





THE ECOSYSTEM OF EVIDENCE

Lessons learned in the pandemic era and future challenges

10th International Conference for EBHC Teachers and Developers 10th Conference of the International Society for EBHC Taormina, 25th - 28th October 2023

#EBHC2023



Al evidence for use in clinical practice

The good, the bad and the ugly – and what now for the EBHC community?

Per Olav Vandvik

CEO, MAGIC Evidence Ecosystem Foundation, Oslo Professor, Faculty of Medicine, University of Oslo Acting consultant, Department of Medicine, Lovisenberg Diaconal Hospital Trust, Senior researcher, Norwegian Institute for Public Health

Declarations of interest: CEO of MAGIC, no AI expert (and perhaps an EBM dinosaur). No financial COI

Agenda

- Perspective of my talk*
 - Advances in EBHC and role of guidelines
 - An encounter with AI, what is it and why the fuzz?
 - Where does AI fit in the evidence ecosystem?
- Al evidence for use in clinical practice
 - The good, the bad and the ugly
 - Pandemic kessons learned: living AI evidence?
 - Making the evidence ecosystem work for AI
- What now for the EBHC community?
 - Critical appraisal of AI evidence; Ready?
 - Al in EBHC education; Keeping up?
 - A call for urgent engagement and collaboration





Picture made by GPT-4

*Slides will be shared, including a glossary of AI terms and links to useful podcasts and papers

Perspective of my talk: Use of AI evidence in clinical practice

Great advances in standards, methods, tools and processes in the evidence ecosystem EBHC shift towards use of pre-appraised evidence and tools: guidelines are critical

MAGIC Evidence Ecosystem Foundation	Home	MAGICapp	Research and Innovation	Publications	About us	Contact
COVID-19: MAGIC making a	difference	and MAGICapp	o now available to develop Li	ving Guidelines.	More news	

Improving patient care through trustworthy guidelines, evidence summaries, policy and decision aids

MAGIC is a non-profit. Our vision is to increase value and reduce waste in healthcare through a digital and trustworthy evidence ecosystem. MAGICapp is our core platform, bringing digitally structured and user-friendly guidelines, evidence summaries and decision aids to clinicians and patients.



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Meet myself, with bodily symptoms and concerns spring 2023

Asked <u>www.healthily.com</u> offering AI platform for self- care in the NHS, keen on Norway



Response after 10 minutes of queries: "You may have pancreatic cancer or sacroileitis. You should see a doctor within 2 days!"

My GP ordered lots of blood tests, MRI of my back + colonoscopy I am still a bit shaken; Is this a case of the ugly AI?

Colonoscopy did not detect any disease (I still have IBS)

Should I have met AI Genius? Computer Assisted Detection (CADe) of polyps is popular now My gastroenterologist apologized: "This AI device simply too expensive..."



How can clinicians, citizens and patients make well-informed decisions, based on Al evidence (aligned with EBHC principles)?

Breakthrough for AI 2023: the Large Language Models (LLM)*

How many have ChatGPT in your pockets? 180 million users , fastest growing app ever Can it answer my overarching question today? It takes 1 minute, I have spent 6 weeks

🥵 Web Browsing	
PE How can clinicians, citizens and patients make well-informed decisions, based on AI evidence (aligned with EBHC principles)?	How can clinicians, citizens and patients make well-informed decisions, based on AI evidence (aligned with EBHC principles)?
 Willizing Artificial Intelligence (AI) in alignment with Evidence-Based Image: Construct of the second second	< 2/2 Integrating Artificial Intelligence (AI) with Evidence-Based Health Care (EBHC) can be a powerful approach to improve clinical decision-making, patient care, and public health. Here are some steps and considerations for clinicians, citizens, and patients to make well-informed decisions based on AI evidence while adhering to EBHC principles:
 structured approach on how this can be achieved: 1. Education and Literacy: Al Literacy: It's crucial that all stakeholders have a basic understanding of Al, including its capabilities, limitations, and the implications of its use in healthcare. EBHC Literacy: Stakeholders should also have a sound understanding of EBHC principles which emphasize the use of current best evidence in making decisions about the care of 	 Understanding AI and EBHC: It's crucial for clinicians, citizens, and patients to have a basic understanding of both AI and EBHC principles. Education and training can provide the necessary background to interpret AI findings within the framework of EBHC. Transparent AI Systems: AI systems should be designed to be transparent, explaining their predictions in understandable terms. Transparency facilitates trust and enables users to evaluate the evidence generated by AI against EBHC principles. Validated AI Algorithms:
individual patients. 2. Development of Trustworthy Al Tools: • Validation and Verification: Al tools should be rigorously teste Se Regenerate and validated against established medical benchmarks to ensure and a message	 Validation of Al algorithms through rigorous testing against real-world data is essential. This ensures that the Al system is reliable and its predictions are evidence-based. Incorporation of Al in Clinical Guidelines: Al can be incorporated into clinical guidelines to assist with decision-making. These guidelines should be developed and reviewed by medical experts to ensure align with EBHC principles. Regenerate

*LLM : A type of Natural Language Processing (NLP) model comprising large neural networks trained over large amounts of text, usually to output continuations of texts from corresponding prefixes.+

What is Artificial Intelligence (AI) and how is it progressing?

The science of developing computer systems that can perform complex tasks approximating human intelligence



Where and how will AI enhance the evidence ecosystem?

Al acceleration across steps (a topic for another day) Explosion of Al models, products & services, already implemented in practice



Vandvik PO, Brandt L. Future of Evidence Ecosystem Series: Evidence ecosystems and learning health systems: why bother? *Journal of Clinical Epidemiology.* 2020. <u>https://doi.org/10.1016/j.jclinepi.2020.02.008</u>

Agenda

- Setting the scene
 - Progress in EBHC and guidelines; clinical practice perspective
 - What is AI and why the fuzz?
 - Where does AI fit in the evidence ecosystem?
- Al evidence for use in clinical practice
 - Examples of the good, the bad and the ugly
 - Lessons learned in the pandemic, time for living AI evidence?
 - Does the evidence ecosystem work for AI?
- What now for the EBHC community?
 - Critical appraisal methods up for the challenge?
 - Al in EBHC education; are we keeping up?
 - A call for urgent engagement and collaboration

Use of AI evidence in clinical practice

to answer questions on diagnosis, prognosis, and treatment Examples of the good, the bad and the ugly (from evidence producers)

India Fights Diabetic Blindness With Help From A.I.





A technician screening a patient at the Aravind Eye Hospital in Madurai, India. The hospital is using a Google system that relies on artificial intelligence to diagnose a retinal problem from such a scan. Atul Loke for The New York Times

AI- assisted diagnosis: The good

Excellent performance (similar to specialists) and worked real-time in Thailand

ghlighted implementation challenges

Editorial pages 2366 and 2368

Supplemental content

me diabetic retinopathy screening by deep learning in isite national screening programme: a prospective entional cohort study

EALTH CARE DELIVERY

oonsuk, Richa Tiwari, Rory Sayres, Variya Nganthavee, Kornwipa Hemarat, Apinpat Kongprayoon, Rajiv Raman, Brian Levinstein haekermann, Roy Lee, Sunny Virmani, Kasumi Widner, John Chambers, Fred Hersch, Lily Peng, Dale R Webster:

Diabetic retinopathy is a leading cause of preventable blindness, especially in low-income and middleatries (LMICs). Deep-learning systems have the potential to enhance diabetic retinopathy screenings in s, yet prospective studies assessing their usability and performance are scarce.

did a prospective interventional cohort study to evaluate the real-world performance and feasibility of deep-learning system into the health-care system of Thailand. Patients with diabetes and listed on the etes registry, aged 18 years or older, able to have their fundus photograph taken for at least one eye, and ening as per the Thai Ministry of Public Health guidelines were eligible for inclusion. Eligible patients Application of these methods to d with the deep-learning system at nine primary care sites under Thailand's national diabetic retinopathy ation. rogramme. Patients with a previous diagnosis of diabetic macular oedema, severe non-proliferative nopathy, or proliferative diabetic retinopathy; previous laser treatment of the retina or retinal surgery; m for automated detection of diabetic abetic retinopathy eye disease requiring referral to an ophthalmologist; or inability to have fundus us photographs. taken of both eyes for any reason were excluded. Deep-learning system-based interpretations of patient es and referral recommendations were provided in real time. As a safety mechanism, regional retina ver-read each image. Performance of the deep-learning system (accuracy, sensitivity, specificity, positive to and work distribution action lue [PPV], and negative predictive value [NPV]) were measured against an adjudicated reference standard fellowship-trained retina specialists. This study is regi 02002.

20-

on of a Deep Learning Algorithm etinopathy

phs

C. Stumpe, PhD; Derek Wu, BS; Arunachalam Narayanaswamy, PhD; /Eng; Jorge Cuadros, OD, PhD; Ramasamy Kim, OD, DNB; **1PH: Dale R. Webster, PhD**

I methods that allow an algorithm to that demonstrate the desired ecificity of the algorithm for detecting

Findings Between Dec 12, 2018, and March 29, 2020, 7940 patients were screened for inclusion. 7651 (96.3%) patients were eligible for study analysis, and 2412 (31.5%) patients were referred for diabetic retinopathy, diabetic macular oedema, ungradable images, or low visual acuity. For vision-threatening diabetic retinopathy, the deep-learning system had an accuracy of 94.7% (95% CI 93.0-96.2), sensitivity of 91.4% (87.1-95.0), and specificity of 95.4% (94.1-96.7). The retina specialist over-readers had an accuracy of 93.5 (91.7-95.0; p=0.17), a sensitivity of 84.8% (79.4-90.0; p=0.024), and specificity of 95.5% (94.1-96.7; p=0.98). The PPV for the deep-learning system was 79.2 (95% CI 73.8-84.3) compared with 75.6 (69.8-81.1) for the over-readers. The NPV for the deep-learning system was 95.5 (92.8–97.9) compared with 92.4 (89.3–95.5) for the over-readers.

Interpretation A deep-learning system can deliver real-time diabetic retinopathy detection capability similar to retina specialists in community-based screening settings. Socioenvironmental factors and workflows must be taken into consideration when implementing a deep-learning system within a large-scale screening programme in LMICs.

Funding Google and Rajavithi Hospital, Bangkok, Thailand.

Machine learning: computer systems able to learn from data without following explicit instructions Deep learning: use of multiple layers in an artificial neural network

Neural networks: a collection of connected nodes, loosely modeling neurons in a biological brain



BMJ Medicine 2023;**2:**e000193. doi: 10.1136/bmjmed-2022-000193

AI to inform treatment decisions: The ugly?

Can not reliably tell what works (relative effects of interventions) With heterogenous effects; can AI reliably predict responses to treatment? I found lots of studies in oncology, no systematic reviews so I asked ChatGPT

EXCLUSIVE

IBM's Watson supercomputer recommended 'unsafe and incorrect' cancer treatments, internal documents show

By Casey Ross 🖤 and Ike Swetlitz 🎔 July 25, 2018

STAT+

Reprints

PE

With heterogenous effects; can AI reliably predict responses to treatment?

The reliability of AI in predicting responses to treatment in the presence of heterogeneous effects (differences in treatment effects across individuals or subgroups) is a nuanced and multi-faceted issue. The application of AI and machine learning can indeed be powerful in understanding and predicting treatment responses, yet several challenges and considerations persist.

In conclusion, while AI has the potential to reliably predict responses to treatment considering heterogeneous effects, the success of such endeavors relies on addressing the mentioned challenges and considerations.

LLM answering clinical questions at the point of care: The good?

Very rapid progress, but still need validation in clinical settings Preprint May 2023 outdated already? <u>arXiv:2305.09617</u>



¹Google Research, ²DeepMind,

LLM answering clinical questions at the point of care

ChatGPT more high quality and empathetic responses to patient questions

JAMA Internal Medicine | Original Investigation

Comparing Physician and Artificial Intelligence Chatbot Responses to Patient Questions Posted to a Public Social Media Forum

John W. Ayers, PhD, MA; Adam Poliak, PhD; Mark Dredze, PhD; Eric C. Leas, PhD, MPH; Zechariah Zhu, BS; Jessica B. Kelley, MSN; Dennis J. Faix, MD; Aaron M. Goodman, MD; Christopher A. Longhurst, MD, MS; Michael Hogarth, MD; Davey M. Smith, MD, MAS

RESULTS Of the 195 questions and responses, evaluators preferred chatbot responses to physician responses in 78.6% (95% CI, 75.0%-81.8%) of the 585 evaluations. Mean (IQR) physician responses were significantly shorter than chatbot responses (52 [17-62] words vs 211 [168-245] words; t = 25.4; P < .001). Chatbot responses were rated of significantly higher quality than physician responses (t = 13.3; P < .001). The proportion of responses rated as *good* or *very good* quality (\geq 4), for instance, was higher for chatbot than physicians (chatbot: 78.5%, 95% CI, 72.3%-84.1%; physicians: 22.1%, 95% CI, 16.4%-28.2%;). This amounted to 3.6 times higher prevalence of *good* or *very good* quality responses for the chatbot. Chatbot responses were also rated significantly more empathetic than physician responses (t = 18.9; P < .001). The proportion of responses rated empathetic or *very empathetic* (\geq 4) was higher for chatbot than for physicians: 4.6%, 95% CI, 2.1%-7.7%; chatbot: 45.1%, 95% CI, 38.5%-51.8%; physicians: 4.6%, 95% CI, 2.1%-7.7%). This amounted to 9.8 times higher prevalence of *empathetic* or *very empathetic* responses for the chatbot.

CONCLUSIONS In this cross-sectional study, a chatbot generated quality and empathetic responses to patient questions posed in an online forum. Further exploration of this technology is warranted in clinical settings, such as using chatbot to draft responses that physicians could then edit. Randomized trials could assess further if using AI assistants might improve responses, lower clinician burnout, and improve patient outcomes.

ChatGPT and revisiting role of trustworthy guidelines revisited

The robot can not write trusttworthy guidelines

Perhaps they are optimal EBM point of care resources? Now, or in next version?



The WHO Therapeutics and COVID-19: living guideline contains the Organization's most up-todate recommendations for the use of therapeutics in the treatment of COVID-19. The **latest** version of this living guideline is available in <u>pdf</u> format (via the 'Download' button) and via an online platform, and is updated regularly as new evidence emerges.

Lessons learned during the pandemic: Living evidence

From trigger trials to updated guidelines at record speed, perfect for AI? Risk prediction remains a challenge; living prognosis review not helped by AI

living WHO guideline on	Therapeutics and COVID-1): living guideline	Home Acc		
<i>MJ</i> 2020 ; 370 doi: https://doi.org	v13.1 published on 1/13/23 Edit	PUBLIC			
Visual summary of re	Sections	References 175 Evidence 66 Recommendations 39 Su	bscribe PDF 🕛		
iii Population	1. Summary of the guideline	For patients with non-severe COVID-19 at highest risk of hospitalization			
This recommendation applies only to people with these characteristics:	2. Abbreviations	Strong recommendation for	Update		
Patients with confirmed	3. Introduction	We recommend treatment with nirmatrelvir-ritonavir (strong recommendation for).			
covid-19	4. What triggered this update and what is coming next?	 See Section 6.1 for help to identify patients at highest risk. Several therapeutic options are available: see <u>decision support tool</u> that displays benefits and harms of nirmatrelvir-ritonavir, molnupiravir and remdesivir 			
5. Understanding and applying the WHO severity definitions		 The GDG concluded that nirmatrelvir-ritonavir represents a superior choice because it may have greater efficacy in preventing hospitalization than the alternatives; has fewer concerns with respect to harms than does molnupiravir; and is easier to administer than intravenous remdesivir and the antibodies. 			
Strong recommendations in favour	6. Recommendations for therapeutics	 Clinicians should review all medications and not consider nirmatrelvir-ritonavir in patients with possible dangerous drug interactions (note: ma drugs interact with nirmatrelvir-ritonavir). Fully informed shared decision-making should determine whether nirmatrelvir-ritonavir should be used in pregnant or breast-feeding women, possible benefit and residual uncertainty regarding potential undesirable effects. 			
For those with highest risk of hospital admission	 - 6.1 Overview of drugs, recommendations and key issues to consider when applying 	Nirmatrelvir-ritonavir should be administered as soon as possible after onset of symptoms, ideally within 5 days.			
The panel recommended that the intervention should s	them	Research evidence (3) Evidence to decision Justification Practical info Decision Aids			
be reserved for those at a risk above 10% of being admitted to hospotal with covid-19. the multiple	- 6.2 Nirmatrelvir-ritonavir (updated 13 January 2023)	×			
comparison tool to compare Typical characteristics of people at high risk include:	- 6.3 Remdesivir (updated 16 September 2022)	For patients with non-severe COVID-19 at low risk of hospitalization			
Lack of vaccination Older people Immunodeficiency	- 6.4 Janus kinase inhibitors (updated 16 September 2022)	Conditional recommendation against We suggest not to use treatment with nirmatrelvir-ritonavir (conditional recommendation against).	① Update		
Chronic diseases	- 6.5 Sotrovimab (updated 13 January 2023)	✓			
J	6.6 Casirivimab-imdevimab	 In the GDG's assessment, only a minority of low-risk patients will choose to consider using nirmatrelvir-ritonavir. Trials on antivirals included patients with some risk factors for hospital admission, resulting in a baseline risk of 3% that the GDG applied to generate the recommendation. The risk of hospitalization is likely to be lower in the general population. 	\bigcirc		

Making the evidence ecosystem loop work for AI

Moving to living guidelines for AI, exemplified by AI Genius (CADe, CADx to come) Current standards and methods works just fine, also from Evidence to Decisions (EtD)



randomized trials on 18232 patients nigher in the CADe group than in up (44.0% vs. 35.9%; relative risk, -certainty evidence), corresponding 0.35 to 0.58]) relative reduction in evidence). More nonneoplastic pol-

Computer Aided Detection (CADe) Colonoscopy vs Routine Practice Colonoscopy

People undergoing colonoscopy for any indication (screening, surveillance, clinical indications)

15 Outcomes Graphical view

Outcome Timeframe	Study results and measurements	Absolute ef Routine Practice Colonoscopy	fect estimates Computer Aided Detection (CADe) Colonoscopy	Certainty of the Evidence (Quality of evidence)	Plain language summary
 Colorectal cancer incidence 10-years Critical 	(CI 95% —)	82 per 10.000 Difference: 9 f (CI 95% 8 fev	• 73 per 10.000 •wer per 10.000 wer — 10 fewer)	Low	Computer aided detection (CADe) colonoscopy may have little or no difference on colorectal cancer incidence No imp. diff.
Colorectal cancer related deaths 10-years 8 Critical	Relative risk (Cl 95% —)	15 per 10.000 Difference: 2 f (Cl 95% 2 fer	13 per 10.000 ewer per 10.000 wer — 3 fewer)	Low	Computer aided detection (CADe) colonoscopy may have little or no difference on colorectal cancer related deaths No imp. diff.

Looking beyond individual examples for clinical application of AI

84 RCTs by now, mostly bad (if not ugly)

129 systematic reviews, mostly bad (2022): We need high-quality umbrella living SR





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Are we ready to deal with the flood of AI publications?

Nature survey 2023: Optimisms and concerns from scientists

The number of **AI publications** worldwide more than doubled from 2010 to 2021, growing from 200,000 to nearly 500,000.



https://aiindex.stanford.edu/report/.



A *Nature* survey finds that scientists are concerned, as well as excited, by the increasing use of artificial-intelligence tools in research. **By Richard Van Noorden and Jeffrey M. Perkel**

672 | Nature | Vol 621 | 28 September 2023

terms has risen in every field over the past decade, according to an analysis for this article by

Nature. Machine-learning statistical techniques are now well established, and the past few years

have seen rapid advances in generative AI,

Machine learning challenging standards for proof and truth

"The main problem is that AI is challenging our existing standards for proof and truth," said Jeffrey Chuang, who studies image analysis of cancer at the Jackson Laboratory in Farmington, Connecticut.

NEGATIVE IMPACTS OF AI

Q: Considering machine-learning methods, what do you think are negative impacts of AI in research? (Choose all that apply.)



LLM most impressive and most concerning for scientists

proliferation of misinformation, mistakes, fraud, and entrenched with bias

Respondents added that they were worried about faked studies, false information and perpetuating bias if AI tools for medical diagnostics were trained on historically biased data. Scientists have seen evidence of this: a team in the United States reported, for instance, that when they asked the LLM GPT-4 to suggest diagnoses and treatments for a series of clinical case studies, the answers varied depending on the patients' race or gender (T. Zack *et al.* Preprint at medRxiv <u>https://doi.org/ktdz</u>; 2023) – probably reflecting the text that the chatbot was trained on.



Conclusion (T.Zack et al) : *"Urgent need for comprehensive and transparent bias assessments of tools like GPT-4 for every intented use case before integrated into clinical care"*

Can we adequately review AI papers? Any reporting standards?

Many of us probably lack skills to appraise/ peer-review , checklists are emerging

When asked if journal editors and peer reviewers could adequately review papers that used AI, respondents were split. Among the scientists who used AI for their work but didn't directly develop it, around half said they didn't know, one-quarter thought reviews were adequate, and one-quarter thought they were not. Those who developed AI directly tended to have a more positive opinion of the editorial and review processes.

QUALITY OF AI REVIEW IN RESEARCH PAPERS

Q: Do you think that journal editors and peer-reviewers, in general, can adequately review papers in your field that use AI?

🗖 Yes 🛛 📕 No 🔅 Don't know/cannot tell

Respondents who study AI





"Reviewers seem to lack the required skills and I see many papers that make basic mistakes in methodology, or lack even basic information to be able to reproduce the results," says Duncan Watson-Parris, an atmospheric physicist who uses machine learning at the Scripps Institution of Oceanography in San Diego, California. The key, he says, is whether journal editors are able to find referees with enough expertise to review the studies.



Fig. 1 | Comparison of development pathways for drug therapies, AI in healthcare and surgical innovation. The colored lines represent reporting



OPEN

Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension

Blackbox problem* and the Explainability of Al

- Lack of transparency raises challenges with bias, accountability and responsibility leading to also ethical and legal problems
- Explainable AI (XAI) aims to address these issues by developing models that are more interpretable and transparent
- XAI has 3 main problems (thought provoking from Dr. Ghassemi @NEJM AI Grand Rounds podcast)
 - Squishy definition
 - Too simple methods to explain, turns of critical thinking (see preprint below)
 - Medicine has lots of black boxes, we need to know well calibrated, how to use in clinical contexts
- A key critical appraisal challenge for the EBHC community?



* Blackbox problem: The challenge of understanding how AI systems and machine learning models operate, especially in processing data and making predictions or decisions



Marzyeh Ghassemi | Harva...

AI in EBHC education; are we keeping up?

Inevitable that health care professionals need to learn, why not link to EBM? 2 week elective AI course for medical students at University of Oslo lots of fun;-)



KURS_KOMITEEN: (f.v) Medisinstudent Birk Hunskaar, professor Per Olav Vandvik, lege i spesialisering Ishita Barua og universitetslektor Anja Fog Heen utgjør kurs-komiteen til MED3065 – AI, innovasjon, big data og beslutningsstøtte. Foto: Anita Aalby

Medisinstudenter kan nå lære om kunstig intelligens, stor-data og innovasjon

Studenter ved Universitetet i Oslo (UiO) kan for første gang denne våren lære om kunstig intelligens, stordata og innovasjon koblet til beslutningsstøtte for helsetjenesten.



»All should understand how to best use AI tools, their limitations and evidence-base that surrounds them» NEJM AI Grand Rounds Podcast Dr. Alan Karthikesalingam Research lead at Google

Summary: Al evidence for use in clinical practice 2023

What now for the EBHC community?

- AI will increasingly inform (and accelerate) the evidence ecosystem
- Current AI evidence mostly the bad and the ugly but likely to change rapidly
- Start dancing with AI folks, right now
- If my talk did not make sense; askChatGPT and be positively surprised;-)





Glossary of key terms for Al

- AI: The science of developing computer systems that can perform complex tasks approximating human intelligence
- **Machine learning**: computer systems able to learn from data without following explicit instructions
- **Deep learning**: use of multiple layers in an artificial neural network
- **Neural networks**: a collection of connected nodes, loosely modeling neurons in a biological brain
- **Generative AI**: Can generate text, images, or other media, using patterns of input training data
- **Natural Language Processing (NLP):** A branch of artificial intelligence that seeks to enable computers to interpret and manipulate human text
- Large Language Model (LLM): A type of NLP model comprising large neural networks trained over large amounts of text, usually to output continuations of texts from corresponding prefixes.+
- **GPT:** Generative Pre-trained Transformer

Useful resources for learning more

• NEJM AI Grand Rounds