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Invited Review

What will Happen in the World of COPD 2030?

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Abstract

2030 may seem to be a long way into the future, but it's not. We live in a world of relentless rapid change in modern medicine and our approach to our patients with chronic diseases such as chronic obstructive pulmonary disease (COPD) will need to evolve at speed. This review looks at what may occur in society and medicine that will influence the way we manage COPD. The article is the opinion of the authors and is based upon current research at the cutting edge of management with a degree of gazing into a dimly lit crystal ball. COPD is a current epidemic, and this is likely to continue. Legislative efforts to reduce smoking will continue and hopefully accelerate, but this will not be globally accepted or successful. Technological advances will occur that will lead to miniaturization and the rise of near patient testing. This itself will enable a personalised approach to management with the ability to measure rapidly biomarkers which will direct therapy. The blood eosinophil is the most promising of these and is available now. New developments in the identification of disease clusters and phenotypes will also enhance a more personalised approach. Through both these epidemiological studies and also new developments in the understanding of basic mechanisms it is hoped that in the future patients will be given treatments that may fundamentally change the prognosis of COPD. Small molecule and antibody directed therapies may, if given early enough, stop and even possibly reverse the effects of COPD on cells and organs. Of course, the most important step which is achievable now is to ban all tobacco-based products from the world.

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INTRODUCTION

At present chronic obstructive pulmonary disease (COPD) is a global epidemic [1]. It is already a major global cause of morbidity and mortality. In spite of treatments and management approaches which are effective we have made few inroads into this difficult condition. We have not delivered change for our patients in a coo-ordinated or effective manner. Can we see a time when this will change? Will the world truly respond to this epidemic and a robust way? This article aims to suggest a few ways in which the world will have changed by 2030. There will clearly be challenges but there are also great opportunities.

We have attempted to only suggest what is feasible and foreseeable at this time. More opportunities for improvements will certainly arise. But truly to make global changes we have to plan and implement now to be ready for 2030.

Before we consider COPD, it is important to consider some of the changes which may occur in society which will impact healthcare. This is of course particularly relevant to the impact of new technologies.

Already plans are being made for new generations of aeronautical mass transport. We have moved from small commercial planes, which were only accessible to the rich elite, to the current large commercial jets which are capable of carrying large cargo loads or many hundreds of passengers. By 2030 it is likely that commercial aircraft will be even larger, and we hope will be more fuel efficient and less polluting [2, 3]. This in itself is a worthwhile venture. Improving international communication links and opening travel to even more people, in our opinion, just serves to shrink the world. It may improve education and open travel to more people and has the potential to spread good practice in healthcare [2, 3].

Of potentially more direct medical application is the future of personalised, miniaturized technologies. Mobile phones are a global phenomenon, in the main, for good. They used to be simple communication devices, but now they act as a

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portable source of information essential for life itself. Phone time is used as currency in many developing countries and it is likely that we have barely scratched the surface of this transformative technology [4]. By 2030 it is possible that data storage and portable communication devices will be implantable and thus directly accessible via suitable optical interfaces. This will impact healthcare. Patients will be able to hold and store contemporaneous notes and then access them when needed. This will increase patient autonomy and possibly improve their knowledge and ability to direct their care. Healthcare professionals should not be concerned and should embrace this technology as it provides a mechanism for the reduction of risk in healthcare, no more looking for missing notes!

Smoking

What about cigarette smoking by 2030? The World Health Authority predicts significant changes in the prevalence of smoking globally [5]. The patterns for men and women are quite different. For men, there will be general reductions across the globe, except in Africa which will see a dramatic increase. Women will again generally decrease the levels of smoking except for in the Russian Federation, Southern Europe and sub-Saharan Africa. More men, than women, will smoke and in general high levels of male and female smoking will be seen in the Russian Federation. Women will smoke at significantly increased levels by 2025 in North America, South America and Europe and Australia.

We must respond now to these concerns. As a respiratory community we need to drive forward local, national and global anti-smoking policies. These need to be linked to public health smoking cessation services for all current smokers. Countries such as Australia and Singapore are leading the way in tobacco control and new initiatives are being developed in the Philippines that will put the so-called developed world to shame [6, 7].

New and more effective treatments for nicotine addiction will be developed. We may see a nicotine vaccine and better nicotine receptor blockers [8]. There are potential threats from the enormous growth of e-cigarettes and especially their use in the adolescent population. Tobacco and all tobacco products should be globally banned. The world will be a better place for all if this occurred.

COPD Cluster Identification

Personalised, precision medicine requires us to identify characteristics, traits and phenotypes which respond to specific targeted treatments. We are now beginning to understand that COPD in this way and divide it into clusters of patients with similar characteristics [9-11]. The large national cohort studies, especially being performed in the United States are already bringing this to the forefront [12, 13]. We hope that over the next ten years we can also define pathological processes which are then amenable to novel, specific treatments. So rather than treating everyone in the same way we will be able to give treatments to patients which are truly effective.

Co-morbidities

Chronic obstructive pulmonary disease rarely exists in isolation. We are beginning to appreciate that many diseases co-exist with COPD and they also interact. This is obviously the case for cardiovascular disease, but even in this case we are relatively poor at appropriate risk assessment [14]. It can be envisaged that COPD patients may be seen as having inter-dependent multi-morbidities which will likely include: Ischaemic heart disease, stroke, diabetes, musculoskeletal, psychological and potentially those with no co-existing problems. By 2030 we will have an understanding of this and be able to appropriately risk assess and manage each of these diseases. It is also possible that we will be able to use the pattern of co-morbidities to suggest similar underlying mechanisms and thus individually personalised treatments.

Technology

The pace of technological change is relentlessly increasing. This will have great benefits for healthcare in general and for the care of patients with COPD as well. It should be obvious that health technology will become faster, smaller, more accessible and cheaper. Take pulse oximetry for example. This development started as an expensive large cumbersome tool but within a few years has become smaller than a wristwatch and many patients have their own. Technology will become personalized [4]. Perhaps linked and driven through mobile phone technology allowing data collection and sharing between the patient, wherever they may be, and health care practitioners. Indeed, the development of autonomous healthcare decision making algorithms may allow the patients to self-manage their airways disease and thus improve outcomes and reduce cost. Platforms for the management of COPD already exist which are being purchased by healthcare providers [15-18]. These may improve adherence, increase activity and do monitor an individual's healthcare status. It is yet to be seen that they are truly effective or cost effective, but the author believes that this type of technology will only now increase.

There are potential problems and challenges raised by health technology development. New developments will have to be shown to be clinically and cost effective. They have the potential to be disrupting and may destabilise existing care structures. This may not be a bad thing, in that challenge to the status quo is essential for advances to be made. However, there may be changes which are damaging that were not anticipated before a technological intervention was initiated. Other issues, which are currently occupying law makers, lawyers, physicians and patients, are those of consent for data sharing, data security and governance and control. This is an issue which goes beyond healthcare alone, but which has the potential to severely limit health technology advances.

Telehealth

Given the potential for practical technical change there is an opportunity to further develop telehealth approaches to the management of COPD. Studies conducted thus far have shown mixed results and have not resulted in cost effective positive clinical outcomes. We can already remotely monitor disease to some extent [15]. This will increase in both the ability of technology to capture data from multiple sources (pulse oximetry, pulse, respiratory rate, temperature, autonomic activation, activity) and also in the ability to use this data in real-time. By 2030 we will be able to have a patient

healthcare practitioner dialogue improving decision making and allowing urgent interventions to occur.

COPD: The Disease

We are slowly increasing our understanding of COPD and the mechanisms and physiological changes which underpin the impact of COPD on our patients. Over the next ten years changes to the way we assess COPD will occur. These will be in the basic areas of anatomy, physiology and also pathology. We have already discussed how we may improve outcomes by taking a multi-morbidity approach to COPD and how similar underlying pathological processes may be in play. This will perhaps have the greatest impact when considering cardio-pulmonary crossover and the ability of these two organs to affect each other.

Driven by changes in imaging technology (xenon-MRI and improving CT techniques) we are beginning to resolve the anatomy and physiology of COPD in real time [19, 20]. Other techniques (time-resolved measures of gas exchange) are changing our understanding or air flow in the lung and will likely lead to developments in the delivery of inhaled medication. More fundamentally, these advances have the potential to change or understanding of the disease itself. The authors can envisage a time where Spirometry is redundant as the tool for diagnosing COPD [21, 22]. We may be able to access directly the changes occurring in small airways and obtain data for individual patients as to their airway inflammatory status. Moreover, during an acute exacerbation we currently do not really understand the airflow changes that occur, leading to breathlessness. New imaging modalities may unlock this issue, leading to new therapeutic approaches.

An Individualised Approach to Basic Mechanisms

The goal for the future has to be a truly personalised approach to the understanding and treatment of COPD [23]. This needs to begin at the most basic level of the underlying inflammation driving the disease in each individual and the changes that then occur. Recent insights into the role of eosinophils in COPD seems to be one useful avenue to pursue [24, 25]. Blood eosinophil levels do predict exacerbation risk and the potential for response to inhaled cortico-steroids for an individual patient [26]. By understanding what is underpinning this observation new paths to treatment may reveal themselves.

It can be envisaged that we may remove entirely the diagnosis of COPD and for any individual patients define "their" disease based upon a truly integrated approach to inflammation, response, pathology and physiological change [23]. Each may be subtly different requiring individualised treatments. The determinants of COPD will likely be due to interactions between susceptibility genes and the environment. In an individual this interaction will lead to an amplification of inflammation resulting in pathological change and thus finally the clinical manifestations of the disease. No single gene (save for alpha-1 antitrypsin) have been found to be a determinant of COPD. Many candidates exist, and they are all likely to play small parts in any individual [27-29]. The environmental factors are essential to the development of disease, cigarette smoking being the most well recognized. Exposure to biomass and air pollution are also significant [30-32]. Cellular responses to the exposure from a variety of cells (neutrophils, eosinophils, Macrophages, Tc1 cells and TH17 cells) will vary in an individual and determine the inflammatory pattern then seen [33]. The pathological changes which then occur will also vary from predominantly small airways disease to emphysema. The clinical features also will vary and have the potential to be individualised. Some patients will be high mucus producers, others will have rapid disease progression or an increase in the incidence of acute exacerbations. Treatment response will also vary and may well have genetic determinants. Receptor polymorphisms, metabolism polymorphisms and tissue response polymorphisms all may occur and interact for any individual [33].

The cellular mechanisms of COPD have been defined, but there are likely to be pathways and other effectors that we are yet to discover. Our current knowledge allows us to look ahead and see some potential for new treatments within the next ten years. Smoking and the need for better smoking cessation strategies has already been discussed. It will be possible to reduce cellular response to pro-inflammatory stimuli by blocking chemotaxis of macrophages and neutrophils and also in blocking the chemokines and cytokines that the cells produce [34]. LTB_4 antagonists as well as anti-TNF and IL-1 blockers are being developed and being submitted to clinical trials [8, 35]. Protease inhibitors may be developed and have utility as will mucoregulators and inhibitors of EGFR [8]. The inhibition of more fundamental up-stream inflammatory pathways with inhibitors of PDE4, p38 MAPK, IKK-2, PI3K-γ, and JAK mediated inflammation is attractive and may be amenable to the use of small molecule inhibitors. Finally, fibrosis inhibitors (TGFγ inhibitors and PPAR-γ agonists) may have a role in the pathology of COPD. The inhibition of all of these pathways is potentially attractive. However, we need careful trials which look for unexpected downstream effects with the potential for disaster. Our inflammatory system works for a reason and if any part is up or down regulated then we may see a change in our ability to manage infections or dysregulated cell production.

Have we any data now that can help us manage COPD in a more effective way? The latest GOLD strategy suggests that there are options based upon a treatable trait approach [36]. While this has merit, in practice it can be difficult to apply. The latest strategy asks the clinician to prioritise which clinical any individual problem has: exacerbations or symptoms. In reality, this is nearly impossible to do as both issues coexist. The blood eosinophil may be a way of making this simpler. The authors believe that by 2030 this approach will be accepted and based upon a prospective set of intervention studies, putting its value beyond doubt. A recent analysis studying the response rates to inhaled cortico-steroids has shown that to select for a positive response the level of eosinophil in an individual varies depending upon the response selected [37]. To prevent exacerbations 50% of the time a patient needs an individual to have a blood eosinophil of 340 cells/micro litre or more. To achieve a significant benefit in lung function the level of eosinophils needed is 270 cells/ microliter, for quality of life (as measured by the SGRQ 4-point change) it needs to be 480 cells/microliter. By 2030 we will

be assessing our patients by a set of clinical and biochemical biomarkers which have been validated and predict treatment. We will then be optimising the treatment for an individual based upon these biomarkers with specific inhibitors of the drivers of the inflammation in COPD>.

Finally, the ultimate aim for the treatment of COPD should be lung regeneration. Exciting studies have been performed in rats using retinoic acid which have demonstrated positive results with increases in lung tubule development [38]. This is thought to be essential for lung regeneration. Unfortunately, rodent models do not always translate into humans, and this has been the case thus far. Perhaps we will be able to switch on elastin production again, regenerate airways and alveoli and "regrow" lungs in our patients [39]. This is yet to be seen. What we must do now, is to stop our patients from smoking, or even better, stop them starting to smoke.

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