Translational Artificial Intelligence (AI): The Need to Translate from Basic Science to Clinical Value

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Translational Artificial Intelligence (AI): The Need to Translate from Basic Science to Clinical Value

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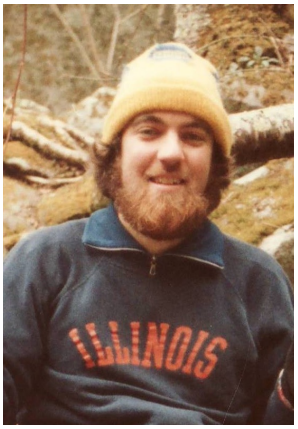
1

Competing and other interests

- Funding for EHR cohort discovery research from
  - Alnylam Pharmaceuticals
  - PTC Pharmaceuticals
- Thanks to the 35 who have completed and the 7 currently enrolled in the 10x10 course



2

Translational AI – outline

- Promise of artificial intelligence (AI) and machine learning (ML) in medicine
- Current state of clinical impact of AI
- Research aiming to diagnose rare disease using ML
- Educating clinicians and informaticians
- Future directions

3

One-slide history of AI and ML in medicine

- A major activity of clinical informatics has been application of AI with aim of improving patient care (Shortliffe, 2019)
- First generation in 1960s-1980s
  - Focus on hand-crafted knowledge bases
  - Computers lacking data, processing power, GUIs, Internet, etc.
  - Led to "AI winter" in late 1980s and beyond
- Resurgence in 21st century
  - Driven by advances in ML, especially deep learning
  - Based on plentiful data, computer power, and networks
  - Overviews – Topol (2019), NAM (2019), Cohen (2022)
  - Still modest impact (as of 2023) in clinical settings

4

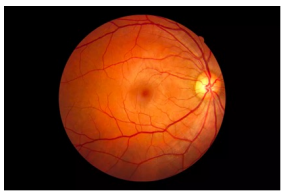
Promise of ML and AI in medicine

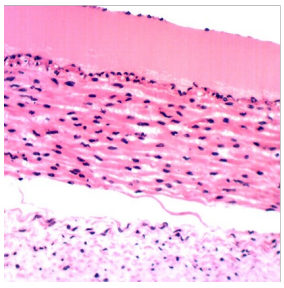
- Imaging
- Other applications
- Systematic reviews
- Building the evidence base

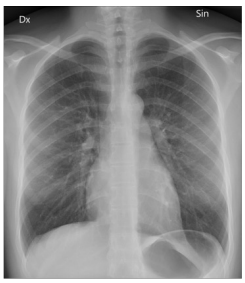
5

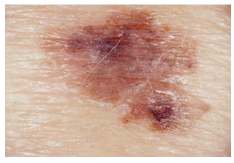
Imaging

- Earliest success for ML and AI
  - Diabetic retinopathy (DR) (Gulshan, 2016; Ting, 2017)
  - Histology of cancer (Bejnordi, 2017) and metastases (Veta, 2019)
  - Tuberculosis (Lakhani, 2017) and pneumonia (Rajpurkar, 2018)
  - Skin cancer (Esteva, 2017; Haenssle, 2018; Tschandi, 2019)
- Systematic review (Liu, 2019)
- State of the art (Esteva, 2021)





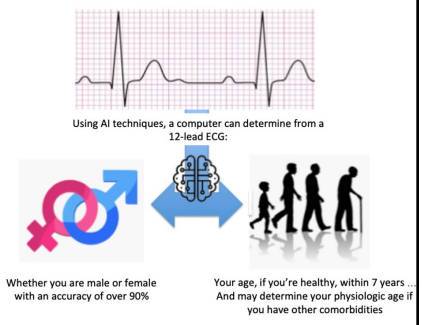




6

Many, many other application areas

- Wave forms – use of ECGs to determine age and sex (Attia, 2019)
- Age and sex determination from retinal images (Poplin, 2018)
- Length of stay, mortality, readmission, and diagnosis at two large medical centers (Rajkomar, 2018)
- Automatically charting symptoms from patient-physician conversations (Rajkomar, 2019)
- "Weakly supervised" (using clinical diagnoses) interpretation of pathology slides would allow pathologists to exclude 65–75% of slides while retaining 100% sensitivity (Campanella, 2019)
- AI system helped physicians extract relevant patient information from EHR in shorter time while maintaining high accuracy (Chi, 2021)



7

And now, large language models (LLMs)

- Building large models based on general and/or clinical text
- BERT models have transformed natural language processing capabilities, including in medicine, e.g., (Yang, 2022; Lehman, 2023; Li, 2023)
- And of course, ChatGPT has captured the public imagination, with some early successes in medicine
  - Diagnostic and triage accuracy for 45 vignettes comparable to physicians (Levine, 2023)
  - Answers to 21/25 questions about cardiovascular disease prevention deemed acceptable for patient-facing information platform and as AI-generated draft responses to questions sent by patients (Sarraju, 2023)
  - Performed at or near passing for three levels of USMLE (Kung, 2023)
  - My own experience (documented in my blog): some correct answers but also confabulation and not admitting it does not know

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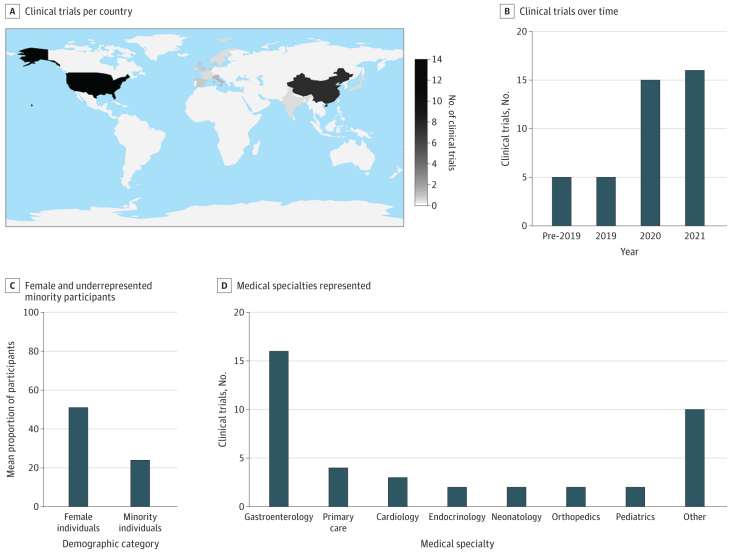
Current state of impact of AI

- From pubmed.gov
  - Tens of thousands of studies applying ML or AI
  - Hundreds of systematic reviews of ML and AI studies – mostly of models applied to clinical topics
- How many studies assessing ML/AI interventions using gold standard, RCT?
  - Collated in systematic reviews – earlier ones did not assess as rigorously, e.g., (Zhou, 2021; Lam, 2022)
  - Most recent and rigorous (Plana, 2022)

Systematic review of RCTs of ML/AI in healthcare (Plana, 2022)

- Exhaustive search of literature databases to identify RCTs of ML/AI interventions through October, 2021
- Excluded studies of non-RCT design, absence of original data, and evaluation of nonclinical interventions
- Identified 41 RCTs for further analysis
- Analyzed RCT characteristics, including primary intervention, demographics, adherence to CONSORT-AI reporting guideline, and Cochrane risk of bias

Where, when, who, and what (Plana, 2022)



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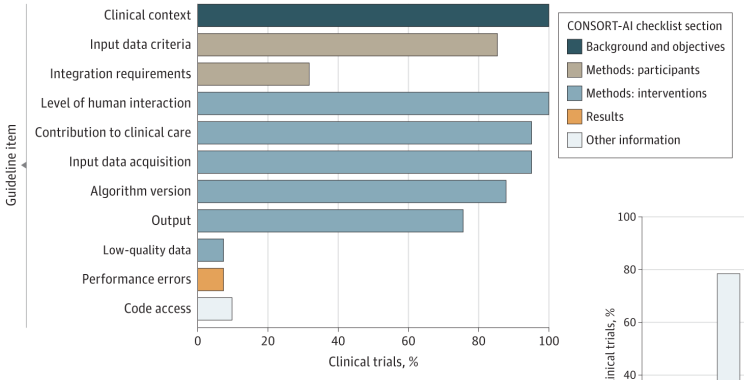
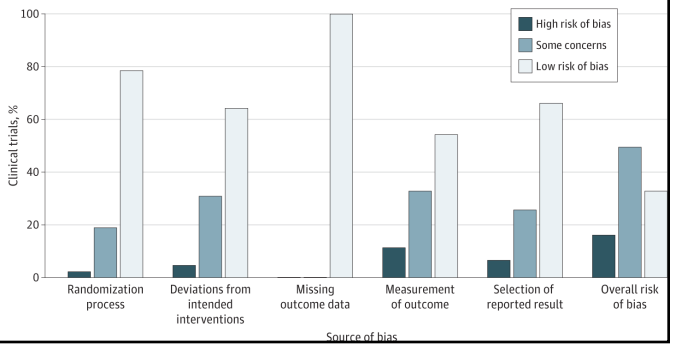
Adherence to reporting guidelines and risk of bias (Plana, 2022)



- No assessment of study outcomes, unlike Zhou (2021) showing about 60% positive
- No attempted meta-analysis



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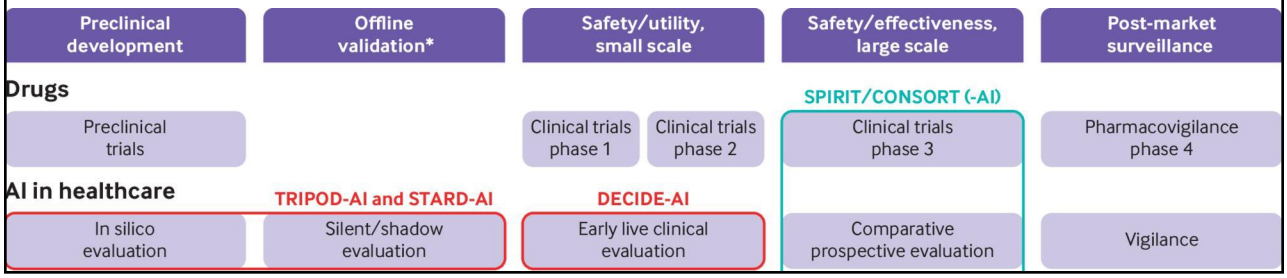
Clear need to build evidence base

- As with all evidence-based medicine (EBM), major questions that guide patient care to ask about ML/AI include
  - Diagnosis – "test" for a "disease"
    - Ideally from comparison with "gold standard"
    - Predictive models are type of diagnostic test
  - Treatment – therapy or intervention to prevent or treat disease; ideally from randomized controlled trial (RCT)
- Studies of both questions can be aggregated into systematic reviews that may (if data allow) be combined via meta-analysis
- Appraisal tools being developed for AI studies (Ibrahim, 2021)



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My work: applying information retrieval (search) to EHR data

- Use cases
  - Cohort discovery
  - Detection of rare diseases
- Data set
  - 100-300K records extracted from OHSU Research Data Warehouse (fully identifiable)
- Funded by grants from
  - NLM 1R01LM011934
  - Alnylam Pharmaceuticals
  - PTC Pharmaceuticals
- With help from OHSU collaborators
  - Steven Bedrick
  - Steven Chamberlin
  - Aaron Cohen
  - Tom Deloughery

(Hersh, 2020)

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Cohort discovery

- Methods (Wu, 2017) and results (Chamberlin, 2020) for collection of 100K records
- R01 with Mayo and UT Houston renewed; updating data, systems, and methods
  - Standardizing on OMOP to share tools and methods across sites
- Major challenges
  - Heterogeneous records
  - Privacy concerns

Adults with IBD who haven't had GI surgery	Adults with inflammatory bowel disease who haven't had surgery involving the small intestine, colon, rectum, or anus.
Adults with a Vitamin D lab result	Adults with a lab result for 25-hydroxy Vitamin D collected between May 15 and October 15.
Postherpetic neuralgia treated with topical and systemic medication	Adults with postherpetic neuralgia ever treated by concurrent use of topical and non-opioid systemic medications.
Children seen in ED with oral pain	Children who were seen in the emergency department with herpetic gingivostomatitis, herpangina or hand, foot, and mouth disease, tonsillitis, gingivitis, or ulceration (aphthae, stomatitis, or mucositis) not due to chemotherapy or radiation.
3rd trimester prenatal visit with midwife or Ob/Gyn	Women who had a pregnancy with a 3rd trimester outpatient prenatal visit with an obstetrician and gynecologist or midwife.

Rare disease detection

- Over 1200 known rare disorders that affect < 1 in 200K patients worldwide, many under-diagnosed (https://rarediseases.org/; Haendel, 2020)
- Acute Intermittent Porphyria (AIP, aka Acute Hepatic Porphyria)
  - Rare genetic disease of heme biosynthesis – variable penetrance
  - Incidence 1 per 100K in population
  - Often undiagnosed for long time
  - Significant morbidity and effect on quality of life
  - "Neurovisceral" symptoms common with other diseases
    - Abdominal pain
    - Nausea and vomiting
    - Psychiatric changes
  - Diagnosed by inexpensive urine porphobilinogen test
  - New highly effective (and highly expensive) treatment available – RNA-silencing molecule givosiran (Balwani, 2020)

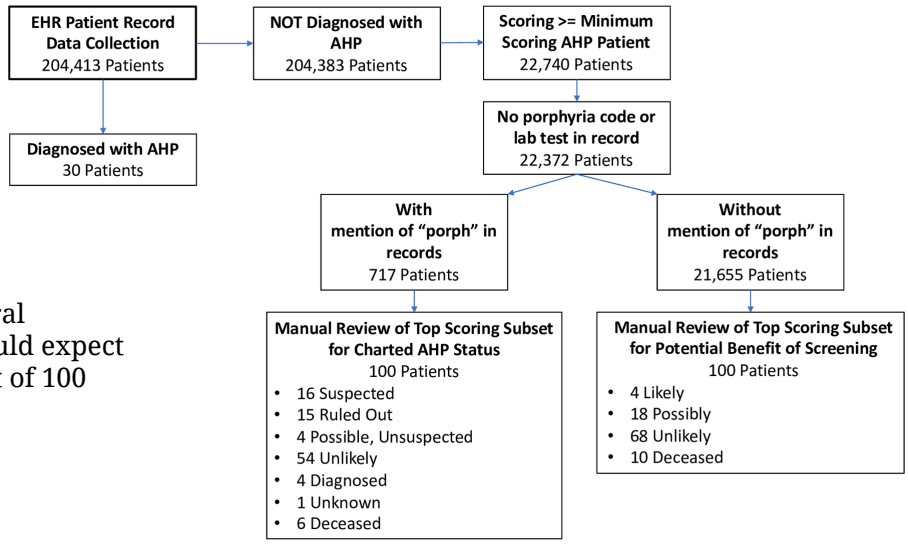
Can we detect rare diseases earlier using population-based techniques with EHR data?

- Funding from Alnylam Pharmaceuticals
- Expanded EHR data set to 200+ K patients
  - Updated base data set to 200K patients
    - Including from post-2015 era of ICD-10-CM coding
  - Enriched with 5,571 additional patients having "porph" in diagnoses, lab tests, and notes
- Preparation for machine learning
  - Positive training cases from ICD-10-CM E80.21 (47) with manual review to verify (30)
  - Negative training cases were the rest

ML approach (Cohen, 2020)

- Parsed EHR record into features – scored by frequency of appearance, labeled features by the EHR source document
- Univariate feature analysis – manually choose features not directly tied to provider attributes or suspecting patient had porphyria
  - e.g., "DeLoughery" and "cimetidine"
- Trained on full dataset, with best performance using support vector machine (SVM) with radial basis function (RBF) kernel
- Applied trained model back to full data set – ranked patients by margin distance

Aimed to identify patients with symptoms but no consideration of diagnosis of AIP

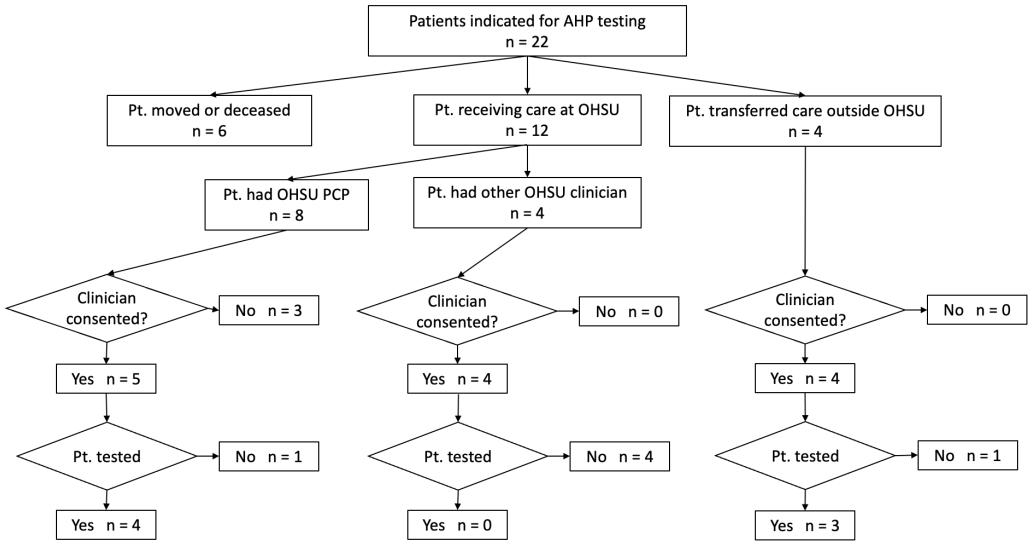


Note with natural prevalence, would expect 0.0005 cases out of 100

Clinical study (Hersh, 2022)

- Hindered by prolonged IRB process and COVID-19 pandemic, study was launched in late 2020
- IRB protocol required initial contact with primary care physician and, if they approved, offering the patient urine porphobilinogen testing
- Aimed to contact and enroll all 22 patients with AIP symptomatology but "unrecognized"

Clinician and patient participation



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And the results showed…

- All 7 patients who came for testing had normal urine porphobilinogen
- Lessons learned
  - Clinical validation of machine learning models essential
  - Two-step approval required for patients not under our care but complicated
  - Rare diseases are rare
  - For other diseases, testing may be expensive and/or harmful
- Next steps
  - Discovery of patients with AADC deficiency (PTC Pharmaceuticals)

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Other aspects of translational AI – clinicians must understand enough to use in practice

- Another competency in clinical informatics (Hersh, 2014; Hersh, 2022)
- Must be prepared for a clinical world influenced by AI (James, 2022)
- Medical schools may be "missing the mark" on AI (Palmer, 2023)
- AI should be taught as a "fundamental toolset of medicine" (Ötleş, 2022)

1. Find, search, and apply knowledge-based information to patient care and other clinical tasks
2. Effectively read from, and write to, the electronic health record for patient care and other clinical activities
3. Use and guide implementation of clinical decision support (CDS)
4. Provide care using population health management approaches
5. Protect patient privacy and security
6. Use information technology to improve patient safety
7. Engage in quality measurement selection and improvement
8. Use health information exchange (HIE) to identify and access patient information across clinical settings
9. Engage patients to improve their health and care delivery though personal health records and patient portals
10. Maintain professionalism through use of information technology tools
11. Provide clinical care via telemedicine and refer patients as indicated
12. Apply personalized/precision medicine
13. Participate in practice-based clinical and translational research
14. Apply machine learning applications in clinical care

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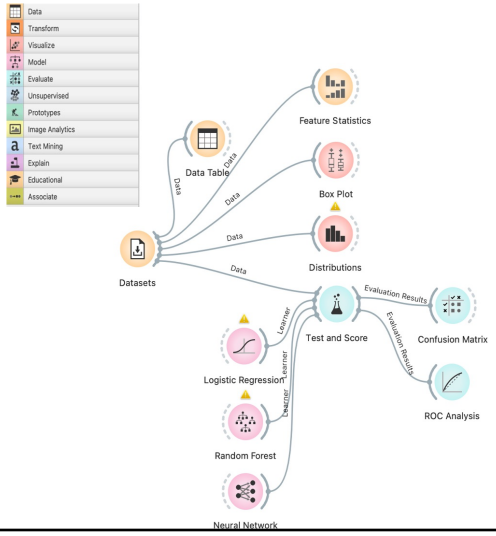
Informaticians must be able to implement and evaluate

- Have implemented "applied" machine learning course at OHSU for those with modest math and programming backgrounds
- Role for visual programming tools, e.g., Orange?
  - (Hoyt, 2022; Hoyt, 2022)
  - https://orangedatamining.com/



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Also cannot forget concerns about AI

- Data and algorithm bias
  - Clinical data may not be complete or accurate (Hersh, 2013)
  - Bias of clinicians and others may be "baked in" to data, leading to biased algorithms (Obermeyer, 2019; DeCamp, 2020)
- Language bias
  - Google searches for "professional" vs. "unprofessional" hair styles reveal racial differences (Alexander, 2016)
  - Training on large amounts of language "learns" biases inherent in text (Sheng, 2019; Logé, 2021)
- Privacy
  - Google, Apple, and others show large language models trained on public data expose personal information (Carlini, 2020; Wiggers, 2020)
  - May be compromised by need for data to be used to improve tools, e.g., Dragon voice recognition (Ross, 2022) and data re-identification (Ross, 2022)
- "Non-human" authors of scientific papers (Liebrenz, 2023; Flanagin, 2023)

How will ML and AI impact healthcare?

- Physicians (Jha, 2016; Jha, 2018; Shah, 2019) and ML (Verghese, 2018) must adapt
- "AI won't replace radiologists, but radiologists who use AI will replace radiologists who don't," (Langlotz, 2019)
  - True for all physicians, even Dr. McCoy?

Future directions

- As in all of medicine, results of basic science advances in AI must achieve clinical translation
- We must be cognizant of all types of bias and ensure fair and trustworthy AI
- As will all informatics, people are more important than technology
- Predictive models are important but must implement and evaluate in clinical settings
- *Great opportunity for informatics research and researchers!*

Thank you!

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