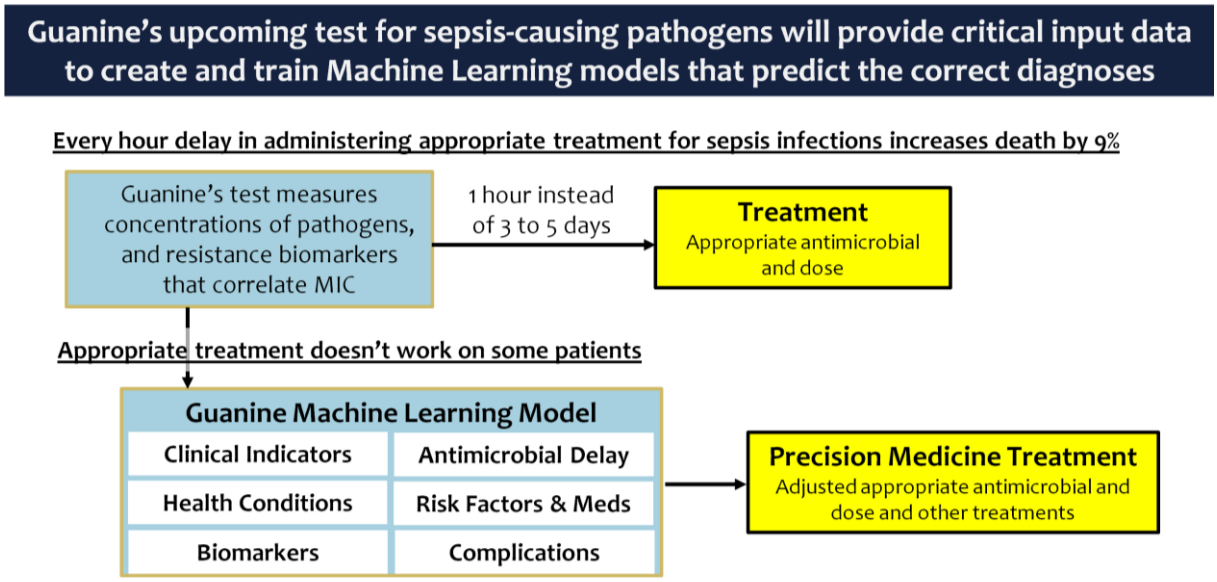
Advancements in medical AI and precision medicine are constrained by antiquated IVD technologies



Medical AI requires input data to create and train models that predict the correct diagnoses. The models improve with use by learning additional correct diagnoses from new cases. The accuracy of the models is dependent on the quality and completeness of the input data. When the input data is frequently incorrect, incomplete and/or has a low correlation with the outcomes, the model fails to deliver the expected accuracy.

Simple medical diagnoses are routinely made using symptoms, vital signs, physical cues and history as the input data. Complex diagnoses require additional information about components in body structures using imaging and/or components in body fluids using in vitro diagnostics (IVDs).

Images of body structures are easy to collect. Technologies such as X-rays, ultrasounds and MRI penetrate the skin and generate images of various structures. These images are interpreted by skilled professionals to determine abnormal structures and anomalies.

Machine learning models can also be used to interpret images by decomposing body structures into patterns and creating layers of objects that are associated with specific outputs such as cancer tumors and bone fractures. The percentage of correct predictions can be improved by exposing the models to new images, and allowing machine learning algorithms to find improved patterns, objects and associations between the input images and the model's output diagnoses.

Contents of body fluids are more difficult to interpret since they are measured with technologies that have limited or highly variable outcomes. As experienced with COVID testing, the same patient can have a negative result with an antigen test and a positive result with a PCR test. This is because PCR tests employ a technique to amplify the detection signal in order to detect lower concentrations. In general, antigen tests have a detection limit of about 1,000,000 targets per mL while PCR tests have a detection limit of about 1,000 targets per mL, which is able to detect targets at about 1,000 times lower concentrations. So if a patient is infected with 50,000 COVID particles per mL, then the patient would be positive with a PCR test and negative with an antigen test. If the antigen test was the input for a machine learning model, then an incorrect diagnosis would be made and allow the infected person to transmit COVID to other people.

Another important consideration is that a patient with COVID can only infect other people within about 4 to 10 days of being infected. However COVID RNA can be present for up to 6 weeks. So a PCR test would be positive weeks after the infective period has ended. A machine learning model based on a positive PCR test could require a non-infective person to be unnecessarily quarantined. In contrast an antigen test does not detect COVID RNA but instead detects the COVID particle's membrane and would correctly provide a negative result after the infective period. So in this case the antigen test would be more effective. Clearly a better test providing the COVID concentration for presence and a second test for infectivity by measuring the increase or decrease in COVID concentration would be a better input for a machine learning model. Quantitative PCR is a cumbersome and expensive technique.

A major opportunity for medical AI is sepsis, which is a life threatening medical condition caused by a blood infection. Sepsis causes 270,000 US deaths/yr (11 M global) with $24 billion US medical cost/yr and 50% of hospital costs are not reimbursed. Sepsis is somewhat difficult to diagnose due in part to the different ways used to define sepsis. More importantly is that sepsis can be extremely difficult to treat. Different sepsis-causing pathogens are killed with specific antimicrobials depending on the pathogen type, its resistance to specific drugs, and the dose needed to kill the pathogen. Antimicrobial resistant pathogens can have mechanisms for defending themselves against antimicrobials such as producing enzymes that destroy a drug's structure or proteins that prevent antibiotics from binding to and subsequently killing the pathogen.

Sepsis treatment is currently determined with a series of blood cultures. A blood sample is added to a culture containing nutrients that allow pathogens to reproduce. Some pathogens like *E.coli* double in about 15 minutes, while other pathogens double in 1 to 24 hours. Some pathogens such as viruses and unculturable bacteria provide a negative culture result even though they can be the source of sepsis-causing blood infections.

When bacteria in cultures reproduce to at least 100,000 cfu targets/mL, samples are furthered cultured to identify the specific pathogen, then subcultured with varying concentrations of antimicrobials to find the best suited antimicrobials based on the minimum inhibitory concentration (MIC) of the drug that stops further pathogen growth. This process takes 3 to 5 days. Unfortunately doctors have to decide on antimicrobial treatment in about 1 hour. Doctors and potentially machine learning models have to rely on guidelines and experience instead of test results which often leads to providing appropriate treatment days later when the culture results are available. When appropriate treatment is delayed, patients have a higher incidence of incurring poor outcomes including sepsis shock where hospitalization extends from 4.5 to 16.5 days, and mortality increases from about 30% to 80%. Many patients incur post-sepsis

syndrome with a 20% chance of re-hospitalization and lifelong complications. The use of the wrong antimicrobial can harm the patient, activate latent *C.difficule* in the gut and increase the incidence of drug resistance.

Efforts to use machine learning to predict sepsis treatment without knowing the pathogen type, drug resistance, and virulence are not likely to succeed. A publication by Fleuren et al. evaluated 130 machine learning models from 28 papers that attempted to predict the early onset of sepsis. They concluded that only three had clinically implemented models with mixed results. In the multivariate analysis, temperature, lab values, and model type contributed most to model performance. What the models didn't do was to incorporate information about the pathogen since culture results were not available.

For machine learning to make advances in complex diagnoses such as sepsis that require input data on the contents of body fluids, two critical issues need to be addressed. First is a better IVD test technology. Regarding sepsis, every hour delay in administering appropriate treatment increases death by 9%. So there should be a great incentive to adopt a faster IVD technology rather than relying on cultures. Syndromic testing which uses a 12 hour culture followed by multiplex PCR is not fast enough for making the initial antibiotic decision. Multiplex PCR detects a wide range of pathogens and drug resistance biomarkers to identify the drug type but they do not provide concentrations that can be used to derive the appropriate drug dose.

Secondly the appropriate treatment does not work on every patient. Multiple patient factors can reduce treatment efficacy such as comorbidities, co-infections, medications that impact the immune system and/or antimicrobials, complications, patient age, medical conditions, etc. Machine learning along with a faster test have the opportunity to enable precision medicine treatments that further improve patient outcomes.

Complex diagnoses that rely on the contents of body fluids along with other information extend beyond infectious diseases and can include cancers, neurological diseases and cardiac diseases. The ideal IVD technology needs to measure low concentrations, multiple targets per test including both nucleic acids and proteins when appropriate, and provide target concentrations instead of just presence or absence. Testing should also be rapid, mobile and inexpensive. These capabilities are not available with the current IVD tests due in large part to the limitations of decades old optical detection methods. A different approach is needed.

Guanine has developed an IVD technology based on electrochemistry that changes the detection signal from optical to electrical. Electrochemistry is a widely used for measuring electroactive materials such as glucose, metals and chemicals. Electroactive materials can be stimulated to emit electrons and produce an electrical current that is easily converted to concentration. The process is fast, mobile, and low cost. The only limitation is that the electroactive target can only be detected in very high concentrations reaching millions or billions of targets/mL. This limits the use of the technology.

Guanine has developed a signal amplification technology that allows electrochemical detection to attain detection limits similar to PCR. Nucleic acid and protein targets attach to microparticles bound with millions of electroactive guanine molecules. The target-microparticle complexes form sandwiches on biosensor electrodes and produce an electrical current proportional to the target's concentration. The signal is further amplified by filtering a large sample

volume such as 20 mL of whole blood to deliver more targets for detection. Magnetic separation removes nonspecific materials that cause false detection outcomes. A biosensor with dozens of electrodes allows multiple targets to be detected from the same sample using a cocktail of microparticles. Not only is the process rapid and mobile, target concentrations can be available in 60 minutes in a digital format that can be used as the input for machine learning models with precision medicine.

Guanine is part of Mount Sinai Health System's Elementa Labs. Guanine's signal amplification technology was derived from its predecessor company that was spun out of NASA's Ames Research Center. For more information contact neil.gordon@guanineinc.com.