

DNA

AI and Genomics

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Doctors are facing new technology challenges



Patient 1

- Software engineer working in AI in his late 20's
- Has a rare endocrine disorder
- Patient evaluated his clinical findings with an LMM and requested genetic testing from his endocrinologist
- Per patient - requested genetic testing multiple times but could not convince the provider
- Endocrinologist finally gives in and orders sequencing



Patient 2

- Stay at home mother of child with complex disorder
- Mother has no background in medicine or computer science
- Child has several clinical findings
- Mother uses LMM and requests pediatrician to order a single gene test



Patient 3

- Business professional on a 10 year diagnostic odyssey for her child
- Finally gets referred to genetics and is frustrated with path it took to get there
- “I am ok with my physician using Grok or ChatGPT in front of me, in fact I feel more comfortable that they do because then I know they have the best information”



Dr Google is out. Now LMM's take on clinicians.

- We have to have access to the same technologies that patients do
- If we don't:
 - Patient's lose confidence
 - We miss diagnoses
 - We become obsolete
- According to study presented at ASHG, LMM's outperform clinical geneticists at rare disease diagnosis



LMM's Delivering Genomic Information

- Improving constantly
- Became much less conversational as accuracy improves
- Guardrails in place but what are they?
- Based on a set point in time, how do you update?
- Controversial content can take precedent due to frequency
- Can use qualifiers to get more up to date recommendations
- Can be so convincing you second guess your own knowledge

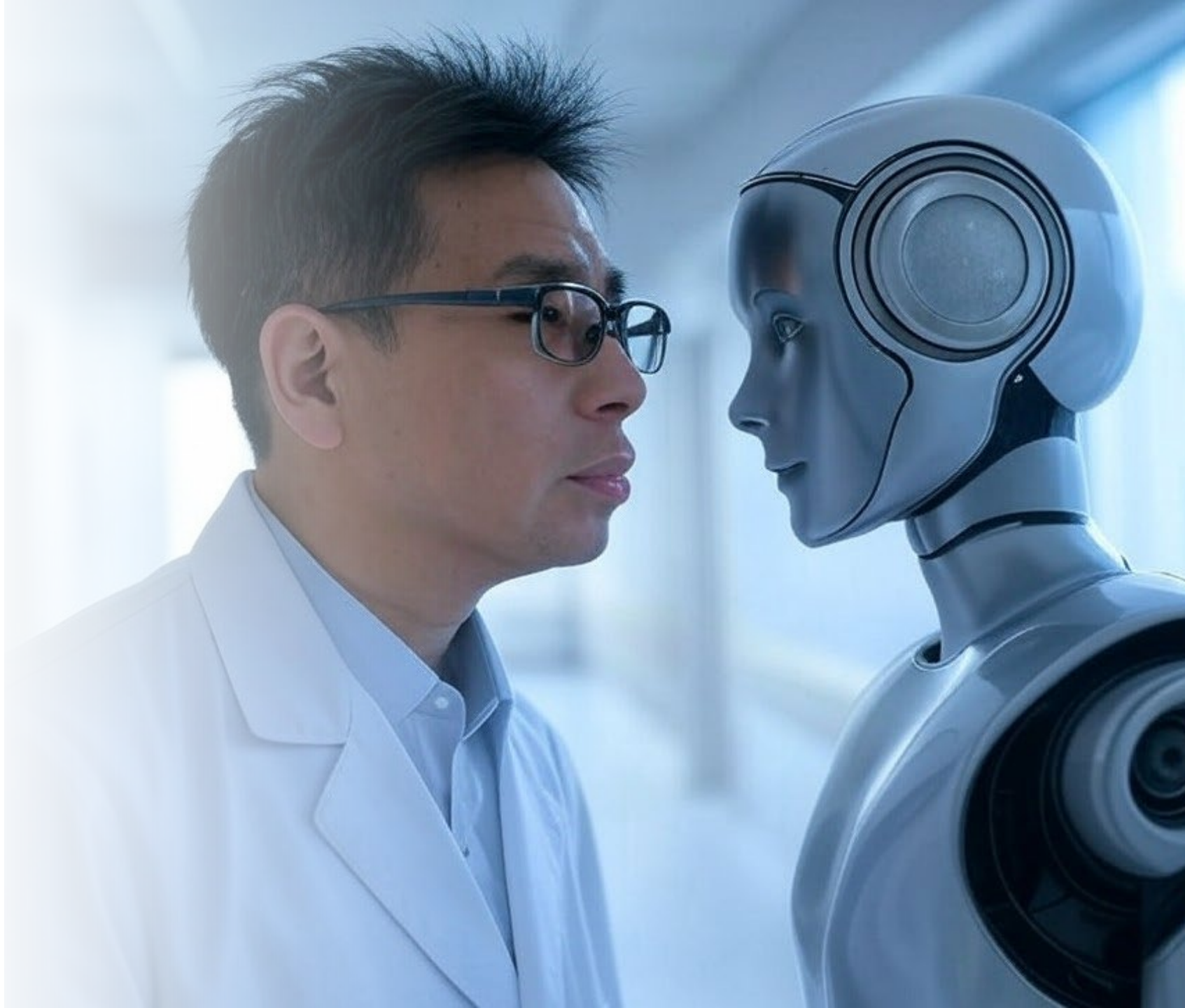
Walton NA, Kozel BA, Danford CJ, McGrath SP. Evaluating ChatGPT as an Agent for Providing Genetic Education. bioRxiv [Preprint]. 2023 Oct 29:2023.10.25.564074. doi: 10.1101/2023.10.25.564074. PMID: 38076902; PMCID: PMC10705538.

McGrath SP, Kozel BA, Gracefo S, Sutherland N, Danford CJ, Walton N. A comparative evaluation of ChatGPT 3.5 and ChatGPT 4 in responses to selected genetics questions. J Am Med Inform Assoc. 2024 Oct 1;31(10):2271-2283. doi: 10.1093/jamia/ocae128. PMID: 38872284



How do we evaluate / trust LMM's

- Need to move away from scripted interactions
- Comparison to Residency
 - Experience in the field with oversight
 - Expectation "No Errors" vs "Better than Humans"

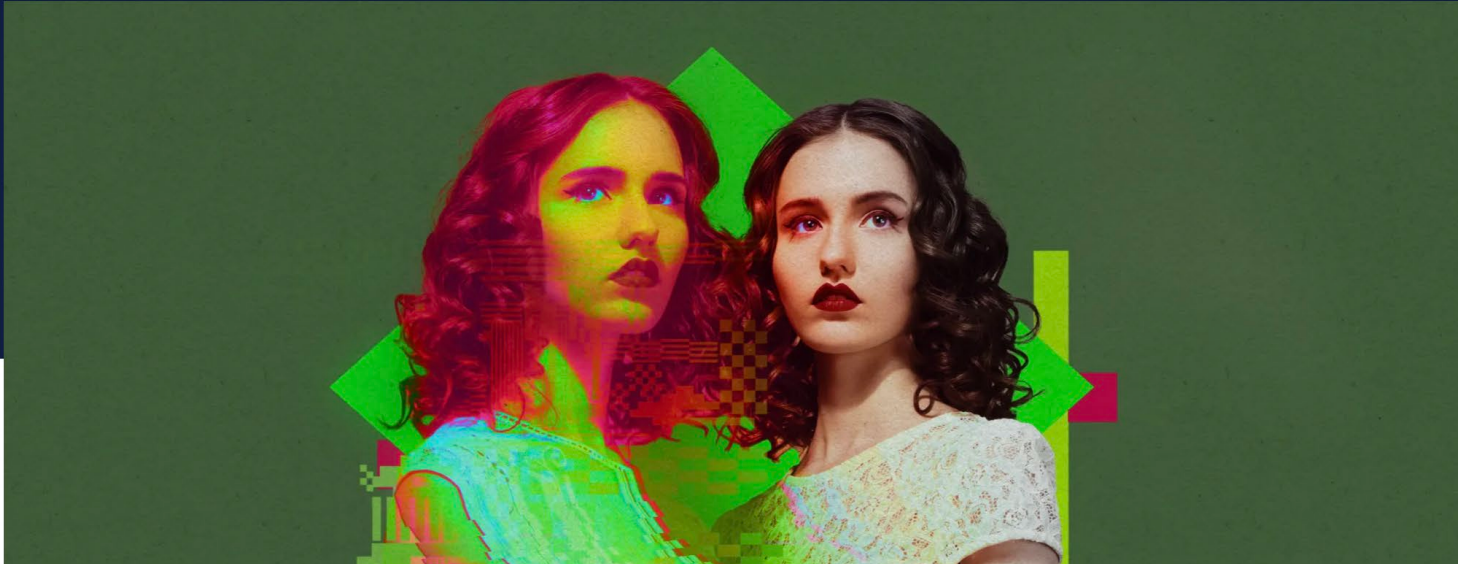


AI can now create a replica of your personality

A two-hour interview is enough to accurately capture your values and preferences, according to new research from Stanford and Google DeepMind.

By James O'Donnell

November 20, 2024



Generative Agent Simulations of 1,000 People

Authors: Joon Sung Park^{1*}, Carolyn Q. Zou^{1,2}, Aaron Shaw², Benjamin Mako Hill³, Carrie Cai⁴, Meredith Ringel Morris⁵, Robb Willer⁶, Percy Liang¹, Michael S. Bernstein¹

- Accuracy:** The generative agents achieved an average normalized accuracy of 85% on the General Social Survey, which is comparable to how well participants replicated their own answers two weeks later.

- Personality and Behavior Prediction:** Agents performed well in predicting personality traits and outcomes in experimental settings, similar to how humans behave.

- Bias Reduction:** The approach showed reduced accuracy biases across racial and ideological groups when compared to traditional models that rely solely on demographic descriptions.

PRS with Personality

- Model and predict human behaviors
- Use these models with polygenic risk scores to come up with better prediction models of disease risk
- Model interventions based on what individuals are likely to do

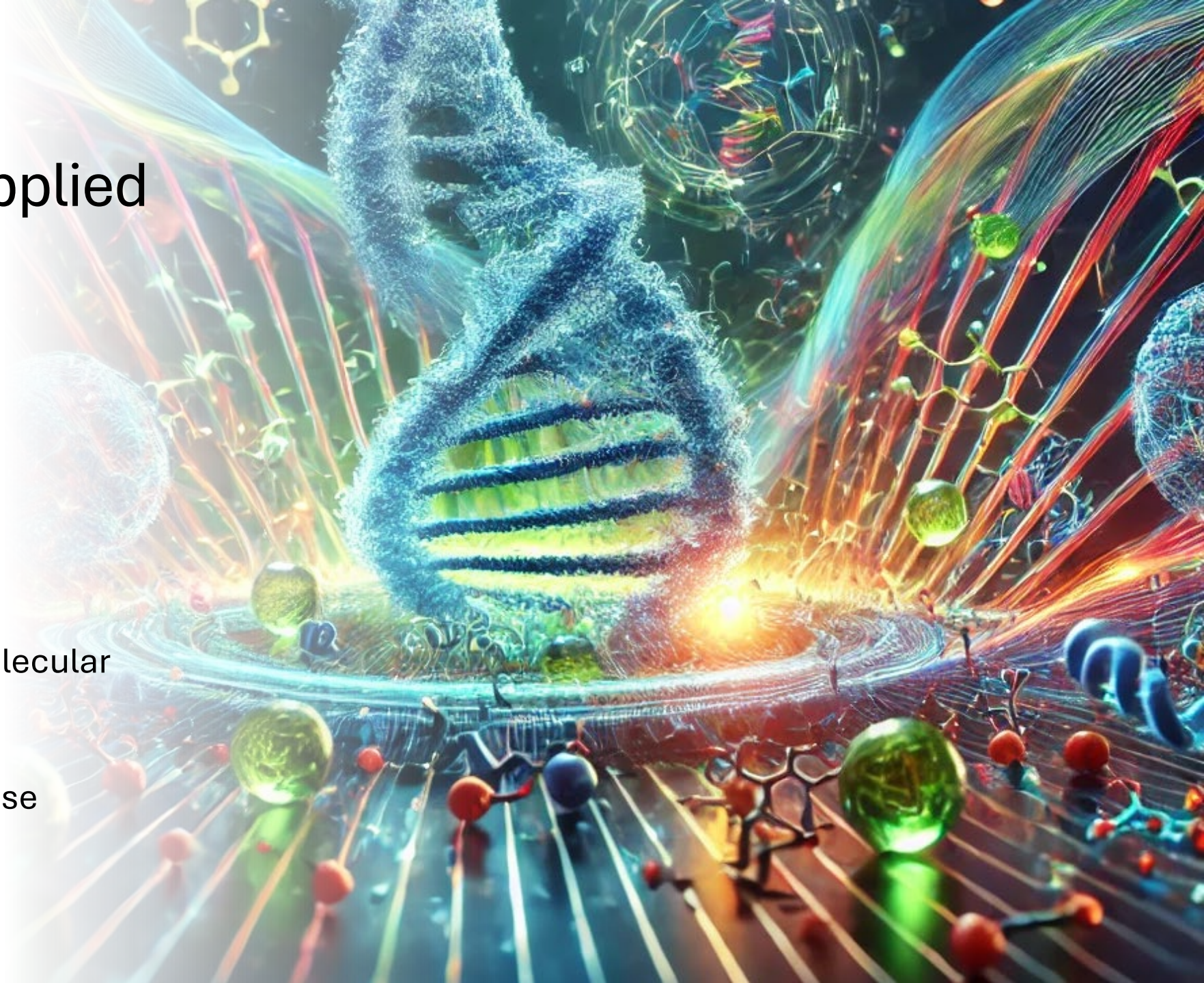


Same treatment - different results – why?

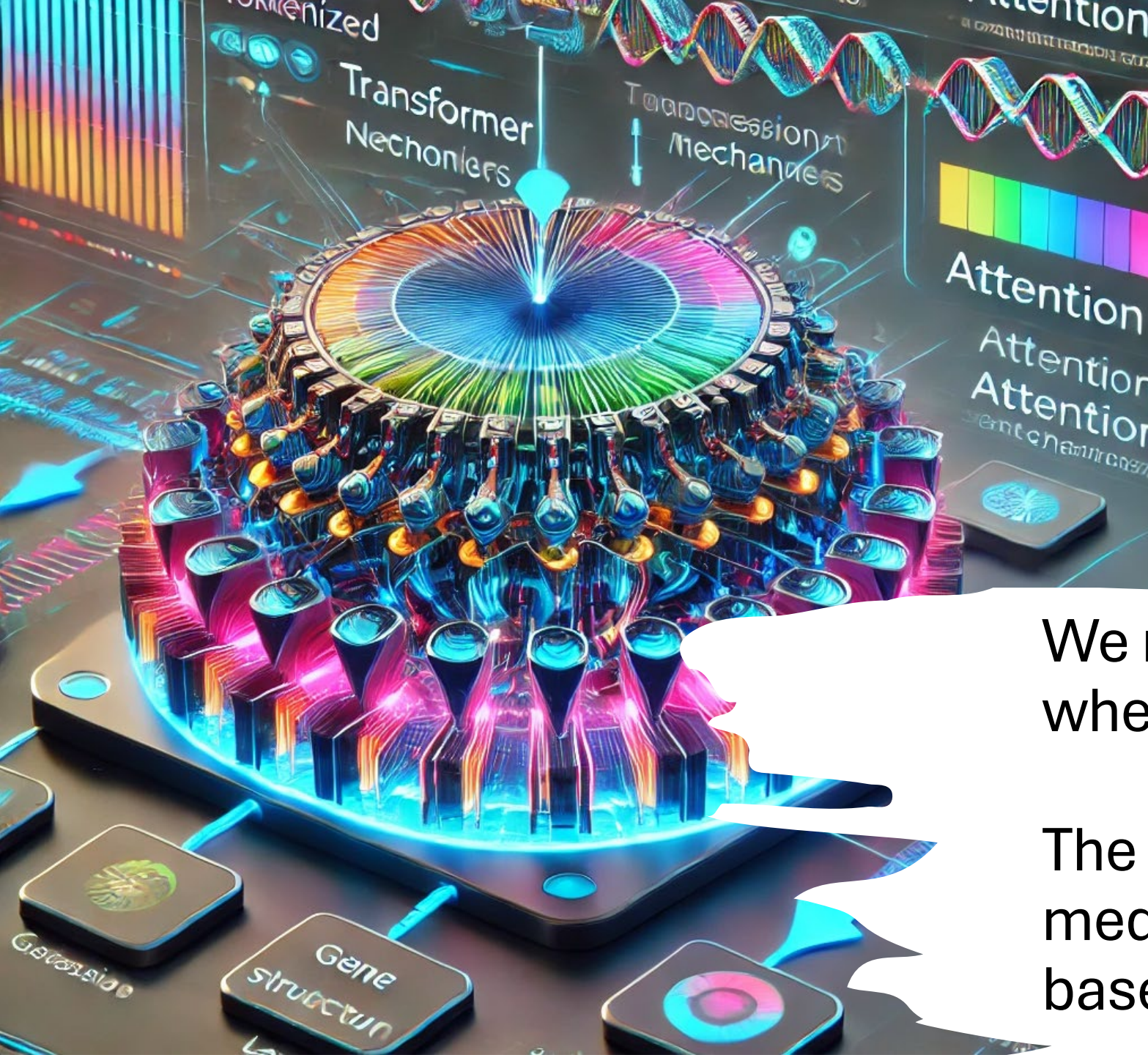


Transformer architectures applied to genomics

- DNABert-2
 - Enformer
 - GenomeGPT
 - Evo-2
-
- Primarily focused on molecular level events
 - Potential for uncovering complex origins of disease



Attention Is All You Need



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We need to pay attention to
where attention is being paid

The largest obstacle to AI in
medicine will be evidence
based guidelines



How do we deliver to patients?

- We cannot scale genomics or AI without delivery at the front lines
- Needs to be streamlined and simple
- Has to fit in a 10-15 minute encounter

National Human Genome Research Institute. (2024, April 10–11). *Defining a clinical data ecosystem for genomic health* [Meeting summary]. Washington, DC. Retrieved August 21, 2024, from <https://www.genome.gov/event-calendar/defining-a-clinical-data-ecosystem-for-genomic-health>

Intermountain Experience

- Delivered information to primary care providers at the point of care
- Very brief management information
- Ability to digest and utilize information in a 10 – 15 minute encounter
- Links to more detail if needed
- Delivered similar information to patients

Walton NA, et al. The Development of an Infrastructure to Facilitate the Use of Whole Genome Sequencing for Population Health. J Pers Med. 2022 Nov 8;12(11):1867. doi: 10.3390/jpm12111867. PMID: 36579594; PMCID: PMC9693138.



HFE Hereditary Hemochromatosis Information Sheet

Hereditary Hemochromatosis is caused by having mutations in both copies of the *HFE* gene, one inherited from each parent. Individuals with Hereditary Hemochromatosis have a tendency to absorb and store too much iron in their body (called iron overload). If left untreated, the extra iron can build up over time and may cause damage to organs, such as the liver and heart. Many people with hereditary hemochromatosis will have high levels of iron in their blood (serum ferritin and transferrin saturation), but not everyone will experience organ damage. Early diagnosis and treatment can prevent organ damage in individuals with very high iron levels.

Health Risks

	Risk for elevated iron levels	Risk for organ damage (if untreated)
Males	75-90%	Approximately 30% Typically occurs in the 4 th to 6 th decade of life
Females	50-75%	Approximately 1-2% Typically occurs after menopause

Signs and Symptoms of Iron Overload

Organ	Damage
Liver	Hepatomegaly, cirrhosis, liver cancer (hepatocellular carcinoma)
Heart	Heart failure, arrhythmia
Pancreas	Type 2 diabetes
Skin	Hyperpigmentation
Pituitary	Decreased libido, irregular menses

Arthralgias, abdominal pain, weakness, and weight loss are also common presenting symptoms

Medical Care Recommendations

