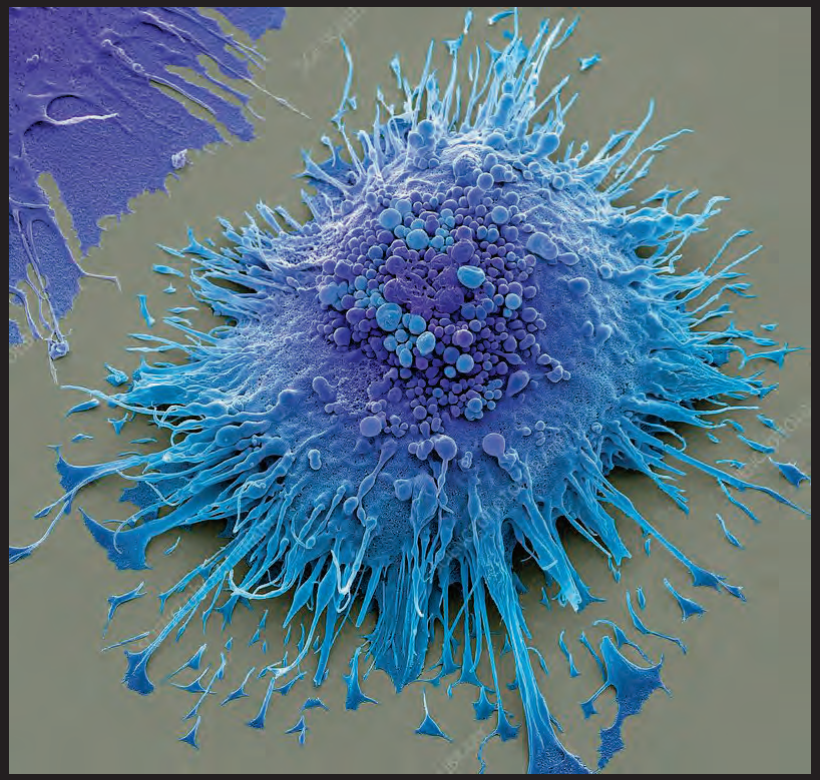
Clinical Informatics & Standards
Duke's first EHR initiative

At Duke, I learned a little about the complexities of sharing health information.

More importantly, I learned the value of having a mentor.



We've finally persuaded the interns to use the new EHR.



Biomedical informatics & an Introduction to Research

I wrote my doctoral dissertation on a computer model of the macrophage.

It’s a strange little white cell that (mostly) does not circulate, but it is the gateway to the immune system.

“You can accomplish anything in life,
if you don’t mind who gets
the credit.”

Harry Truman

Biomedical informatics & an Introduction to Research

Nearly 5 decades later, someone agreed that I got it (mostly) right.

At the NIH Clinical Center & the Lombardi Cancer Center
I got some lessons in clinical research.

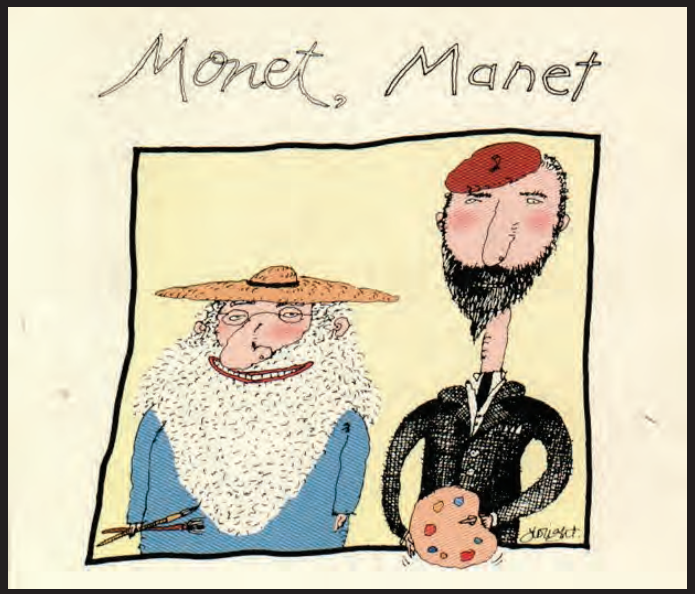
I also was schooled in publication politics.

“How much easier it is to be critical than to be correct.”

- Benjamin Disraeli

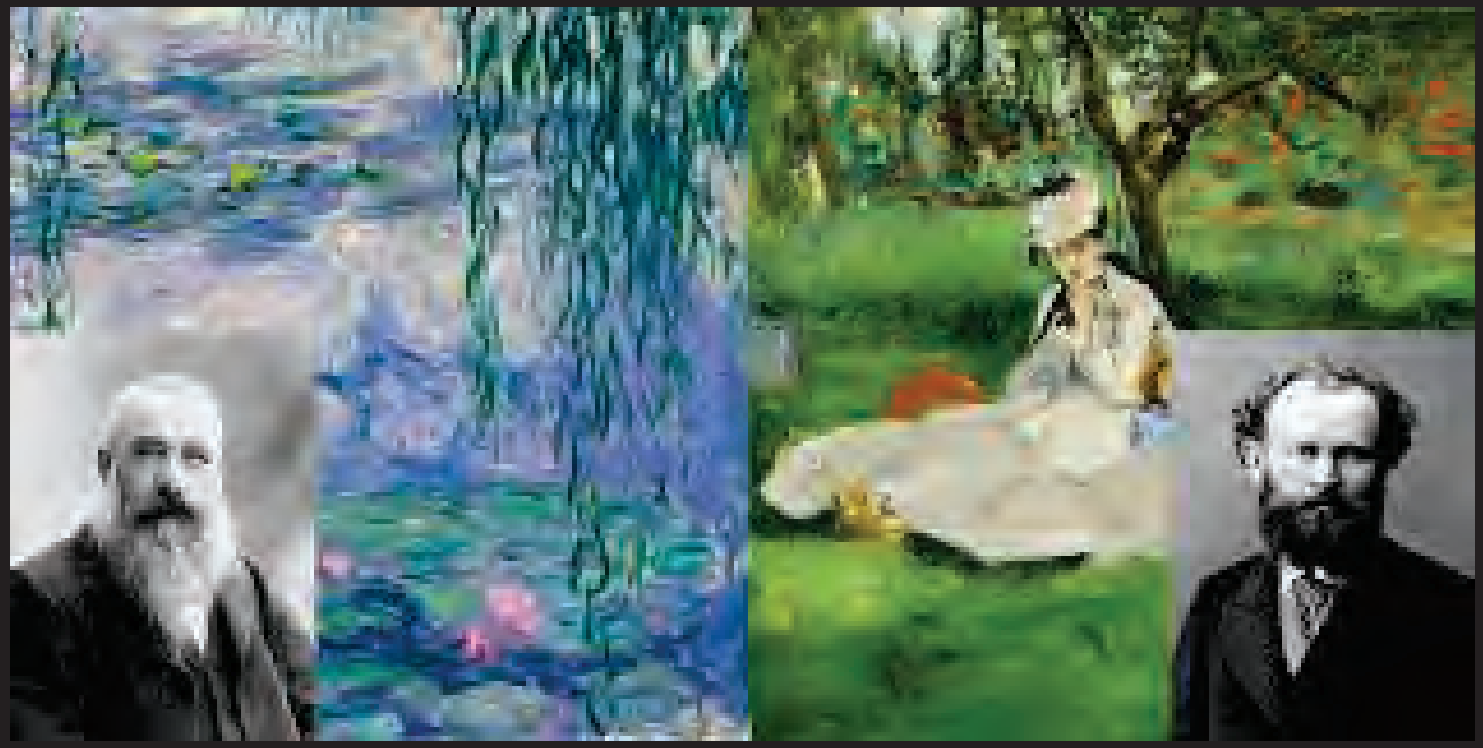
NIH & the Lombardi Cancer Center

The struggles over things that don’t matter



Apparently, there’s a difference.

- Is it the *Alternate Pathway* or the *Alternative Pathway*?
- Complement: Apparently immunologists can’t count, either.



I couldn’t allow you to worry about it.

Scripps & the Clinical Research Years

“Finding the evidence in Evidence Based Medicine”

Clinical Care & Clinical Research

In 1987 Ed Hammond and 3 colleagues develop an experiment that he called HL7

- Syntactic interoperability is established in the transport layer*
- The “how” becomes clearer.
  The what, not so much.

* Exchanging research data is someone else’s problem.

Well, I tried.

Apple Newton

Introduced: August 2, 1993
Discontinued: February 27, 1998
Just 15 years too early

Intel Digital Health

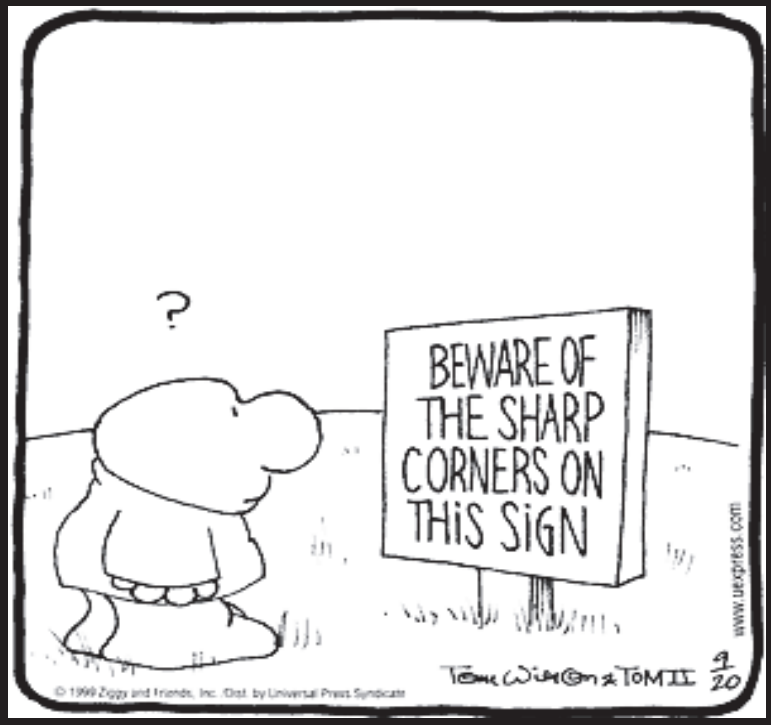
"Well then…try to forgive."

- The notion of open standards begins to charm the industry.
- Interoperability takes a leap forward and a step back
  - 1995: HL7 introduces the *RIM and version 3**
- The *Personal Health Record* gains a following
  - Intel and Microsoft embrace PHR standards,
  - Microsoft introduces *Health Vault*. It lasts a decade.*

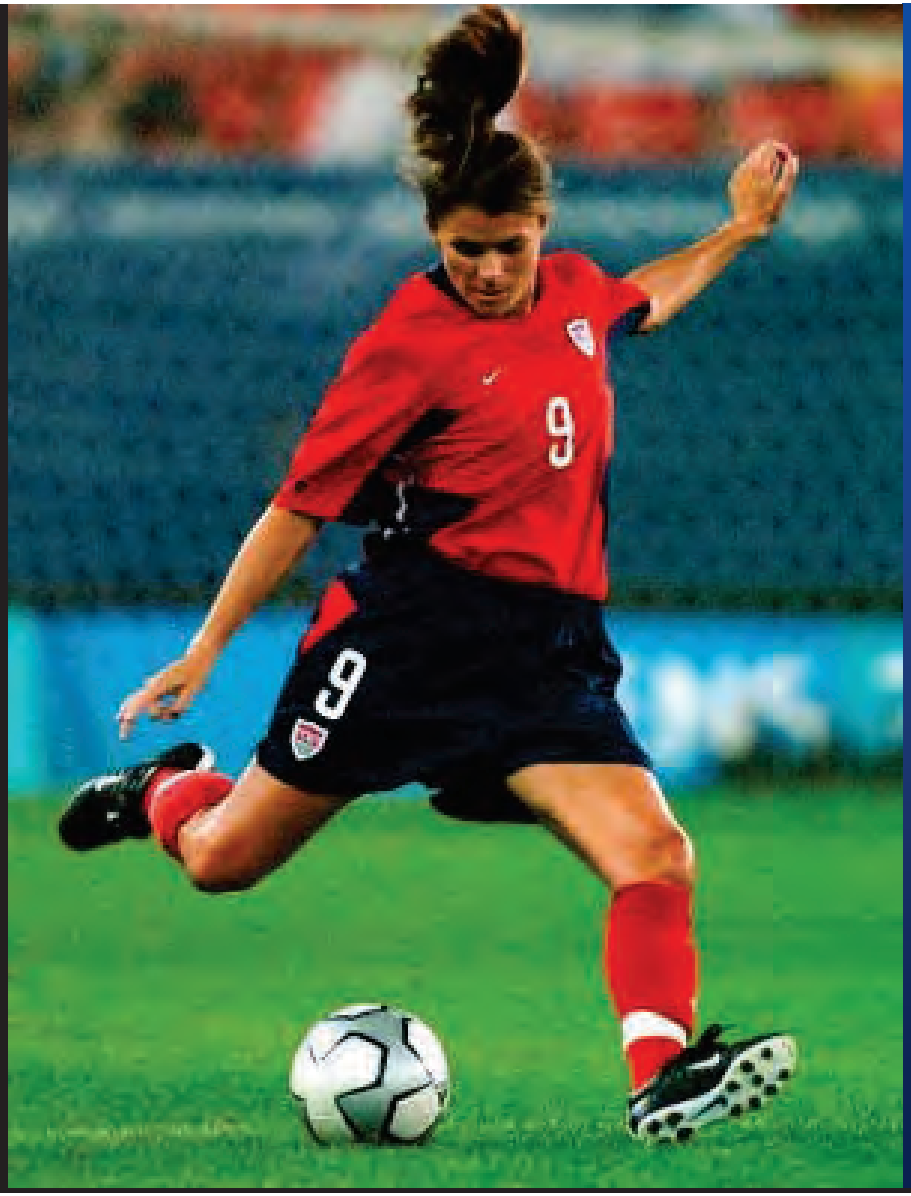
* Maybe it was not a good idea to allow patients to change professionally sourced data.

Intel Digital Health

- **Big Pharma** has an appetite for Intel chips, but not so much for open standards.
- **ISO** thinks it's a good idea to sell standards. So does **IHTSDO**.
  - NLM buys into it.
- **CDISC** convinces (some of) the FDA that it has the solution to bringing clinical data into research. The idea lasts a long time. **Nothing lasts forever**.
- Some vendors thrive trying to connect EHRs that are not interoperable.



Quo vadis?

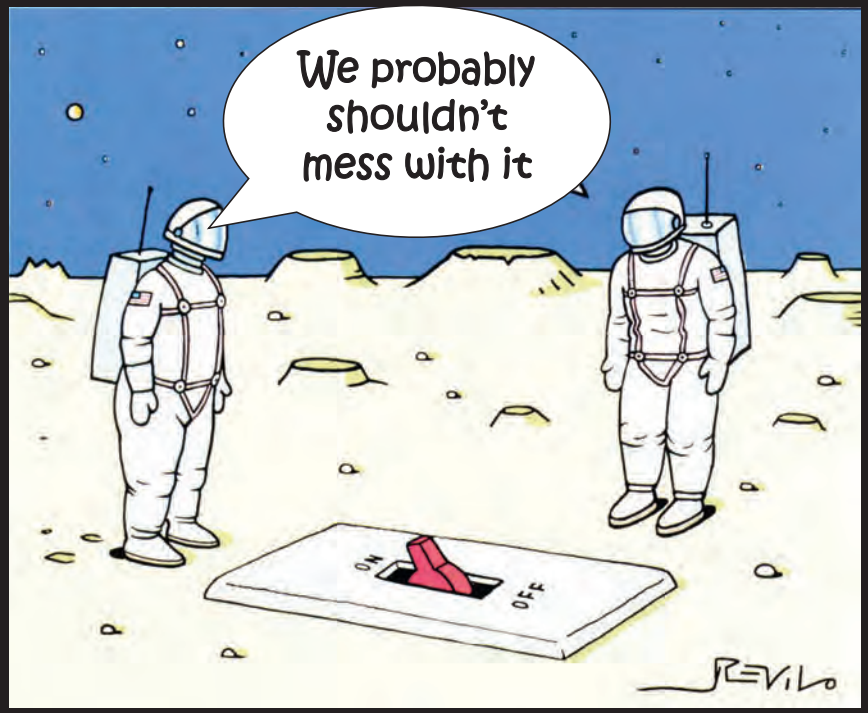


My coach said that I kick like a girl.

I told him that if he tried harder, he could too.

Mia Hamm

Health Level 7: FHIR



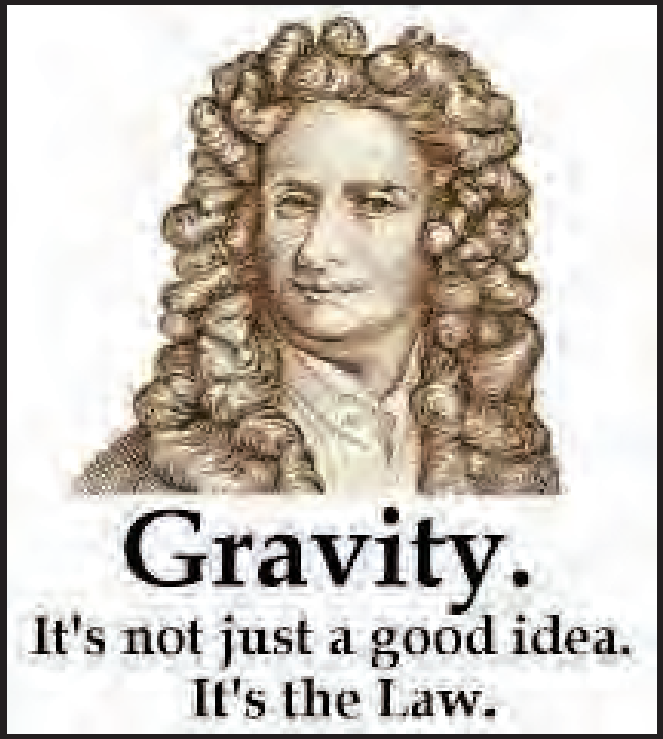
It's all about change management

- ASTM introduces the Continuity of Care Record
  - AAFP threatens to sue HL7 over technical issues.
- 2012: HL7 introduces *FHIR**.
  - *SMART* from Boson Children's adds "identity and authorization"
- *CDA* is reborn as Consolidated-CDA. It's named in Meaningful Use.

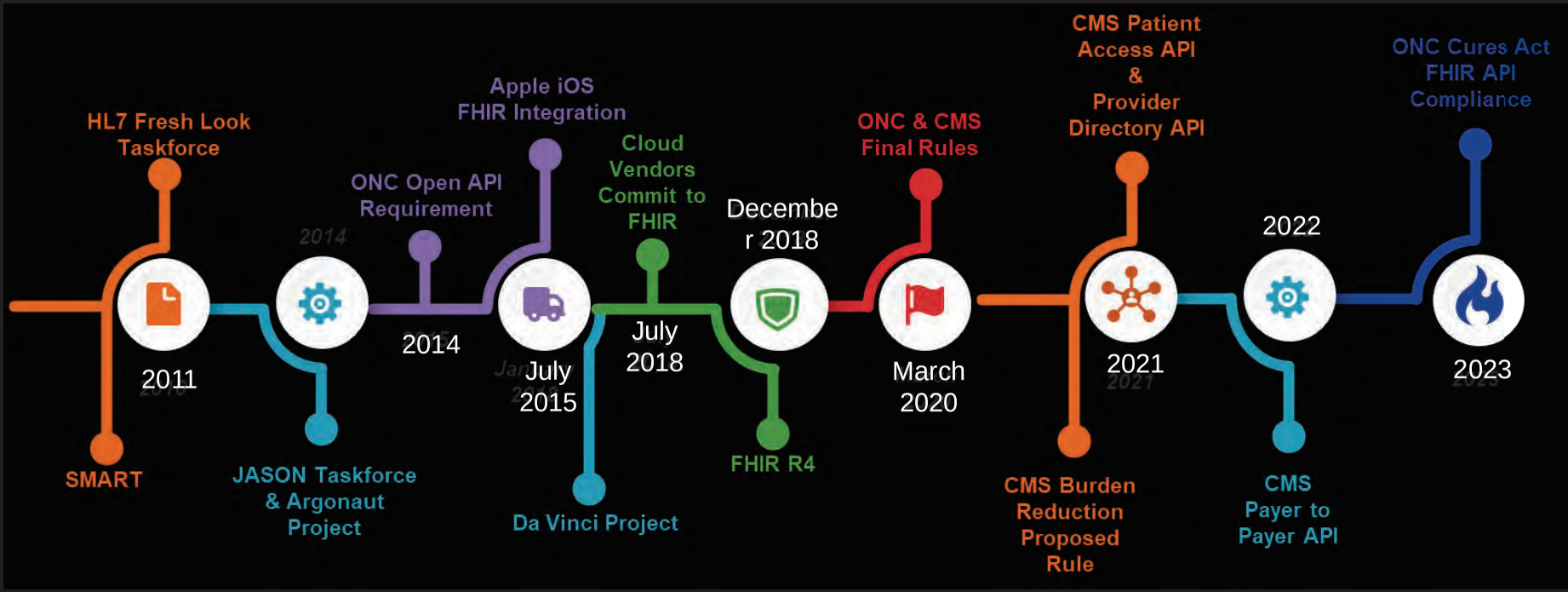
* FHIR is unique. It provides a transport platform and defines the meaning of terms..

Health Level 7: FHIR

- 2013: **HL7 makes all its standards free.**
  - Big Pharma views that as a valid reason to abandon HL7.
  - The rest of the world gets a real opportunity to embrace FHIR.
  - Half of the world's health information is still exchanged with v2.
- 2014: The JASON Task Force identifies open APIs as the future of interoperability.
  - The Argonaut Project is born.



HL7 FHIR: And the rest is history



“If you’re doing something the same
way for ten years,
the chances are you are
doing it wrong.”

Charles Kettering

Health Level 7: AI

HL7 evaluates the ***life-cycle*** of its standards. FHIR is one of them.

2023: After a decade of helping to standardize LLM and machine learning, HL7 commits to supporting AI.

By leveraging a history of standardizing the concept of provenance, HL7 begins an initiative to reduce fraud and abuse.

All in a lifetime

“We cannot solve our problems with
the same thinking we used to create them.”

Albert Einstein

Thank you

cjaffe@HL7.org

UC San Diego
School of Medicine

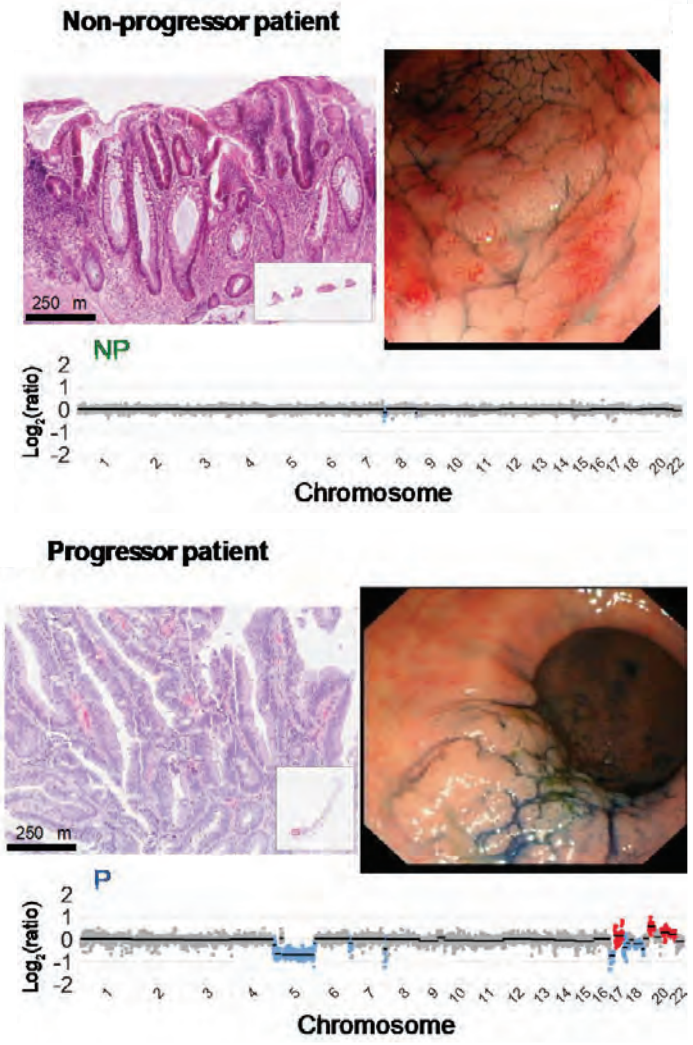
Diving into Genetics, Genomics, and Multimodal Data that Advance Equity through Informatics

Moderators: Kit Curtius, Tiffany Amariuta

Division of Biomedical Informatics

Jan 24, 2025

DBMI 15 year anniversary symposium



Al Bakir & Curtius et al. *Gut* 2025

ABOUT OUR SPEAKERS

Dr. Sandip P Patel

Professor, UCSD
Department of Medicine
Moores Cancer Center

Co-Leader, Experimental Therapeutics
Deputy Director, San Diego Center for Precision Immunotherapy
Director, Clinical Trials Office

Dr. Hannah Carter

Professor, UCSD
Division of Genomics and Precision Medicine
Department of Medicine
Moores Cancer Center

Dr. Amit R Majithia

Associate Professor, UCSD
Division of Endocrinology & Metabolism
Department of Medicine

UC San Diego
School of Medicine

Machine Learning Innovations to Improve Design and Diversity of Oncology Trials

Sandip Patel MD

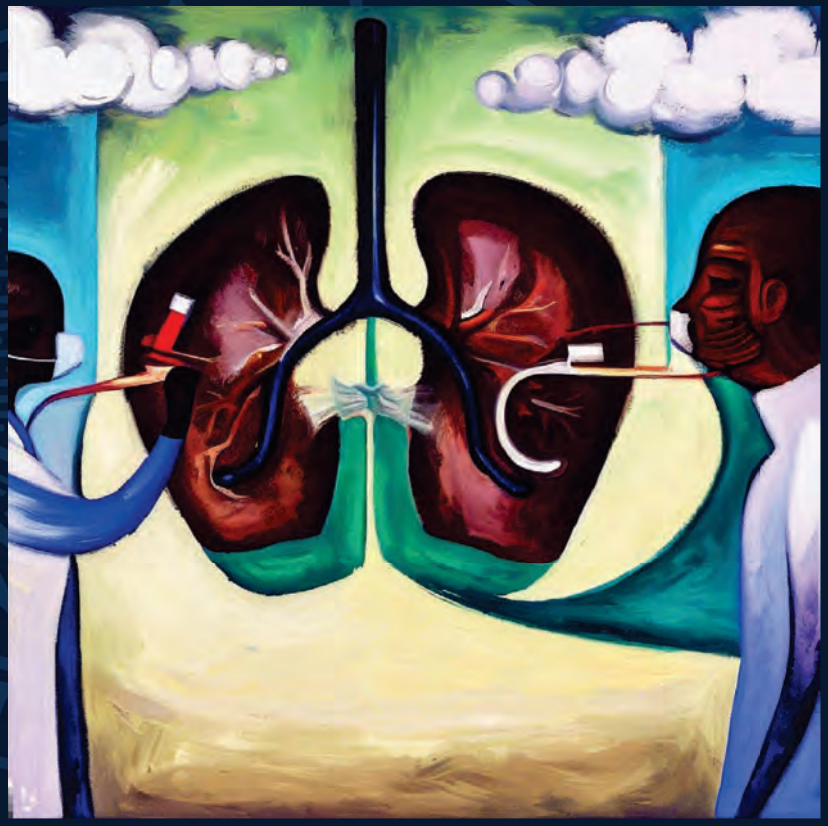
Professor, University of California San Diego

Medical Director, Clinical Research Informatics

Leader, Experimental Therapeutics

Co-Leader, Solid Tumor Therapeutics Program

Deputy Director, Sanford Stem Cell Clinical Center



"painting in the style of Dali 'La persistencia de la memoria' with two lungs being treated with cancer immunotherapy and a doctor and a nurse" image generated by OpenAI's DALL·E 2, March 5, 2023

UC San Diego
MOORES CANCER CENTER

Racial Disparities in NSCLC: Background

- Advanced NSCLC is a heterogeneous disease and national guidelines recommend comprehensive biomarker testing for actionable mutations and PD-L1[1,2]
  - Genomic testing identifies optimal therapy for a given patient and is often required for clinical trial eligibility
  - Receipt of biomarker-driven therapies improves survival[3,4]
- Despite improved outcomes in NSCLC overall, racial disparities in OS persist[5,6]
- Current retrospective analysis investigated racial differences in biomarker testing, use of targeted therapies, and clinical trial enrollment among US patients with advanced or metastatic NSCLC[7]

1. Ettinger. J Natl Compr Canc Netw. 2021;19:254. 2. NCCN Clinical Practice Guidelines in Oncology: NSCLC v.4.2021. nccn.org. 3. Kris. JAMA. 2014;311:1998. 4. Garon. JCO. 2019;37:2518. 5. Howlander. NEJM. 2020;383:640. 6. Blom. Ann Am Thorac Soc. 2020;17:186. 7. Bruno. ASCO 2021. Abstr 9005.

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Racial Disparities in NSCLC: Rates of Biomarker Testing and Receipt of Targeted Therapies

Variable, n (%)	Overall (N = 14,768)				Nonsquamous (n = 10,333)			
	All (N = 14,768)	White (n = 9793)	Black (n = 1288)	P Value*	All (n = 10,333)	White (n = 6705)	Black (n = 922)	P Value*
Biomarker testing								
▪ Ever tested	11,297 (76.5)	7477 (76.4)	948 (73.6)	.03	8786 (85.0)	5699 (85.0)	764 (82.9)	.09
▪ Tested prior to first-line tx	--	6064 (61.9)	784 (60.9)	.47	--	4881 (72.8)	662 (71.8)	.52
▪ Ever NGS tested	7185 (48.7)	4904 (50.1)	513 (39.8)	<.0001	5494 (53.2)	3668 (54.7)	404 (43.8)	<.0001
▪ NGS tested prior to first-line tx	--	3081 (31.5)	332 (25.8)	<.0001	--	2452 (36.6)	274 (29.7)	<.0001
Use of targeted therapy								
▪ During first line	1784 (12.1)	999 (10.2)	118 (9.2)	.24	1703 (16.5)	959 (14.3)	113 (12.3)	.09
▪ During second line	796 (5.4)	456 (4.7)	69 (5.4)	.36	719 (7.0)	416 (6.2)	62 (6.7)	.56
▪ In any line	2328 (15.8)	1323 (13.5)	170 (13.2)	.76	2153 (20.8)	1229 (18.3)	156 (16.9)	.30

- Rate of biomarker testing significantly lower in Black patients vs White patients at any time during their care, even in nonsquamous cohort where testing rate expected to be higher
- Overall rates of targeted therapy use similar between groups, with trend in nonsquamous cohort toward inferior first-line use in Black patients

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Bruno. ASCO 2021. Abstr 9005.

Racial Disparities in NSCLC: Clinical Trial Participation

	Overall (N = 14,768)			Nonsquamous (n = 10,333)		
Analysis Variable	**n**	**Evidence of Clinical Trial Participation,* n (%)**	**P Value**	**n**	**Evidence of Clinical Trial Participation,* n (%)**	**P Value**
All	14,768	484 (3.3)	--	10,333	343 (3.3)	--
By race						
▪ White	9793	385 (3.9)	.0002	6705	261 (3.9)	.006
▪ Black	1288	24 (1.9)	--	922	19 (2.1)	--
By NGS testing						
▪ Ever tested	7185	318 (4.4)	<.0001	5494	236 (4.3)	<.0001
▪ Never tested	7583	166 (2.2)	--	4839	107 (2.2)	--

*In the absence of a specific variable for clinical trial participation in EHR database, evidence of clinical trial participation defined as receiving 1 or more drugs indicated as "clinical trial drug" at any time after diagnosis.

- Rate of clinical trial participation by Black patients one half that of White patients
- Patients who received NGS testing significantly more likely to participate in a clinical trial

Bruno. ASCO 2021. Abstr 9005.

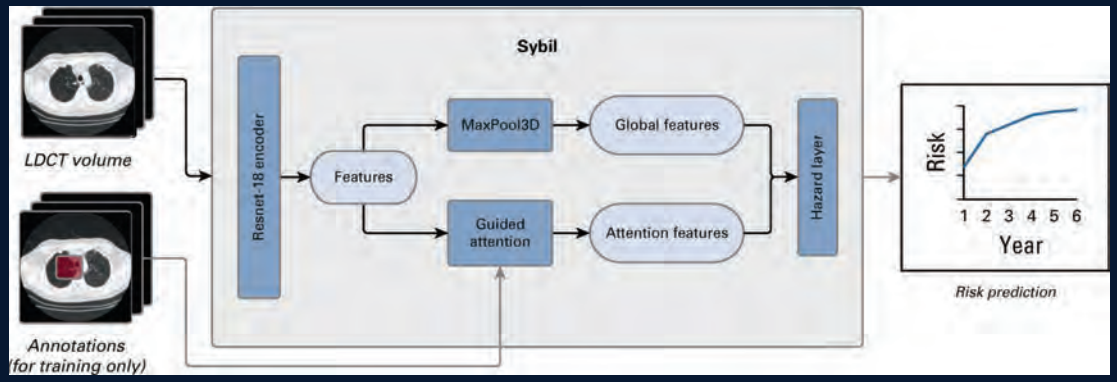
Racial Disparities in NSCLC: Covariates Related to Clinical Trial Participation Among White and Black Patients

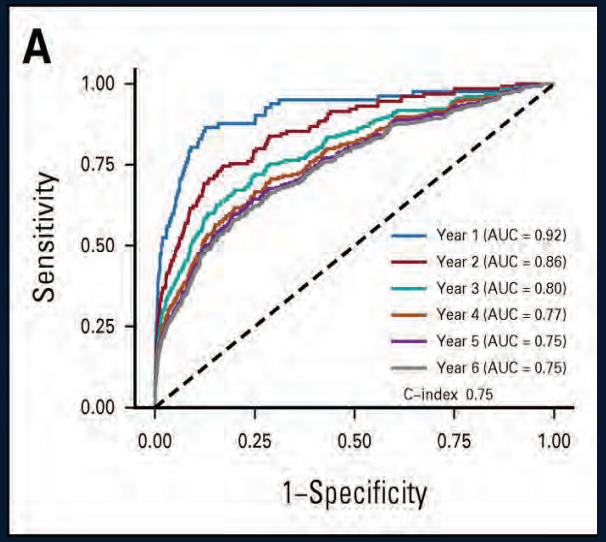
Variable	Odds Ratio (95% CI)	P Value
Biomarker testing prior to first-line therapy (yes vs no)	2.29 (1.64-3.20)	<.0001
Ever NGS tested (yes vs no)	2.41 (1.56-3.70)	<.0001
Race (Black vs White)	0.45 (0.26-0.79)	.005

- In logistic regression, biomarker testing prior to first-line therapy or ever having been NGS tested more than doubled the likelihood of clinical trial participation
- However, Black patients were 55% less likely to participate
- Additional factors associated with clinical trial participation included young age at diagnosis, squamous histology, stage IV disease (vs III), and being treated at a high-volume practice

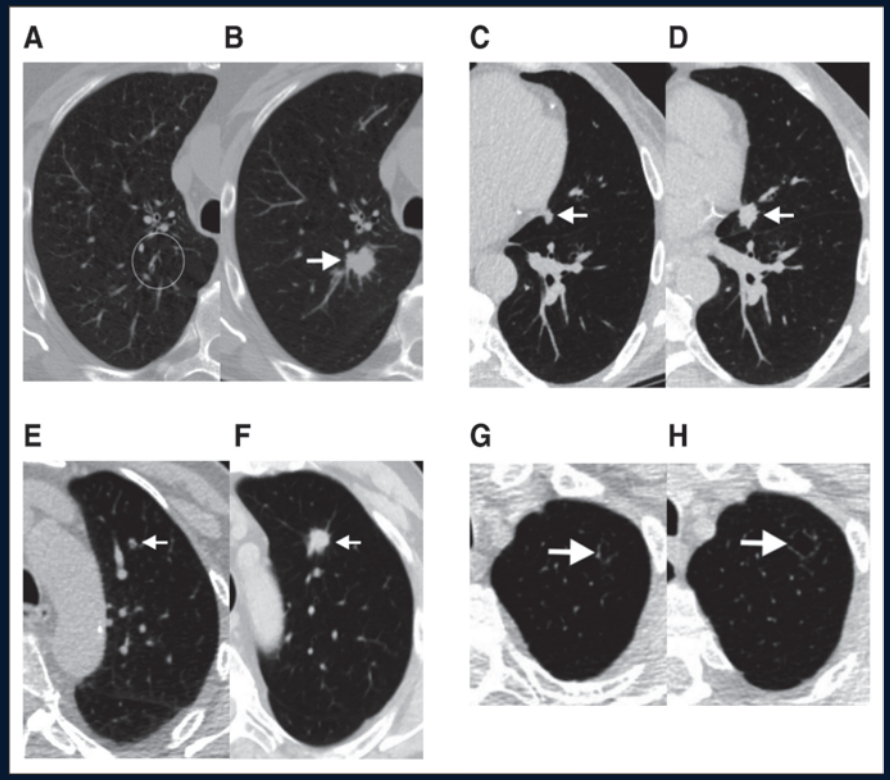
Bruno. ASCO 2021. Abstr 9005.

AI-Assisted LDCT for Lung Cancer Screening





NLST

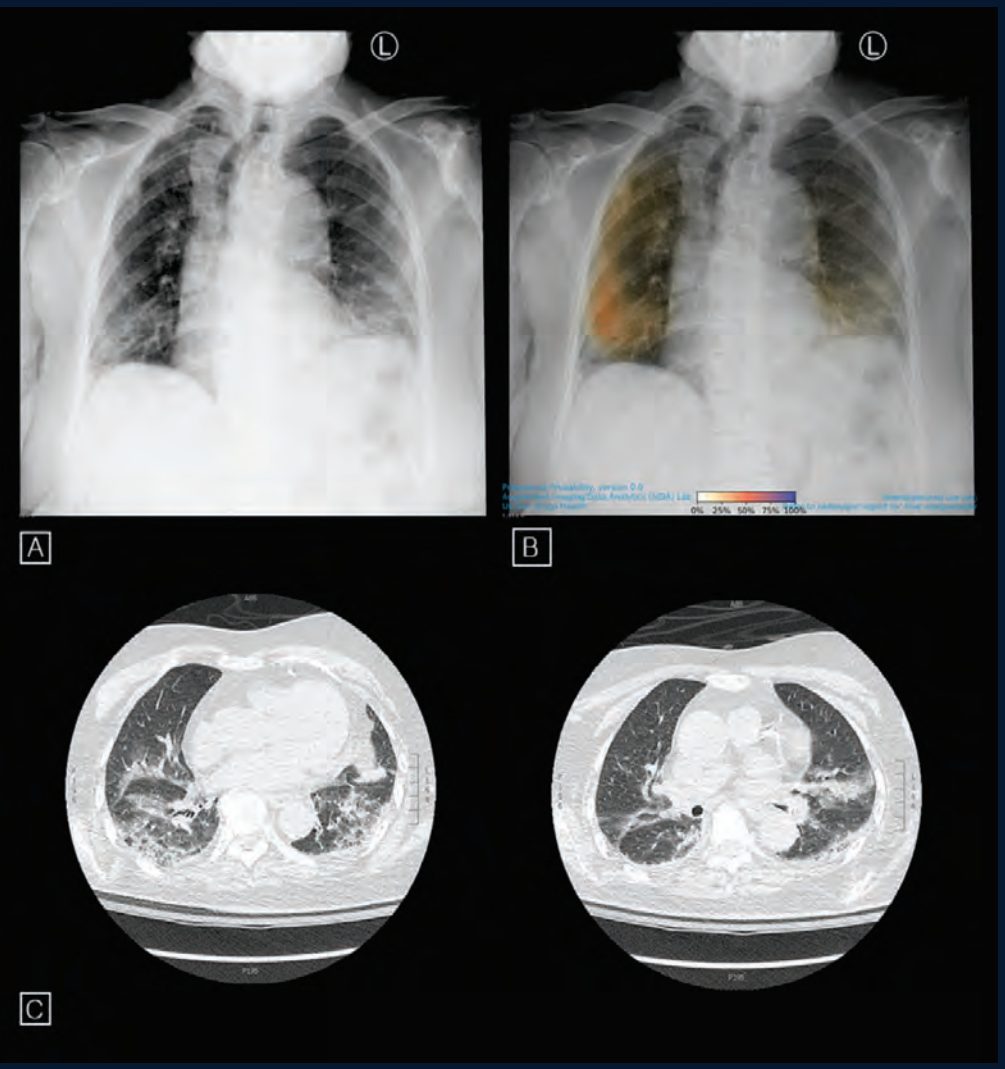


Clinically negative, but Sybil (MGH)+

Mikhael et al. JCO 2023

UC San Diego
Moores Cancer Center

UCSD Deployment of artificial intelligence for radiographic diagnosis of COVID-19 pneumonia in the ER



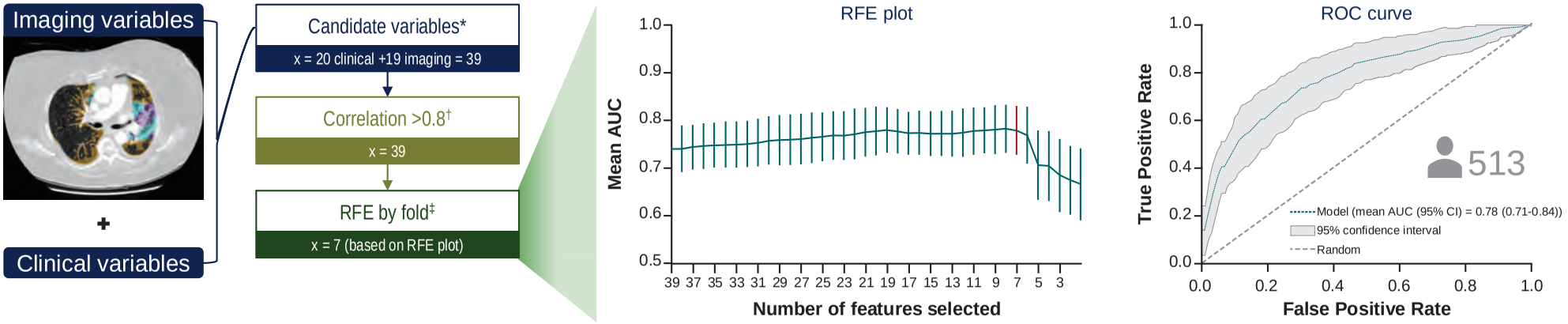
	Question 1: The AI-augmented overlay was easy to use in my existing workflow				
	Strongly agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Strongly disagree
Overall cohort (n = 202)	150 (74%)	28 (14%)	15 (7%)	1 (0%)	8 (4%)
Resident cohort (n = 70)	61 (87%)	6 (9%)	3 (4%)	0 (0%)	0 (0%)
Attending cohort (n = 132)	89 (67%)	22 (17%)	12 (9%)	1 (1%)	8 (6%)

	Question 2: Did the AI-augmented overlay contribute to your medical decisionmaking?	
	Yes	No
Overall cohort (n = 202)	41 (20%)	161 (80%)
Resident cohort (n = 70)	18 (26%)	52 (74%)
Attending cohort (n = 132)	23 (17%)	109 (83%)

Carlile et al. JACEP Open 2020

UC San Diego
MOORES CANCER CENTER

Radiomic prediction of pneumonitis: AI model trained on imaging and clinical data improved predictiveness



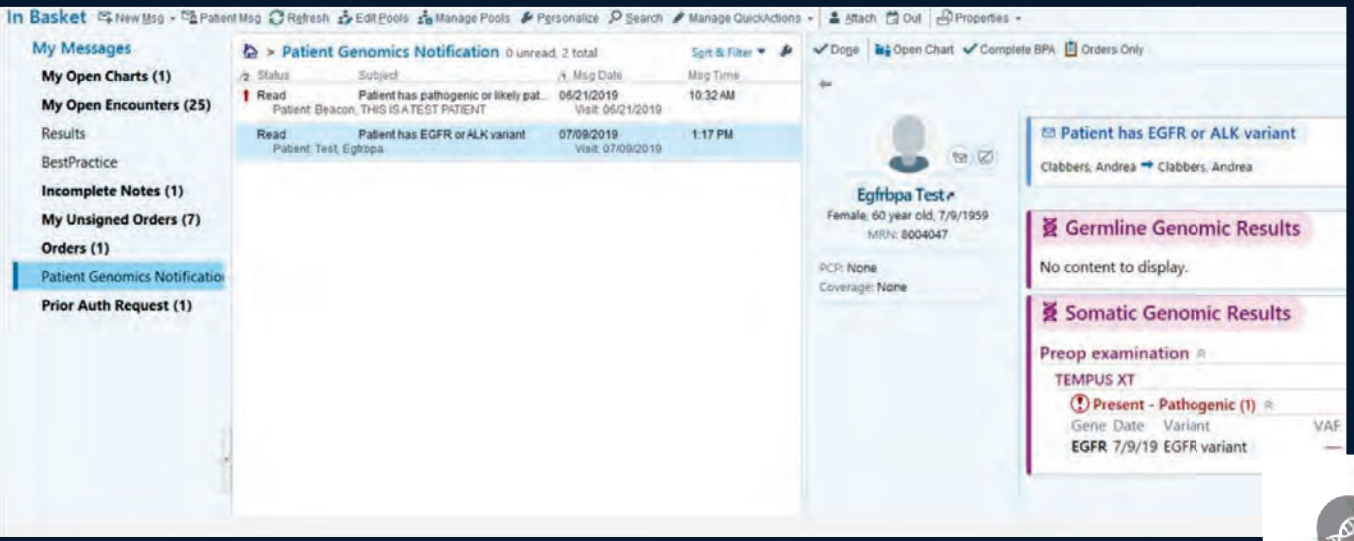
Discriminative power: AUC (95% CI) = 0.78 (0.71–0.84) PPV§ (95% CI) = 0.46 (0.35–0.56) NPV§ (95% CI) = 0.93 (0.90–0.96)

Variables included in the AI model after RFE		
Model feature	OR‡	95% CI‡
Asian race	3.35	2.78–3.91
Neutrophil count	2.02	1.87–2.17
Reticulation volume/TLC	1.90	1.71–2.08
Stage IIIA disease	1.69	1.41–1.96
Etoposide treatment	1.68	1.33–2.03
Treatment arm = durvalumab	1.58	1.31–1.85
Male gender	0.46	0.39–0.53

BARCELONA 2024 ESMO congress

Courtesy: Dr. Naidoo

A path forward: Having the EMR work for you

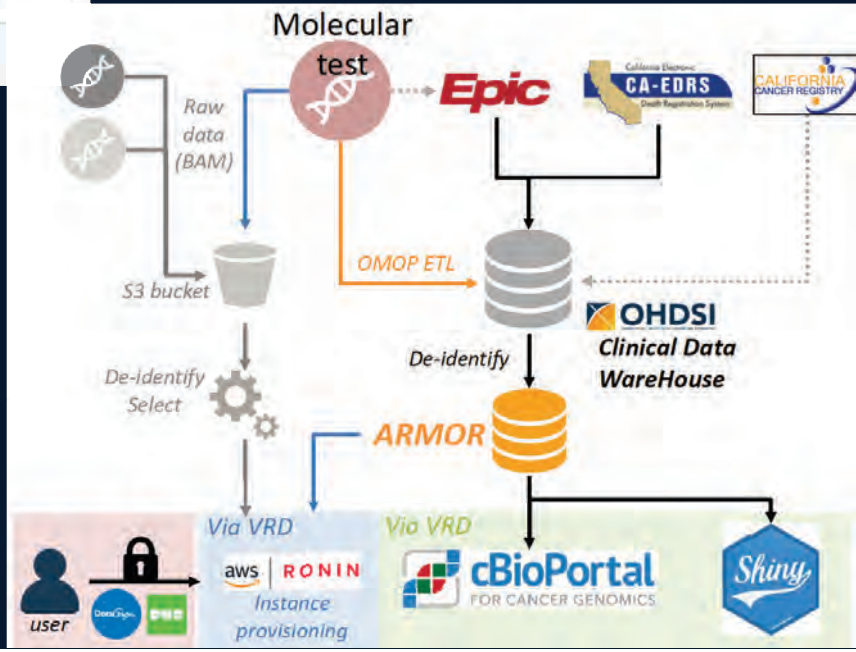


Discrete genomics allows for triggering of EMR alerts

- Screening for molecularly-guided clinical trials
- Pharmacogenomics for toxicity

Parallel raw data allows for translational research

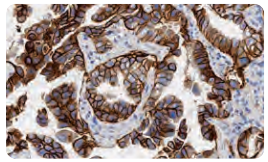
- University of California system-wide molecular database
- Pan-UC



TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

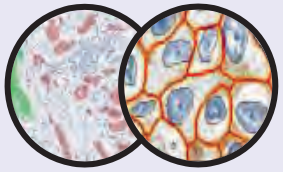
QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay



2 Whole Slide Imaging

3 Automated Image Analysis (QCS)

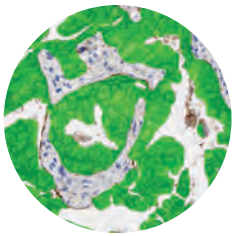


4 Patient Biomarker Status Determination

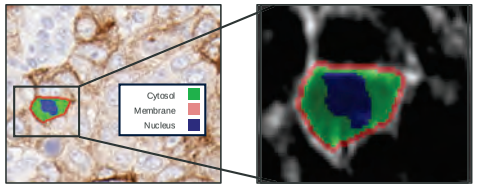
\+ ≥75% of tumor cells with TROP2 NMR ≤0.56

\- <75% of tumor cells with TROP2 NMR ≤0.56*

Differentiates tumor from non-tumor



Measures OD in each tumor cell



Membrane and cytoplasm optical density (OD)

Calculates TROP2 NMR for every tumor cell

$$\frac{\text{Membrane OD}}{\text{Membrane OD + Cytoplasm OD}}$$

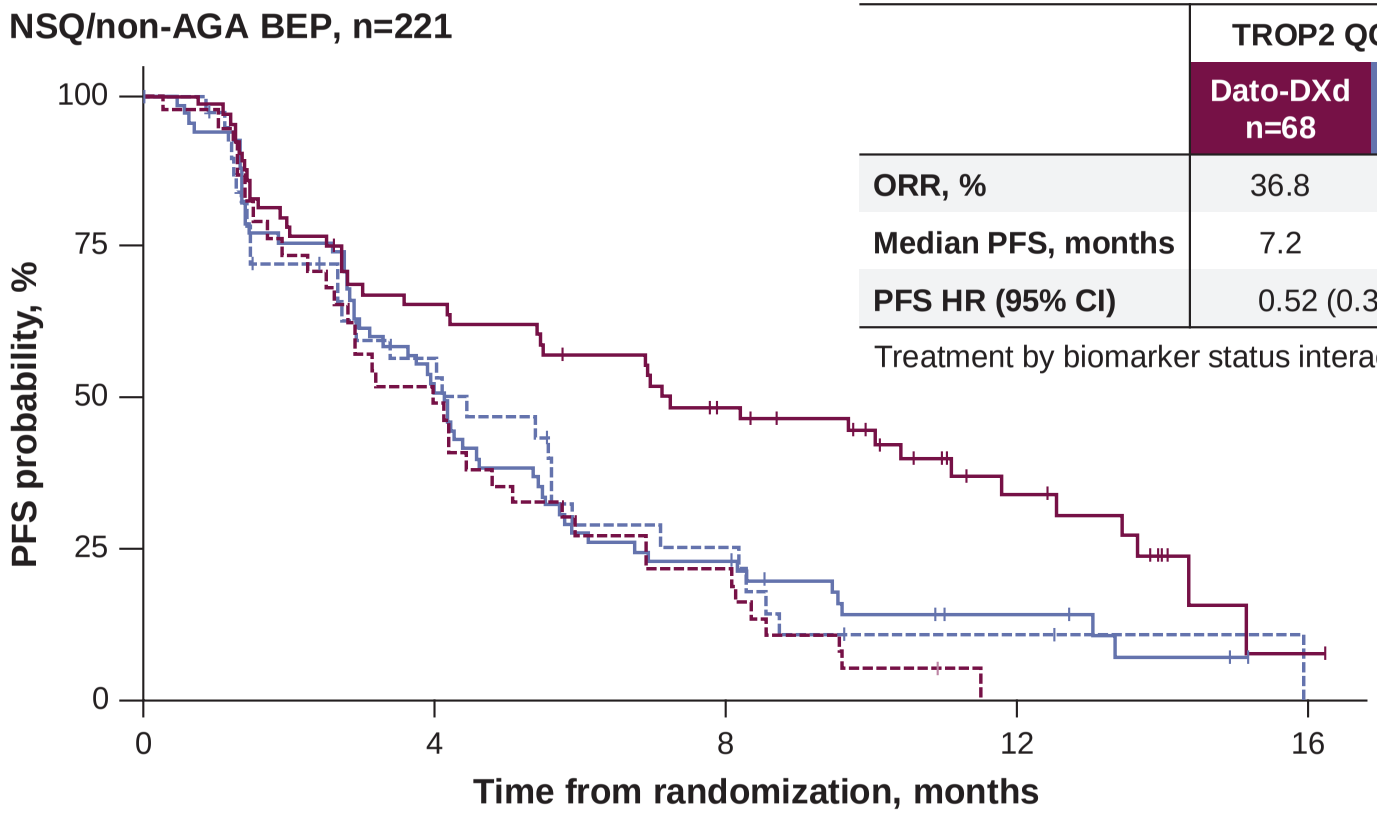
Lower NMR → higher cytoplasm proportion

Courtesy: Dr Garassino

*Or >25% of cells with an NMR >0.56

NSQ/non-AGA BEP: Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the NSQ/non-AGA biomarker-evaluable population



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=68	Docetaxel n=72	Dato-DXd n=40	Docetaxel n=41
ORR, %	36.8	15.3	22.5	12.2
Median PFS, months	7.2	4.1	4.0	4.4
PFS HR (95% CI)	0.52 (0.35–0.78)		1.22 (0.74–2.00)	

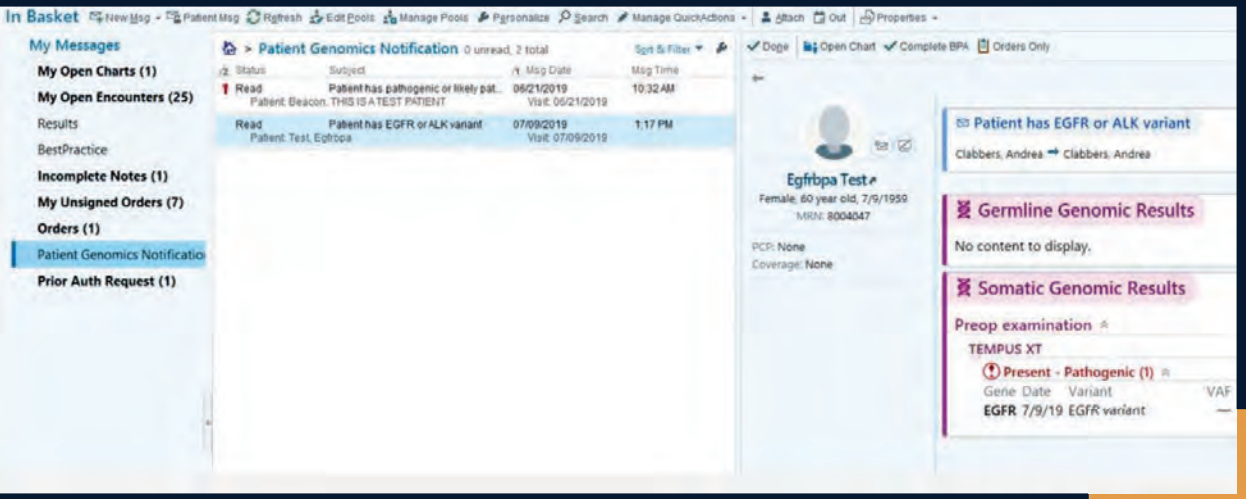
Treatment by biomarker status interaction: p=0.0098

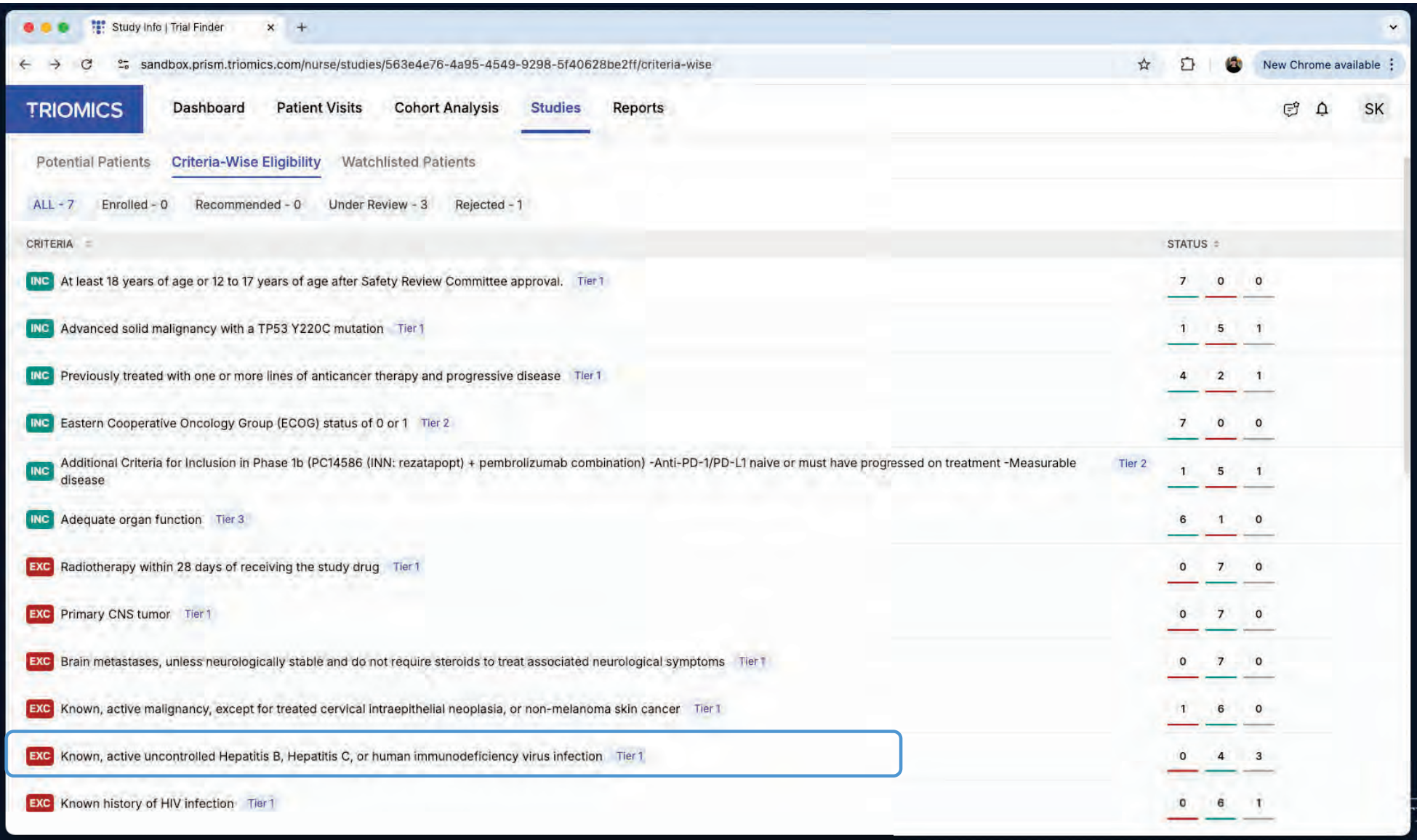
Dr Marina Chiara Garassino | Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is Predictive of Clinical Outcomes in TROPION-Lung01

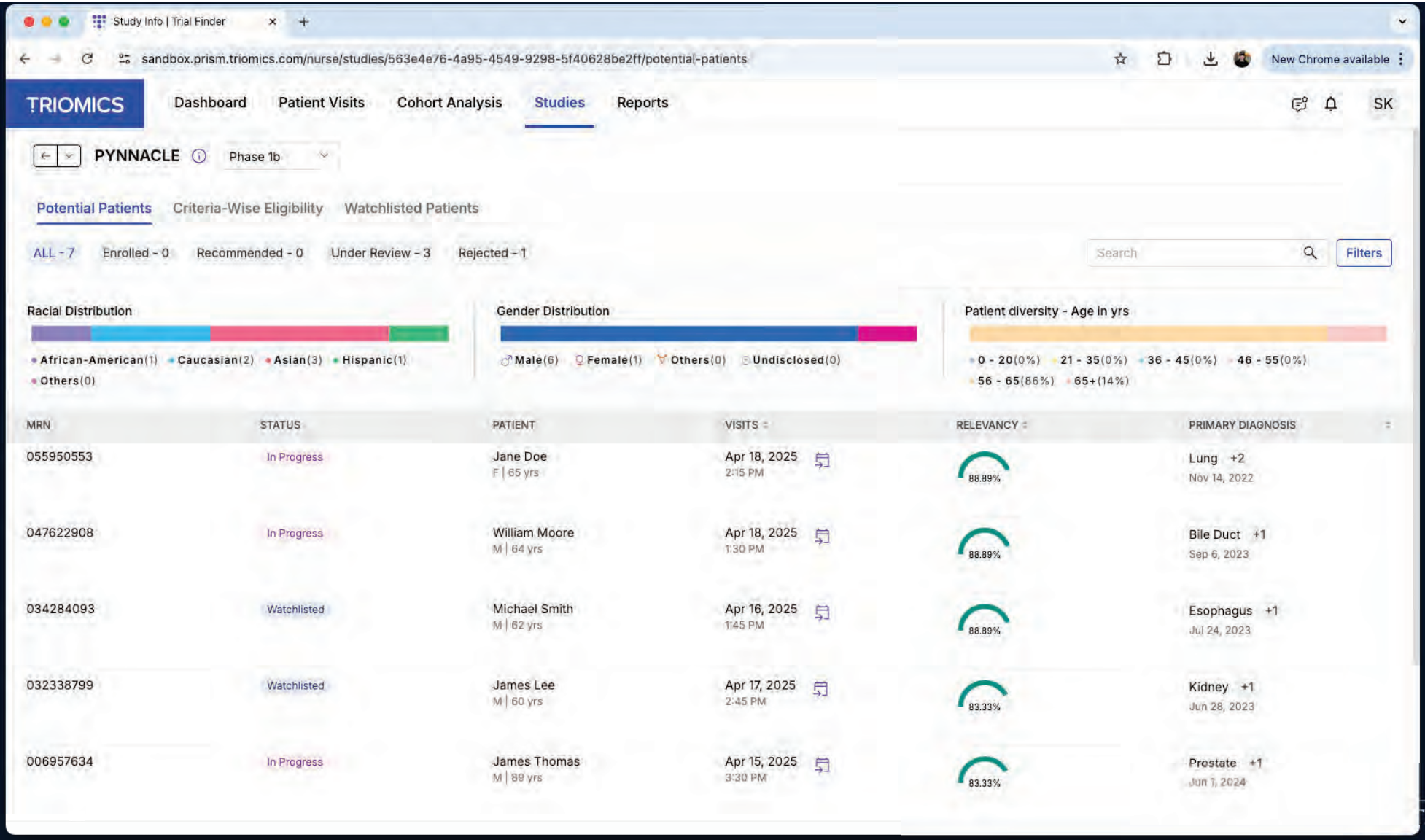
Data cutoff: March 29 2023

PFS HR (95% CI) by TROP2 QCS-NMR status (+ vs -) within treatment: Dato-DXd: 0.40 [0.25-0.64]; Docetaxel:0.94 [0.60-1.49]

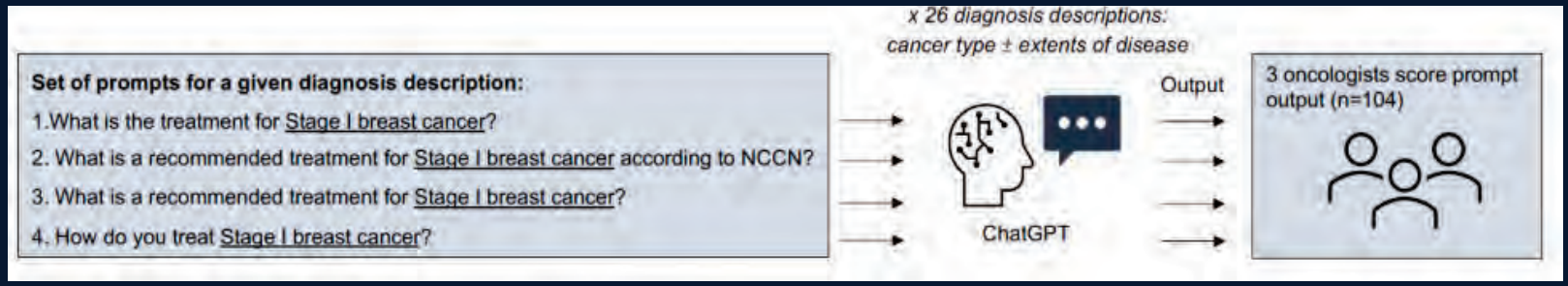
Genomics, Clinical Trials, and AI-assisted matching




Study Info | Trial Finder
sandbox.prism.triomics.com/nurse/studies/563e4e76-4a95-4549-9298-5f40628be2ff/criteria-wise
New Chrome available
TRIOMICS
Dashboard
Patient Visits
Cohort Analysis
Studies
Reports
SK
Potential Patients
Criteria-Wise Eligibility
Watchlisted Patients
ALL - 7
Enrolled - 0
Recommended - 0
Under Review - 3
Rejected - 1
CRITERIA
STATUS
INC At least 18 years of age or 12 to 17 years of age after Safety Review Committee approval. Tier 1 7 0 0
INC Advanced solid malignancy with a TP53 Y220C mutation Tier 1 1 5 1
INC Previously treated with one or more lines of anticancer therapy and progressive disease Tier 1 4 2 1
INC Eastern Cooperative Oncology Group (ECOG) status of 0 or 1 Tier 2 7 0 0
INC Additional Criteria for Inclusion in Phase 1b (PC14586 (INN: rezatapopt) + pembrolizumab combination) -Anti-PD-1/PD-L1 naive or must have progressed on treatment -Measurable disease Tier 2 1 5 1
INC Adequate organ function Tier 3 6 1 0
EXC Radiotherapy within 28 days of receiving the study drug Tier 1 0 7 0
EXC Primary CNS tumor Tier 1 0 7 0
EXC Brain metastases, unless neurologically stable and do not require steroids to treat associated neurological symptoms Tier 1 0 7 0
EXC Known, active malignancy, except for treated cervical intraepithelial neoplasia, or non-melanoma skin cancer Tier 1 1 6 0
EXC Known, active uncontrolled Hepatitis B, Hepatitis C, or human immunodeficiency virus infection Tier 1 0 4 3
EXC Known history of HIV infection Tier 1 0 6 1


Study Info | Trial Finder
sandbox.prism.triomics.com/nurse/studies/563e4e76-4a95-4549-9298-5f40628be2ff/potential-patients
New Chrome available
TRIOMICS
Dashboard
Patient Visits
Cohort Analysis
Studies
Reports
SK
PYNNACLE
Phase 1b
Potential Patients
Criteria-Wise Eligibility
Watchlisted Patients
ALL - 7
Enrolled - 0
Recommended - 0
Under Review - 3
Rejected - 1
Search
Filters
Racial Distribution
African-American(1) Caucasian(2) Asian(3) Hispanic(1)
Others(0)
Gender Distribution
Male(6) Female(1) Others(0) Undisclosed(0)
Patient diversity - Age in yrs
0 - 20(0%) 21 - 35(0%) 36 - 45(0%) 46 - 55(0%)
56 - 65(86%) 65+(14%)
MRN
STATUS
PATIENT
VISITS
RELEVANCY
PRIMARY DIAGNOSIS
055950553
In Progress
Jane Doe
F | 65 yrs
Apr 18, 2025
2:15 PM
88.89%
Lung +2
Nov 14, 2022
047622908
In Progress
William Moore
M | 64 yrs
Apr 18, 2025
1:30 PM
88.89%
Bile Duct +1
Sep 6, 2023
034284093
Watchlisted
Michael Smith
M | 62 yrs
Apr 16, 2025
1:45 PM
88.89%
Esophagus +1
Jul 24, 2023
032338799
Watchlisted
James Lee
M | 60 yrs
Apr 17, 2025
2:45 PM
83.33%
Kidney +1
Jun 28, 2023
006957634
In Progress
James Thomas
M | 89 yrs
Apr 15, 2025
3:30 PM
83.33%
Prostate +1
Jun 1, 2024

LLM Only Concordant with NCCN Guidelines Only 1/3 The Time



"All outputs with a recommendation included at least 1 NCCN-concordant treatment, but 35 of 102 (34.3%) of these outputs also recommended 1 or more nonconcordant treatments.

Responses were hallucinated (ie, were not part of any recommended treatment) in 13 of 104 (12.5%) outputs. Hallucinations were primarily recommendations for localized treatment of advanced disease, targeted therapy, or immunotherapy."

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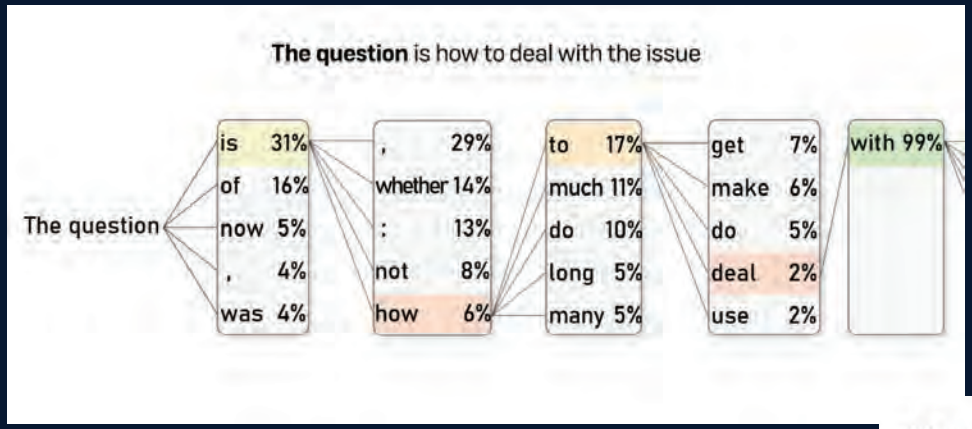
Chen S et al. JAMA Oncology 2023

Language Modeling Errors



How many feet fit in a shoe?

A shoe usually holds two feet, but it depends on the shoe. Some shoes hold up to four feet.

How = 12.38%
A = 5.04%
The = 3.68%
What = 3.40%
I = 2.96%
One = 2.14%
There = 2.09%
If = 1.85%
It = 1.65%
This = 1.42%

Answer the question:

Question: How many feet fit in a shoe?

Answer: One.

One = 8.76%
A = 6.26%
Dep = 4.62%
The = 4.17%
It = 3.24%
Two = 2.85%
If = 2.72%
I = 2.50%
None = 2.07%
10 = 1.93%

Sobieszek et al MM 2022

Summary

- Artificial intelligence is a tool that can augment human intelligence
  - Current “AI” systems are large language models – statistical language autocomplete

- Potential for AI to augment medical tasks
  - Image detection/toxicity interception (pneumonitis prediction)
  - Biomarker discovery and pathologic diagnosis (ADC efficacy prediction)
  - Clinical support
  - Clinical research support

- Important to have representative models that include patients from population that model will be applied to

- Human interventions with AI-assistance most likely to be effective

Questions?

Sandip Patel, MD

Email: patel@ucsd.edu

Bluesky/Twitter/Threads: @PatelOncology

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Precision Immuno-oncology: Uncovering the genomic determinants of immunotherapy response

Hannah Carter, PhD

Professor of Medicine, UCSD

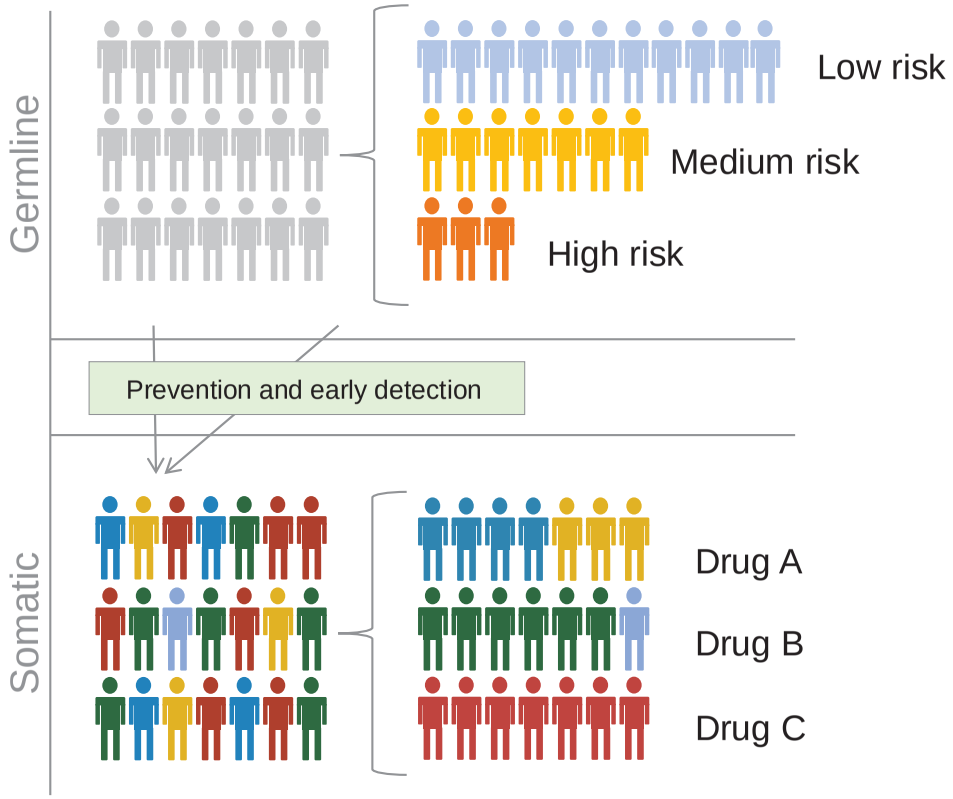
January 24th, 2025

NCI Designated Comprehensive Cancer Center

UC San Diego Moores Cancer Center

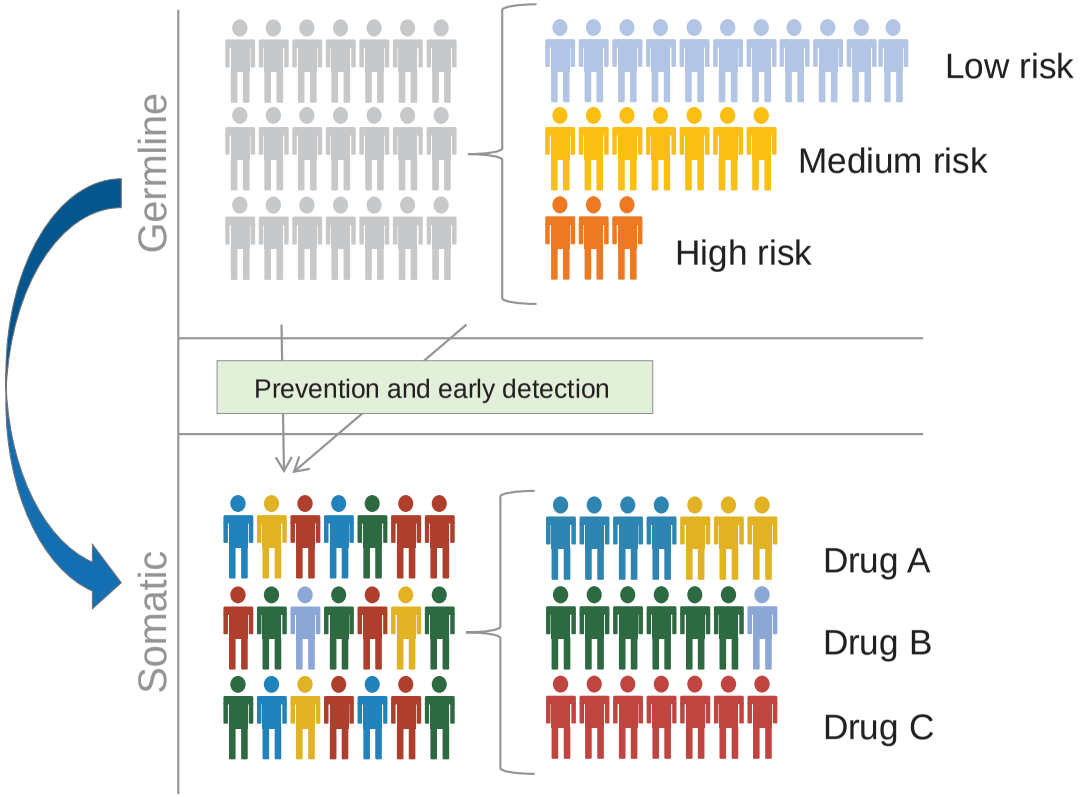
Precision Cancer Medicine

- Identify individuals at risk
- Preventative measures and screening for early detection
- Patient stratification for prognostic or treatment purposes

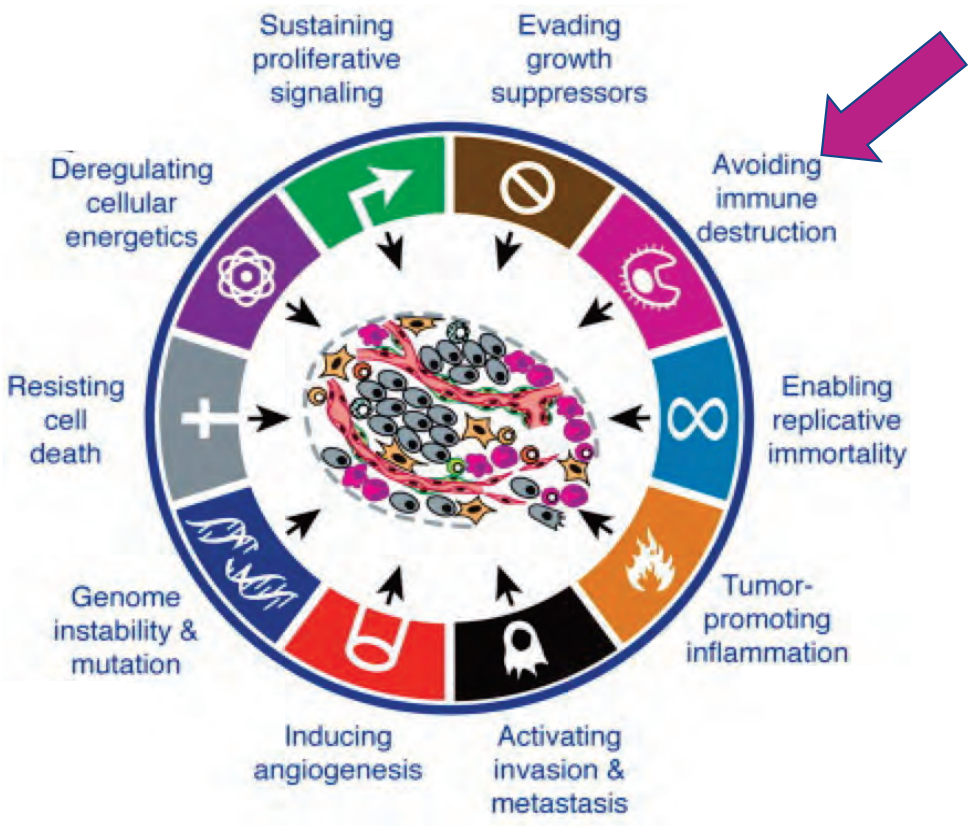


Precision Cancer Medicine

- Identify individuals at risk
- Preventative measures and screening for early detection
- Patient stratification for prognostic or treatment purposes

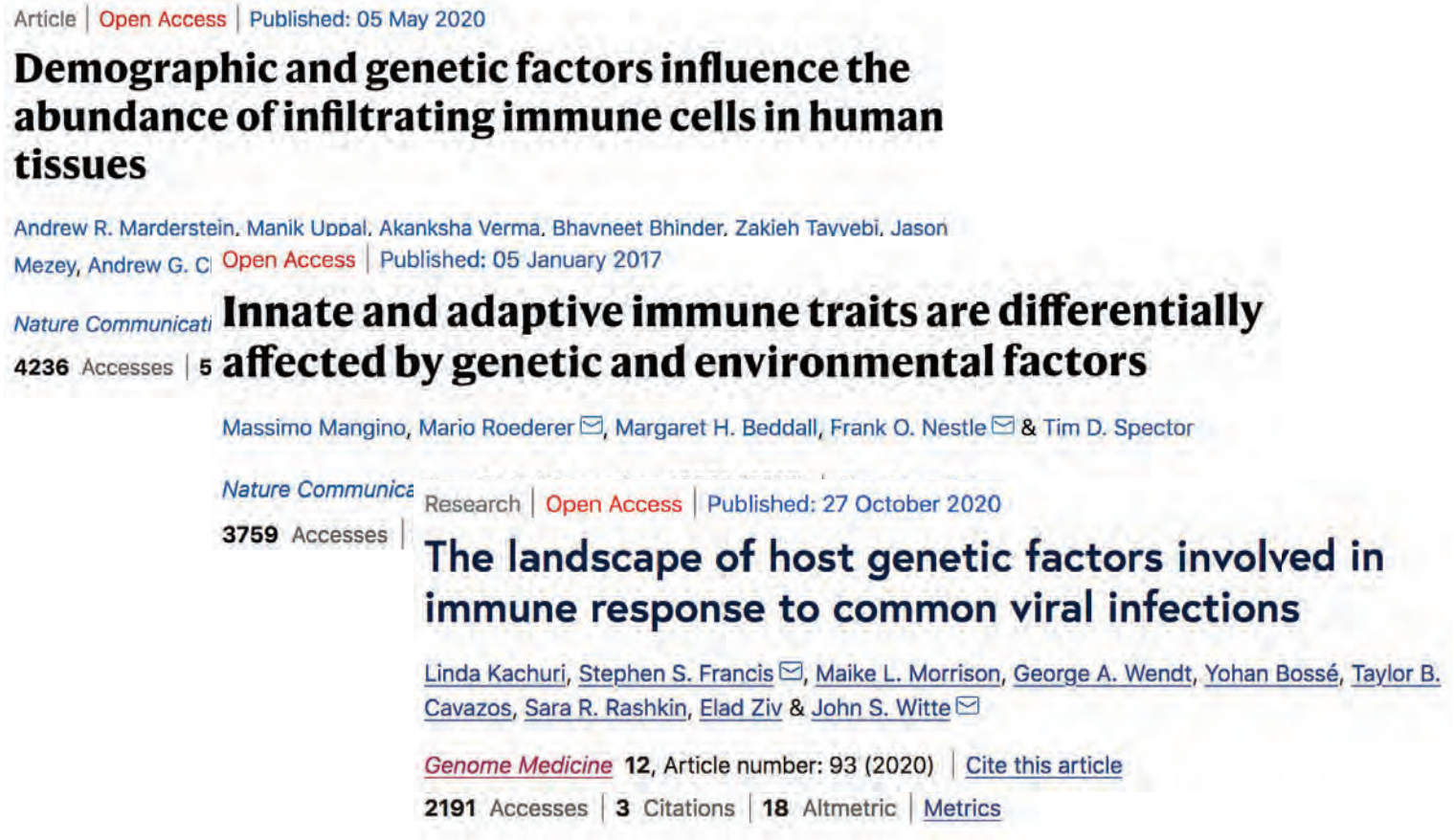


Neoplastic behaviors implicate selective pressure acting on cancer cells



Hanahan, Weinberg **Hallmarks of Cancer: The Next Generation** Cell Volume 144, Issue 5, 2011, 646 – 674

Germline influence on immunity



Article | Open Access | Published: 05 May 2020

Demographic and genetic factors influence the abundance of infiltrating immune cells in human tissues

Andrew R. Marderstein, Manik Uppal, Akanksha Verma, Bhavneet Bhinder, Zakieh Tayyebi, Jason Mezey, Andrew G. C

Open Access | Published: 05 January 2017

Nature Communicati

4236 Accesses | 5

Innate and adaptive immune traits are differentially affected by genetic and environmental factors

Massimo Mangino, Mario Roederer, Margaret H. Beddall, Frank O. Nestle & Tim D. Spector

Nature Communica

3759 Accesses |

Research | Open Access | Published: 27 October 2020

The landscape of host genetic factors involved in immune response to common viral infections

Linda Kachuri, Stephen S. Francis, Maike L. Morrison, George A. Wendt, Yohan Bossé, Taylor B. Cavazos, Sara R. Rashkin, Elad Ziv & John S. Witte

Genome Medicine **12**, Article number: 93 (2020) | Cite this article

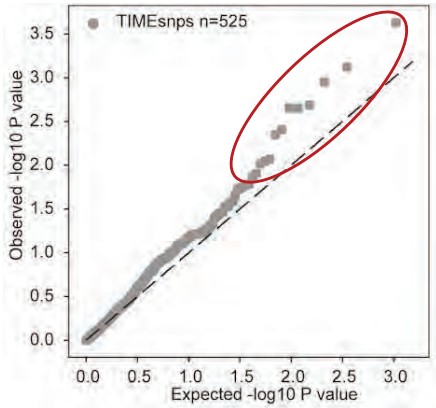
2191 Accesses | **3** Citations | **18** Altmetric | Metrics

Immune eQTL SNPs in immunotherapy response

TIME SNPs imputed from exome sequencing data for 6 published cohorts treated with ICB

Dataset	Cancer	Female/Male/?	# of individuals	RNA Available
Hugo et al	**Melanoma**	**11/27/-**	**38**	**27**
Van Allen et al.	**Melanoma**	**32/78/-**	**110**	**40**
Miao et al.	RCC	24/44/2	70	33
Riaz et al.	**Melanoma**	**31/37/-**	**68**	**92**
Rizvi et al.	NSCLC	18/26/-	34	0
Snyder et al.	**Melanoma**	**25/39/-**	**64**	**0**

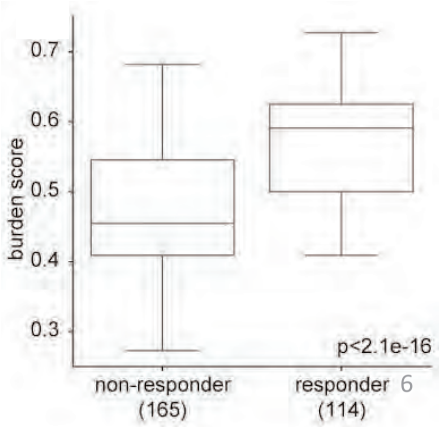
1084 germline variants → >0.01 MAF in all 6 studies → 525 germline variants



METAL
Meta-analysis

Some immune eQTLs are nominally associated with ICI response

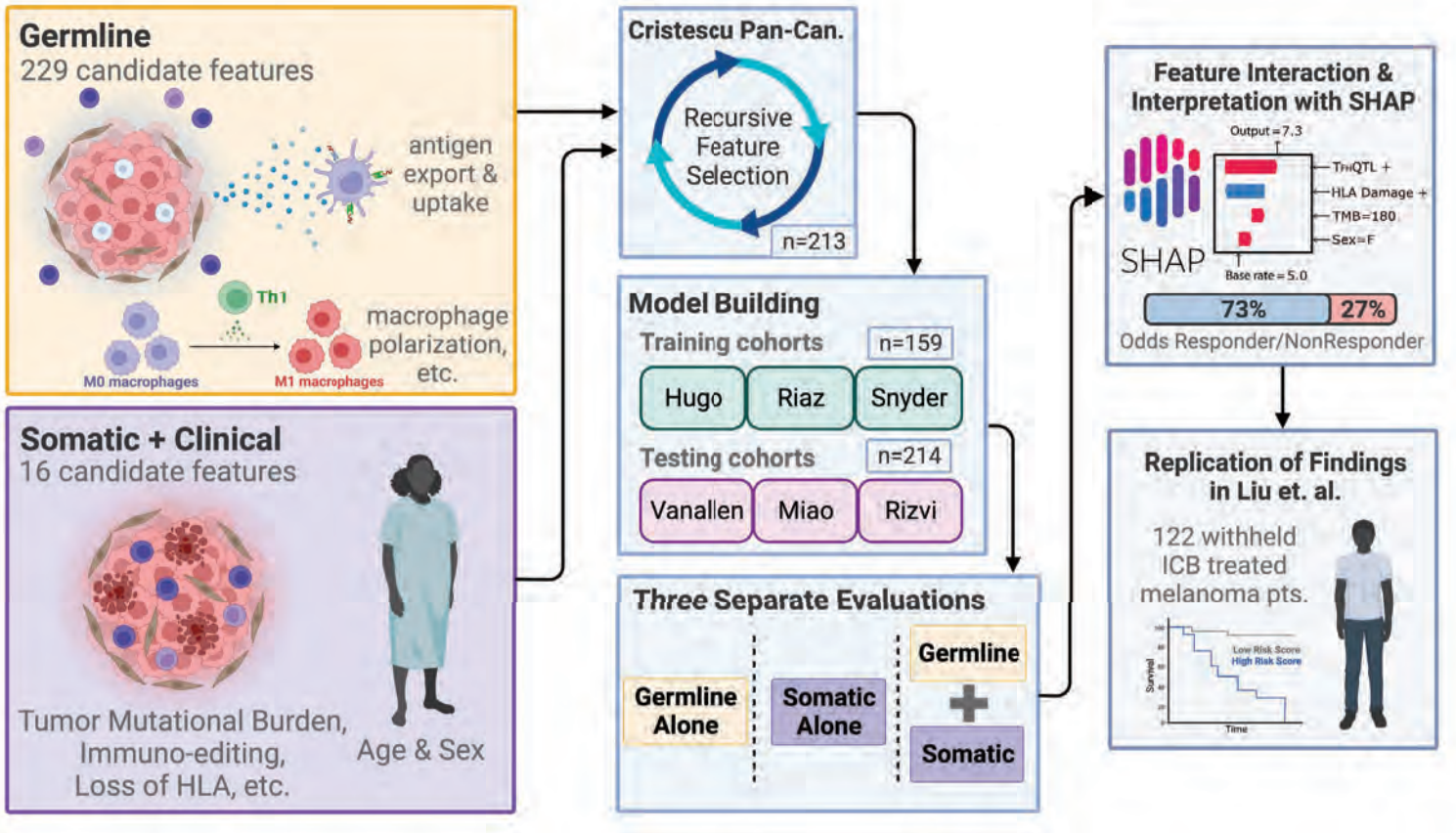
Responders tend to have more response alleles
-> Polygenic Scores could work



Pagadala *et al Nat Comm 2023*

Combining germline and somatic features

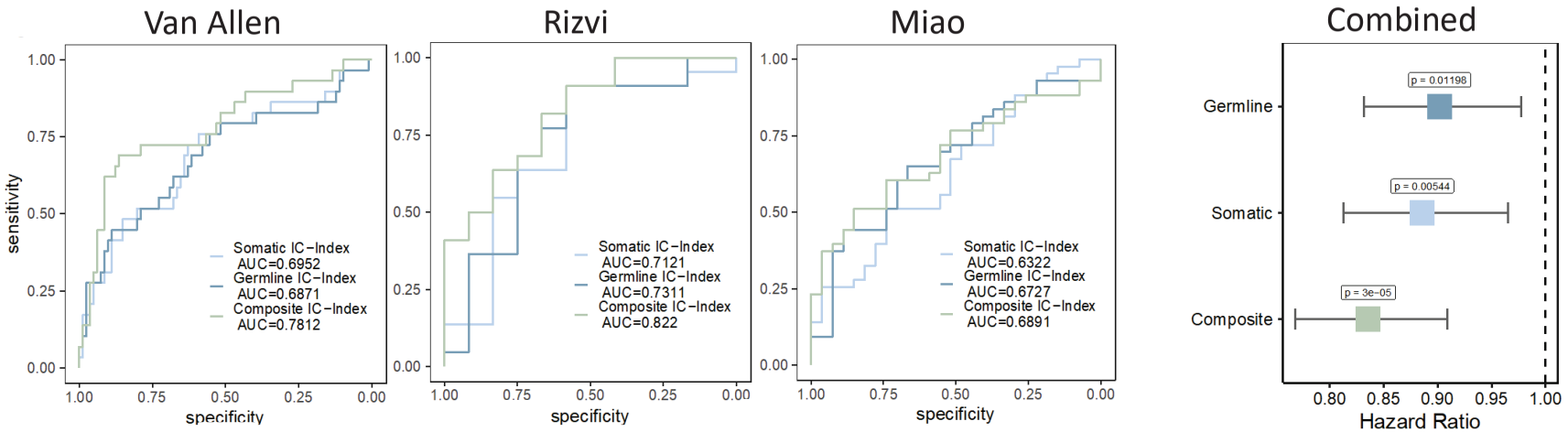
DNA based features



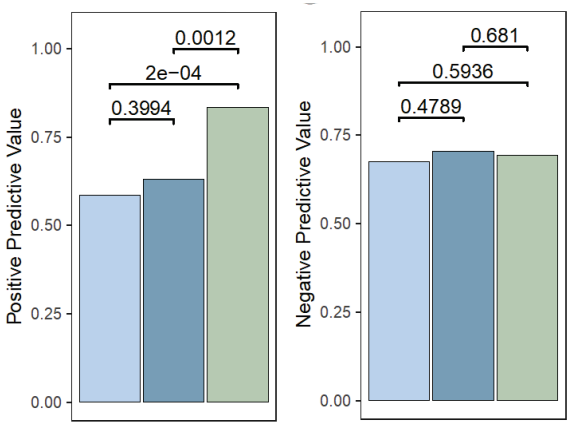
TJ Sears

Sears *et al, in press at Cancer Immunology Research*

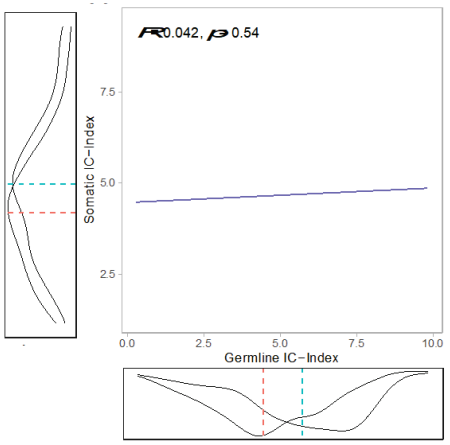
Using both germline and somatic features boosts performance



Composite score has higher PPV



Predictions based on germline and somatic features separately are uncorrelated



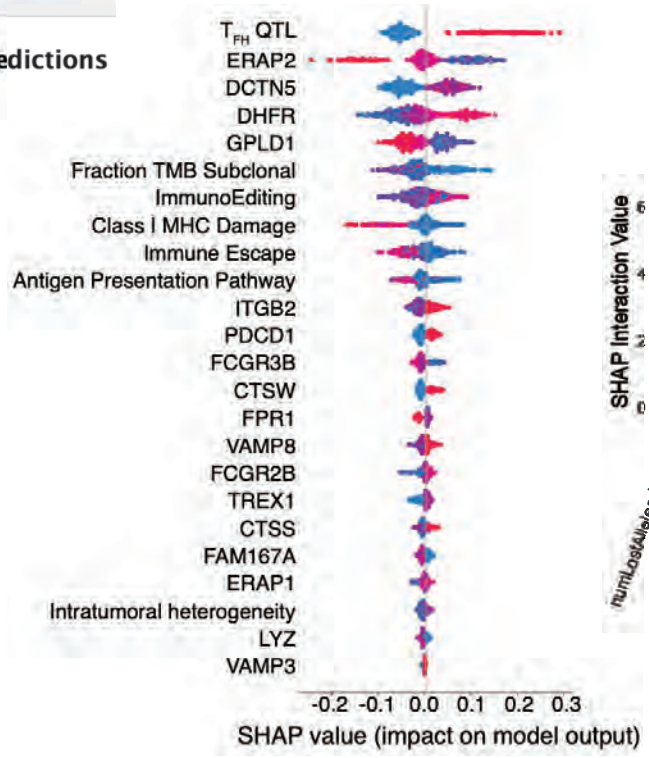
Sears *et al, in press at Cancer Immunology Research*

Non-linear polygenic models implicate interactions

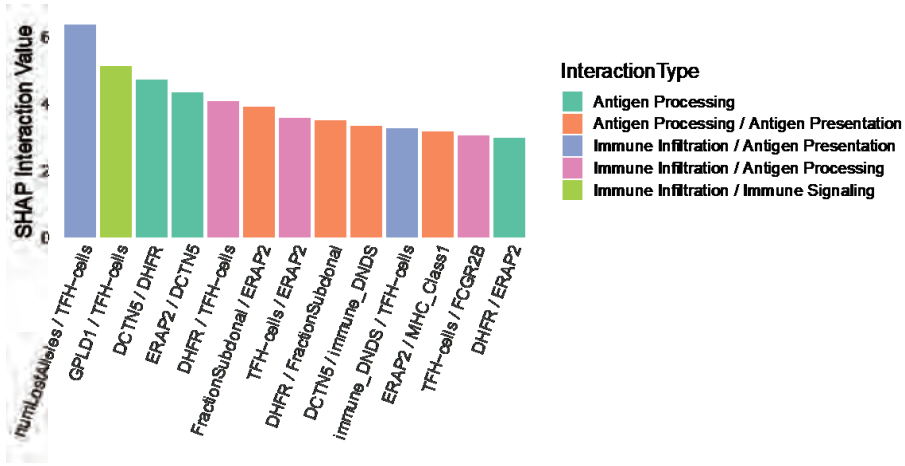
Shapley Values

$$\varphi_i(\upsilon) = \frac{1}{\text{n features}} \sum_{\substack{\text{num subsets} \\ \text{including feature i}}} \frac{\text{marginal contribution of } f_i \text{ in subset}}{\text{num subsets of this size that exclude } f_i}$$

Extract feature importances

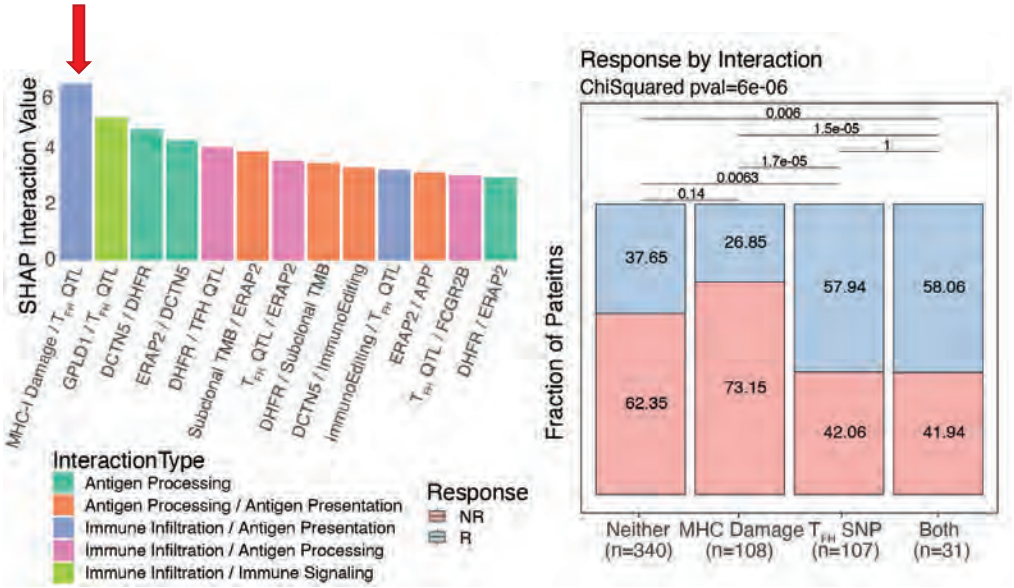


Extract feature interactions



Sears *et al, in press at Cancer Immunology Research*

T_{fh} SNP rescues MHC-I loss

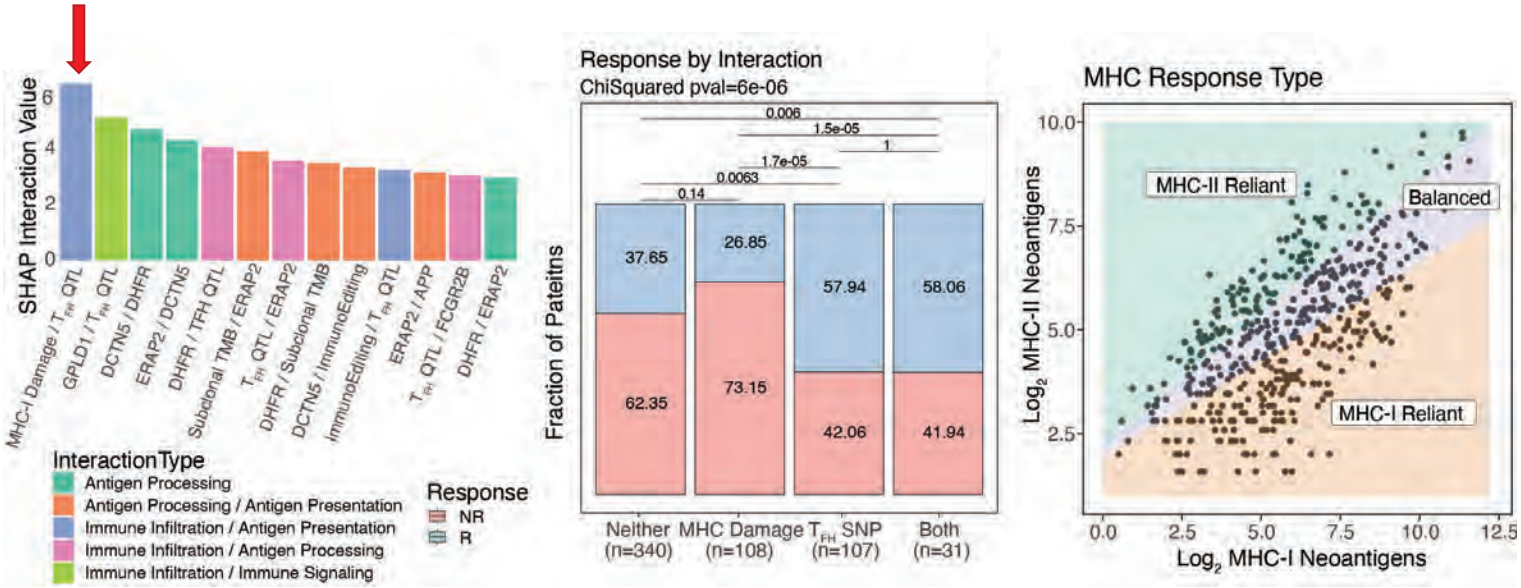


Does this mean that CD4 T cell responses can mediate immunotherapy response in the absence of CD8 T cell responses?

In that case, what happens if you have more neoantigens specific for MHC II versus more for MHC I??

Sears *et al, in press at Cancer Immunology Research*

T_{fh} SNP rescues MHC-I loss



Sears *et al, in press at Cancer Immunology Research*

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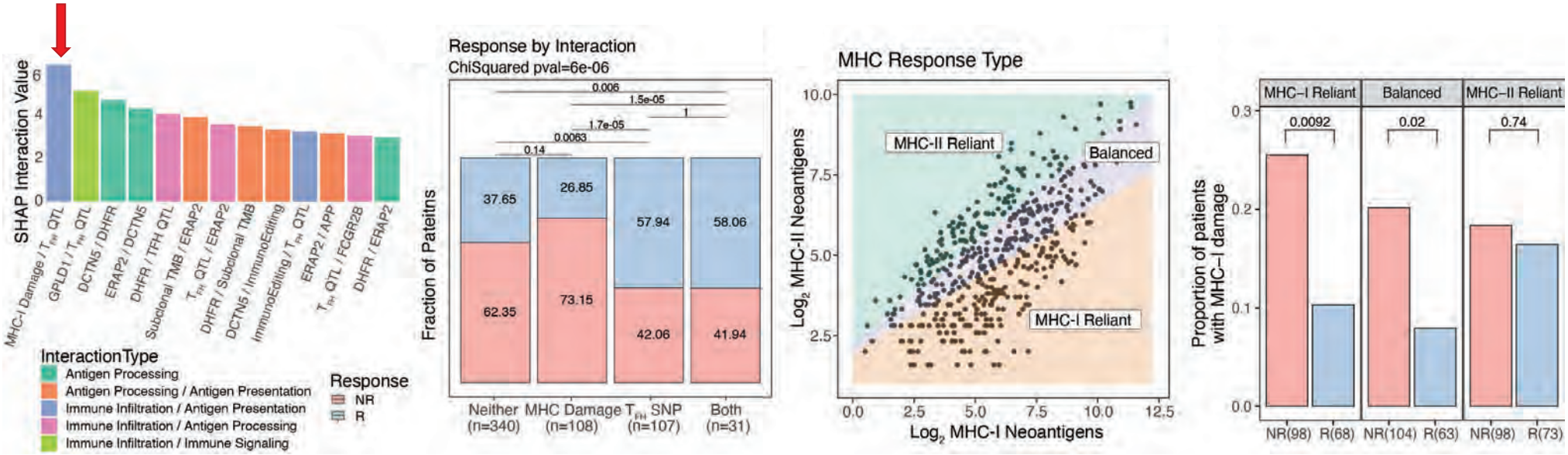


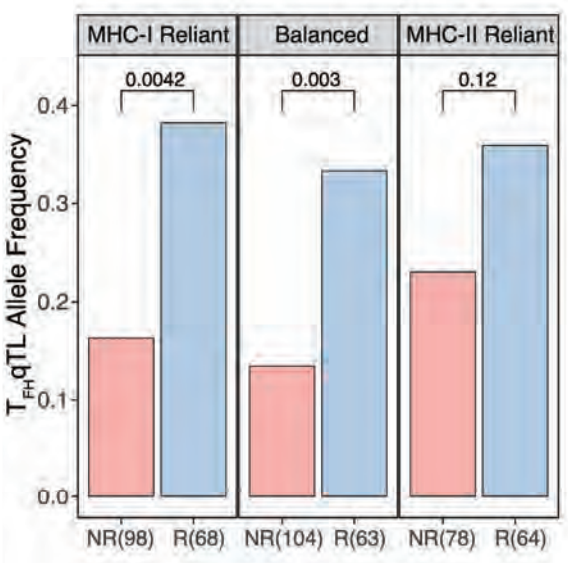
Having more MHC-II NeoAgs counters the effect of MHC-I loss

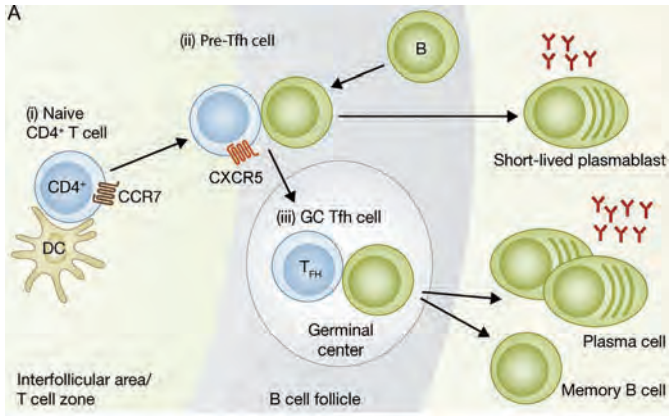
Abundant MHCII NeoAgs provides similar benefit to T_{fh} SNP

Association of T_{fh} SNP with response is stronger in patients that have more MHC-I NeoAgs

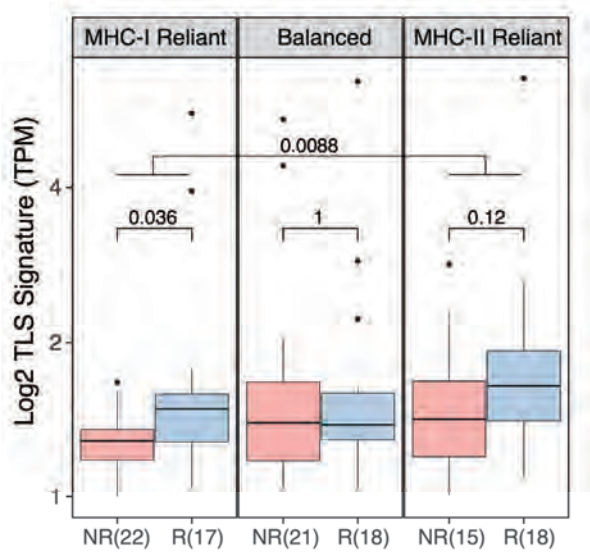
T_{fh} cell identity indicates antigen presentation by B cells – could indicate the presence of Tertiary Lymphoid Structures (TLS)

TLS-like signature more strongly associated with responders in MHC-I reliant tumors





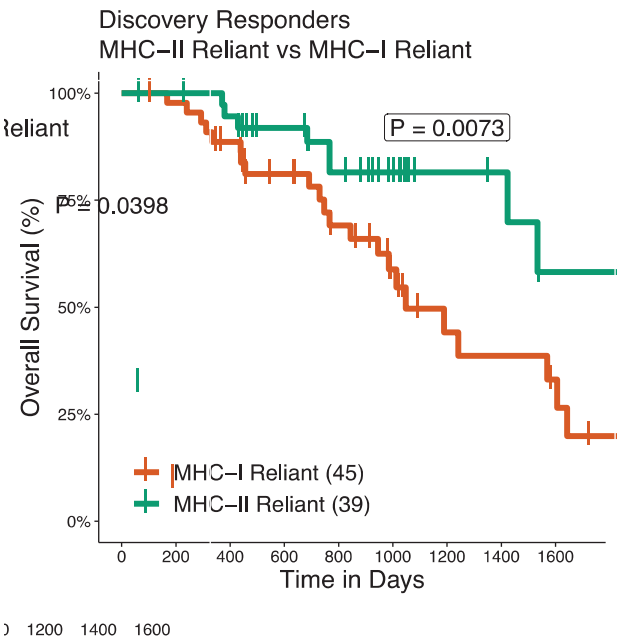
J Exp Med. 2012;209(7):1241-1253. doi:10.1084/jem.20120994



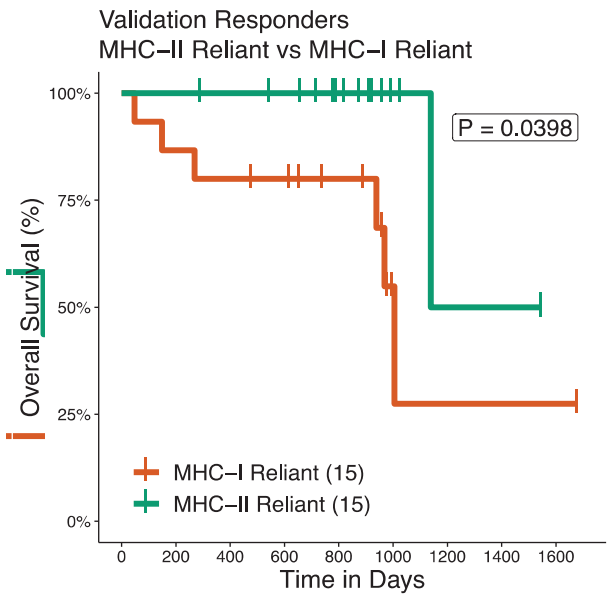
Sears *et al, in press at Cancer Immunology Research*

Longer survival post ICB treatment in patients with more MHC-II NeoAgs

Responders only all 7 ML cohorts



Responders only Liu dataset

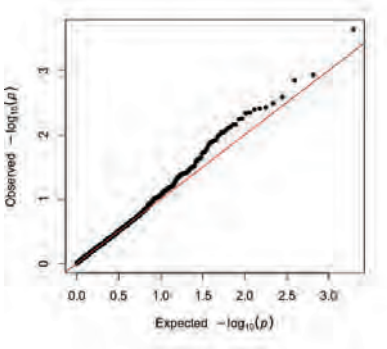


Cross-population portability

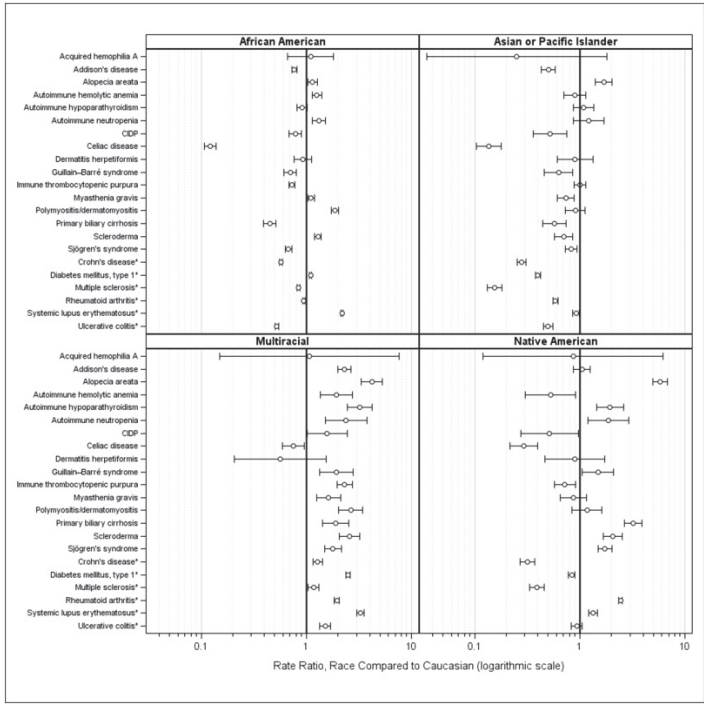
Allele frequency of SNP rs71510648 most predictive of CPI response across populations

#Study	Population	Sample Size	Ref Allele	Alt Allele	BioSample ID
ALFA (dbGaP)	European	12044	G=0.90070	C=0.09930	SAMN10492695
ALFA (dbGaP)	African	2548	G=0.9796	C=0.0204	SAMN10492703
ALFA (dbGaP)	**Hispanic**	**548**	**G=1.000**	**C=0.000**	**SAMN10492700**
ALFA (dbGaP)	**Asian**	**112**	**G=1.000**	**C=0.000**	**SAMN10492704**
1000Genomes_30x	African	1786	G=0.9138	C=0.0862	SAMN07486022
1000Genomes_30x	Europe	1266	G=0.8081	C=0.1919	SAMN07488239
1000Genomes_30x	South Asian	1202	G=0.8003	C=0.1997	SAMN07486027
1000Genomes_30x	**East Asian**	**1170**	**G=0.9983**	**C=0.0017**	**SAMN07486024**
1000Genomes_30x	Admixed American	980	G=0.887	C=0.113	SAMN07488242

64 out of 977 immune eQTLs tested were nominally associated with lung cancer risk in Asians and Hispanics in MVP



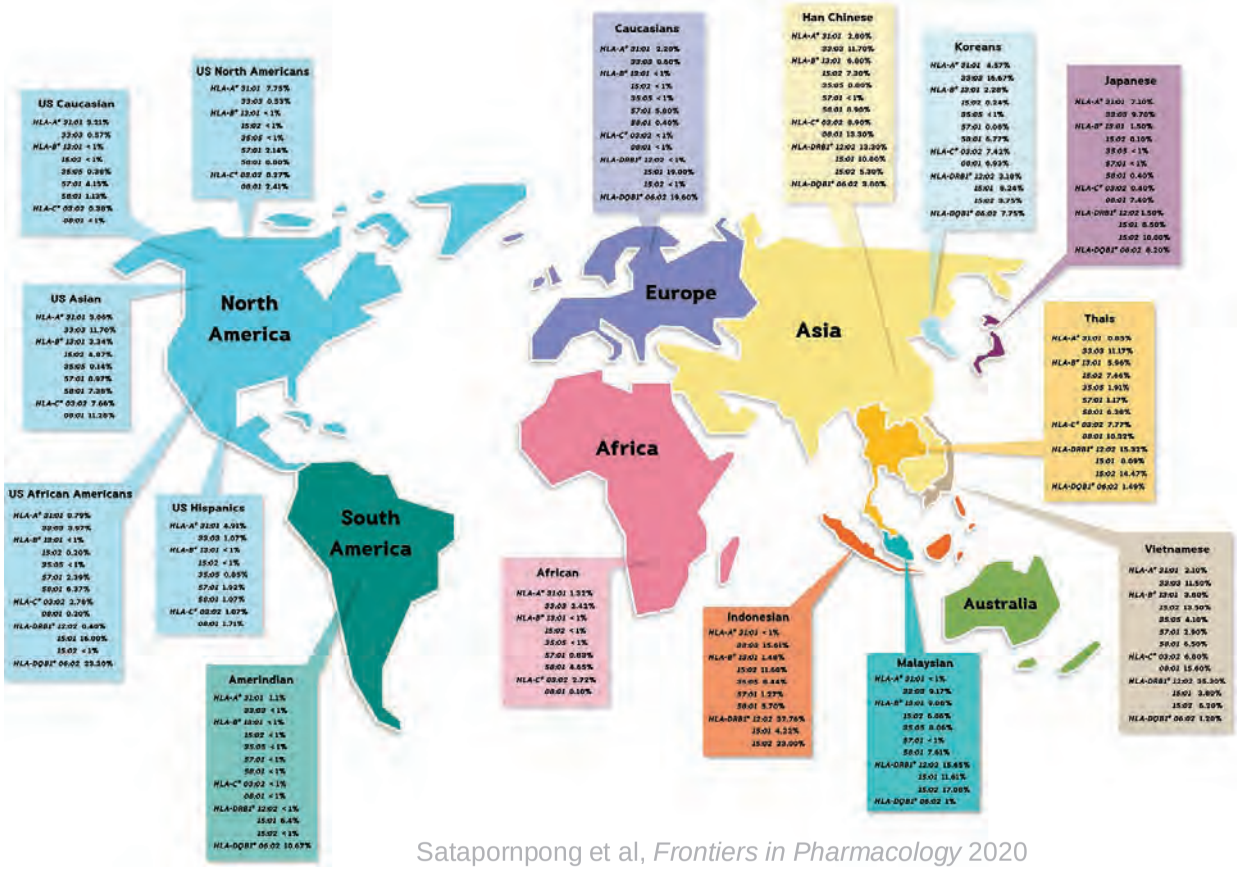
MILLION VETERAN PROGRAM



Roberts and Erdei, *Autoimmunity Reviews* 2020

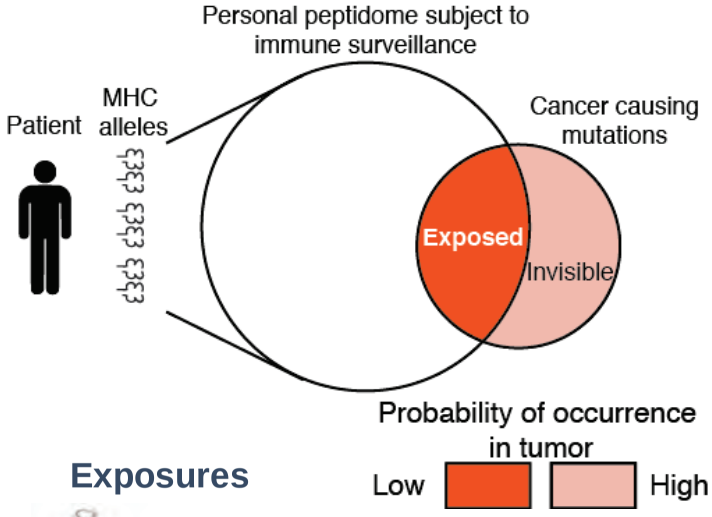
Cross-population portability

HLA allele frequencies differ across populations



Sataporpong et al, *Frontiers in Pharmacology* 2020

Mutations -> NeoAgs



Exposures

Marty et al, *Cell* 2017

Conclusions

The inherited genome influences host anti-tumor immunity

Germline variants at immune loci affect the tumor immune microenvironment to influence cancer development and response to immunotherapy

Antigen presentation by MHC-I versus MHC-II appear to drive divergent immune activities that result in differences in immunotherapy response

Studying SNP associations with selection-driven molecular characteristics of tumors implicates relevant biology and new entry points for therapy

But we need to be careful to be inclusive of population diversity and admixture to ensure precision immuno-oncology approaches benefit everyone.

Acknowledgements

Lab Members

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LJI
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Benjamin Schmiedel
Cristian Gonzalez-Colin

https://carterlab.info/

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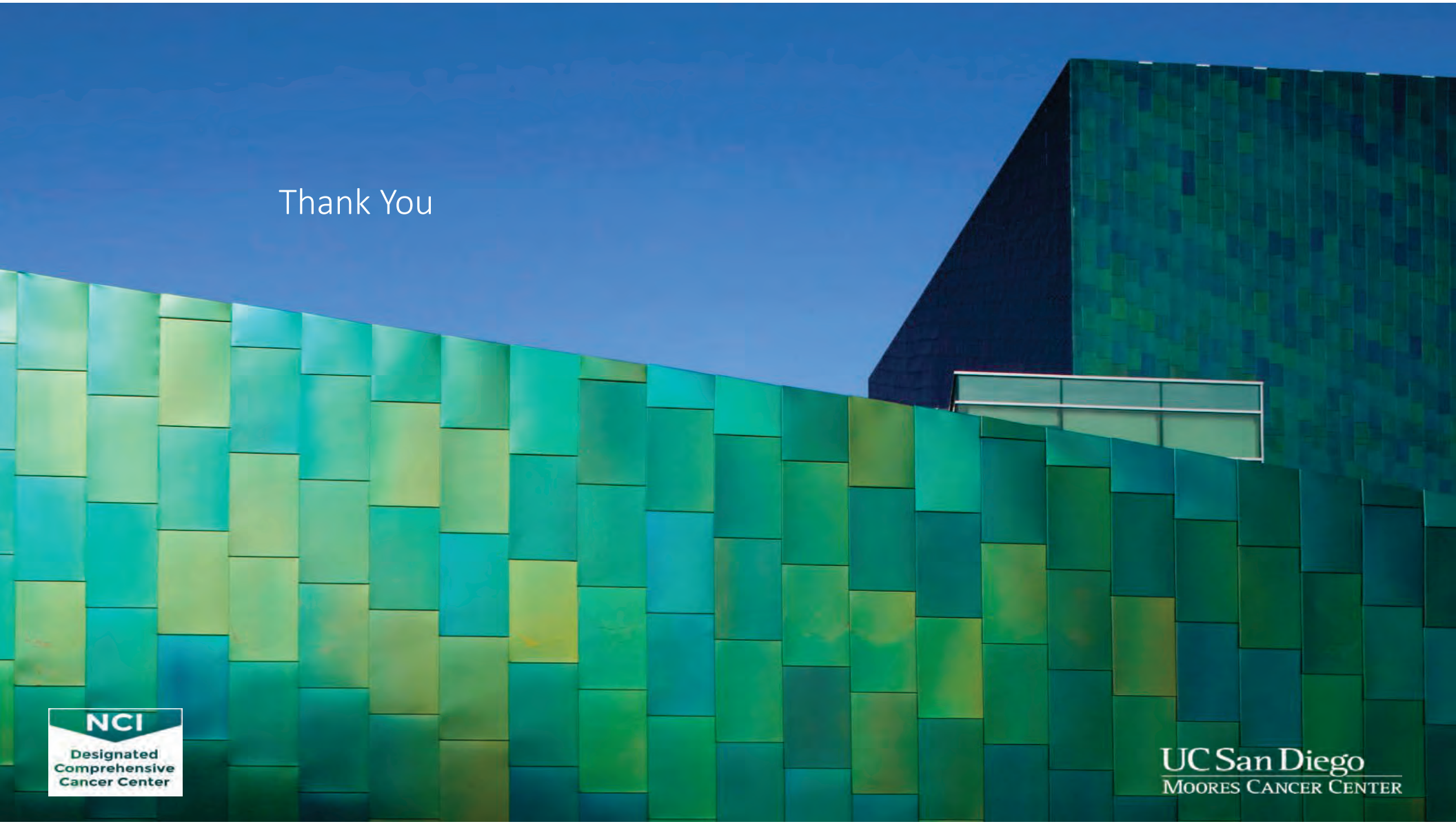
NIH NATIONAL CANCER INSTITUTE
EARLY INDEPENDENCE AWARD
CIFAR CANADIAN INSTITUTE FOR ADVANCED RESEARCH
CCMI


Thank You
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Cancer Center
UC San Diego
Moores Cancer Center

Considering ancestry in biomarker discovery and personalized genomics in metabolic disease

Amit R. Majithia, MD
Associate Professor of Medicine
January 24, 2025

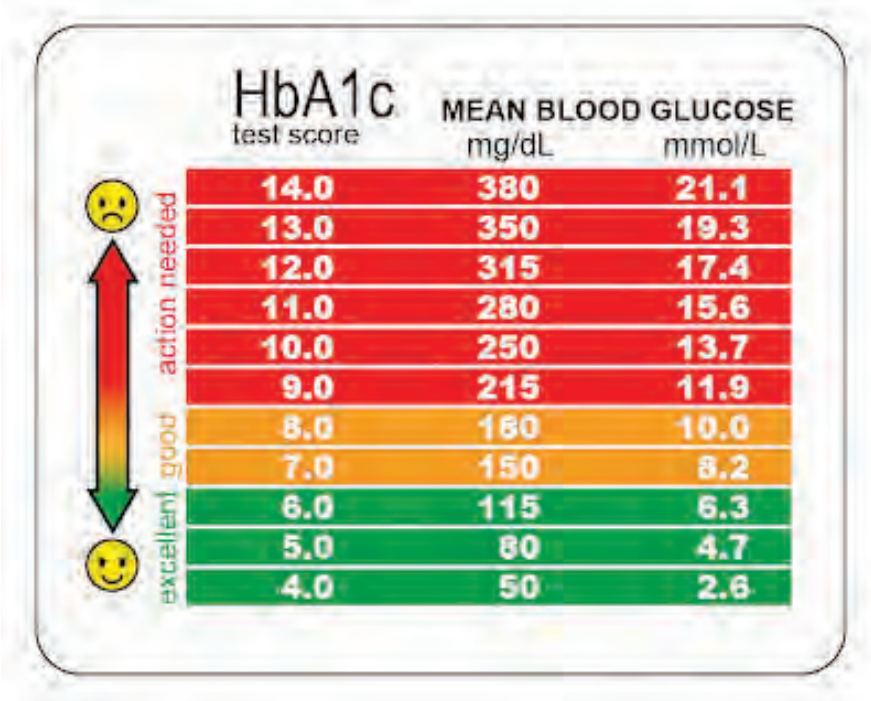
majithialab.ucsd.edu

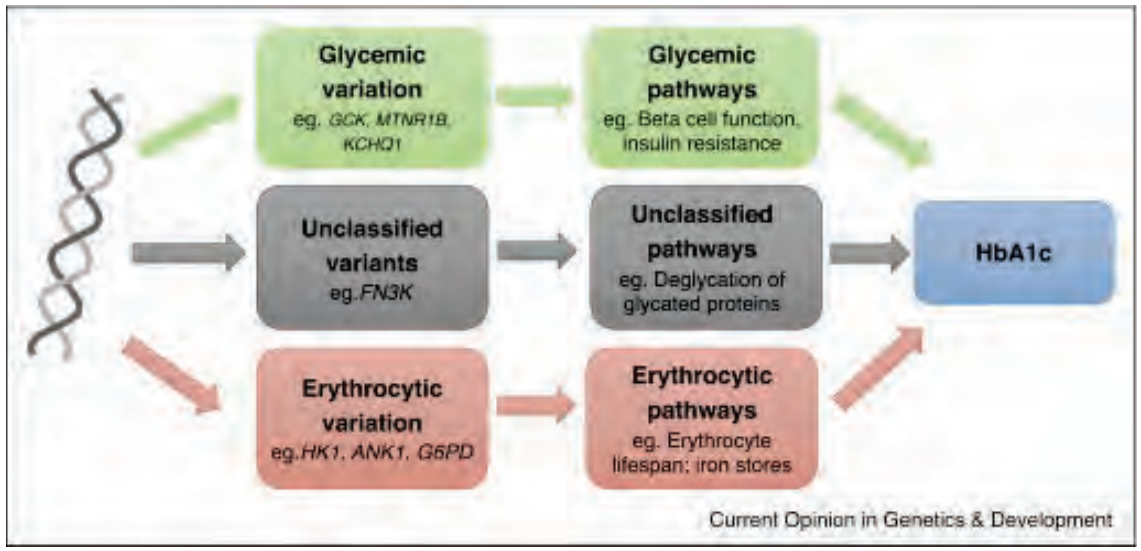
Outline

The importance of ancestry in:

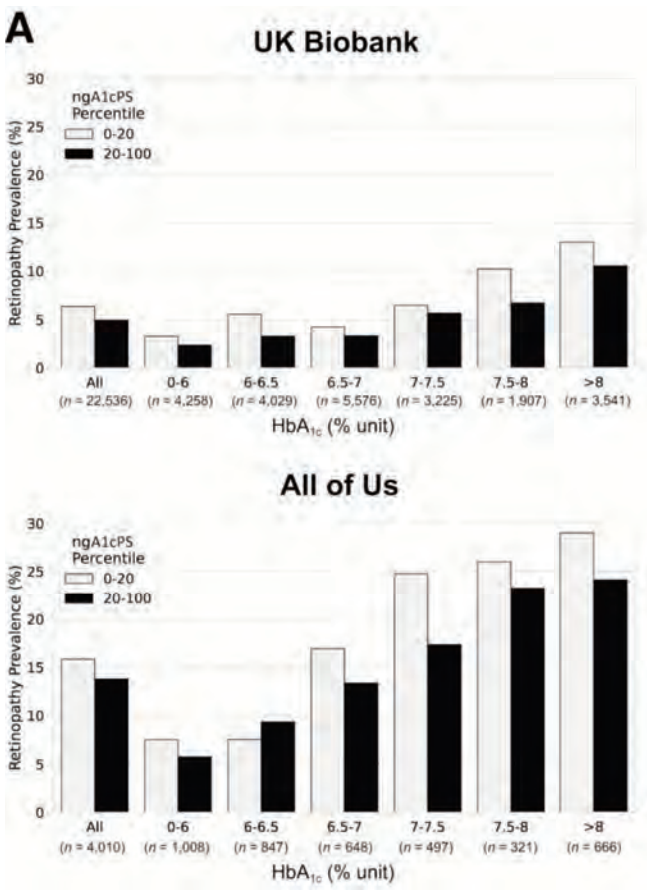
1. Biomarkers/omics
2. Polygenic risk scores

Ancestry specific genetic basis of biomarkers impacts diagnosis





Ancestry specific genetic basis of biomarkers impacts diagnosis



Mandla et. al, *Diabetes Care* 2024

Plasma Lipid Metabolites, Clinical Glycemic Predictors, and Incident Type 2 Diabetes

https://doi.org/10.2337/dc24-2266

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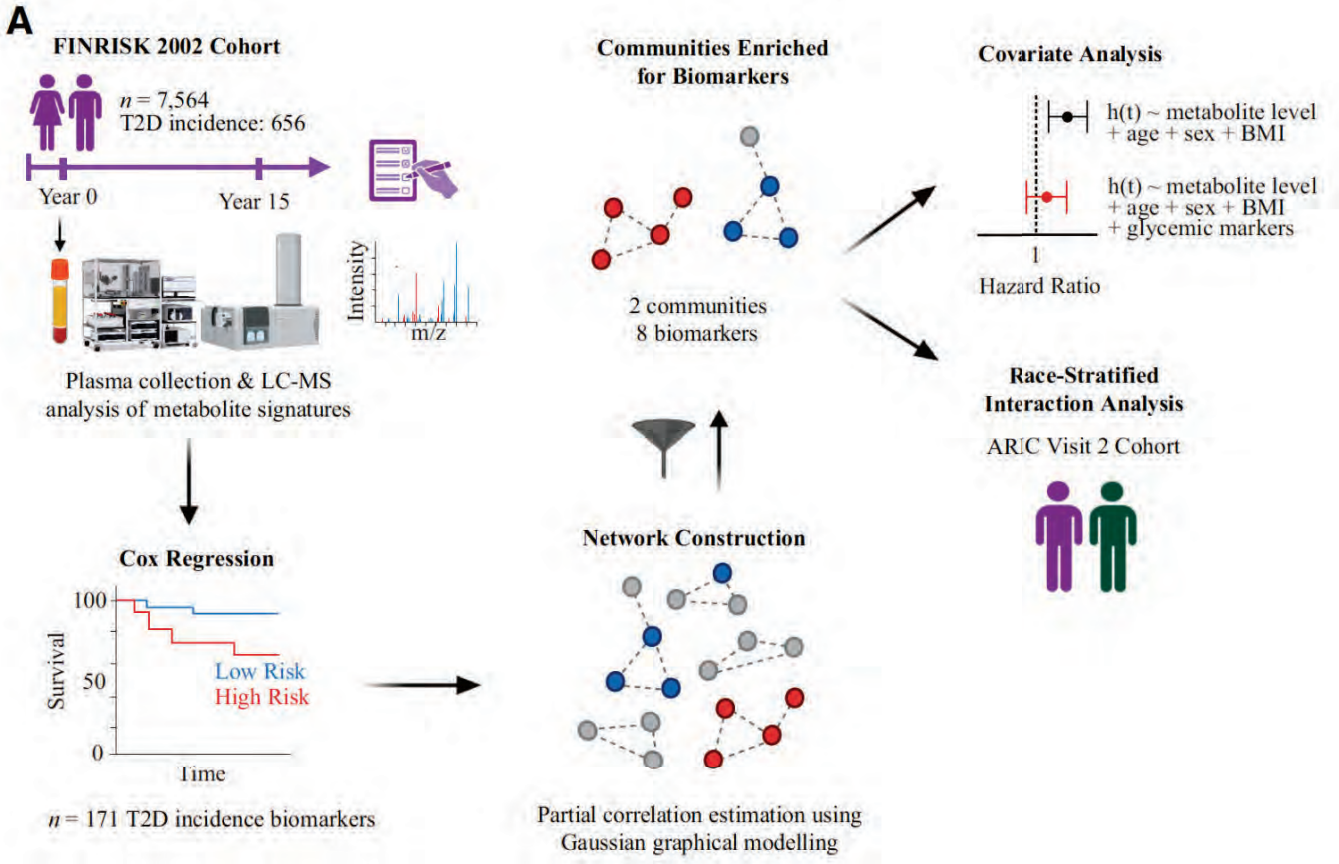
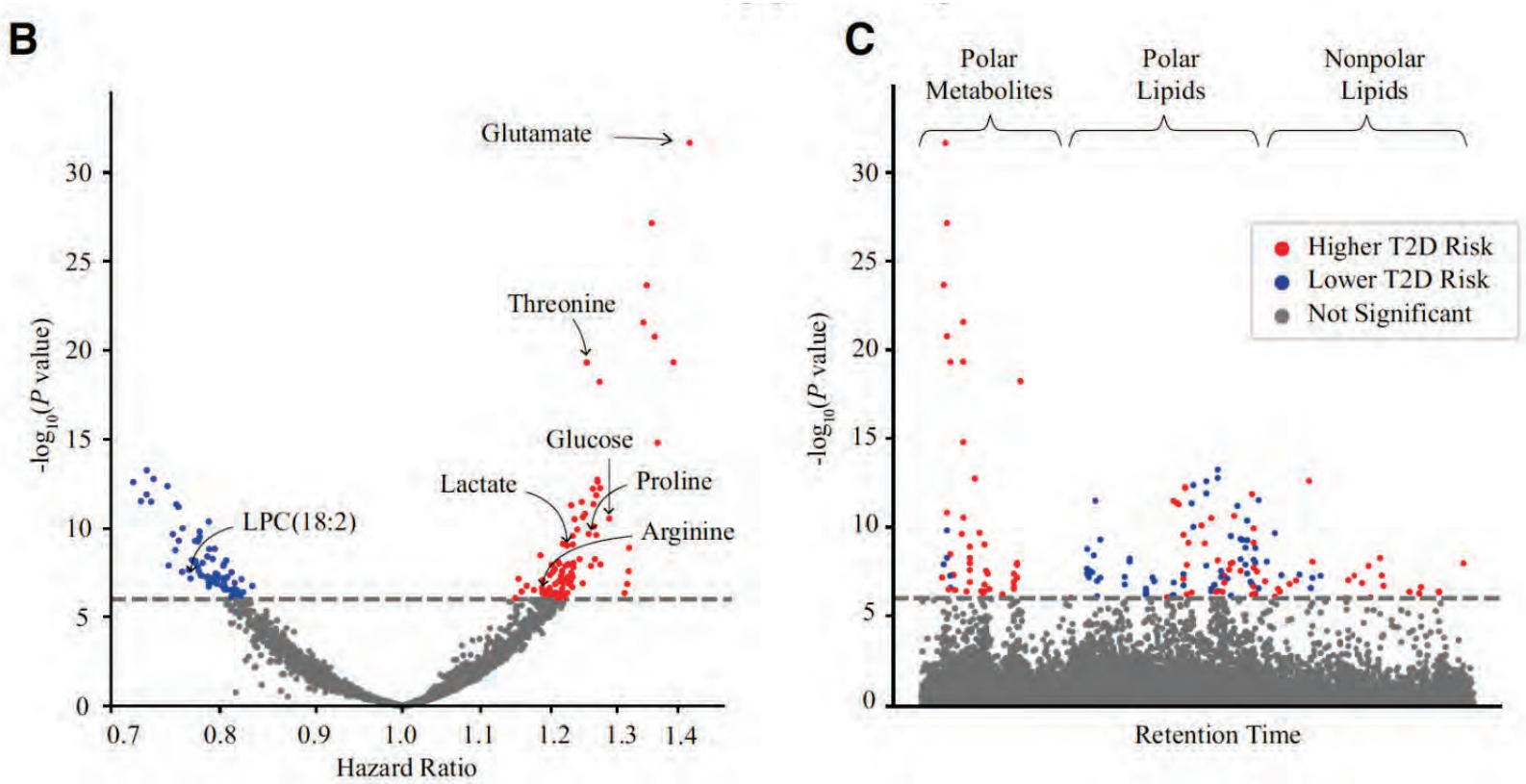
DAG and PC Biomarkers of Type 2 Diabetes Risk



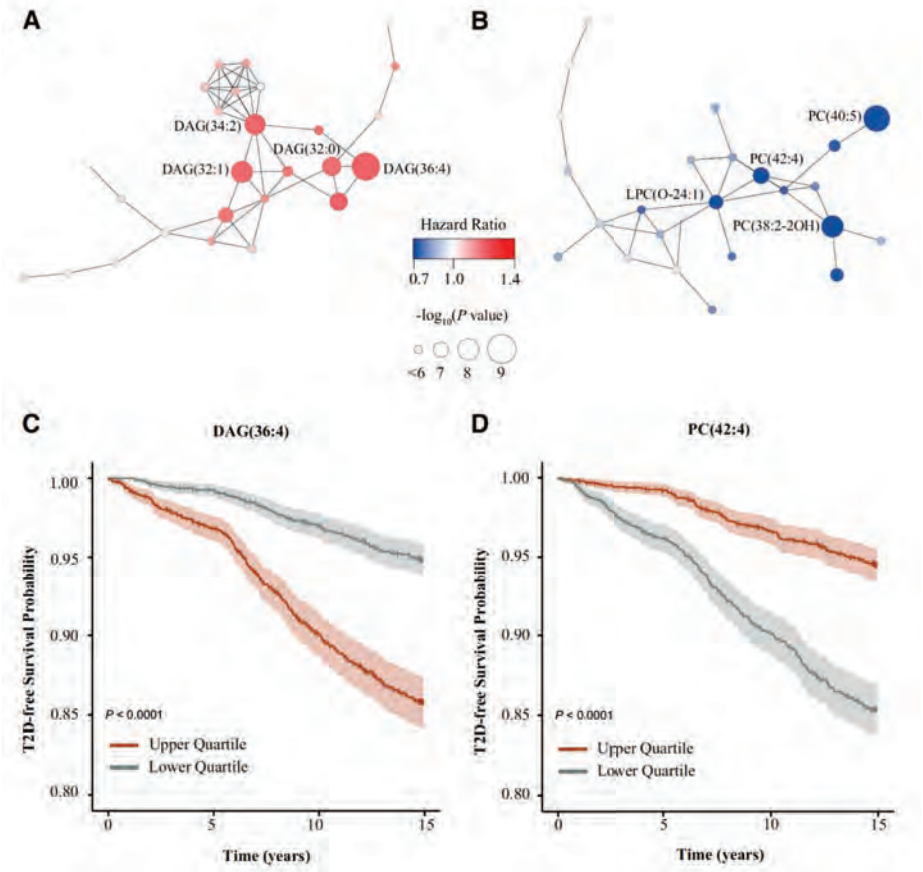
Begzati A, et al. *Diabetes Care 2025*

DAG and PC Biomarkers of Type 2 Diabetes Risk



Begzati A, et al. *Diabetes Care 2025*

DAG and PC Biomarkers of Type 2 Diabetes Risk

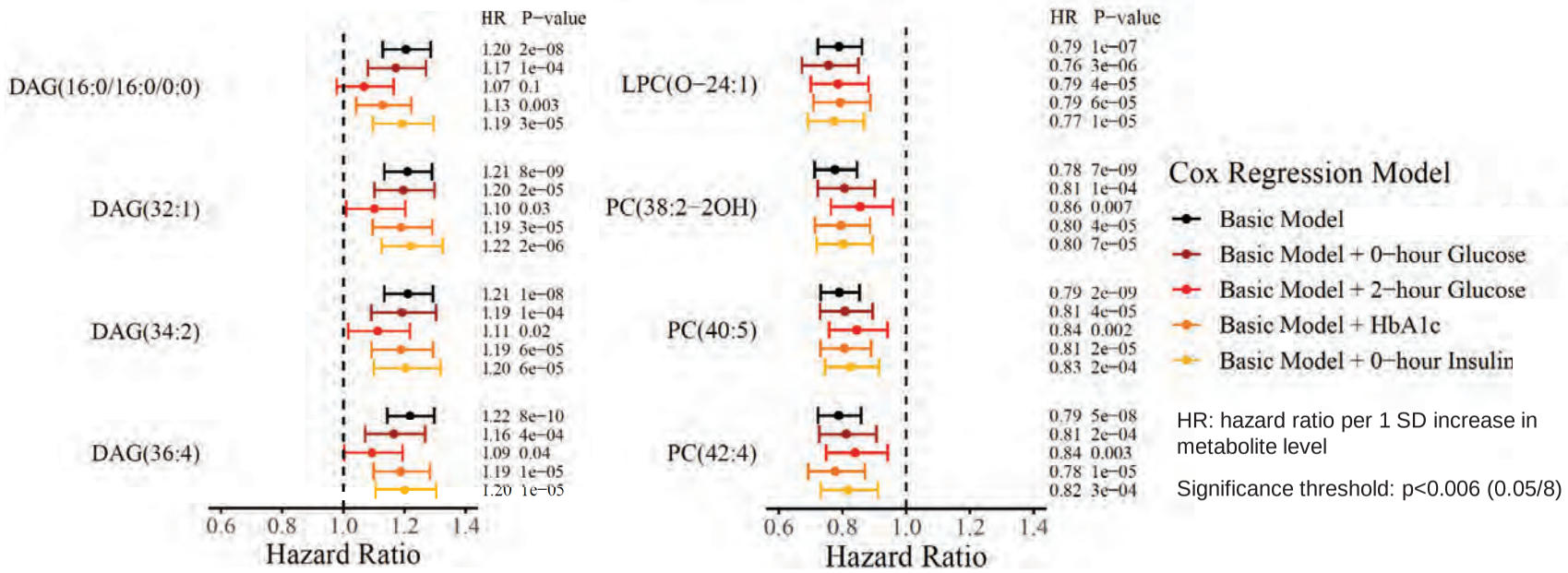


Begzati A, et al. *Diabetes Care 2025*

Circulating DAGs and PCs predict T2D risk independent of most standard clinical T2D risk markers

Time-to-T2D ~ metabolite + age + sex + BMI + clinical marker

Basic Model



HR: hazard ratio per 1 SD increase in metabolite level

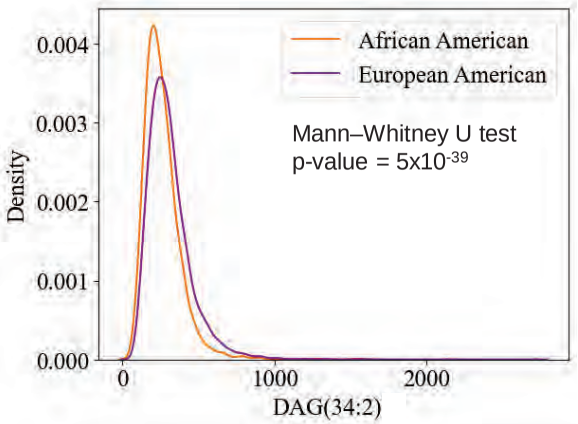
Significance threshold: p<0.006 (0.05/8)

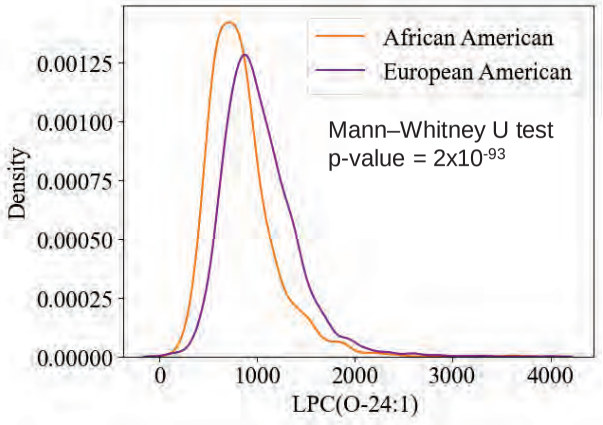
Characteristics of the Atherosclerosis Risk in Communities (ARIC) cohort

ARIC™	**European American (n = 6145)**	**African American (n = 1417)**	**Total (n = 7562)**
Age, years	58 (6)	56 (6)	57 (6)
Male	2809 (46%)	536 (38%)	3345 (44%)
BMI, kg/m^2	27 (5)	29 (6)	27 (5)
Follow up time, years	13 (8)	12 (8)	12 (8)
Incident T2D cases	899 (15%)	312 (22%)	1211 (16%)

Data are mean (SD) or n (%).

DAG and PC biomarkers have different levels in populations of different ancestry





	Metabolite Biomarker	Median Ratio (EA/AA)	Mann–Whitney U test P-value
DAGs	DAG(16:0/16:0/0:0)	1.06	9e-04
	DAG(32:1)	1.21	1e-31
	DAG(34:2)	1.18	5e-39
	DAG(36:4)	1.08	2e-07
PCs	LPC(O-24:1)	1.24	2e-93
	PC(38:2-2OH)	0.95	1e-06
	PC(40:5)	1.03	1e-05
	PC(42:4)	1.15	1e-40

Significance threshold: $p<0.006$ (0.05/8)
EA: European American, AA: African American

DAGs and PCs have similar risk association in European Americans and African Americans

Table 1—Cox regression statistics for DAG and PC biomarkers with incident T2D

Biomarker	FINRISK HR	FINRISK *P* value	ARIC HR	ARIC *P* value	Biomarker-race interaction *P* value
DAG(32:0)	1.20	2.00×10^{-8}	1.12	2.66×10^{-5}	0.5
DAG(32:1)	1.21	7.62×10^{-9}	1.18	1.67×10^{-12}	0.8
DAG(34:2)	1.21	1.03×10^{-8}	1.20	8.95×10^{-15}	0.6
DAG(36:4)	1.22	7.65×10^{-10}	1.16	8.23×10^{-11}	0.8
LPC(*O–24*:1)	0.79	1.17×10^{-7}	0.78	2.44×10^{-13}	0.7
PC(38:2-2OH)	0.78	7.06×10^{-9}	0.81	6.69×10^{-11}	0.3
PC(40:5)	0.79	1.52×10^{-9}	0.78	2.00×10^{-15}	0.4
PC(42:4)	0.79	5.22×10^{-8}	0.78	1.05×10^{-12}	0.8

Begzati A, et al. *Diabetes Care 2025*

DAG and PC Biomarkers of Type 2 Diabetes Risk

- Diacylglycerols (DAGs) capture type 2 diabetes (T2D) risk information related to 2-hour post-challenge glucose.
- Phosphatidylcholines (PCs) predict incident T2D risk independent of glycemic markers and insulin.
- No significant interaction between race and DAG or PC biomarkers was found.

Begzati A, et al. *Diabetes Care 2025*

Outline

The importance of ancestry in:

1. Biomarkers/omics
2. Polygenic risk scores

Human genetics Personalized medicine: Polygenic risk scores

What do your genes say about type 2 diabetes?

23andMe can tell you if your genetics are associated with a higher than typical likelihood of developing type 2 diabetes. The 23andMe Type 2 Diabetes Health Predisposition report estimates your chances of developing type 2 diabetes by looking at more than 1,000 places in your DNA. The report also equips you with information and tools to help you take action. You can get the Type 2 Diabetes Health Predisposition report and more with 23andMe's Health + Ancestry Service.

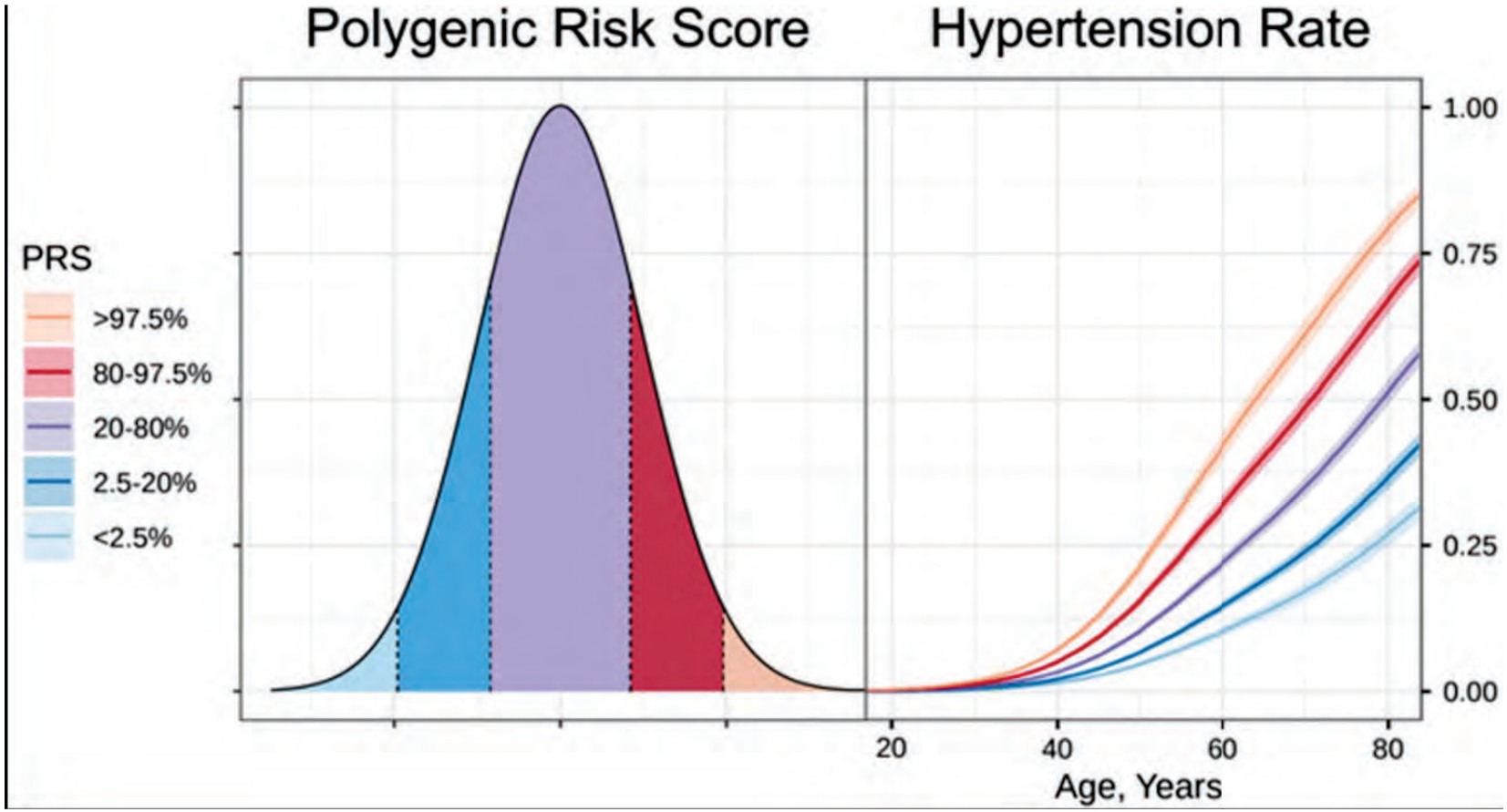
Health + Ancestry Service

Learn more

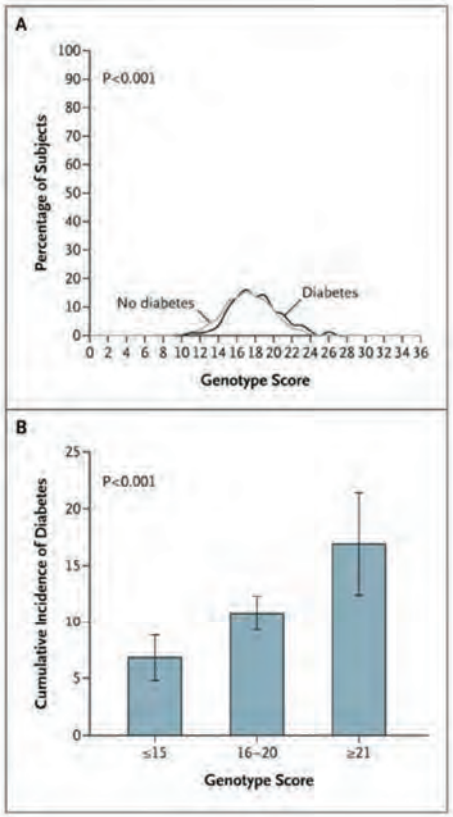
Please note:

- The 23andMe Type 2 Diabetes Health Predisposition report does not diagnose type 2 diabetes or prediabetes and should not be used to make medical decisions.
- The report was developed by 23andMe scientists using data and insights gathered from thousands of customers who participate in our research. Reports based on 23andMe research provide an estimate of your likelihood of developing a condition based on your genetics and other factors. This report does not account for lifestyle or family history.
- The report does not account for every possible genetic variant that could affect your likelihood of developing type 2 diabetes.

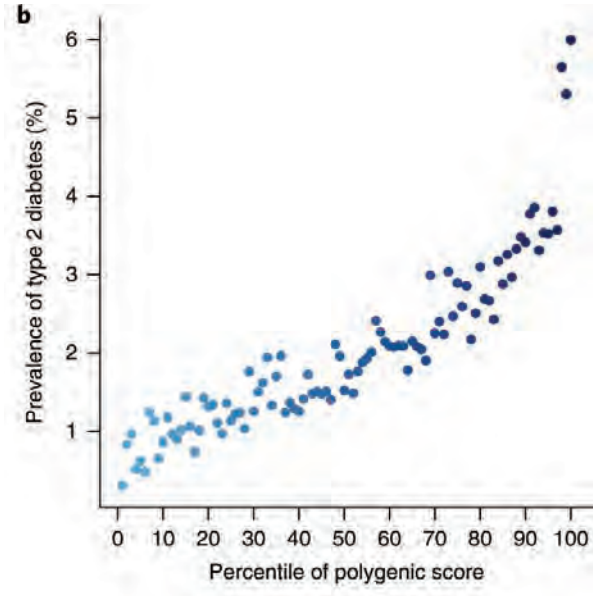
Polygenic risk scores: the concept



Polygenic risk scores: not a new idea

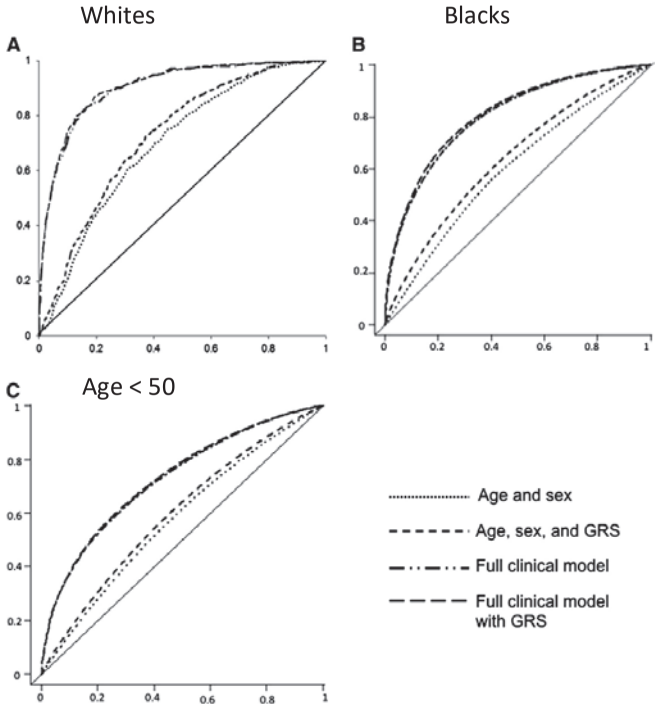


Meigs J.B., *NEJM* 2008



Khera A.V., *Nature Genetics* 2018

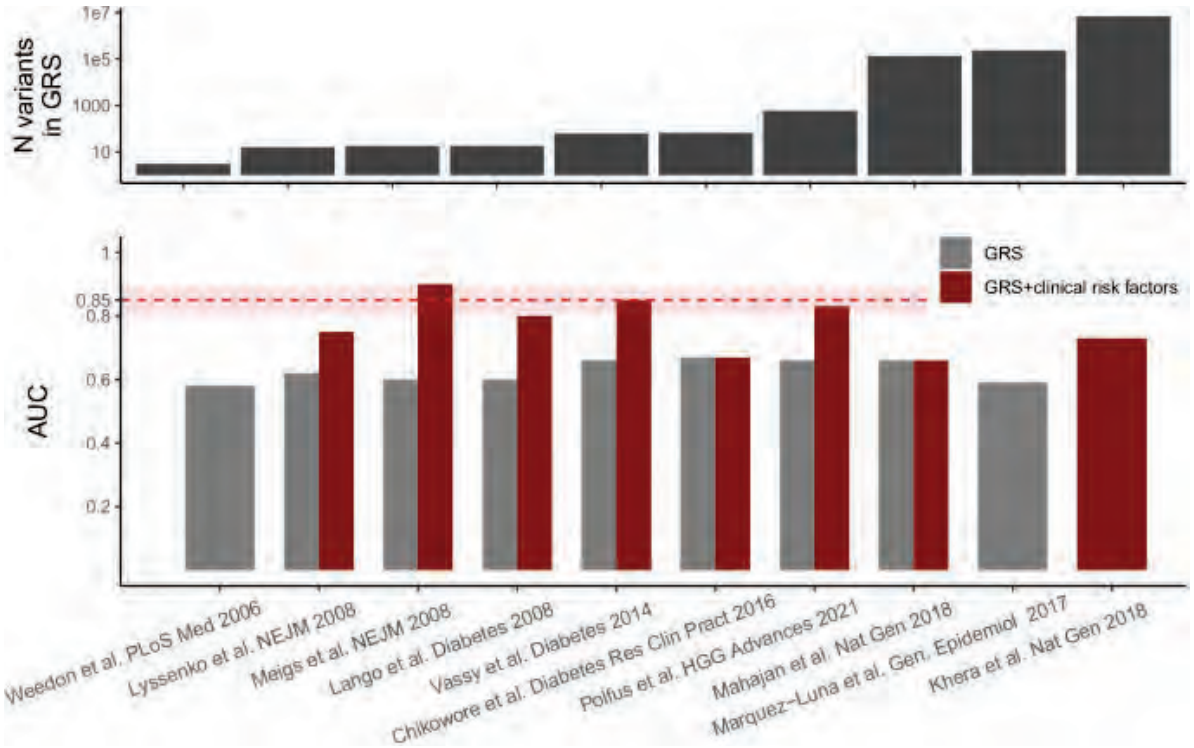
Polygenic risk scores: not much improvement over traditional risk factors



full clinical model is adjusted for age, sex, parental diabetes (yes vs. no), BMI, systolic blood pressure, fasting glucose, HDL cholesterol, and triglyceride levels.

Vassy J.L., *Diabetes* 2014

Polygenic risk scores: not much improvement over traditional risk factors



Natalie DeForest, B.S.

UCSD Biomedical Sciences

DeForest N. *Curr Diabetes Reports* 2022

Polygenic risk scores: large variation in ancestry specific performance

Table 1. Absolute and Relative Reduction in Risks of Disease and Other Conditions with ESPS.*

Condition	Lifetime Risk in United States (%)	Absolute Risk Reduction (Preferred)†			
		EUR	AMR	EAS	AFR
		percentage points (95% confidence interval)			
Type 1 diabetes	0.34	0.12 (0.08–0.14)	0.09 (0.07–0.13)	0.09 (0.06–0.11)	0.07 (0.05–0.07)
Type 2 diabetes	35.3	5.5 (3.9–7.1)	4.4 (3.2–5.6)	3.9 (2.8–5.0)	2.6 (1.9–3.3)
Breast cancer (women)	12.9	1.9 (1.1–2.7)	1.5 (0.92–2.2)	1.3 (0.77–1.9)	0.91 (0.52–1.3)
Prostate cancer	12.1	4.0 (2.5–5.6)	3.2 (2.0–4.5)	2.9 (1.8–3.9)	1.9 (1.2–2.7)
Malignant melanoma	2.3	0.50 (0.44–0.55)	0.40 (0.32–0.46)	0.33 (0.29–0.42)	0.23 (0.18–0.33)
Testicular cancer	0.41	0.14 (0.11–0.15)	0.10 (0.09–0.12)	0.09 (0.08–0.12)	0.07 (0.06–0.08)
Coronary artery disease	6.7	1.1 (0.53–1.7)	0.89 (0.39–1.4)	0.79 (0.38–1.2)	0.55 (0.27–0.79)
Hypercholesterolemia	11.7	3.2 (3.1–3.3)	2.5 (2.4–2.5)	2.3 (2.2–2.3)	1.5 (1.5–1.6)
Hypertension	46.0	8.5 (8.3–8.6)	6.6 (6.5–6.7)	5.9 (5.9–6.1)	4.0 (3.9–4.1)
Idiopathic short stature	2.3	1.8 (1.7–1.8)	1.5 (1.5–1.5)	1.3 (1.3–1.4)	0.95 (0.95–0.98)
Intellectual disability	2.3	0.87 (0.78–0.90)	0.67 (0.63–0.73)	0.60 (0.56–0.67)	0.41 (0.38–0.45)

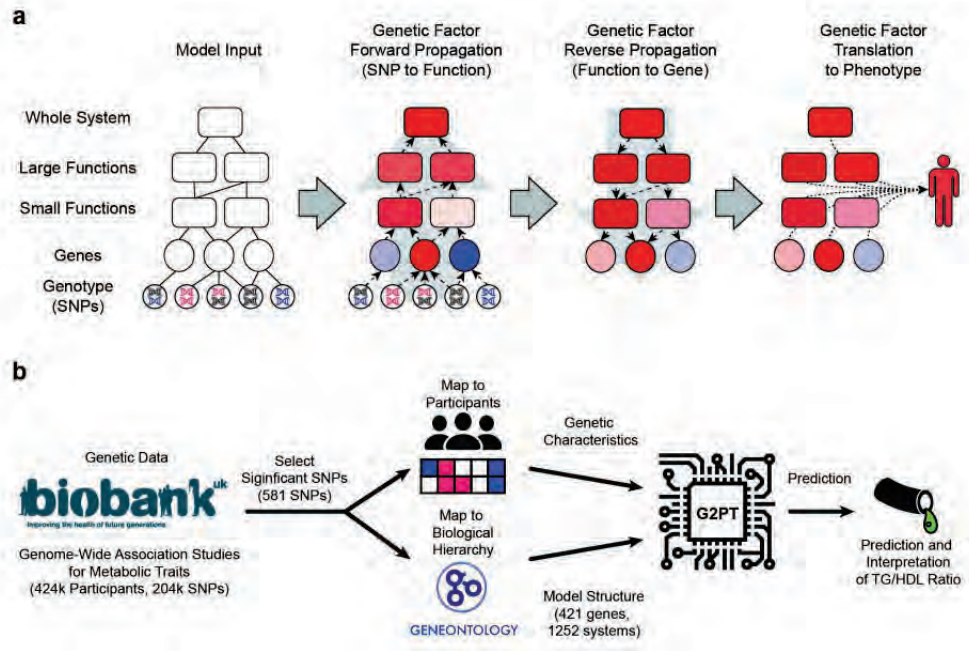
Turley P., *NEJM* 2021

The future: interpretable polygenic risk scores

Mechanistic genotype-phenotype translation using hierarchical transformers

Ingoo Lee, Zach Wallace, Sungjoon Park, Hojung Nam, Amit R. Majithia, Trey Ideker

doi: https://doi.org/10.1101/2024.10.23.619940



Outline

The importance of ancestry in:

1. Biomarkers/omics - must be validated in populations close to use
2. Polygenic risk scores - interpretability is key to clinical use in metabolic disease. This depends on accurate ancestry specific estimates

Thank you!

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VA

NIH

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Overview of Center for Data-driven Insights & Innovation (CDI2) Resources

Pagan Morris, MPH

Director for Research Initiatives

University of California Office of the President

Division of Biomedical Informatices 15-Year Symposium | January 24, 2025

UC San Diego

Rising Stars in Biomedical Informatics Flash Talks

Highlighting Trainees in DBMI

Moderated by:
Aaron Boussina, PhD & Timothy Wen MD, MPH

Disclosures

- Timothy Wen
  - Delfina Care, Inc. (Advisor)
- Aaron Boussina
  - Clairyon, Inc. (Co-founder & CTO)

DBMI Training By the Numbers

14 current PhD Candidates

4 Major Training Programs

5 current Postdoctoral Fellows

>100 Alumni from the DBMI Training Programs

DBMI Trainee Highlights

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Brian Johnson & Kit Curtius

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Volume 32, Issue 2
February 2025

Article Contents

JOURNAL ARTICLE

Distributed, immutable, and transparent biomedical limited data set request management on multi-capacity network

Yufei Yu, BS, Maxim Edelson, MS, Anh Pham, PhD, Jonathan E Pekar, PhD, Brian Johnson, BS, Kai Post, MS, Tsung-Ting Kuo, PhD ✉ Author Notes

Journal of the American Medical Informatics Association, Volume 32, Issue 2, February 2025, Pages 296–307, https://doi.org/10.1093/jamia/ocae288

Published: 21 November 2024 **Article history**

Flash Talks

- **Leveraging LLMs for Infection Identification in Cirrhosis Patients**
  - Grace Yu
- **Improving Inflammatory Bowel Disease (IBD) PRS prediction, interpretability, and clinical utility in the Million Veterans Program (MVP)**
  - Hyrum Eddington
- **GenVarLoader: An accelerated dataloader for applying deep learning to personalized genomics**
  - David Laub
- **From Manual to Massive: Using LLMs to Scale the “Gold Standard”**
  - Brian Johnson

Leveraging LLMs for Infection Identification in Cirrhosis Patients

Yufei (Grace) Yu

The Nemati Lab

DBMI 15 Year Anniversary Flash Talk

This research was supported by grant #T15LM011271

Why Infection Identification in Cirrhosis Matters

Cirrhosis Patients Face High Risks:

- **4–5 times higher risk of infections**, accounting for 25–35% of hospital admissions.
- Infections increase **mortality by 4-fold**, with 30% at 1 month and 63% at 1 year.

Impact of Delayed or Missed Diagnosis:

- Overlapping symptoms complicate diagnosis.
- Delays in identifying infections worsen outcomes.

Ekpanyapong S, Reddy KR. Infections in Cirrhosis. Curr Treat Options Gastroenterol. 2019 Jun;17(2):254-270. doi: 10.1007/s11938-019-00229-2. PMID: 30980335; PMCID: PMC7101776.
This research was supported by grant #T15LM011271

The Challenge: Establishing a Gold Standard for Infection Labels

Limitations of Current Methods:

- ICD Codes:
  - Often misclassify or miss infections, limiting reliability
- Manual Chart Review:
  - The **"gold standard"** but labor-intensive, costly, and impractical for large datasets.

The Gap in Infection Labeling:

- A **scalable**, consistent labeling method is needed for both research and clinical use.

Leveraging AI to Bridge the Gap:

- **Large language models (LLMs)** can automate infection identification and classification.

This research was supported by grant #T15LM011271

Method

Infrastructure:

- **Claude 3.5 Sonnet** on a **HIPAA-compliant AWS instance**.

Cohort and Data:

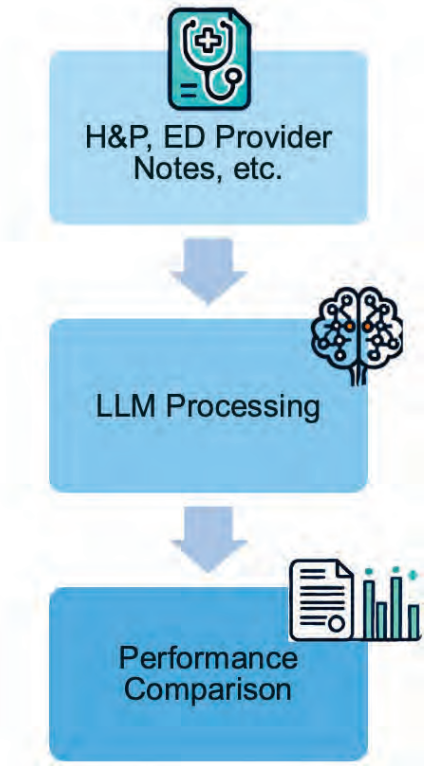
- Cirrhosis patients with hospital stays **>48 hours.**
- First 48 hours of **clinical notes** concatenated.

Gold Standard Validation:

- Manual infection labeling by two physicians.

Performance Comparisons (LLMs vs. ICD Codes):

1. General infection identification (Infection vs. No Infection).
2. Identification of infection types and sites.



This research was supported by grant #T15LM011271

Preliminary Results

(Based on 69 chart-reviewed cases)

Overall Performance for Infection Identification

Accuracy: 0.942

Sensitivity: 1.000

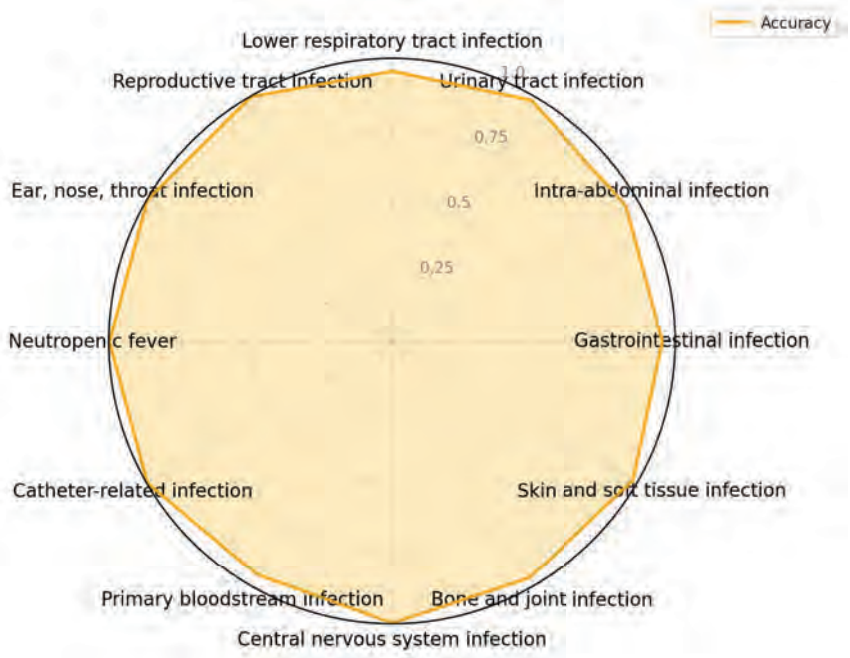
Specificity: 0.871

PPV: 0.905

Key Insights:

- High overall accuracy and sensitivity.
- LLM effectively identified infections, including cases with multiple infection types.

Accuracy by Bacterial Infection Subtype



This research was supported by grant #T15LM011271

Next Steps and Impact

Next Steps:

1. Expand the study to a **1,000 patient cohort**.
2. Develop a **prediction model** for early infection diagnosis

Impact:

- **Validated LLMs** for accurate infection classification in cirrhosis patients.
- Demonstrated **scalable, efficient** silver-standard labeling solutions.
- Established a foundation for future AI-driven infection management tools.

This research was supported by grant #T15LM011271

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The Nemati Lab @UC San Diego

Bioinformatics & Systems Biology

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DEPARTMENT OF BIOMEDICAL INFORMATICS

This research was supported by grant #T15LM011271

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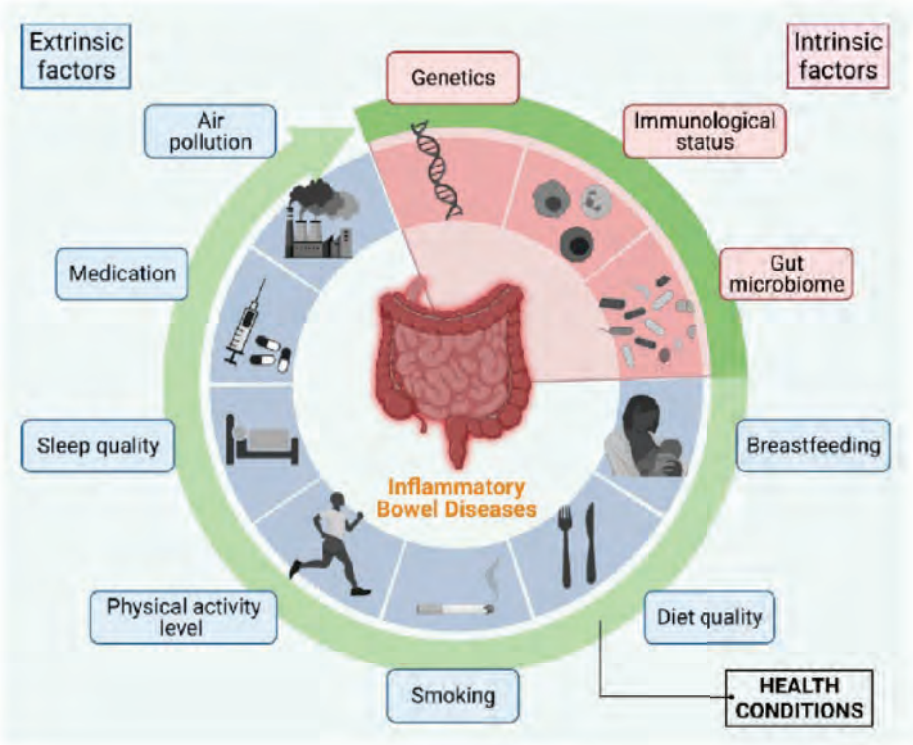
Improving Inflammatory Bowel Disease (IBD) PRS prediction, interpretability, and clinical utility in the Million Veterans Program (MVP)

Hyrum Eddington, 2nd year (Carter & Curtius lab)

BMI 15th anniversary | Jan 24, 2025

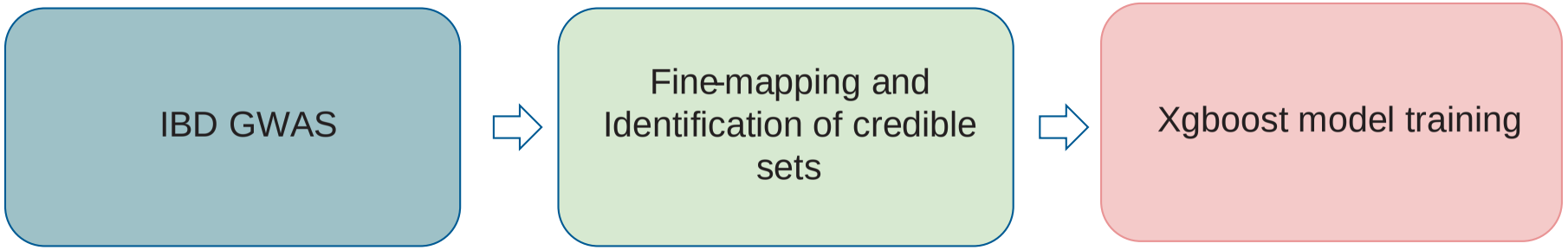
Challenges facing IBD prediction



- Improve PRS prediction with ML methods
- Leverage clinical predictors in IBD prediction
- Utilize both genetic and environmental contributors to IBD's complex disease trajectory

MILLION VETERAN PROGRAM

PRS Model development pipeline

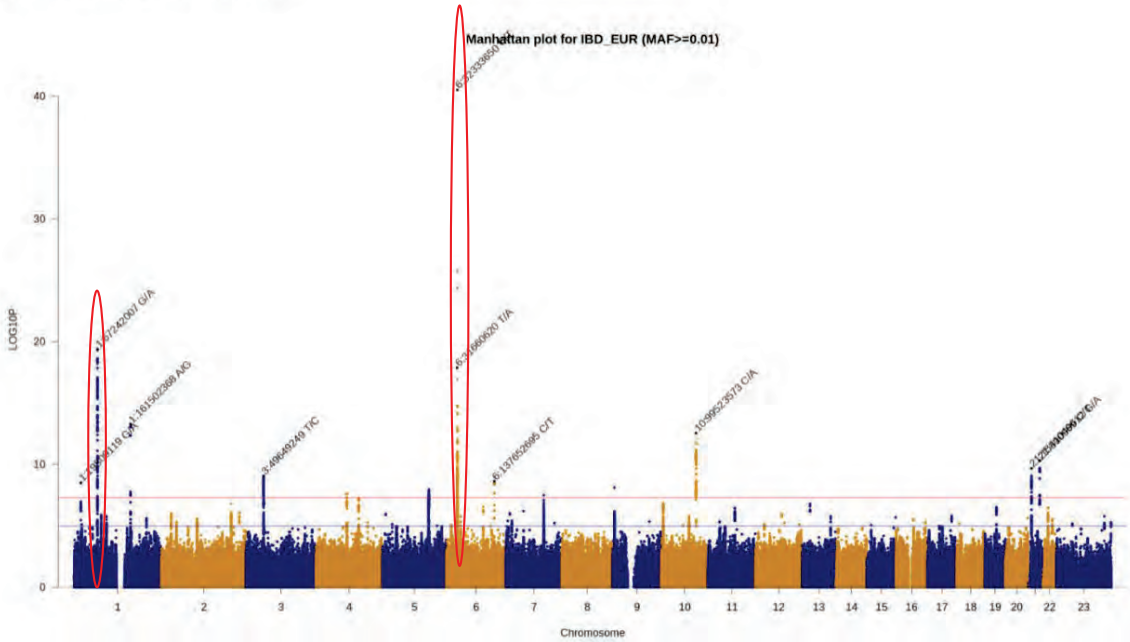


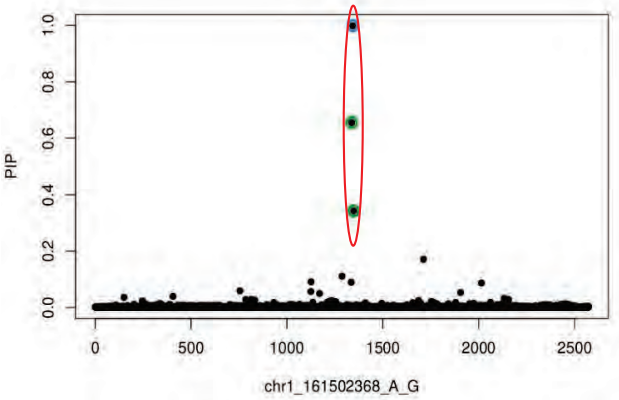
Feature selection using GWAS/SuSIE

UC San Diego

EUR

10374 cases, 454314 controls

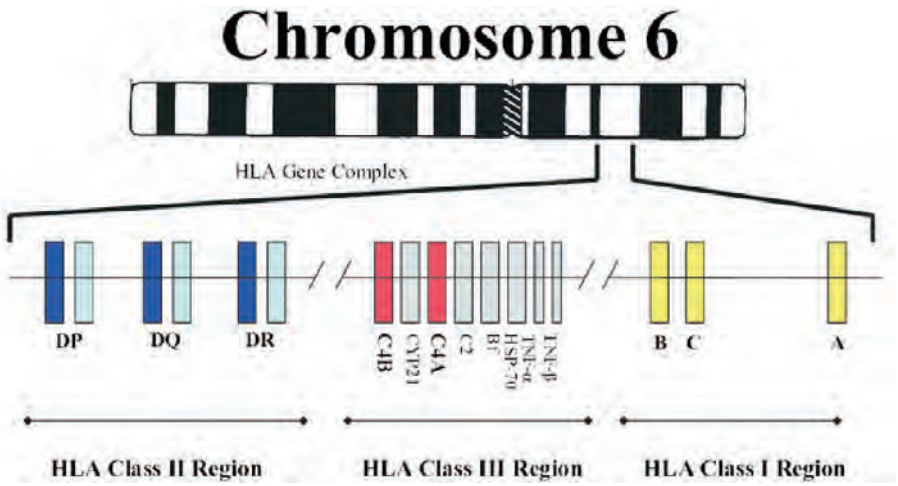


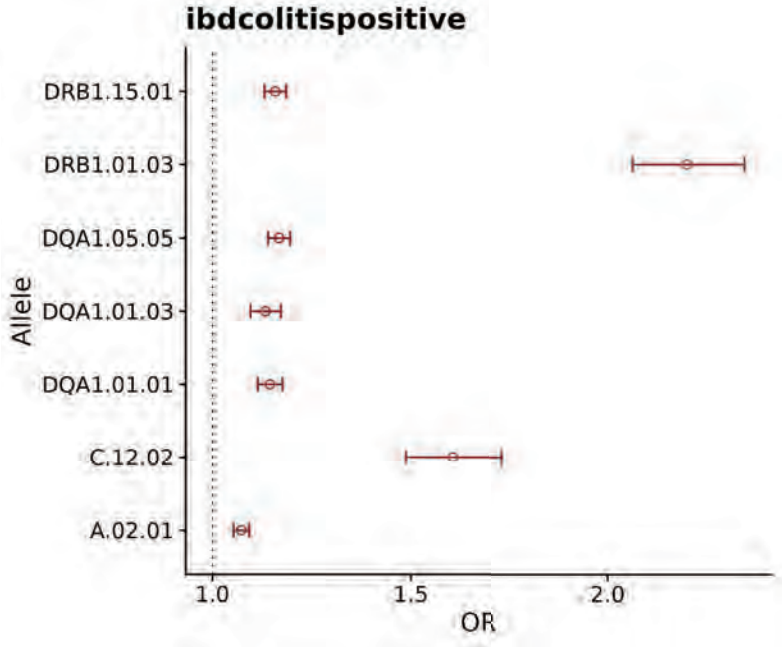


Top Loci

Marker	RSID	Nearest Gene
6:32333650 C/T	rs115378818	TSBP1-AS1
1:67242007 G/A	rs11581607	IL23R
6:31660620 T/A	rs148844907	C6orf47
1:161502368 A/G	rs10800309	FCGR2A

IBD-associated HLA alleles

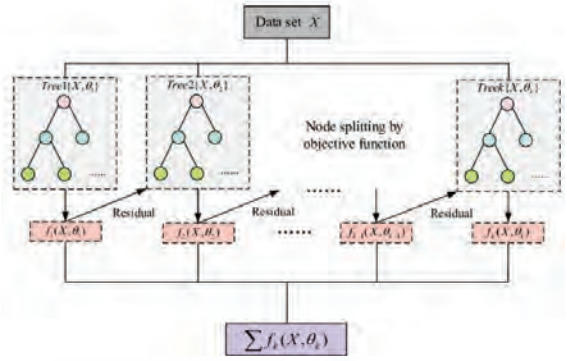


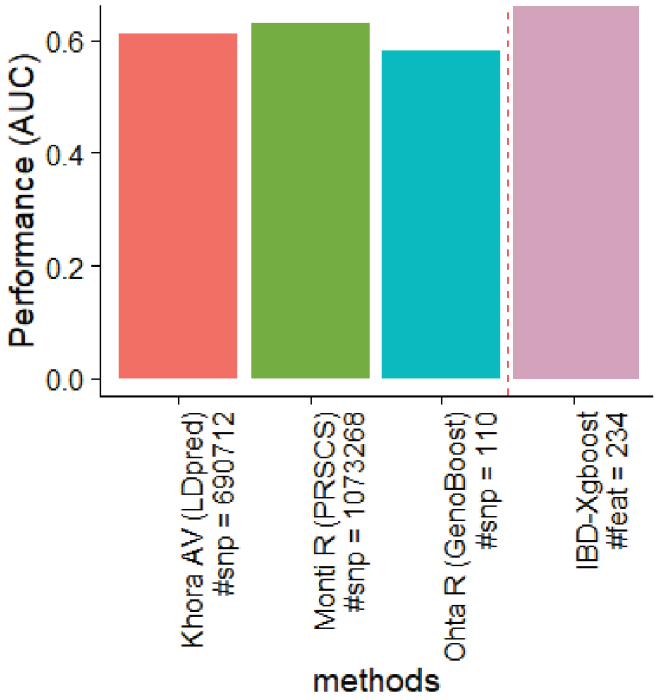


Xgboost vs. Other PRS methods

289 SNPs (fine mapping)

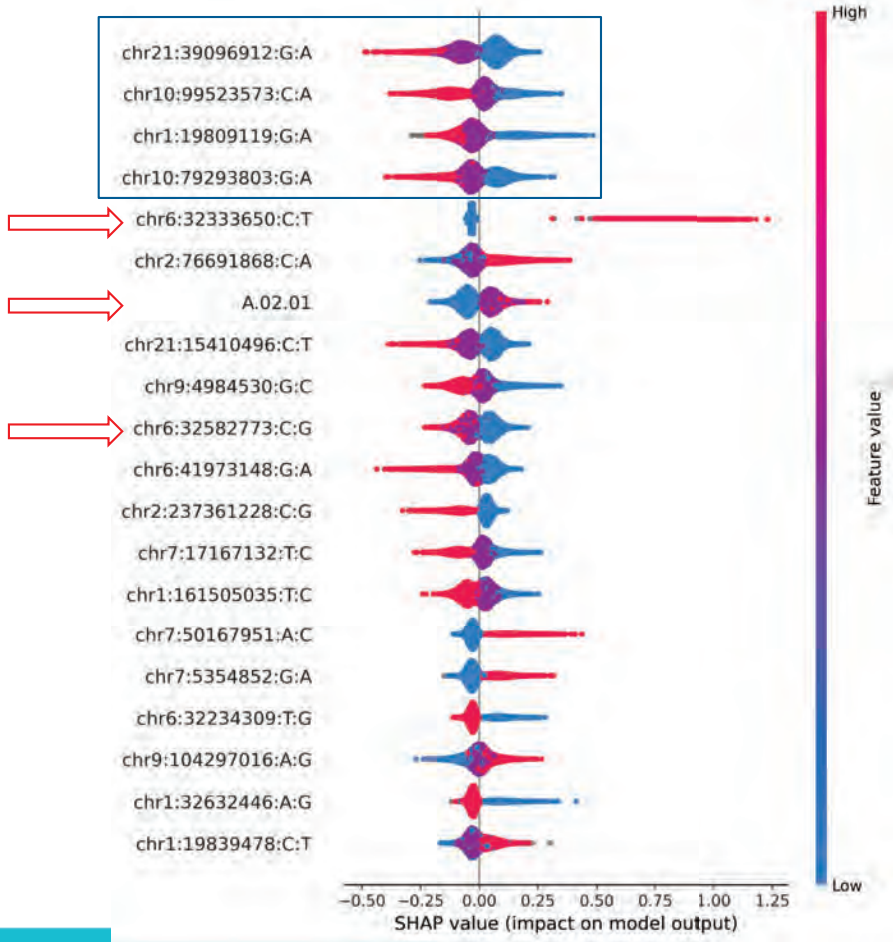
8 HLA alleles (iterative regression)

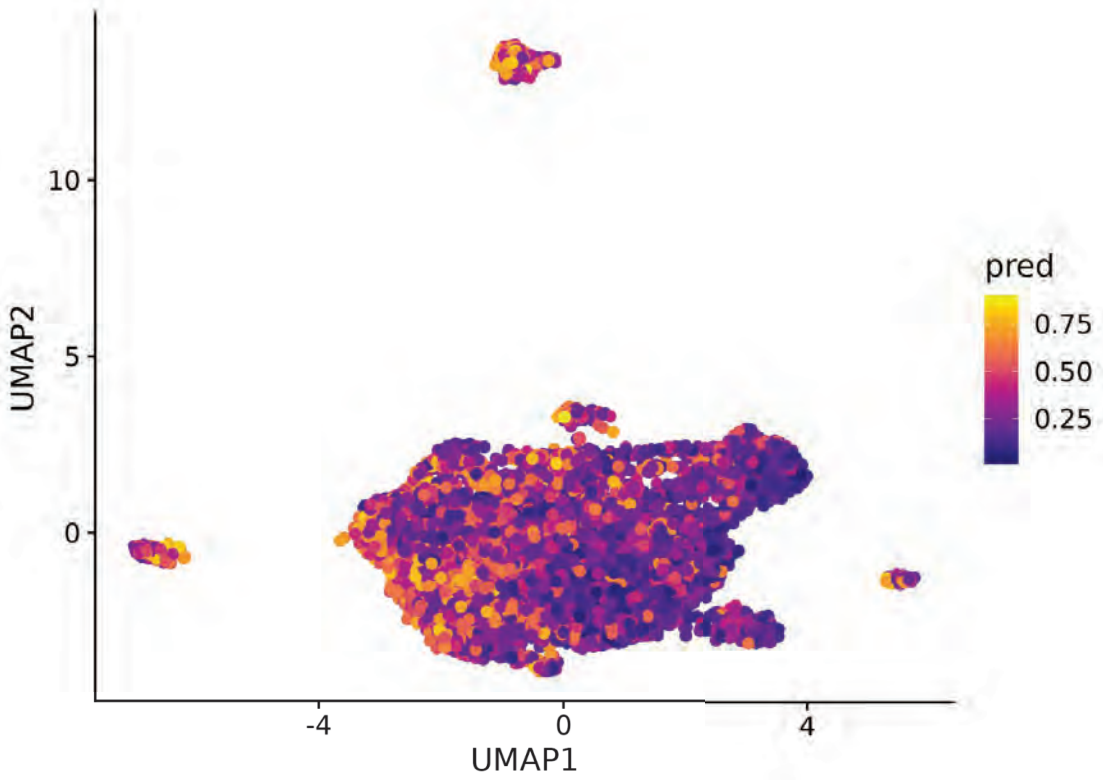




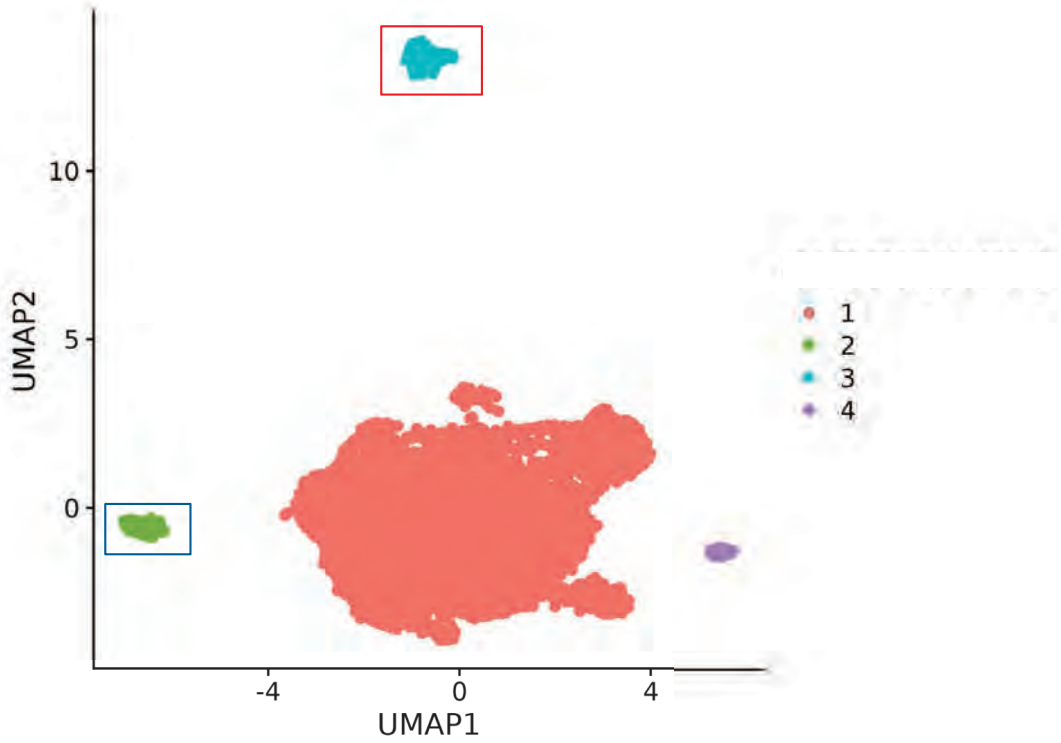
- AUC = .65, Xgboost model achieves equal or better performance to other methods with fewer features

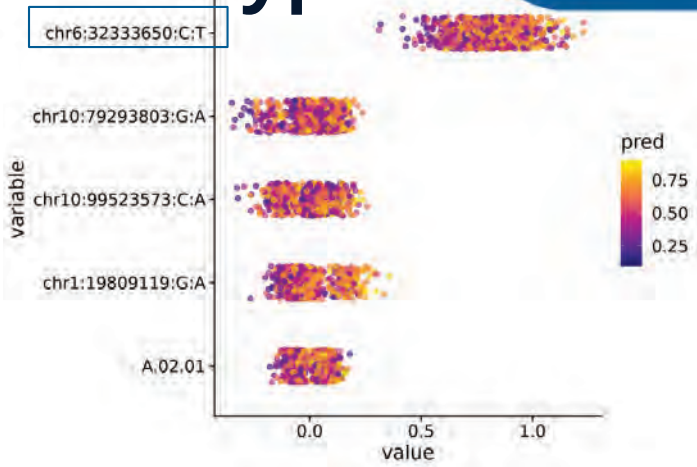
Model reveals important extra HLA contribution

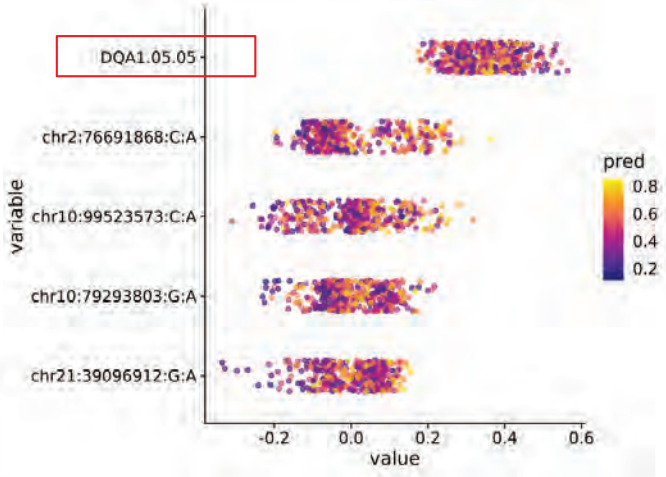




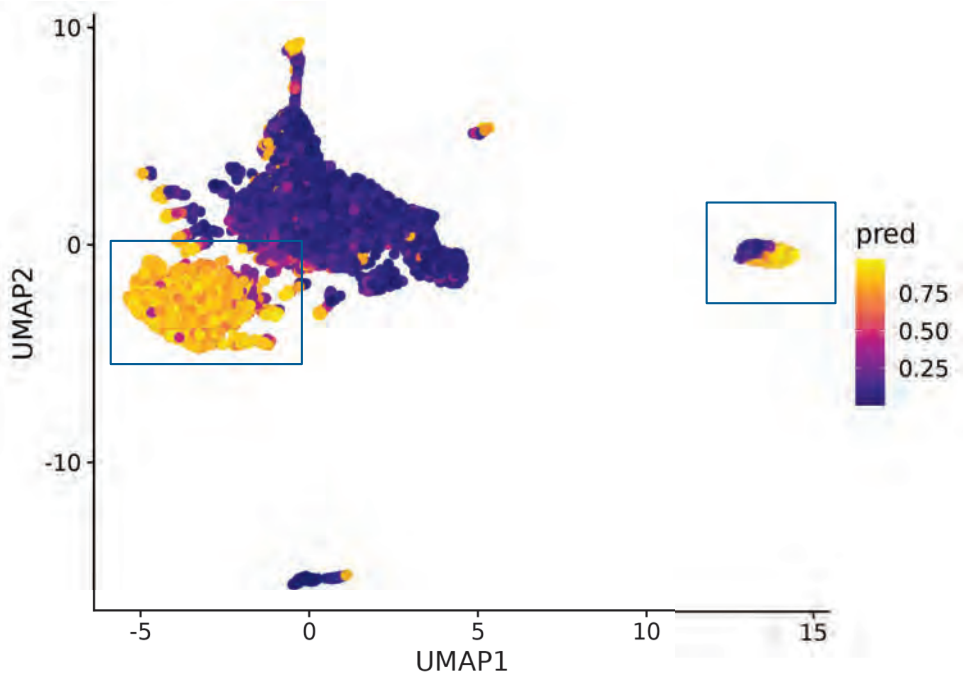
Clustering highlights genetic subtypes

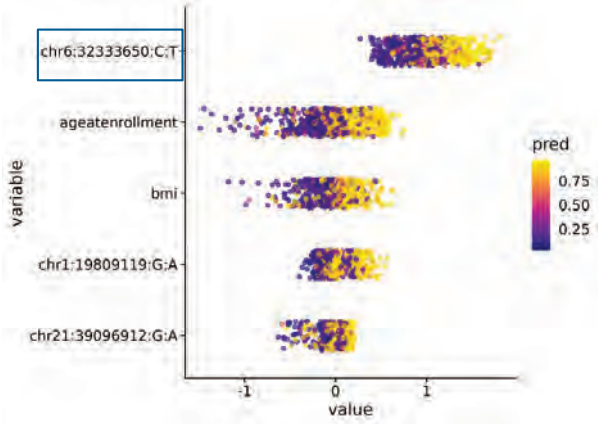


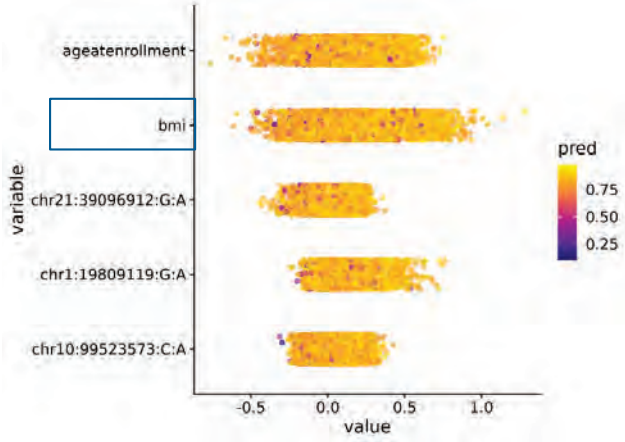




Clinical factors generate additional clusters in prediction







Conclusions

- Fine-mapping plus Xgboost demonstrates on par performance with enhanced interpretability of feature contributions, highlighting putative genetic disease subtypes

Next steps include:

- Improving performance of additional of other environmental contributors such as:
  - psychiatric disorders/stressors e.g. PTSD
  - military chemical exposures e.g. Agent orange
- Association of patient sub-clusters with clinical outcomes
  - disease severity
  - Elevated cancer incidence e.g. colorectal

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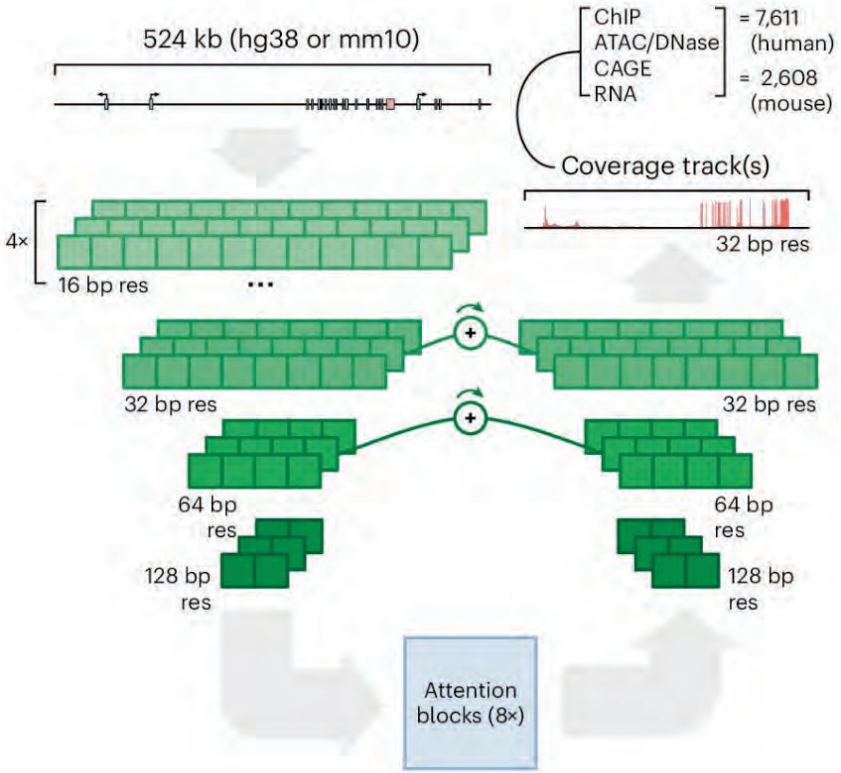
UC San Diego

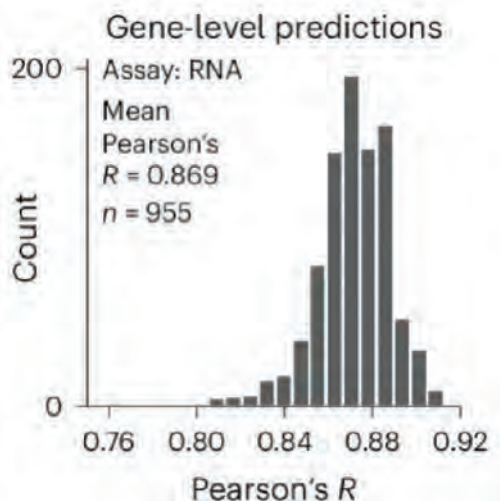
GenVarLoader: an accelerated dataloader for applying deep learning to personalized genomics

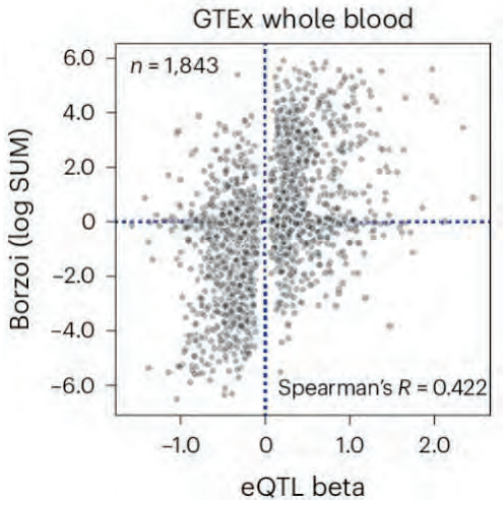
David Laub, 4th year, Carter Lab

BMI 15th anniversary | Jan 24, 2025

Deep learning sequence models are trained on reference genomes to predict gene expression

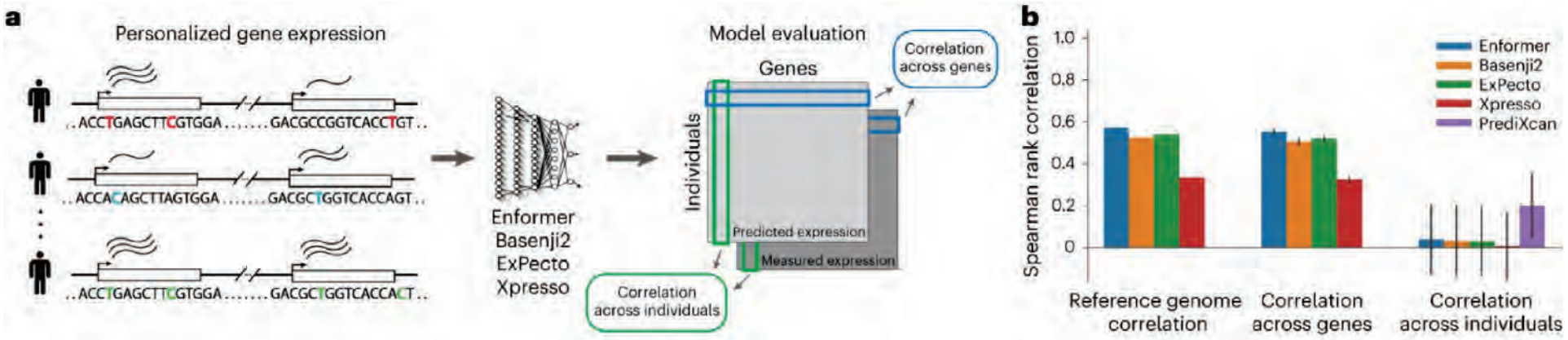






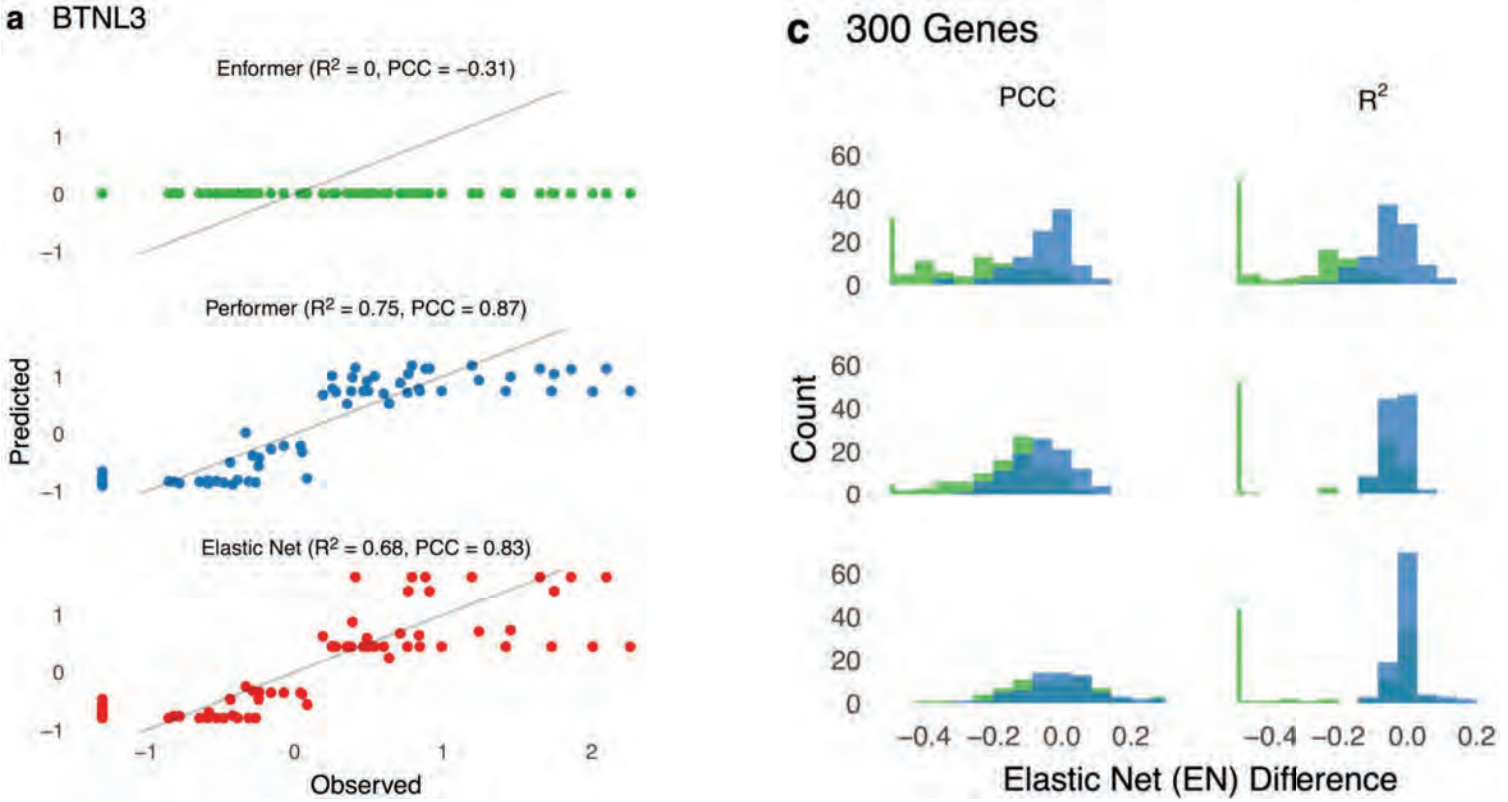
Linder et al. Nat Genet 2025

…however they struggle to predict personal gene expression



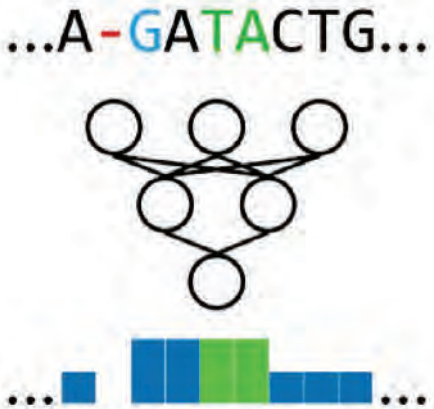
Huang et al. Nat Genet 2023

Training on personal genomes improves predictions to be ~par with SOTA



Drusinsky et al. bioRxiv 2024

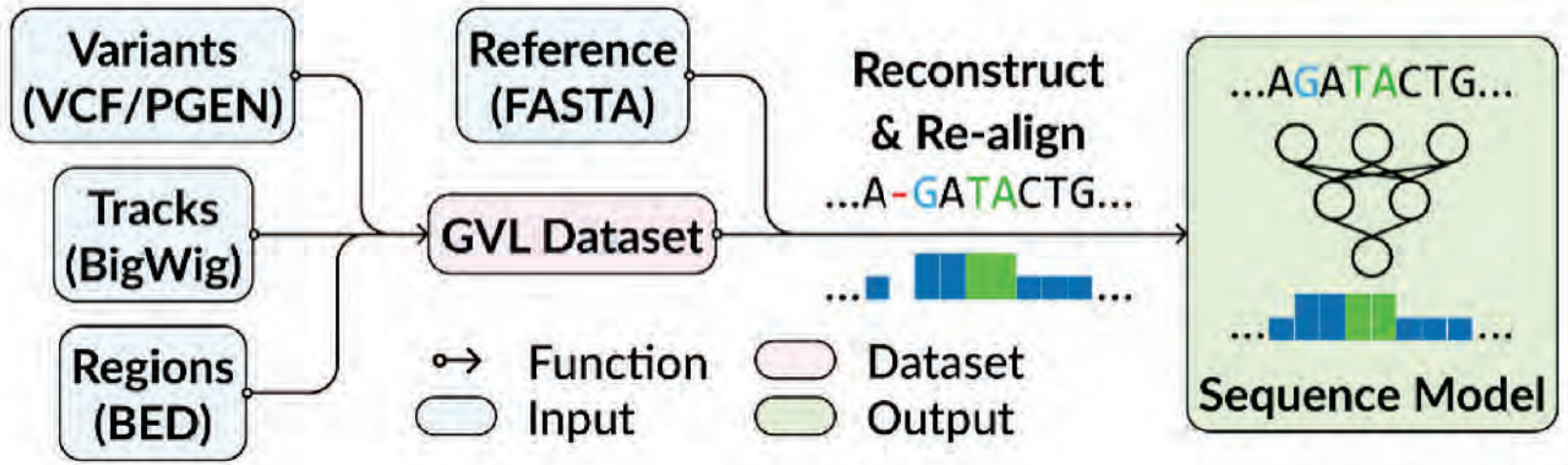
…but methods to use personalized genomics are compute intensive



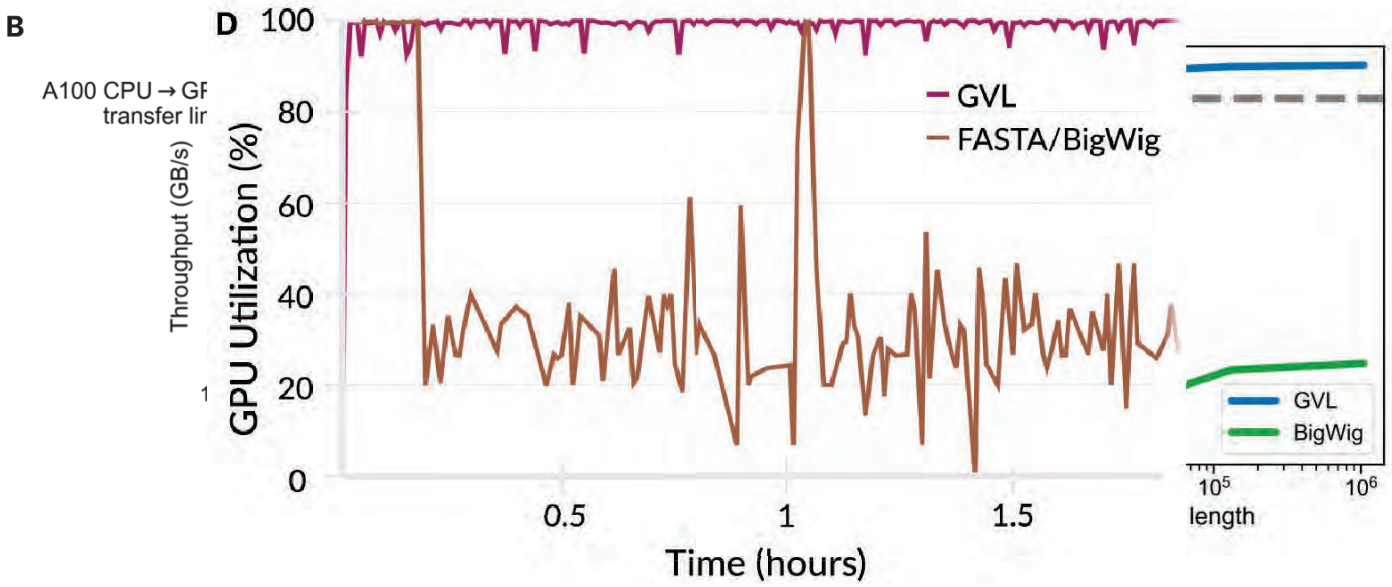
1 genome ≈ 1.8 GB

thousands of genomes ≈ terabytes, petabytes

GenVarLoader fixes this and streamlines the dataloading workflow

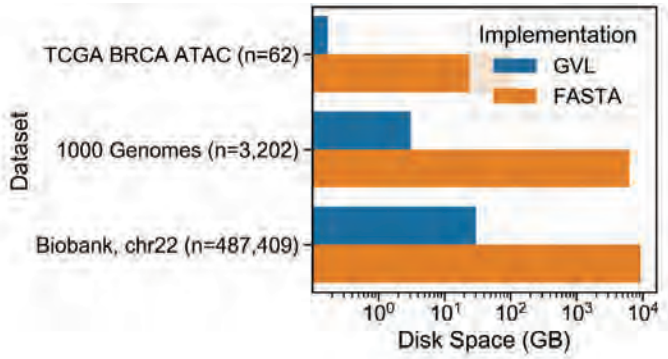


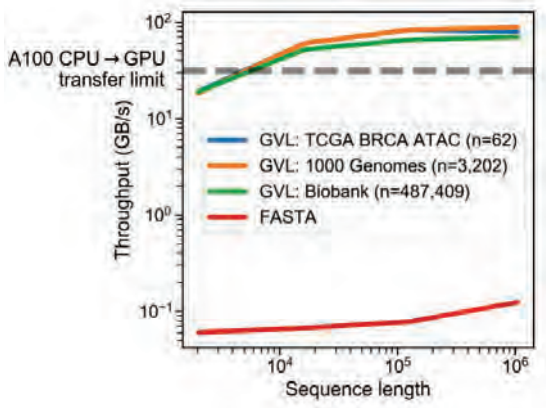
GenVarLoader reduces storage requirements and eliminates bottlenecks



Conclusion

- Improves throughput by up to 1,000x and compression by 2,000x
- Lowers the barrier to applying sequence models to personalized genomics
- Envision sequence models:
  - complementing existing gene expression imputation e.g. TWAS
  - applied to genotypeto-phenotype tasks e.g. GWAS





Acknowledgements

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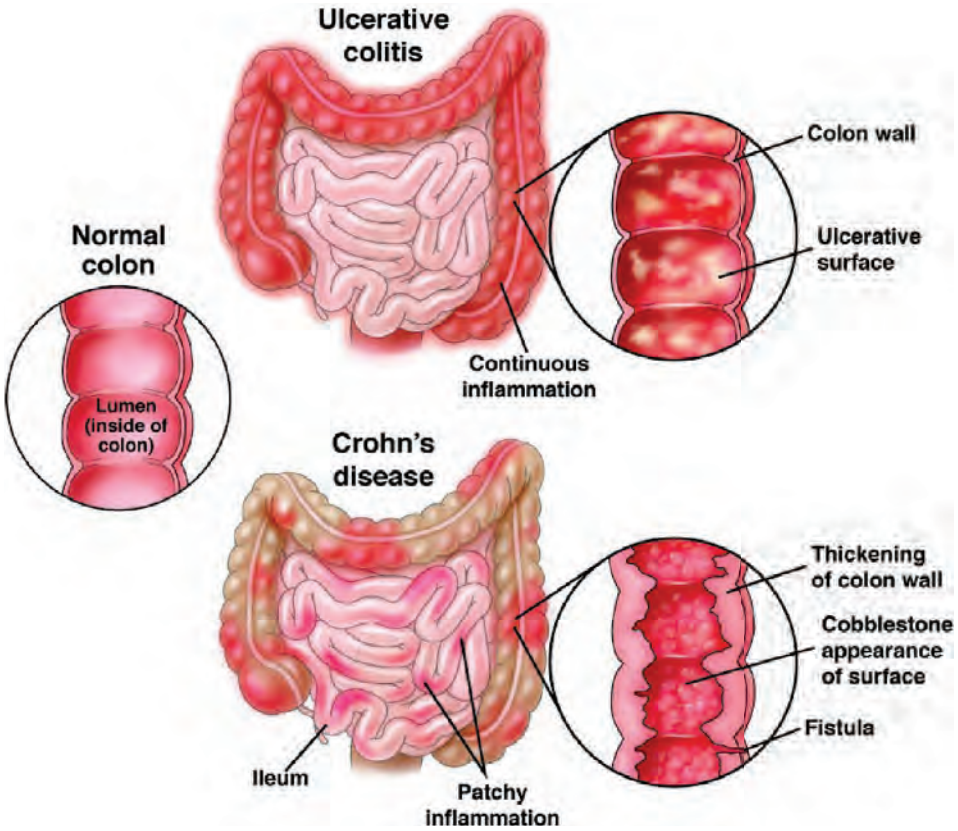
Jeff Jaureguy

UC SAN DIEGO HEALTH
DEPARTMENT OF BIOMEDICAL INFORMATICS

From Manual to Massive: Using LLMs to Scale the “Gold Standard”

Brian Johnson

Quantitative Cancer Control Laboratory · UCSD

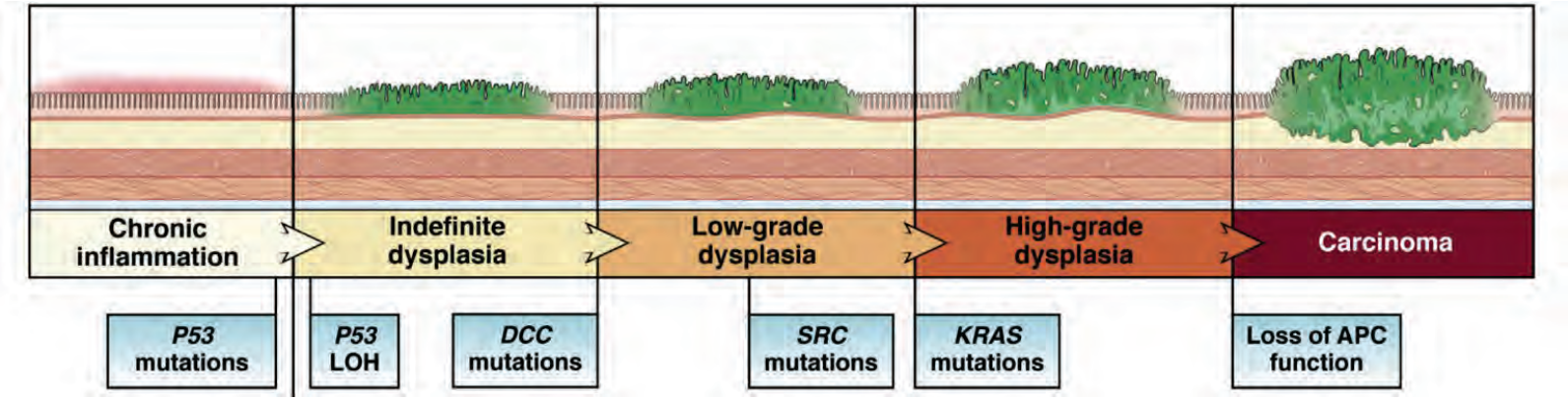


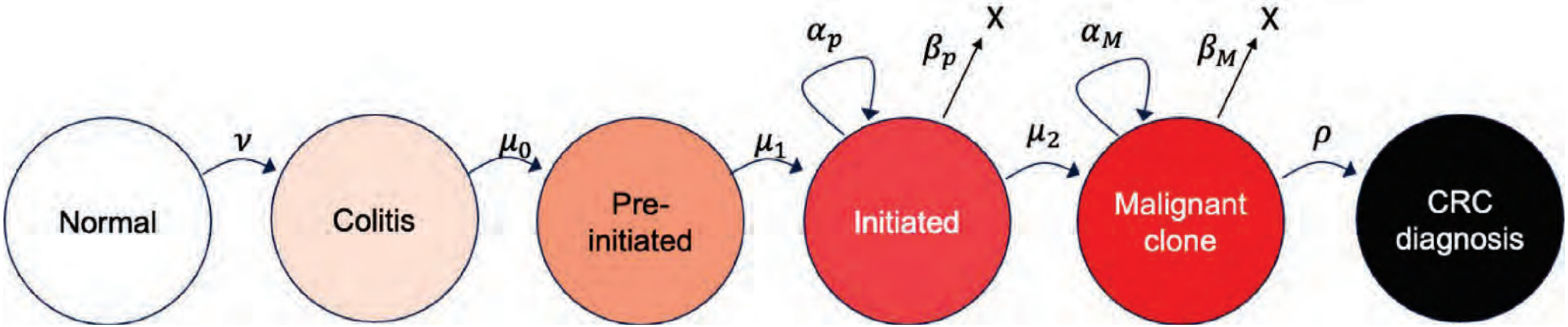
patient.gastro.org/inflammatory-bowel-disease-ibd/

UC = Ulcerative colitis
CD = Crohn's Disease
SIR > 1 means increased risk of CRC

Year	Author	IBD	SIR	CI-	CI+	Weight
1988	Gilat	UC	0.9	-0.4	2.2	8.85%
1988	Rutegard	UC	8.3	-1.1	17.8	0.33%
1995	Stewenius	UC	2.6	1.1	4.1	7.45%
2000	Wandall	UC	1.5	0.3	2.7	9.16%
2000	Palli	UC	1.8	0.7	2.9	9.81%
2004	Jess	CD	1.4	-0.2	2.9	7.02%
2006	Jess	UC	1.1	0.2	2.1	11.40%
2006	Jess	CD	1.4	-0.2	2.9	7.09%
2007	Jess	UC	1.1	0.5	1.6	13.87%
2009	Soderlund	UC	2.7	2.3	3.2	14.66%
2009	Soderlund	CD	2.1	1.1	3.1	10.37%
			1.7	1.2	2.2	100%

Lutgens, Maurice WMD, et al. "Declining risk of colorectal cancer in inflammatory bowel disease…" *Inflammatory bowel diseases* 19(4) 2013. PMID: 23448792





Shah, Shailja C., and Steven H. Itzkowitz. "Colorectal cancer in inflammatory bowel disease: mechanisms and management." Gastroenterology 162(3) 2022. PMID: 34757143

VA Corporate Data Warehouse (CDW)

13-22 million Veterans

~ 60-100k IBD colitis patients

VA | U.S. Department of Veterans Affairs

Million Veteran Program (MVP)

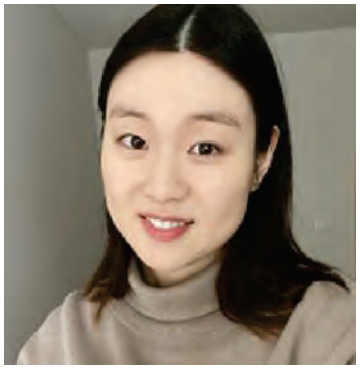
1 million + Veteran volunteers

10-15k IBD colitis patients

CDW data and **germline genetic information**

MVP MILLION VETERAN PROGRAM

Tyler Bath



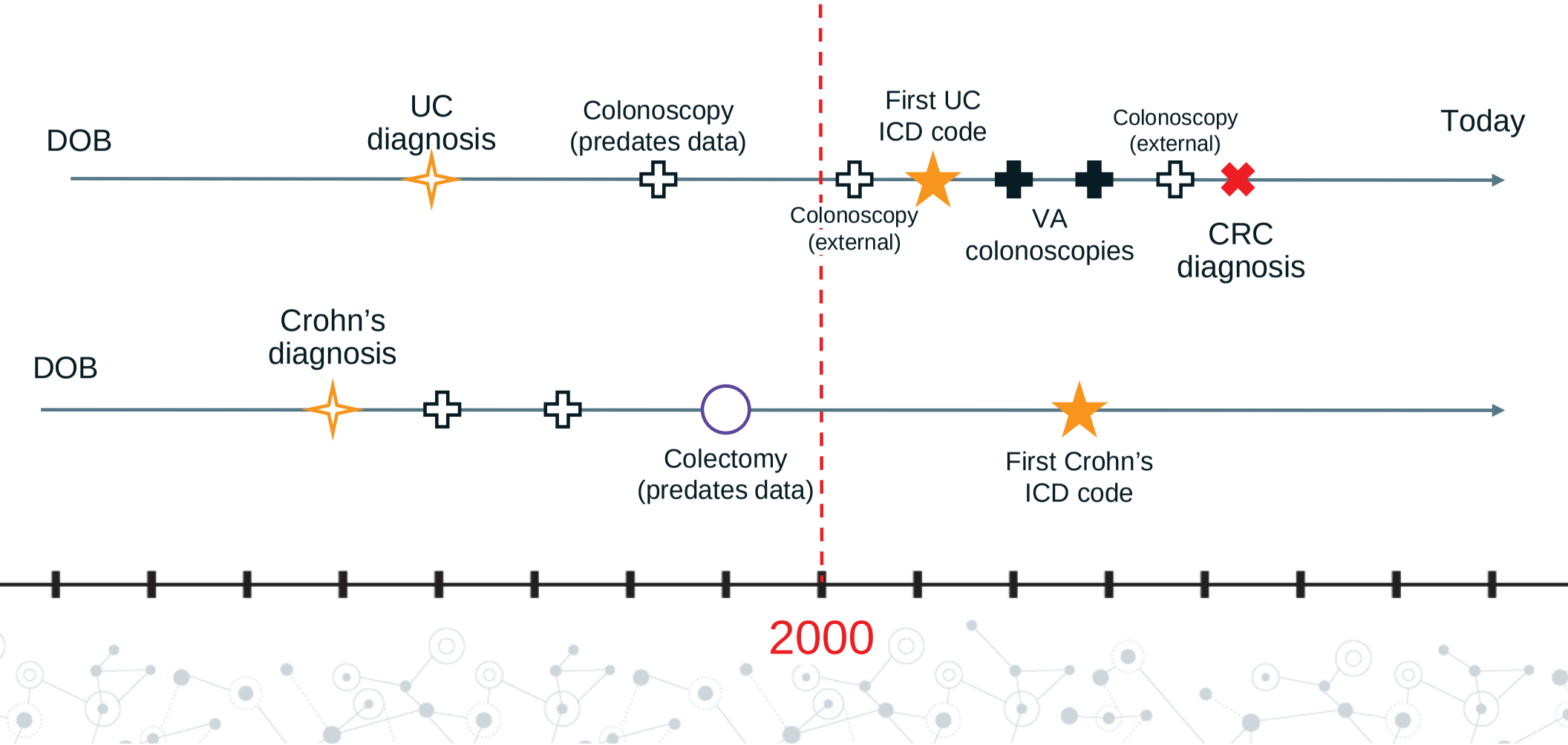
Cindy Huang

Initial results:
Identifying diagnoses from pathology reports

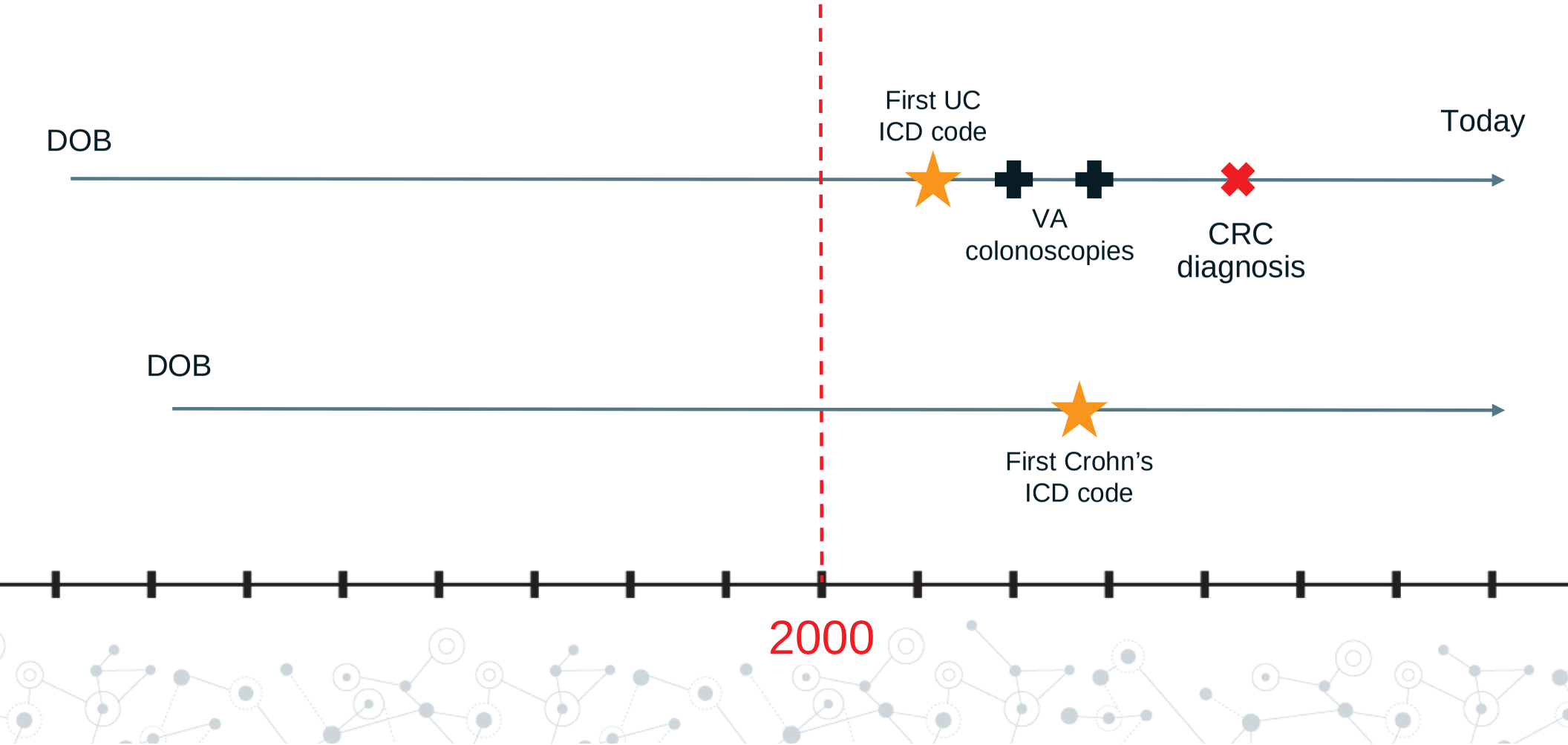
Task	PPV (LB - UB)	NPV (LB - UB)	Recall (Sensitivity)	Specificity	F1	MCC
CRC	0.962 (0.92-0.99)	0.993 (0.96-1.00)	0.980	0.987	0.971	0.961
HGD/CRC	0.961 (0.92-0.99)	0.993 (0.96-1.00)	0.968	0.992	0.964	0.957
Dysplasia	0.987 (0.95-1.00)	0.987 (0.95-1.00)	0.956	0.996	0.971	0.963

Johnson, Brian, et al. "Large language models for extracting histopathologic diagnoses from electronic health records." *medRxiv* (2024): 2024-11.

WIP: full patient timelines



WIP: full patient timelines (what we see now)



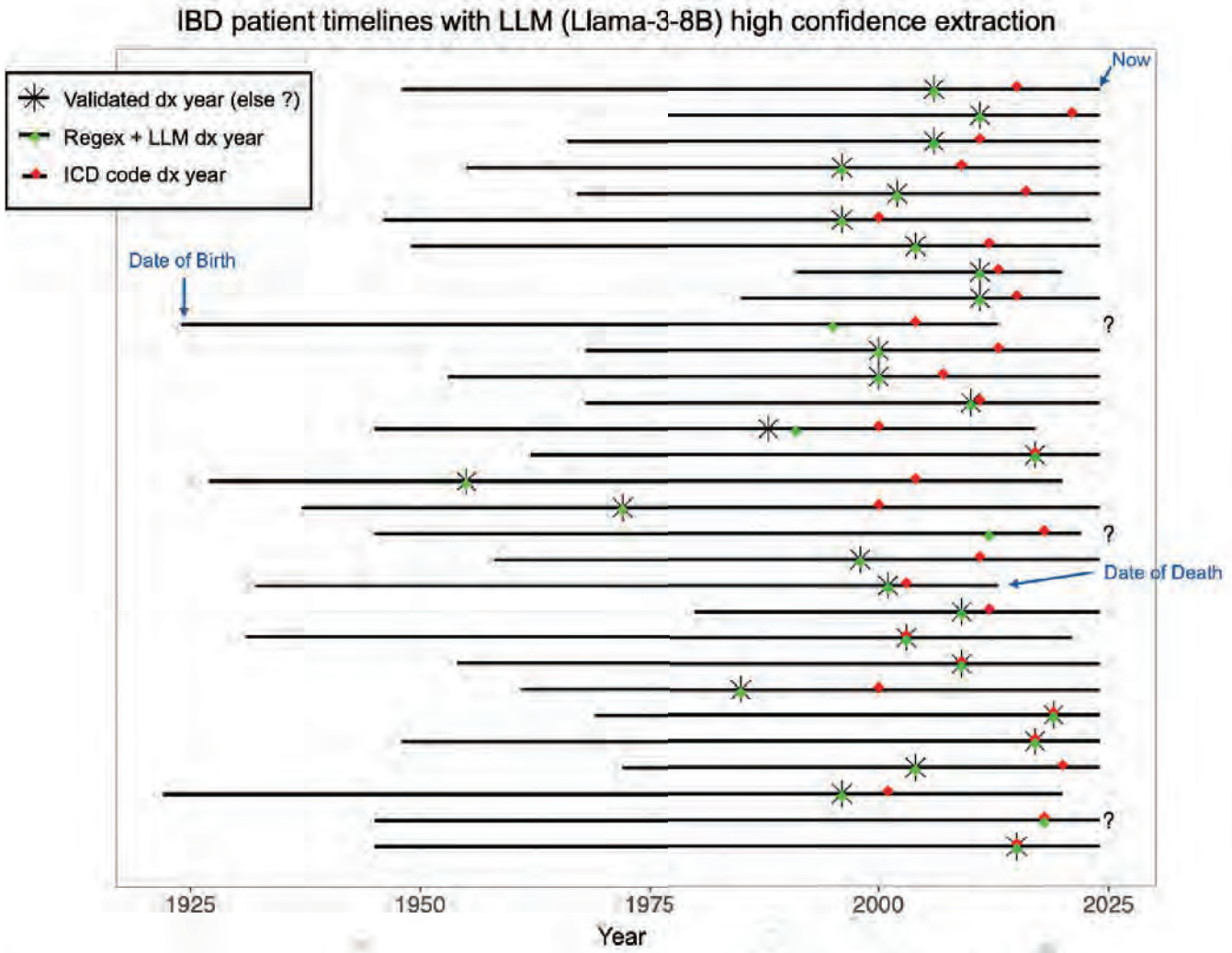
Match terms and three lines of context

Patient Name: John Doe
Date of Birth: January 15, 1950
Date of Visit: June 9, 2024
Chief Complaint: Follow-up visit post-colonoscopy.
History of Present Illness: Mr. John Doe presents for a follow-up appointment following his recent colonoscopy. The procedure was performed on June 5, 2024, and the results were clean with no polyps or malignancies detected.
Medical History:
•Ulcerative Colitis (UC) - Diagnosed 15 years ago.
•Medication: Mesalamine 2.4g daily.
Current Medications:
•Mesalamine 2.4g daily.
Review of Systems:
•GI: No abdominal pain, no diarrhea, no blood in stool.
•Overall: Symptoms are mostly managed well with occasional mild flare-ups.
Physical Examination:
•Vitals: Stable
•Abdomen: Soft, non-tender, no masses.
•Rectal Exam: Deferred
Assessment:
1.Ulcerative Colitis - stable on current medication.
Plan:
1.Continue mesalamine 2.4g daily.
2.Routine follow-up in 6 months unless symptoms worsen.
3.Patient advised to return if experiencing any new or worsening symptoms.
Notes:
•Patient expressed relief at the clean colonoscopy results.
•Discussed the importance of medication adherence and regular monitoring of symptoms.

[System prompt]

<<<
[Input Text 1]
[Input Text 2]
[Input Text 3]
...
>>>
Instruction
Determine the calendar year of original IBD colitis diagnosis.

Original year of diagnosis: 2009, Confidence: High
Colitis type: Ulcerative colitis, Confidence: Certain


IBD patient timelines with LLM (Llama-3-8B) high confidence extraction
Validated dx year (else ?)
Regex + LLM dx year
ICD code dx year
Now
Date of Birth
Date of Death
?
?
?
1925
1950
1975
2000
2025
Year

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Anna Dornisch

Samir Gupta
Shailja C. Shah
Lily J. Jih
Mark Lamm
Ashley Earles
Joshua Demb

UC San Diego

Advancing Humanism and Health Outcomes Through Artificial Intelligence

Moderator: Jejo Koola, MD

Panel:

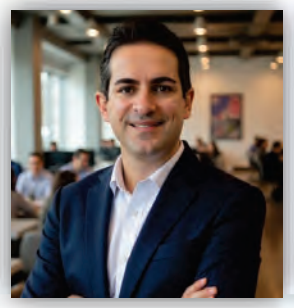
- Karandeep Singh, MD
- Chris Longhurst, MD
- Robert El-Kareh, MD

Division of Biomedical Informatics 15-Year Symposium | January 24, 2025

UC San Diego

PANEL DISCUSSION

Industry Perspectives on Digital Health and Academia/Industry Collaborations



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Assoc. Professor of Biomedical Informatics

Brenda Schmidt

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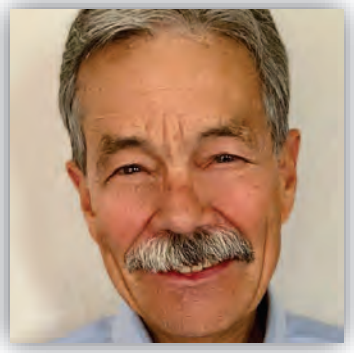
Kei Nakagawa, MD

Director of Strategic Growth & Impact
UCSD
Jacobs Center for Health Innovation

Ben Sperling

VP, Enterprise Intelligence Services
Siemens – Healthineers



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Tech Coast Angels / NuFund

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