White paper

Predictive medicine Solution for patients with chronic respiratory disease



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Executive summary

For centuries, individuals have sought medical interventions for their health concerns. Much like the past, today's landscape is still fraught with diseases that manifest few or ambiguous symptoms, leading to misdiagnoses. The progression of diseases varies widely among individuals; some require a vigilant "watch and wait" approach, while others necessitate early and aggressive treatment. In an era of burgeoning scientific knowledge, these intricate medical decisions challenge even the most skilled physicians.

The digital revolution has inundated the healthcare sector with information. With the ongoing digitization of healthcare systems, unprecedented opportunities to enhance patient care are emerging. Cutting-edge technologies like machine learning and artificial intelligence (AI) are now unlocking vital insights from routinely collected health data. They pose crucial questions: Who is likely suffering from a disease yet remains undiagnosed? Which patients are at high risk of disease progression, and who would benefit most from novel therapies ?

In this white paper, we unveil practical case studies that leverage AI in medical care. We delve into the pivotal methodologies for developing what are termed predictive algorithms and illustrate how these algorithms are currently revolutionizing healthcare practices. Furthermore, we explore the future potential of predictive algorithms in routine medical applications and discuss the possible barriers to their widespread adoption. Biosency, with its Bora care® Solution, stands at the forefront of this transformative era, offering a predictive monitoring solution that promises to redefine the management of Chronic Obstructive Pulmonary Disease (COPD) and beyond. By actively participating in the advancement of healthcare systems, Biosency is dedicated to shaping a future where patient care is not only more effective but also more accessible and patient-centric.

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Biosency sets a new standard in COPD management, providing a predictive solution that not only detects exacerbations early for proactive prevention but also enhances patient quality of life and eases the economic impact of the disease.

The challenge of managing COPD

Chronic obstructive pulmonary disease (COPD) is an irreversible pathology characterized by chronic progressive dyspnea impacting drastically the quality of life of affected patients. It encompasses various chronic obstructive pulmonary conditions characterized by airflow limitation and respiratory symptoms; COPD is mainly caused by exposure to noxious particles (for example due to occupational exposure or smoking) and is usually diagnosed in people aged 40 years or more, often presenting comorbidities like cardiovascular diseases, hypertension, or obesity.

COPD affects more than 480 million persons worldwide although more than 50% of patients might be undiagnosed ; in 2020. The projected increase in COPD cases is 112 million, reaching a total of 592 million by 2050, which represents 9.5% of the overall eligible population. This marks a relative rise of 23.3% from 2020 to 2050 [1]. 3.23 million people died because of COPD, the third leading cause of mortality worldwide [2, 3].

COPD progresses over time, with acute worsening episodes known as exacerbations caused by a drop in blood oxygenation. Patients face exacerbations twice every year on average [4], although they are largely under-reported and under-diagnosed; they lead to hospitalization in 10% of the cases and symptoms can last several weeks, thus impacting dramatically the quality of life of patients as well as the socio-economic burden of COPD. Exacerbations are associated to an accelerated irreversible decline of respiratory function, an increased risk of cardiovascular disease and a risk of further exacerbations. Severe exacerbations often result in hospitalisation and are life-threatening events; the risk of severe exacerbation [5]. In the European Union, the total direct costs of respiratory diseases are estimated at 6% of the annual healthcare budget. Within this, COPD constitutes 56% of the total respiratory disease costs, amounting to €38.6 billion [6]. Furthermore, the annual costs of healthcare and lost productivity due to COPD in Europe are estimated at €48.4 billion. [7]

In the United States (US), 16 million people are diagnosed with COPD and the disease costs 50 billion US dollars (USD) each year, divided into 30 billion USD for direct health care and 20 billion USD for indirect costs. Exacerbations result in more than 700,000 hospitalizations per year in the US [8], while the loss of productivity is estimated between 1,053 and 1,527 USD per COPD patient every year [9].

What is the treatment for COPD ?

The treatment of COPD is based on bronchodilators helping directly breathing and inhaled corticosteroids aiming at reducing inflammation of the airways. Patients are encouraged to get vaccinations to avoid respiratory infections. They receive antibiotics in case of bacterial ones; antibiotics are also commonly prescribed in case of exacerbations, although less than one third of these acute worsening episodes are actually linked to bacterial infections. Management of COPD should include lifestyle recommendations (quitting smoking, diet, physical activity) and patienttailored pulmonary rehabilitation is encouraged to improve both physical and psychological condition.

Conventional care of COPD patients includes regular assessment of lung function parameters and oxygenation status of arterial blood during medical visits, so that healthcare professionals can adjust treatment and general care. When blood oxygenation is low in spite of the treatments described hereabove, oxygen therapy – which can be received at home – is prescribed. Non-invasive ventilation (NIV) reduces the work of breathing and improves respiratory mechanics. In severe COPD, hyperinflation of the lungs due to emphysema and small airway disease results in increased lower airway resistance and diaphragm muscle atrophy; together with airflow obstruction, this contributes to increased respiratory muscle load. NIV aims to achieve control of spontaneous breathing and minimize diaphragm activity, thus reducing chronic hypercapnia.

Conventional treatment of COPD aims at reducing dyspnea as well as the risk of exacerbation and mortality, but this strategy based on months-apart respiratory function evaluation does not entirely represent the course of the disease and cannot detect, let alone anticipate, the exacerbations which are a keystone in patient's worsening, with 26% of them dying within the year following their first exacerbation [10].

It is now widely recognized that early detection of COPD exacerbations is central in improving patient's overall quality of life, the quality of patient care, and reduce the COPD economic burden - two thirds of the costs being attributable to exacerbations only. Early detection and management of exacerbations have indeed been shown to correlate with faster recovery, reduced risks of hospitalization, and a better quality of life [11]; in this study, the regression model adjusted for symptom severity showed that each day of delay in treatment initiation after the beginning of the exacerbation increased the duration of symptoms by 0,52 day. Early detection of exacerbations has been demonstrated to prevent further exacerbations, to slow down COPD progression and to reduce mortality [12]. Moreover, patients failing to recognize and/or report exacerbations miss out on receiving appropriate treatment, thus worsening their prognosis and overall quality of life.

Biosency innovates in the field of remote patient monitoring for COPD by focusing on the early detection and prediction of exacerbations through advanced algorithmic analysis.

Remote monitoring of patients offers a variety of solutions and has been shown to reduce hospital days, exacerbation-related readmissions, as well as overall mortality by helping detect acute exacerbations of COPD [13]; home monitoring solutions for COPD patients include pulse oximeters, spirometers and various hands-free devices but their accuracy and forecasting abilities are limited [14] and rely on the patient's ability to read and understand the results provided.

In this context, prompted by the ambition of developing a telemonitoring solution that would early detect COPD exacerbations and alert remote healthcare professionals, Marie Pirotais and Yann Le Guillou created Biosency in 2017; the first prototypes of their telemonitoring solution called Bora care[®] were locally produced in Brittany-France in January 2018.

Biosency has set their mission in detecting exacerbations at an early stage while impacting the less possibly the quality of life of patients. The development of Bora care[®] solution was driven by a triple constraint: home, daily, long-term monitoring requiring no action from the patient. Bora care[®] consists of a connected wrist band (Bora band[®]) and a web platform (Bora connect[®]). The bracelet, worn by the patient, collects vital signs data then transmitted securely to the Bora connect[®] platform. The specificity of Bora care[®] resides in that it includes an advanced algorithm which analyzes trends, enabling the early identification of deteriorating health conditions.

II. Bora care[®]: A unique predictive medecine solution

Bora care[®] is a predictive medecine solution that enables early detection of vital signs decompensation, based on the parameters of each patient.

It consists in a wearable remote monitoring device measuring vital signs and connected to an internet platform, with a patented algorithm analyzing vital signs incoming data. Bora care[®] provides a regular followup of patients and can also detect acute episodes of exacerbation.

Bora care[®] (CE MDR Class IIa) offers comprehensive monitoring solution of patients with chronic respiratory pathologies, centralized on a collaborative web platform for managing all patient lists. The solution offers two different modules for complementary and comprehensive care monitoring :

• Bora band[®] module provides real life measurements of vital signs and activity using a dedicated medical device wrist band. A predictive score, BVS³ (Bora Vital Sign Standard Score), is generated by AI powered algorithm from the vital signs measurements contribututing to early detection of the risk of COPD exacerbation event.





Early detection score of COPD exacerbation

Provides an alert on deviation from average over the last 15 days

- Basal state learning
- Anomaly detection

Clinical decision-making support

- Early management of a COPD exacerbation
- Adapt or confirm treatment
- ✓ Better care coordination and management

Bora band[®] is a remote monitoring device worn on the wrist during daily life including sleeping time. It collects, processes, and stores key parameters for the follow up of patients with respiratory dysfunction: blood oxygen saturation (SpO2), heart rate (HR), respiratory rate (RR), and skin temperature. Data are transmitted via Bluetooth to a Bora box[®] (at home) which then transfers them to the web-based platform Bora connect[®]. A proprietary algorithm filters and interpret accurately entering data, made accessible on Bora connect[®] to both patients and healthcare professionals.

Boraband®

Module for measuring and monitoring vital signs in real life with a connected wristband



Healthcare professionals can follow their patients remotely on Bora connect[®] and adjust their treatment when needed; Bora connect[®] is also interoperable with other platforms and connected devices such as respiratory assistance machines. Customizable alerts, sent by Bora connect[®] when a given parameter falls outside a predetermined range, allow the healthcare professional to both optimize the treatment and take expedited measures to counteract exacerbations.

Bora flow module which collects data from NIV devices, not only meets the French market requirements but is also in the deployment phase across various European countries. It is reimbursed in France and provides data that complements NIV data by offering additional insights beyond vital signs accessible via Bora connect[®].

Boraconnect®

Online platform for visualising vital signs and respiratory support machine data, with clinical dashboard and customisable alerts





- CE MDR Class IIa certified medical platform

- Certified compliant with ANS (Digital Health Agency) requirements (cyber, interoperability, etc.)

interoperable

- Easily interfaces with other platforms (SDK/API) or with other connected devices

EASY TO USE

- Available online using your internet browser

- Patient management via a simple and intuitive dashboard
- Intelligent alert system : alerts on collected data and adapted to the needs of each individual patient

- Reliable vital sign measurements : clinically validated heart rate, respiratory rate and SpO2

- Report export feature

The technologies behind Bora care[®] were developed by Biosency along time and their performances assessed during several studies [15-18] which demonstrated an elevated 3% accuracy for the measurement of SpO2, while the accuracy of HR and RR is of 3 bpm (beats per minute) and 3 rpm (respirations per minute), respectively.



The on-going multi-center **DACRE study** (NCT04034901) included 50 patients hospitalized in a pulmonary ward for an exacerbation episode of BPCO and tele-monitored with Bora care® until one month after discharge while being followed-up as per usual clinical practice. The objective is to collect clinical parameters and analyze their correlation with readmission over the 30-day period to identify the key markers of COPD worsening and develop the algorithm for the prediction of exacerbations. So far, 24 patients with a median age of 66.7 years have been enrolled and monitored for a median duration of 35.5 days. Preliminary results show that the breath rate variation was the main parameter correlation with readmission, followed by heart rate variation, then oxygen saturation [22]. The Dacre study is currently ongoing, with 41 patients having been enrolled.

IV. Predictive Validation Study

The **e-MEUSE study** (NCT04963192) is a prospective clinical study, conducted at one site in France, with the main objective of studying through the SF36 questionnaire the evolution of the quality of life of patients with a chronic respiratory pathology, during an integrated management at home for six months.

The e-Meuse study also serves to conduct a clinical evaluation of the real-life utilization of Bora band[®] and to validate the detection algorithm and the entire Bora connect[®] solution.

The patients were monitored during six months with Bora care[®] and their vital parameters collected :

- SpO2 (peripheral oxygen saturation)
- HR (heart rate)
- RR (respiratory rate)

Data regarding exacerbation and severities were collected as well, and several thresholds and scores to set the alert for early detection of exacerbations episodes were assessed. The compliance and satisfaction of the patients were also evaluated.

A total of 85 patients with COPD took part in the study; they were aged 63,8 years on average, 25% of them were on oxygen therapy and 71% had comorbidities such as hypertension or obesity. Patients wore their Bora Band[®] 90% of the time on average and their vital signs were measured more than 110 times daily, considering the three parameters together; this represents over more than 12 500 monitoring days for the whole study.

During the course of the study, 21 exacerbations were reported and examined to assess the detection algorithm. Among the various thresholds evaluated for early detection of exacerbations, the combined BVS^3 score – with a limit set at 3 – showed the best results: the algorithm elicited a sensitivity of 85.7% and a specificity of 90,9% in the early detection of exacerbations, on average 3 days before their actual beginning, with a standard deviation of +/- 2,7 days with an area under the curve (AUC) of 0.94, signifying a high level of accuracy and discrimination.



ROC Curve : Receiver Operating Characteristic curve Sensitivity: the ability of a test to correctly identify those with the disease (true positive rate)

Specificity is the ability of a test to correctly identify those without the disease (true negative rate)

This clinical study demonstrates that Bora care[®] fulfilled its requirements: a remote monitoring with low impact on patient's life, while predicting exacerbations early enough to take appropriate countermeasures. The results of this study were presented at the American Thoracic Society International Conference in May 2023 [19].

The e-meuse study continues to make significant strides. As of January 2024, the e-meuse study has seen a promising progression, with over 170 patients now included in the research. The study is set to conclude patient inclusion by the second semester of 2024. The Bora care[®] system has proven to be an effective remote monitoring solution, minimally impacting patients' lives while successfully predicting and detecting COPD exacerbation episodes up to seven days in advance, allowing for timely interventions.

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V. Ongoing clinical studies

Two further clinical studies starting in the first quarter of 2024 will further evaluate the Bora care[®] solution.

The **Austraal study** aims to compare conventional care and telemonitoring by Bora care[®] in 400 patients with COPD having frequent exacerbations (at least 1 exacerbation within the last 12 months). The objective of the study is to evaluate whether early detection of exacerbations by Bora care[®] reduces the overall inhospital time. The patients will be randomly assigned to either Bora care[®] or conventional care and followed-up for one year. The primary criterion for evaluation will be comparison of the number of hospitalization days between the two groups.

Secondary objectives include assessing the device's impact on hospitalization frequency and duration, evaluating patients' overall quality of life, measuring compliance with the Bora care[®] device, examining its influence on healthcare organization and quality of care, assessing patient and caregiver satisfaction, and evaluating the device's performance in early exacerbation detection while identifying potential new markers for clinical events.

In summary, the study aims to demonstrate the advantages of telemonitoring with the Bora care[®] solution in improving patient outcomes and healthcare efficiency, potentially leading to the reconfiguration of healthcare pathways.

This multi-center study conducted in France started in March 2024 and will enroll patients until December 2026.

The **React study** will focus on the early detection of acute exacerbations in patients with Idiopathic Pulmonary Fibrosis (IPF), a rare disease affecting five million people worldwide [19]. No real treatment is available so far for this severe disease and the life expectation of patients experiencing acute exacerbations is three or four months in median [21]. The primary objective of the study is to evaluate whether Bora care[®] effectively detects acute exacerbation episodes in IPF patients.

This multi-center feasibility study conducted in France started in April 2024 and will enroll 30 patients until August 2025. Patients will be remotely monitored with Bora care[®] and followed-up for one year.

Through its e-MEUSE and upcoming Austraal and React clinical studies, Biosency is solidifying its role in healthcare's future by leveraging the predictive capabilities of Bora care[®] to enhance the management and quality of life for patients with respiratory conditions, demonstrating a commitment to pioneering predictive health solutions. Patient's quality of life is at the center of Biosency's interest and is part of the assessment of Bora care[®] solution.

During the validation study, as well as during previous studies assessing Bora care[®], its impact on patient's daily life was evaluated. Patients wore their Bora band[®] 90% of the time [22]; overall, 95% of them declared they feel reassured by wearing it. Among patients participating in a pulmonary rehabilitation program, 84% of those using Bora care[®] decided to continue to follow their program. From the healthcare professionals' perspective, 70% of doctors declared that the data collected with Bora care[®] was useful in deciding how to adapt oxygen therapy for their patients, either on fixed or on mobile oxygen concentrators [22]. In France, 160 doctors have already adopted Bora care[®].

Biosency prioritizes patient quality of life, evident in the high satisfaction rates reported by users of Bora care[®], with a significant majority finding reassurance in the Bora band[®] and a substantial number of doctors valuing the data it provides for optimizing patient care.

VII. Conclusion

Clinical studies have underscored the impactful role of Bora care[®] in the predictive remote monitoring of COPD, enabling the detection and early intervention of exacerbations with remarkable reliability and efficiency.

Bora care[®] harnesses a unique algorithm and scoring system to proactively alert healthcare professionals, significantly contributing to the preservation of patient health and life by predicting exacerbations days before they occur. Validated by extensive research and certified by the French Digital Health Agency as well as the European Class IIa medical device standards (23), Bora care[®] is poised for potential health insurance reimbursement, enhancing its accessibility to patients. Moreover, Biosency is expanding its technological forefront to include predictive algorithms that address a broader spectrum of respiratory conditions, further innovating patient care in the respiratory health domain.

Biosency is forward-looking, aspiring to be a key player in the predictive landscape not only for respiratory diseases but also in broader healthcare fields, leveraging their innovative technologies to transform patient outcomes and care practices globally.



VIII. References

1. Boers E, Barrett M, Su JG, et al. Global Burden of Chronic Obstructive Pulmonary Disease Through 2050. JAMA Netw Open. 2023;6(12):e2346598. doi:10.1001/jamanetworkopen.2023.46598

2. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. Lancet Respir Med 10(5), 447-458 (2022).

3. World Health Organisation. Chronic Obstructive Pulmonary Disease. Last assessed on November 21, 2023, at https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).

4. Macintyre N, Huang YC. Acute exacerbations and respiratory failure in chronic obstructive pulmonary disease. Proc Am Thorac Soc 5(4), 530-535 (2008).

5. Sandelowsky H, Weinreich UM, Aarli BB et al. COPD - do the right thing. BMC Fam Pract 22(1), 244 (2021).

6. Rehman AU, Hassali MAA, Muhammad SA, Harun SN, Shah S, Abbas S. The economic burden of chronic obstructive pulmonary disease (COPD) in Europe: results from a systematic review of the literature. Eur J Health Econ. 2020;21(2):181-194. doi:10.1007/s10198-019-01119-1

7. The Burden of lung disease https://www.ersnet.org/wp-content/uploads/2023/01/Overview.pdf

8. Macintyre NR. Toward Reducing COPD Hospitalization. Respir Care 65(1), 127-128 (2020).

9. Patel JG, Nagar SP, Dalal AA. Indirect costs in chronic obstructive pulmonary disease: a review of the economic burden on employers and individuals in the United States. Int J Chron Obstruct Pulmon Dis 9 289-300 (2014).

10. García-Sanz MT, Cánive-Gómez JC, Senín-Rial L et al. One-year and long-term mortality in patients hospitalized for chronic obstructive pulmonary disease. J Thorac Dis 9(3), 636-645 (2017).

Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 169(12), 1298-1303 (2004).
 Vitacca M, Bianchi L, Guerra A et al. Tele-assistance in chronic respiratory failure patients: a randomised clinical trial. Eur Respir J 33(2), 411-418 (2009).

13. Lu JW, Wang Y, Sun Y et al. Effectiveness of Telemonitoring for Reducing Exacerbation Occurrence in COPD Patients With Past Exacerbation History: A Systematic Review and Meta-Analysis. Front Med (Lausanne) 8 720019 (2021).

14. Fan KG, Mandel J, Agnihotri P, Tai-Seale M. Remote Patient Monitoring Technologies for Predicting Chronic Obstructive Pulmonary Disease Exacerbations: Review and Comparison. JMIR Mhealth Uhealth 8(5), e16147 (2020).

15. Dervieux E, Bodinier Q, Uhring W, Théron M. Measuring hemoglobin spectra: searching for carbaminohemoglobin. J Biomed Opt 25(10), (2020).

16. Dervieux E, Théron M, Uhring W. Carbon Dioxide Sensing-Biomedical Applications to Human Subjects. Sensors (Basel) 22(1), (2021).

17. Priem G, Martinez C, Bodinier Q. Clinical grade SpO2 prediction through semi-supervised learning. 20th International Conference on BioInformatics and BioEngineering, (2020).

18. Taoum A, Bisiaux A, Tilquin F, Le Guillou Y, Carrault G. Validity of Ultra-Short-Term HRV Analysis Using PPG-A Preliminary Study. Sensors (Basel) 22(20), (2022).

19. Le Guillou Y, Tilquin F, S. LL. Vital signs remote patient monitoring in real-life for early detection of acute exacerbations of chronic obstructive pulmonary disease. American Thoracic Society International Conference, abstract, (2023).

20. Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. Orphanet J Rare Dis 3 8 (2008).

21. Collard HR, Ryerson CJ, Corte TJ et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med 194(3), 265-275 (2016).

22. Brinchault G, Guy T, Thepault F. Évolution des signes vitaux en vie réelle de patients BPCO : facteurs préventifs d'une réadmission après une hospitalisation pour exacerbation sévère – étude clinique en vie réelle DACRE. Revue des Maladies Respiratoires Actualités 15(1), 70 (2023).

23. European Commission, Guidance on classification of medical devices. Last assessed on November 21, 2023, at https://health.ec.europa.eu/system/files/2021-10/mdcg_2021-24_en_0.pdf.

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