



# **Home-Based Respiratory Care for COPD Patients**

Ricardo G. Figueiredo <sup>1,2,\*</sup>, Caio Laudano <sup>1</sup>, Jaqueline Muniz <sup>2</sup> and José de Bessa, Jr. <sup>1,2</sup>

- <sup>1</sup> Departamento de Saúde, Universidade Estadual de Feira de Santana (UEFS), Feira de Santana 44036-900, Brazil
- <sup>2</sup> Programa de Pós-Graduação em Saúde Coletiva, Universidade Estadual de Feira de Santana (UEFS), Feira de Santana 44036-900, Brazil
- \* Correspondence: rgfigueiredo@uefs.br

Abstract: Despite significant advances in pharmacological treatment over the last few decades, COPD remains a heavy burden on the health systems around the world, affecting approximately 210 million people, with elevated morbimortality and socioeconomic impact. Barriers to healthcare access were even more evident during the coronavirus disease 19 (COVID-19) pandemic and increased patients' vulnerability to physical deconditioning, depression, and social isolation. Home-based respiratory care in patients with COPD provides a valuable contribution to effective disease management, with potential advantages for monitoring, treatment adherence, and cost reduction. Technological innovation allows clinical markers of interest, such as respiratory frequency, pulmonary function, and oxygen saturation, to be tracked remotely from the patients' homes, providing a better understanding of their real needs. Home-based telerehabilitation can also be a viable alternative to hospital-based programs. Here, we highlight the full extent of health benefits of HRC in COPD, particularly for patients with a higher risk of exacerbations, multiple comorbidities, and limited access to health services.

Keywords: COPD; home monitoring; pulmonary rehabilitation



Citation: Figueiredo, R.G.; Laudano, C.; Muniz, J.; de Bessa, J., Jr. Home-Based Respiratory Care for COPD Patients. *Sinusitis* **2022**, *6*, 49–55. https://doi.org/10.3390/ sinusitis6020007

Academic Editor: Gurupreet S. Sethi

Received: 9 May 2022 Accepted: 6 September 2022 Published: 12 September 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/).

# 1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a multisystem inflammatory disorder intimately related to cigarette smoking, occupational factors, and/or biomass combustion, which alters respiratory mechanics and gas exchange [1]. Despite significant advances in pharmacological treatment over the last few decades, COPD remains a heavy burden on the world's health systems, affecting approximately 210 million people, with elevated morbimortality and socioeconomic impact [2]. Management of chronic fatigue, poor exercise tolerance, and depression are often inadequately addressed in COPD [3]. Barriers to accessing medical centers, such as urban disparities, socioeconomic determinants, mobility limitation, and disease severity, contribute to suboptimal clinical management, particularly in rural settings [4,5]. Patients with underlying COPD infected by SARS-CoV-2 are most likely to worsen the progression of the disease, and strong efforts should be directed to avoid COVID-19 infection in this population [6]. In this complex scenario, home-based respiratory care (HRC) plays a crucial role in effective disease management, with potential advantages for monitoring, treatment adherence, and cost reduction.

## 2. Home-Based Respiratory Care

Home-based programs promote easier access to pulmonary rehabilitation, better patient monitoring, and early recognition of acute exacerbations [5]. Ideally, screening patients for HRC should depend on a predefined risk management strategy. Identifying risk factors of COPD, poor outcomes, vulnerable populations, and impaired mobility favors inclusion in HRC programs. This strategy aims to implement preventative health actions in high-risk populations to identify, control, or eliminate related dysfunctions [7]. Due

to the multicausality of acute worsening of respiratory symptoms, one of the significant barriers to the effective management of acute exacerbations in COPD is the lack of reliable predictive biomarkers. However, validated models and risk scales are likely to contribute to predicting the risk of acute exacerbations [8] Therefore, HRC should be available to provide the full extent of health benefits and well-being, particularly to patients with a higher risk of exacerbations, multiple comorbidities, and limited access to health services.

#### 3. Pharmacological Treatment

Adherence to inhaled therapy is strongly associated with mortality and hospital admission due to exacerbations of COPD [9]. Adherence evaluation based on counting remaining doses in the returned inhalers is not entirely reliable [10]. Regular monitoring of inhaler technique and treatment compliance during home respiratory follow-up might improve clinical outcomes.

Treatment decisions should be developed by taking into account patients' individual preferences and current clinical guidelines. Pharmacological treatment can reduce symptoms, reduce the frequency and severity of exacerbations, and improve quality of life and exercise tolerance [2].

## 4. Smoking Cessation

A significant proportion of patients keep smoking after COPD diagnosis [2]. Increasing patients' knowledge about the disease is a significant goal in HRC and might contribute to smoking cessation. A tobacco cessation support program can achieve better results in the home scenario with increased risk perception and multidisciplinary care. A comprehensive approach to smoking cessation is individualized and includes behavioral interventions, accounting for smoking motivation, the environment in which smoking occurs, available resources to quit, and individual preferences [11]. Motivational Enhancement and carbon dioxide feedback delivered by home health care nurses resulted in more quit attempts and significantly more significant reductions in the number of cigarettes smoked per day through a 12 month follow-up [12].

## 5. Pulmonary Rehabilitation

Despite its undoubted benefits for COPD treatment at different severity levels, pulmonary rehabilitation continues to be underused due to limited access to rehabilitation centers and specialized multidisciplinary teams [13]. Home-based pulmonary rehabilitation (HPR) can be a viable alternative to provide equal access to this therapeutic strategy and increase rehabilitation adherence in patients with reduced mobility and advanced phases of the disease [14]. However, data concerning its efficacy and safety are currently limited to studies involving heterogeneous samples with few participants. In a Spanish study involving 60 patients with moderate COPD, a 12-week-long HPR program significantly improved tolerance to exercise, dyspnea, and life quality [15]. A recent systematic review, including twelve randomized controlled trials and two comparative observational studies, showed comparable effectiveness of HPR and usual pulmonary rehabilitation for safety, quality of life, and exercise capacity for patients with the chronic obstructive respiratory disease [16].

Aerobic respiratory exercise at home can alleviate the effects of dynamic hyperinflation during exercise by improving inspiratory capacity and respiratory muscle function [17]. HPR also contributes to greater long-term cardiorespiratory endurance. However, the benefits of exercise capacity and life quality are multifactorial and cannot be attributed exclusively to improved pulmonary function and respiratory muscle training.

Access barriers to pulmonary rehabilitation centers were even more evident during the coronavirus disease 19 (COVID-19) pandemic. The unprecedented worldwide spread of the virus has quickly turned COVID-19 into a critical global public health problem and increased patients' vulnerability to physical deconditioning, depression, and social isolation [18]. This scenario has significantly impacted traditional modes of pulmonary rehabilitation. As most COPD patients are notably susceptible to severe complications of COVID-19, the pandemic has fastened the debate on the implementation and delivery of HPR [19].

A successful HPR should be matched to principles of exercise training and education provision to improve patient outcomes. Nonetheless, telehealth rehabilitation requires some adjustments regarding access and use of technology, available space, adequate training and resources for health professionals, and patient individualization of care [20]. HPR may be an effective, lower-cost alternative for delivering pulmonary rehabilitation for COPD patients.

## 6. Long-Term Non-Invasive Ventilation

Long-term home non-invasive ventilation (LTH-NIV) is an established intervention to improve the prognosis of COPD patients with hypercapnia and chronic respiratory failure [21]. Domiciliary non-invasive ventilation is widely used to correct CO2 levels in stable hypercapnic, reduce hospital admissions and improve quality of life [22].

Severe COPD patients may remain with a  $PaCO_2 \ge 55$  mmHg after hospital discharge following a life-threatening exacerbation. Although LTH-NIV was not associated with increased survival, it may improve dyspnea scores and reduce subsequent exacerbations and rehospitalization after an acute acidotic respiratory failure [23]. A conditional recommendation for targeted reduction of  $PaCO_2$  in hypercapnic patients was proposed by the European Respiratory Society (ERS) task force under low certainty of evidence-driven by minimal potential harms of this intervention [22,24].

## 7. Long-Term Oxygen Therapy

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, supplemental oxygen is indicated for stable patients with arterial hypoxemia, defined as  $PaO_2$  at or below 55 mmHg or  $SaO_2$  at or below 88%. Long-term oxygen therapy (LTOT) should also be prescribed to patients with pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia (hematocrit > 55%) and  $PaO_2$  between 55–60 mmHg or  $SaO_2$  of 88% [2]. Oxygen levels should be monitored after 2 or 3 months to define whether LTOT will still be indicated.

Oxygen levels can vary significantly during the nocturnal period and daily activities. Continuous SpO<sub>2</sub> measurements with wearable finger pulse oximeters may help identify SpO<sub>2</sub> fluctuations in COPD subjects with unexplained dyspnea or severe exercise intolerance [25].

#### 8. Exacerbations

Avoiding exacerbations has significant prognostic implications on health status and is one of the main goals in COPD treatment [2]. A recent multicentric study involving 1150 patients demonstrated the benefits of HRC as an independent predictor for reducing severe exacerbations, hospitalizations, and emergency room visits, to a magnitude of 48%, 36%, and 88%, respectively [26]. Home-based maintenance telerehabilitation consisted of an individualized action plan, physical exercise sessions, and psychological and dietary support during 144 sessions over 12 months. In this study, HRC telemonitoring was considered as effective as hospital rehabilitation. The COPD Patient Management European Trial (COMET), conducted in 4 European countries, evaluated the impact of a comprehensive HRC program involving counseling sessions, a symptoms diary, pulmonary function monitoring, and oxygenation in stable COPD patients [27]. A reduction in mortality has been shown in patients with severe COPD, probably due to early detection and management of acute exacerbations; however, the study did not reach its primary endpoint of reducing hospitalizations over 12 months.

Acute exacerbation leading to hospitalization is associated with poor prognosis, elevated morbimortality, and risk of rehospitalization [2]. These patients usually experience a loss of independence in daily living after hospital discharge. McDowell and colleagues studied the impact of a 5-week-HRC conducted by a nurse on 110 patients with moderate to severe COPD following an acute exacerbation after hospital discharge. Each patient received disease-specific education, including recognition of the signs and symptoms of exacerbation, advice on smoking cessation, and a review of self-management techniques. The intervention group showed a significant reduction in anxiety and a better understanding of the disease. Nonetheless, there was not a significant reduction in rehospitalizations [28].

#### 9. Sociocultural Factors and Patient Education

The health-disease process involves biopsychosocial interactions with significant influence from the environment in which the individual is inserted [3]. An HRC program should be developed under the perspective of health beyond its biological character, considering social aspects and patient preferences. It is essential, therefore, to analyze the complex relationships among sociocultural factors, lifestyle, dietary patterns, and daily routines for a better understanding of the health inequities in COPD patients.

Patients must have adequate knowledge about the disease, the risk, and the benefits of treatment options and behavioral changes to ensure active engagement in health care [29]. Health coaching is a feasible way to promote patient education and counseling in a homebased respiratory care setting. A recent randomized controlled trial with 154 moderate to severe COPD patients showed a significant improvement in self-management abilities and a high degree of program acceptability [30].

#### 10. Home Health-Monitoring Technologies

An approach toward a better experience during COPD treatment is critical to guarantee better results in HRC. In this context, biotechnology solutions and remote monitoring take on increasing importance to offer the patient personalized and multidimensional care (Figure 1). Home health monitoring of pulmonary function, oxygenation, physical activity levels, and exacerbations via applications and videoconferencing by trained teams has proven to be a valuable tool in managing COPD patients [31]. Furthermore, since 2019, many pulmonary rehabilitation programs have been suspended during periods of elevated risk of infection of the SARS-CoV-2 virus. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), technological solutions, such as internet and cellphone applications, can be helpful in encouraging and stimulating patients under HPR during the pandemic [2].

Remote monitoring allows reaching population groups that are generally excluded due to access barriers and provide greater convenience, security, and service efficiency. However, economic evaluation of smart homes and home health monitoring technologies are still relatively rare, and the cost-effectiveness of remote monitoring strategies has yet to be validated by prospective studies [32,33].



**Figure 1.** Home-based respiratory care as a multidimensional health strategy for COPD; HRC: home-based respiratory care.

## 11. Conclusions

Home respiratory care (HCR) represents a valuable tool for promoting personalized health care in patients with COPD. Technological innovation allows clinical markers of interest, such as respiratory frequency, pulmonary function, and oxygen saturation, to be tracked remotely from the patients' homes, providing a better understanding of their real needs. Home-based telerehabilitation can also be a viable alternative to hospital-based programs, with the advantage of amplifying access to this therapeutic modality, especially in light of concerns regarding the biosecurity of patients during the pandemic.

**Author Contributions:** R.G.F., J.d.B.J.; Supervision: J.d.B.J.; Visualization: R.G.F., C.L., J.M.; Writing original draft: R.G.F., C.L., J.M., J.d.B.J.; Writing—review & editing: R.G.F., C.L., J.M., J.d.B.J. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

**Data Availability Statement:** No new data were created or analyzed in this study. Data sharing is not applicable to this article.

**Conflicts of Interest:** R.G.F. has participated in educational meetings funded by AstraZeneca, Boehringer Ingelheim, Chiesi, and GlaxoSmithKline. C.L., J.M., and J.B.J. declare no conflicts of interest.

# References

- Bousquet, J.; Dahl, R.; Khaltaev, N. Global Alliance against Chronic Respiratory Diseases. *Allergy* 2007, 62, 216–223. [CrossRef] [PubMed]
- 2. Global Initiative for Chronic Obstructive Lung Disease. 2022. Global Initiative for Chronic Obstructive Lung Disease—GOLD. 2022. Available online: https://goldcopd.org/ (accessed on 10 January 2022).
- Hermiz, O.; Comino, E.; Marks, G.; Daffurn, K.; Wilson, S.; Harris, M. Randomised controlled trial of home based care of patients with chronic obstructive pulmonary disease. *BMJ* 2002, 325, 938. [CrossRef] [PubMed]
- Guo, B.; Wang, Y.; Pei, L.; Yu, Y.; Liu, F.; Zhang, D.; Wang, X.; Su, Y.; Zhang, D.; Zhang, B.; et al. Determining the effects of socioeconomic and environmental determinants on chronic obstructive pulmonary disease (COPD) mortality using geographically and temporally weighted regression model across Xi'an during 2014–2016. *Sci. Total Environ.* 2021, 756, 143869. [CrossRef] [PubMed]
- Holland, A.E.; Mahal, A.; Hill, C.J.; Lee, A.L.; Burge, A.T.; Cox, N.S.; Moore, R.; Nicolson, C.; O'Halloran, P.; Lahham, A.; et al. Home-based rehabilitation for COPD using minimal resources: A randomised, controlled equivalence trial. *Thorax* 2017, 72, 57–65. [CrossRef]
- 6. Zhao, Q.; Meng, M.; Kumar, R.; Wu, Y.; Huang, J.; Lian, N.; Deng, Y.; Lin, S. The impact of COPD and smoking history on the severity of COVID-19: A systemic review and meta-analysis. *J. Med. Virol.* **2020**, *92*, 1915–1921. [CrossRef]
- Barreto, M.L.; de Almeida Filho, N.; Veras, R.P.; Barata, R.B. Epidemiologia, Serviços e Tecnologias em Saúde; Fiocruz: Rio de Janeiro, Brasil, 1998.
- 8. Adibi, A.; Sin, D.D.; Safari, A.; Johnson, K.M.; Aaron, S.D.; FitzGerald, J.M.; Sadatsafavi, M. The Acute COPD Exacerbation Prediction Tool (ACCEPT): A Modelling Study. *Lancet Respir. Med.* **2020**, *8*, 1013–1021. [CrossRef]
- 9. Vestbo, J.; Anderson, J.A.; Calverley, P.M.A.; Celli, B.; Ferguson, G.T.; Jenkins, C.; Knobil, K.; Willits, L.R.; Yates, J.C.; Jones, P.W. Adherence to inhaled therapy, mortality and hospital admission in COPD. *Thorax* **2009**, *64*, 939–943. [CrossRef]
- 10. Simmons, M.S.; Nides, M.A.; Rand, C.S.; Wise, R.A.; Tashkin, D.P. Unpredictability of deception in compliance with physicianprescribed bronchodilator inhaler use in a clinical trial. *Chest* **2000**, *118*, 290–295. [CrossRef]
- 11. Marlow, S.P.; Stoller, J.K. Smoking cessation. Respir. Care 2003, 48, 1238–1256.
- Borrelli, B.; Novak, S.; Hecht, J.; Emmons, K.; Papandonatos, G.; Abrams, D. Home health care nurses as a new channel for smoking cessation treatment: Outcomes from project CARES (Community-nurse Assisted Research and Education on Smoking). *Prev. Med.* 2005, 41, 815–821. [CrossRef]
- Rochester, C.L.; Vogiatzis, I.; Holland, A.E.; Lareau, S.C.; Marciniuk, D.D.; Puhan, M.A.; Spruit, M.A.; Masefield, S.; Casaburi, R.; Clini, E.M.; et al. An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. *Am. J. Respir. Crit. Care Med.* 2015, 192, 1373–1386. [CrossRef] [PubMed]
- 14. Sebio-García, R. Pulmonary Rehabilitation: Time for an Upgrade. J. Clin. Med. 2020, 9, 2742. [CrossRef] [PubMed]
- 15. Hernández, M.T.E.; Rubio, T.M.; Ruiz, F.O.; Riera, H.S.; Gil, R.S.; Gómez, J.C. Results of a Home-Based Training Program for Patients With COPD. *Chest* 2000, *118*, 106–114. [CrossRef] [PubMed]
- Stafinski, T.; Nagase, F.I.; Avdagovska, M.; Stickland, M.K.; Menon, D. Effectiveness of home-based pulmonary rehabilitation programs for patients with chronic obstructive pulmonary disease (COPD): Systematic review. *BMC Health Serv. Res.* 2022, 22, 557. [CrossRef]
- 17. Lu, Y.; Li, P.; Li, N.; Wang, Z.; Li, J.; Liu, X.; Wu, W. Effects of Home-Based Breathing Exercises in Subjects With COPD. *Respir. Care* 2020, *65*, 377–387. [CrossRef]
- 18. Tsutsui, M.; Gerayeli, F.; Sin, D.D. Pulmonary Rehabilitation in a Post-COVID-19 World: Telerehabilitation as a New Standard in Patients with COPD. *Int. J. Chronic Obstr. Pulm. Dis.* **2021**, *16*, 379–391. [CrossRef]
- 19. Vogiatzis, I.; Rochester, C.L.; Spruit, M.A.; Troosters, T.T.; Clini, E.M. Increasing implementation and delivery of pulmonary rehabilitation: Key messages from the new ATS/ERS policy statement. *Eur. Respir. J.* **2016**, *47*, 1336–1341. [CrossRef]
- 20. Lewis, A.; Knight, E.; Bland, M.; Middleton, J.; Mitchell, E.; McCrum, K.; Conway, J.; Bevan-Smith, E. Feasibility of an online platform delivery of pulmonary rehabilitation for individuals with chronic respiratory disease. *BMJ Open Respir. Res.* 2021, *8*, e000880. [CrossRef]
- Ergan, B.; Oczkowski, S.; Rochwerg, B.; Carlucci, A.; Chatwin, M.; Clini, E.; Elliott, M.; Gonzalez-Bermejo, J.; Hart, N.; Luján, M.; et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. *Eur. Respir.* J. 2019, 54, 1901003. [CrossRef]
- Crimi, C.; Noto, A.; Princi, P.; Cuvelier, A.; Masa, J.F.; Simonds, A.; Elliott, M.W.; Wijkstra, P.; Windisch, W.; Nava, S. Domiciliary Non-invasive Ventilation in COPD: An International Survey of Indications and Practices. COPD J. Chronic Obstr. Pulm. Dis. 2016, 13, 483–490. [CrossRef]
- Lun, C.-T.; Tsui, M.S.; Cheng, S.-L.; Chan, V.L.; Cheung, A.P.; Leung, W.-S.; Chu, C.-M. Differences in baseline factors and survival between normocapnia, compensated respiratory acidosis and decompensated respiratory acidosis in COPD exacerbation: A pilot study. *Respirology* 2015, 21, 128–136. [CrossRef]
- 24. Lukácsovits, J.; Carlucci, A.; Hill, N.; Ceriana, P.; Pisani, L.; Schreiber, A.; Pierucci, P.; Losonczy, G.; Nava, S. Physiological changes during low- and high-intensity noninvasive ventilation. *Eur. Respir. J.* **2011**, *39*, 869–875. [CrossRef] [PubMed]

- Buekers, J.; Theunis, J.; De Boever, P.; Vaes, A.W.; Koopman, M.; Janssen, E.V.; Wouters, E.F.; Spruit, M.A.; Aerts, J.-M. Wearable Finger Pulse Oximetry for Continuous Oxygen Saturation Measurements During Daily Home Routines of Patients With Chronic Obstructive Pulmonary Disease (COPD) Over One Week: Observational Study. JMIR Mhealth Uhealth 2019, 7, e12866. [CrossRef] [PubMed]
- Vasilopoulou, M.; Papaioannou, A.I.; Kaltsakas, G.; Louvaris, Z.; Chynkiamis, N.; Spetsioti, S.; Kortianou, E.; Genimata, S.A.; Palamidas, A.; Kostikas, K.; et al. Home-based maintenance tele-rehabilitation reduces the risk for acute exacerbations of COPD, hospitalisations and emergency department visits. *Eur. Respir. J.* 2017, *49*, 1602129. [CrossRef]
- Kessler, R.; Casan-Clara, P.; Koehler, D.; Tognella, S.; Viejo, J.L.; Negro, R.W.D.; Díaz-Lobato, S.; Reissig, K.; González-Moro, J.M.R.; Devouassoux, G.; et al. COMET: A multicomponent home-based disease-management programme versus routine care in severe COPD. *Eur. Respir. J.* 2018, *51*, 1701612. [CrossRef] [PubMed]
- McDowell, J.E.; McClean, S.; FitzGibbon, F.; Tate, S. A randomised clinical trial of the effectiveness of home-based health care with telemonitoring in patients with COPD. J. Telemed. Telecare 2015, 21, 80–87. [CrossRef]
- Duncan, B.B.; Chor, D.; Aquino, E.M.L.; Bensenor, I.M.; Mill, J.G.; Schmidt, M.I.; Lotufo, P.; Vigo, A.; Barreto, S. Doenças crônicas não transmissíveis no Brasil: Prioridade para enfrentamento e investigação. *Rev. Saúde Pública* 2012, 46, 126–134. [CrossRef] [PubMed]
- 30. Gruman, J.; Rovner, M.H.; French, M.E.; Jeffress, D.; Sofaer, S.; Shaller, D.; Prager, D.J. From patient education to patient engagement: Implications for the field of patient education. *Patient Educ. Couns.* **2010**, *78*, 350–356. [CrossRef]
- Benzo, R.P.; Ridgeway, J.; Hoult, J.P.; Novotny, P.; Thomas, B.E.; Lam, N.M.; Benzo, M.V.; Kramer, K.; Seifert, S. Feasibility of a Health Coaching and Home-Based Rehabilitation Intervention With Remote Monitoring for COPD. *Respir. Care* 2021, 66, 960–971. [CrossRef]
- Orme, M.W.; Weedon, A.E.; Esliger, D.W.; Saukko, P.; Morgan, M.D.; Steiner, M.; Downey, J.W.; Singh, S.J.; Sherar, L.B. Study protocol for Chronic Obstructive Pulmonary Disease-Sitting and ExacerbAtions Trial (COPD-SEAT): A randomised controlled feasibility trial of a home-based self-monitoring sedentary behaviour intervention. *BMJ Open* 2016, 6, e013014. [CrossRef]
- Liu, L.; Stroulia, E.; Nikolaidis, I.; Miguel-Cruz, A.; Rincon, A.R. Smart homes and home health monitoring technologies for older adults: A systematic review. Int. J. Med. Inform. 2016, 91, 44–59. [CrossRef] [PubMed]