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NARRATIVE REVIEW

Machine learning in cystic fibrosis: narrative review

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ABSTRACT

Machine learning (ML) is an emerging area of interest, and it can represent useful tool in cystic fibrosis (CF) to improve a personalized patient-centered care. It can help to evaluate and treat each patient in a specific and appropriate way according to his clinical needs.

The aim of this narrative review is to describe how ML can help and support clinical evaluations and decisions in CF patients, regarding medical aspects, rehabilitation approach, microbiology dimension.

It represents an original and primary evaluation of ML-approach connected with cystic fibrosis; indeed, artificial intelligence (AI) can predict risks with high precision, based on multidimensional clinical and biological datasets. AI gives a great opportunity to tailor early treatments or interventions to each patient with CF.

IMPACT STATEMENT: The review proposed has the aim to underline preliminary the status quo of machine learning in cystic fibrosis, a sort of map trying to clarify hidden aspects of the world of artificial intelligence.

INTRODUCTION

Artificial intelligence (AI) has become a popular interest field both within and outside of the scientific community; a large number of articles in technology and non-technology-based journals have covered the topics of AI, machine learning (ML) and deep learning (DL) (1-6).

ML techniques can facilitate clinical workflows by making individual-level predictions for a patient's prognosis that are tailored to their specific traits, features and medical history (7). Last years showed high levels of ML use: chronic diseases' management starts to use these approaches, so we need to underline the necessary aspects to know about ML. This technology has demonstrated a great ability to extract useful information from large samples of data in a variety of application domains (1). ML models can address patient heterogeneity by learning the underlying complex patterns that govern how individual patient features and traits map to different prognoses.

ML-based models can guide personalized decisions through individual-level predictions on: 1) whether the patient is likely to have an exacerbation, 2) whether a specific new treatment is likely to be effective for that patient, 3) what is the most likely sequence of clinical events that the patient might experience, and 4) what is the relative likelihood of their different competing risks. Moreover, ML-based models trained on patient-generated data recorded on digital devices, in the context of macro-intelligence extracted from registries,

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KEY WORDS
Cystic fibrosis; machine learning; rehabilitation; personalized medicine; chronic disease.

can inform whether a proactive clinical intervention is needed, and even whether a clinic visit is necessary. This care model could help inform the health economics of the high-priced disease-modifying therapies that target specific genotypes within the population of people with cystic fibrosis (CF). It could also help the CF healthcare system as the population of patients grows due to better survival. A CF patient faces a variety of health risks, for instance, infections or deterioration of lung function. Currently, risk evaluation for CF patients, and more generally in the medicine domain, does not fully integrate the wealth of information available about the patient. It is usually done on the basis of a linear model, such as a Cox proportional hazards model (7) (*e.g.*, see (8)), and using a relatively small number of hand-picked features, often chosen by clinical judgment. ML methods would allow us to take such work one step forward by learning patient-specific information that might influence treatment decision. Recent methods have been proposed to extract patient-specific risk factors from ML models using symbolic regression approaches (1) (**Figure 1**).

METHODOLOGIC QUALITY

ML, with the use of digital devices, can transform this model of care. Digital sensors and wearable devices can enhance care in (at least) three ways:

- collecting information that can be used by the treating clinicians (especially in tracking patients' key health indicators and progress);
- collecting information that can be used by the patient to monitor and manage their own progress;
- providing actionable intelligence to the patients including early warnings, reminders, and suggestions for achieving success with medication, exercise, and treatment regimen (1).

Methods

The proposed narrative review will be conducted with no structured and systematic protocol. Narrative reviews have no predetermined research question or specified search strategy. This research is a preliminary step to understand the power of ML in CF. An initial limited search of PubMed was undertaken to identify articles on this topic. We also used databases like Google Scholar and CINHAL. In each database we put the term "machine learning" connected with "cystic fibrosis" through the Boolean operator "and"; we also used the word "rehabilitation" with "machine learning" always linked with "and".

APPLICATION OF ML IN CYSTIC FIBROSIS

There are a lot of studies that underline the necessity to use ML in pulmonary pathologies; CF represents one

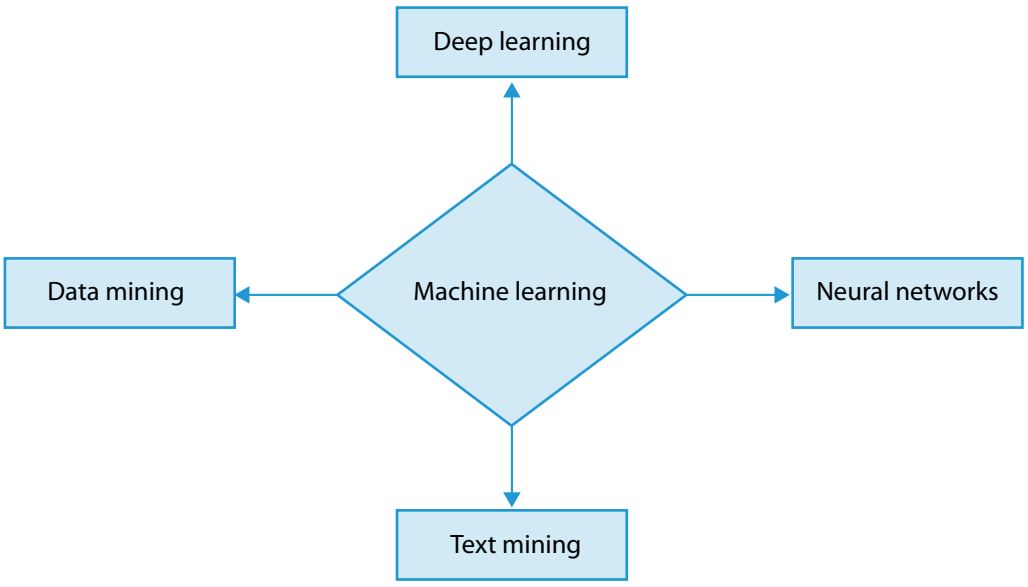

Figure 1. *Machine learning and derivations.*

of the most important respiratory panel, but it was also characterized by a disaffection about multiple organ. In fact, diabetes is the most common complication of CF, affecting at least half of the adult population (8). Early identification and treatment are crucial, as the symptoms are usually not immediately recognized. ML method was also used in this field to optimize the diagnosis of CFRD (Cystic Fibrosis Related Disorders). According to scientists, ML approach represents a good tool and facility to be understood by non-machine learning experts (physicians and other health professionals).

ML algorithms were applied to develop classification models in order to suggest a possible antibiofilm action for each chemical component of the studied EOs (Essential oils). In the present study, we assessed the biofilm growth modulation exerted by 61 commercial EOs on a selected number of *P. aeruginosa strains* isolated from CF patients. Furthermore, ML has been used to underline the EO chemical components likely responsible for the positive or negative modulation of bacterial biofilm formation (9). About data set General Methods Binary classification models development and validation were carried out by an in-house python script based on the scikit-learn machine learning library.

Personalized treatment in CD and in the other chronic diseases could represent a way to reach the goal to build an accurate patient-specific plan, based on a systematic and reproducible approach to obtain values that are necessary to understand the evolution of pathology, and also to analyze small clinical aspects referred to each patient. ML approach could give the correct instruments to apply healthcare protocols based on algorithms, realized thanks to proven statistical analysis.

Deep learning (DL) may also represent a good tool analyze in chronic disease. The huge collected data and related models can be used to establish new possible ways to evaluate strategies to create excellent models, standardized following CF guidelines of care. From one side personalized-medicine represents the true solution to realize a standard of care expression of high-quality health care-related; on the other side the aspect of longitudinal trajectory is the way to collect and measure biomarkers and risk factors repeatedly. Regarding the clinical approach we really get a big opportunity thanks to machine learning, a real and ontologic opportunity to build a consistent new idea of healthcare.

In addition to the therapeutic effects, the big world of deep learning could give a real opportunity to the diagnostic area; for example, it was known the importance of imaging scoring systems in CF lung severity-disease. Brasfield scores are routinely requested by pediatric pulmonologists (10). Moreover, in recent years, studies underling the role of deep learning were published, showing this form of machine learning based on neural networks, often applied for image recognition or classification (11). So, we noticed that deep convolutional neural network (DCNN) model for automated Brasfield scoring was a good tool, but further studies of validation are needed to establish the complete role of this computational approach (**Table 1**).

Table 1. *Possible uses of machine learning in cystic fibrosis (respiratory domain).*

Role of Machine Learning	Clinical implications
Predict the pulmonary exacerbation	Anticipate the lung damage
Try a new possible treatment for each patient	Improve specific and personalized medicine (medical treatments)
Imagine the trajectory of pathology starting from patient issues	Prevent systemic and multi-organ involvement

ML IN MANAGEMENT OF REHABILITATION IN CYSTIC FIBROSIS

ML in physiotherapy practice is becoming a new form of patient measurement data and also it represents a clinical decision support increasingly used. ML could play an important role also as a component of professional development. For physiotherapists this technology system will be an excellent resource, for which all health professionals could improve their knowledge and experiences to change their rehabilitation-approach *in fieri*. There are for example new strategies to assess physical activity in CF (12). Another frontier is virtual respiratory therapy delivered through a smartphone app (13) (Baxter BMJ open research) that allows to make respiratory rehabilitation funnier. New platforms for remote rehabilitation have been tested by some authors, for example Tomlinson *et al*. (Tomlinson *et al*. Journal of Telemedicine and Telecare) proposed Zoom like new tool for tele-rehabilitation for CF patients. In the literature we found Gaming Console

Home-Based Exercise for adult patients with CF to transform standard physical activity in something totally revolutionized, where patients thanks to home-based exergames could improve their physical fitness and respiratory function (14).

In this field ML will be a sort of bridge between technologies and therapists. The target and goal for this approach is to create a new tool for all health professional who are called to change completely their working-mind.

DISCUSSION

ML is a way to build a new dimension of medicine and also rehabilitation. New technology strategies, including ML and DL, are the possible answers to personalized medicine and to rehabilitation. In **Table 2** we list some examples of machine learning and deep learning applications in medicine.

Despite standardization of protocols and a lot of guidelines for therapeutic approaches, it's becoming evident that all areas of medicine need to have a singular development, and also through big data it will be possible to manage a lot of information about a big number of patients; this represents a new frontier for all clinicians. We are at the point of change, where tools like ML, big data, deep learning are the present, but especially they will be the future also for rehabilitation.

All therapists and physicians must understand the completely change set in the way to provide rehabilitation for lot of patients for example with respiratory and cardiological aspects, for neurological approach, to establish a modified pathway building a new idea of medicine.

Computational intelligence (CI) has become a true necessity in the last years, an essential element to build a sort of new world which must be followed by figures trained to use these "new" instruments also in their clinical practice. Using these strategies, we think that all processes around the patients will have a deep change, where clinical practice is supported by CI. However, it's necessary to realize for healthcare professionals to learn the use, in better way, of a lot of instruments provided by ICT to create a modern possibility to reach a multimodal-care system.

CONCLUSIONS

CF in the era of ML is called to transform itself also thanks to these technologies that represent an important part of the care pathway. We will assist a complete upheaval of the approach in the field of chronic disease. We hope that all aspects of artificial intelligence will become an integral part of healthcare, and all clinicians and health professionals will be able to modify their approach to be near at the transformations of health culture that we are experiencing. Further studies are necessary to underline the role of ML in a new era of personalized medicine, where patient will be the center of a global and multidisciplinary approach to develop a real model with mathematical and biological aspects linked together.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors declare no conflict of interests.

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Author contributions

MDM and MC conceived the study. MDM, SB and MC wrote the manuscript. MDM and MC collected data. RC conceived and directed the work thanks to his knowl-

Table 2. *Examples of machine learning and deep learning in medicine.*

Field of work	Study target	Type of analyses
Microbiology	Detect positive or negative modulation of bacterial biofilm formation	Machine learning
Diabetology	Optimize identification of diabetes	Machine learning
Radiographic medicine	Assess skeletal maturity	Deep learning
Neurological rehabilitation	Detect home exercise	Machine learning
Radiographic medicine	Application to Brasfield score	Deep learning
Robotic and virtual rehabilitation	Improve human therapist approach	Machine learning

edge of the subject matter. All Authors analyzed and interpreted patients' data, read and approved the final manuscript.

Ethical approval

Human studies and subjects

N/A.

Animal studies

N/A.

Data sharing and data accessibility

The data presented in this study are available on request from the Corresponding Author.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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