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Collaborative AI and Laboratory Medicine integration in precision cardiovascular medicine

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ABSTRACT

Artificial Intelligence (AI) is a broad term that combines computation with sophisticated mathematical models and in turn allows the development of complex algorithms which are capable to simulate human intelligence such as problem solving and learning. It is devised to promote a significant paradigm shift in the most diverse areas of medical knowledge. On the other hand, Cardiology is a vast field dealing with diseases relating to the heart, the circulatory system, and includes coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions. AI has emerged as a promising tool in cardiovascular medicine which is aimed in augmenting the effectiveness of the cardiologist and to extend better quality to patients. It has the ability to support decision-making and improve diagnostic and prognostic performance. Attempt has also been made to explore novel genotypes and phenotypes in existing cardiovascular diseases, improve the quality of patient care, to enable cost-effectiveness with reduce readmission and mortality rates. Our review addresses the integration of AI and laboratory medicine as an accelerator of personalization care associated with the precision and the need of value creation services in cardiovascular medicine.

1. Setting the scene

Laboratory medicine as a medical discipline is supporting clinicians to improve the diagnosis and treatment of patients across a wide variety of diagnostic disciplines and patient-centered care for better outcomes. Laboratory medicine is facing a rapidly changing health ecosystem, inseparable of emerging technologies [1]. In this transforming health ecosystem, the focus is place on predicting, preventing, and curing disease precisely with a fundamental shift to more proactive and personalized care that empowers people to lead healthy lives.

The impact of emerging technologies can be felt at the pre-analytical, analytical and post-analytical levels. As part of these emerging technologies, data science and the digital transformation are important drivers for the evolution of laboratory medicine [1].

Cardiovascular diseases (CVD) represent a leading cause of mortality and morbidity all over the world [2]. The economic burden of CVD is seriously impacting the healthcare budget and resources. The annual total cost of CVD is estimated to more than $350 billion in the United States [3] and €210 billion for the European Union [2,4]. Laboratory medicine, through biomarker testing is a cornerstone for physicians for the diagnosis and risk assessment of cardiovascular diseases with keynote examples like myocardial infarction (MI) or heart failure (HF) [5,6].

The hype about Artificial Intelligence (AI) is unavoidable and the downstream applications behind AI are incredible. Its rapid development in healthcare appears as a game changer for healthcare workforces [7–9]. The benefit of interconnecting AI and laboratory medicine have already been documented and the example of sepsis prediction through the integration of clinical features and laboratory data through machine learning for real time assessment could be given [10]. There

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are optimistic prospects of the use of AI in cardiovascular medicine. AI technologies have been applied in CVD including precision medicine, clinical prediction, cardiac imaging analysis and intelligent robots.

The physicians may have the potential to reduce workload and to gain time and experience. In the future, cognitive computers, devices trained through machine learning or deep learning algorithms, will help clinicians make accurate decisions and predict patient outcomes. They will benefit of automating measurements and test ordering, making predictions based on big data, and putting clinical findings into an evidence-based context [8,9]. The integration of AI technology and laboratory medicine into cardiovascular medicine could improve the accuracy and speed of diagnosis, help clinical decision-making, and lead to better health outcomes.

This mini-review is focusing on the expected value of the integration of AI and laboratory medicine to improve the outcomes and services related to cardiovascular diseases.

2. Emerging applications

2.1. New horizons for biomarker discovery and research

The integration of AI and cardiovascular medicine requires professional skills, advanced technologies and substantial investment before applications to clinical practices. The power of AI and computational modeling is opening new horizons for research [11]. Different examples could illustrate it for different diseases like atrial fibrillation (AF), coronary artery diseases (CAD) and heart failure (HF).For AF, deep analysis of databases were performed to identify biomarkers associated with the disease [12]. Chua and coworkers reported in their study that two biomarkers identified after databases screening (increased Brain Natriuretic Peptides (BNP) and increased Fibroblast Growth Factor 23 (FGF-23) and three simple clinical risk factors (age, sex, and body mass index) provide a model able to identify patients with AF [12]. For CAD, the combination of “omics” and bioinformatics was applied to discover new biological mechanisms and biomarkers [13]. Machine learning and lipidomics on serum samples of individuals with familial CAD and population-based controls were employed to explore the relationship between serum sphingolipids and CAD [14]. This study validated serum ceramides as candidate biomarkers of cardiovascular disease and suggests that comprehensive sphingolipid panels be considered as measures of CVD. In heart failure (HF) with reduced left ventricular ejection fraction (HFrEF), a combined approach of untargeted metabolomics and machine learning was evaluated to create a simple and potentially clinically useful diagnostic panel for HFrEF [15]. The accuracy of a model based on a panel of metabolites was comparable to BNP and that selected metabolites correlated with clinical, echocardiographic and functional parameters. The combination of quantitative proteomics (multiplexed targeted liquid chromatography-tandem/mass spectrometry-based assay) and machine learning was also efficient to uncover multiplex biomarker panel for Hypertrophic Cardiomyopathy (HCM) and to refine disease monitoring and improve patient risk stratification [16]. Six potentially useful circulating biomarkers related to myocardial substrate changes in HCM were identified and correlate with the estimated sudden cardiac death risk [16].

The comprehensive molecular phenotyping through genomics, metabolomics, proteomics and immunophenotyping combined with data science and machine learning appear as a very attractive approach to identify novel pathophysiological pathways and new biomarkers, to have a better understanding of diseases and complex interplays among them and to target novel treatment [17].

2.2. Engines for early risk estimation

Current approaches to predict cardiovascular risk fail to identify many people who would benefit from preventive measures and treatment, while others receive unnecessary intervention. AI offers opportunity to improve accuracy by exploiting complex interactions between multiple risk factors as well as to characterize cardiovascular risk and predict outcomes [11].

AI can improve cardiovascular risk prediction using routine clinical data. This approach was used in a prospective cohort study using routine clinical data of 378,256 patients from UK family practices, free from cardiovascular disease at outset [18]. Four machine-learning algorithms were compared to an established algorithm (American College of Cardiology guidelines) to predict first cardiovascular event over 10-years. Neural network was the highest achieving algorithm predicting 4998/7404 cases and 53,458/75,585 non-cases. The neural network algorithm showed an added value by correctly predicting 355 (+7.6%) more patients who developed cardiovascular disease compared to the established algorithm. This study demonstrated that machine-learning significantly improves accuracy of cardiovascular risk prediction; increasing the number of patients identified who could benefit from preventive treatment, while avoiding unnecessary treatment of others. The results of the MESA (Multi-Ethnic Study of Atherosclerosis) involving 6814 participants initially asymptomatic population are also promising [19]. The baseline measurements were used to predict cardiovascular outcomes over 12 years of follow-up. Seven-hundred thirty-five variables from imaging and noninvasive tests, questionnaires, and biomarker panels were obtained. The study showed that creatinine, age, and ankle-brachial index were among the top predictors of atrial fibrillation and that TNF-α, IL-2 soluble receptors and NT-proBNP levels were important across all outcomes. The study showed also that the random survival forests technique performed better than established risk scores with increased prediction accuracy. Similarly, data science approaches could be applied to develop panel for predicting incident coronary heart disease [20]. A recent study demonstrated that ensemble set of random forest models consisting of four genetic and four epigenetic loci predicted risk of coronary heart disease better for both genders and very well in the three-year risk prediction window. Lastly, machine-learning algorithms could be helpful in population known for their high risk of developing CVD such diabetes or kidney disease. The use of data science and multiple biomarkers has been shown as a mean for predicting diabetes mellitus development [21] and to predict ischemic heart disease in patients with end-stage kidney disease [22].

AI could therefore participate to a more personalized risk estimation of CVD and identify actionable risk factors that may be leveraged to guide risk modification efforts.

2.3. Improving diagnosis of cardiovascular diseases.

The differential diagnosis of chest pain in the emergency department (ED) is highly subjective and variable and the diagnosis of acute coronary syndrome (ACS) is important and helps physician with his decision to discharge or to hospitalize. In patients presenting to ED with chest pain and compatible with the diagnosis of ACS, machine learning techniques using patient data including age, sex, risk factors, and cardiac biomarkers could improve the diagnosis and then their triage [23]. A study evaluated the performance of four different methods (Support vector machine (SVM), Artificial neural network, Naïve Bayes and Logistic Regression) employing clinical, laboratory, and imaging data of 228 patients presenting to emergency department with chest pain [23]. SVM has the highest accuracy and attained a 99.13% classification success. Data science approaches were also evaluated to reduce misdiagnosis and enhance triage procedures of non ST elevation myocardial infarction (NSTEMI) [24]. An artificial neural network model was built and showed an area under the receiver operating characteristic and an accuracy of 98.4, and 92.86, respectively. Additionally, the sensitivity, specificity, positive predictive value, and negative predictive value of the model were 90.91, 93.33, 76.92, and 97.67 respectively. The appropriate use of troponin testing for the diagnosis of acute myocardial infarction (AMI) is another important feature.

In the efficient triage of AMI, the variations in cardiac troponin

concentrations by age, sex and time between samples should be integrated for more accurate and personalized workup. A study aimed to combine these variables through machine learning [25]. The machine learning algorithm incorporating age, sex, and paired high-sensitivity cardiac troponin I concentrations, was trained on 3013 patients and tested on 7998 patients with suspected myocardial infarction. Using these thresholds, the model performed better than the ESC 0/3-hour pathway and the 99th percentile at any time-point and allowed an individualized and objective assessment of the likelihood of AMI.

Dyspnea and the differential diagnosis of HF are also challenging in ED and AI can help to improve it by integrating multiple factors. Such as the need for personalized prognostication becomes important due to high risk related to HF. As the risk related to HF is also high the need for personalized prognostication is also important. Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome related to high morbidity and mortality. Research was performed to derive HFpEF phenotype-based groups (phenogroups) based on clinical and echocardiogram data using machine learning, and to compare clinical characteristics, proteomics and outcomes across the phenogroups [26]. The authors applied model-based clustering to 32 echocardiogram and 11 clinical and laboratory variables collected in stable condition from 320 HFpEF outpatients. They identified six phenogroups with significant differences in the prevalence of concomitant atrial fibrillation, anemia and kidney disease were observed. These HFpEF phenogroups were related to differential characteristics and outcomes, as well as differential levels of inflammatory and cardiovascular proteins [26].

2.4. Enhanced precision care and outcomes monitoring

The potential of AI in cardiovascular medicine is tremendous. The use of AI appears also as a way to implement precision care and treatment. By using a machine learning-based algorithm, AI can carefully examine the clinician's diagnosis and treatment plan. The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) study tested the hypothesis that a machine learning algorithm utilizing both complex echocardiographic data and clinical parameters could be used to phenogroup a HF cohort and identify patients with beneficial response to cardiac resynchronization therapy [27]. In more than a thousand of patients, their analysis identified four phenogroups, significantly different in the majority of baseline clinical characteristics, biomarker values, measures of left and right ventricular structure and function and the primary outcome occurrence. Two phenogroups included a higher proportion of known clinical characteristics predictive of CRT response and were associated with a substantially better treatment effect of CRT-D on the primary outcome than observed in the other groups.

Another study evaluated the performance of machine learning models compared to traditional risk stratification methods for the prediction of major adverse cardiovascular events and bleeding in patients with ACS treated with antithrombotic therapy [31]. Data on 24,178 ACS patients were pooled from four randomized controlled trials and used to compare the efficiency of a super learner ensemble algorithm selected weights for 23 machine learning models in comparison to traditional models. The efficacy endpoint was a composite of cardiovascular death, myocardial infarction, or stroke. The safety endpoint was a composite of TIMI major and minor bleeding or bleeding requiring medical attention. For the major adverse cardiovascular event (MACE) outcome, the super learner model produced a higher c-statistic than logistic regression, the thrombolysis in myocardial infarction (TIMI) risk score, and a new cardiovascular risk score developed in the dataset. For the bleeding outcome, the super learner demonstrated a similar c-statistic as the logistic regression model. This analysis demonstrates the valuable application of machine learning to guide antithrombotic therapy treatment decisions.

Improvement of health outcomes could also be a short-term perspective of the application of AI to laboratory medicine and cardiovascular diseases. Outcomes are consistently improving when they are routinely measured, monitored and when the feedback is provided back to physicians and healthcare teams. The nonprofit International Consortium for Health Outcomes Measurement (ICHOM) recommends a set of outcomes and other patient information to be measured for all patients with CAD [28] and HF [29].

Reduction of preventable hospital readmissions, that result from chronic or acute conditions like stroke, HF or AMI, remains a significant challenge improving the readmission rate outcome and decreasing the cost of healthcare delivery [30,31]. Compared to existing predictive models for HF readmission rates, results from data driven machine learning applied to electronic medical record predictive model are encouraging and could help to improve this important contemporary outcome [30].

3. Translating value based cardiovascular medicine to practice

Big data are providing new insights and opportunities to personalize therapy. AI, used to predict likely outcomes, automatic generation of management decisions in addition of the “human neural network” which integrates the clinical, personal, environmental, and social aspects of each individual patient.

The application of AI and the precision biology in imagery is going to reduce cost and improve medical value at the stage’s interpretation, and decision-making. In addition, Artificial intelligence is attracting growing amounts of investment, as the technologies develop; its potential value in health is likely to grow.

Therefore, some policy innovations are needed to cope with these rapidly evolving technologies. But given the scale of the beneficial impact on health, the economy and society, the goal should not be to constrain the adoption and application of AI, but rather to encourage its beneficial and safe use. It becomes essential to switch resources from lower value to higher value healthcare [32]. Data science and AI appear as potential accelerators for value based laboratory medicine.

3.1. Data aggregation and integration of omics

The analysis of genome, transcriptome, proteome and metabolome are instrumental in identifying biomarkers of disease, to gain insight into mechanisms underlying the development of cardiovascular disease and for the sub-phenotyping of patients [33]. AI can clearly improve the comprehensive analyses of such large volumes of data from multi-omics and trigger the identification of relationships between complex features in the data and sub-classification of diseases [33]. In our multi-omics era, such a use of AI for integrative approaches is mandatory in order to gain further insights on oncological phenomena, and to move forward toward the precision medicine paradigm [34].

3.2. Resources stewardship and demand management

The need for value based care has led to assess laboratory test reordering and to develop models to reduce unnecessary testing [35]. A recent study performed data analysis of laboratory test ordering in one major teaching hospital and one rural hospital in the same health district. The investigators showed that computerized physician ordering of urea, creatinine and full blood count could save approximately AU $400/inpatient bed per year. Another study investigated specific interventions including reduction of obsolete or misused testing, duplicate orders, and daily routine lab testing [36]. The authors observed that hard stops significantly decreased duplicate testing and educational sessions significantly decreased and rationalized daily orders of routine labs. They also estimated a related saving of about $100 000 during the study period. AI will also allow translating a real time integration of guidelines and recommendations into demand management and daily practices.

The efficient integration of AI and laboratory medicine to support

Table 1
Emerging applications in cardiovascular medicine based on the collaborative integration of AI and laboratory medicine.

Clinical perspectives	Biomarkers discovery and better understanding of complex disease pathways Engines for early risk estimation Improving diagnosis of AF, ACS, AMI or HF Enhanced precision care and outcomes monitoring
Supporting value based care	Data aggregation and integration of omics Resources stewardship and demand management Real time monitoring of diseases or risk components

cardiovascular medicine will contribute to value-based care. Beside substantial improvements in cardiovascular health, and according to a 1% hypothesis of efficiency of the integration, €2 billion a year could be saved at the EU level.

3.3. Future perspectives

The usage of AI in cardiovascular medicine requires absolute professional skills, advanced technologies and importantly with appropriate considerable investment. It would necessitate the easy access and monitoring of AI technology with real-time updates and evaluation. Future AI projects may draw attention of giant technology firms to develop potential interest in developing sensor technology to risk stratification algorithms. The latest Apple watch series 4 has a new transducer that measure ECG. Recently, Microsoft announced that they are going to help clinicians in writing algorithms for predicting the risk factors for CVD in cooperation with Apollo Hospital, India. Thus, AI technology will help to detect the early warning signals and associated health risks with the help of machine-learning based solutions in high burden diseases [9,37].

4. Overcoming challenges

Multiple challenges are still paving the way for a fast and efficient integration of AI and laboratory medicine to improve cardiovascular medicine [38–40]:

- Regulatory and ethical challenges need to be addressed [7–9]. Fortunately, ethical principles and legal framework have been proposed for a trustworthy AI [41].
- The need of liability of the AI community, from developers to users [42].
- The need to guarantee data privacy and patient safety [7].
- The need to improve the education and awareness of healthcare workforces about the strengths and weaknesses of data science and AI. This will be parallel to the development of digital skills and competences.
- The need of inter-operability and scalability of AI solutions. This is associated to use of structured data. A specific challenge will be the exchanges of data between public and private sectors.
- The need for state supported health data space to aggregate and exchange data for building dynamic care pathways relying on AI.
- The need to define the value and business models around AI tools and carefully assess the benefits in terms of clinical outcomes, patient experience, and costs.
- The need to support scientific research and development in the field.
- The need to consider medico-legal aspects [7]. The active involvement of healthcare workforces will be mandatory for the construction and validation of AI solutions and decision support systems. The input of healthcare workforces will also be critical for the building of care pathways and for the integration the most recent clinical decision standards as well as to avoid biases in the delivery of healthcare or tampering with the allocation of scarce resources.

5. Concluding remarks

AI has already been adapted for health care in areas such as predictive analysis, in health management, clinical decision-making, and many other trend or analytics-based solutions. Managing population health is a critical component of value-based care—but it's no easy task. Understanding broader patient health needs within a target population, defining care gaps that impact patient health, mining social determinants data to tailor care plans, is still challenging. CVD remain a major killer and burden for healthcare economies. The rising prevalence of cardiovascular diseases is putting pressure and additional costs on healthcare systems worldwide. Expanded CVD surveillance, advances in evaluation and economic modeling of primary prevention, and use of behavioral economics to identify new prevention strategies is vital. The combination of AI techniques and laboratory medicine can be used to address some of these challenges with due focus on improving the quality of research (Table 1).

AI is providing new tools to improve research but also to enhance early risk estimation of diseases and diagnostic performances. The combination of AI and laboratory medicine appears also as an accelerator for value-based care and a contributor to more dynamic care pathways, better processes, and better integration of evidence to practices. Several challenges are there and it is fundamental to support the training and development of a laboratory workforce with expertise in AI, data science.

CRediT authorship contribution statement

Damien Gruson: Conceptualization, Writing - review & editing. **Sergio Bernardini:** Writing - review & editing. **Pradeep Kumar Dabla:** Writing - review & editing. **Bernard Gouget:** Writing - review & editing. **Sanja Stankovic:** Writing - review & editing.

Declaration of Competing Interest

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