CHAPTER 1

Introduction

The main theme in this thesis is the development of patient centered disease management in primary care respiratory diseases. This thesis describes how contemporary patient centred care can be organized for asthma and chronic obstructive pulmonary disease (COPD) patients. Until the end of the 20th century it was difficult to provide patient centred management. Many recent and past developments have led to a shift towards tailored healthcare. The introduction gives a brief historical overview of changes in disease diagnostic and management. The focus of the introduction will be on respiratory diseases. This overview illustrates how respiratory healthcare changed from "one size fits all" to patient centred disease management.

A HISTORICAL OVERVIEW OF DISEASE DIAGNOSTIC AND MANAGEMENT

The change from infectious diseases to non-communicable diseases

Nowadays, chronic non-communicable illnesses are common but before the 20th century communicable diseases were prevalent. Severe epidemics have affected the world population in the past. For example, in the 14th century one third of the world population died because of the plague. Other examples are the diseases cholera and tuberculosis (TBC). Improvements in hygiene and sanitary developments, the discovery of antibiotics and the use of vaccinations have dramatically reduced the impact of communicable disease. Life expectancy in Europe has increased from 40 years for children born in 1800 to 80 years or more for children born in 2005(1).

This has led to a shift in illness prevalence. With ageing of the population, the prevalence of chronic diseases like hearth disease, stroke, cancer, chronic respiratory diseases and diabetes increased. These are called non-communicable diseases and they cause 40 million deaths each year(2), 70% of all global deaths. Especially tobacco use accounts for 7 million deaths each year and this number is increasing because the number of smokers keeps increasing worldwide(3). Non-communicable illnesses require more patient involvement because they need to manage their disease for, in general, many years. It is therefore important to educate patients about disease management.

Although the current leading cause of death is ischaemic hearth disease with 7.4 million deaths each year, it is noteworthy that 3 out of 10 deadliest diseases are respiratory diseases. In 2015 3.2 million people died from COPD and 3.2 million people died from lower respiratory tract infections. Trachea, bronchus and lung cancers were responsible for 1.7 million deaths in 2015. In total these respiratory diseases are responsible for more deaths than ischaemic hearth disease (8.1 million deaths in 2015)(4).

Diagnosing patients(5,6)

The challenge for every physician is make an adequate and timely diagnosis. Diagnosing is *"The art of identifying a disease from its signs and symptoms(7)."* The diagnosis is the starting point of the treatment. In the past two centuries the diagnostic procedure has developed impressively as will

be illustrated in a short summary of diagnostic history: in the late 19th century the *"Edwin Smith Papyrus"* was discovered. An important finding because this was the first document in which the diagnostic procedure of patients was described. The "*Edwin Smith Papyrus*" was written in the ancient Egyptian world around 2700 BC.

Impothep, an Egyptian physician is expected to be the writer of the *"Edwin Smith papyrus"*. These first diagnoses were based on only visual observations by the physician. Laboratory tests were developed a few centuries later. The Greek physician Hippocrates who lived around 400 years BC started examining urine, listening to the sound of the lungs and evaluating skin colour to diagnose his patients. He assumed that health depended on the balance between bodily fluids, called humors. In the middle ages, diagnosing patients became less important because in general diseases were thought to be a punishment for sin or caused by witchcraft. The most common treatment in that time was prayer. Despite this, some physicians in the middle ages started using uroscopy. In the 17th century Athanasius Kircher was probably the first who used a microscope for diagnostic purposes. Phrenology became popular in the 18th century. In this procedure the form of the skull and face was thought to predict patient's character and possible mental illness.

Although medical diagnostics changed between the ancient Egypt's until the 18th century, the biggest and most remarkable changes took place in the 19th and 20th century. In the early 20th century the diagnostic and treatment possibilities were limited. This is illustrated by the following citation about a general practitioner in the early 20th century who was not able to treat his patients.

"During the Spanish flu outbreak in the Netherlands (early 20th century) general practitioner de Bruijne was visiting his patients. His arrival was announced by the coachman: "GP is coming! Bare your chest!". GP de Bruijne hurried from door to door. He used his stethoscope to listen to the lungs, patted patients on their back and said: "Keep it up brother, see you tomorrow!" This ritual was repeated daily until the epidemic was over(8). *"*

De Bruijne could not do anything but monitor his patients and hope that the flu would disappear soon. Fortunately, new diagnostic tools were developed and survival rates after surgery and injuries improved a lot because hygiene became important. At the end of the 19th century the thermometer and stethoscope became commonly used as diagnostic tools. Although cures were not yet developed, chemical laboratory tests were widely available and physicians could now detect TBC, cholera, typhoid and diphtheria. Physicians started using blood pressure and pulse rate to assess their patients.

The 20th century was the century of huge technological changes. By that time, human anatomy had been mapped in detail. It became possible to look inside the body without invasive procedures. Advanced microscopes made it possible to study human cells in the brain and the brainstem. The electrocardiogram was introduced and in the beginning of the 20th century, hospitals started using X-rays to diagnose their patients(9). Also, nuclear radiology and magnetic resonance imaging were developed.

Diseases can now often be detected and treated in an early stage. Additionally, physicians can assess the severity of the disease and adapt the management to the severity stage. This has led to a variation of treatments between patients with the same disease.

The need for medical guidelines(10,11)

The new radiology and visual imaging methods were helpful but also dangerous. After several incidents in the beginning of its use, guidelines and protocols were developed to achieve safety and effectiveness. Guidelines are used to standardise procedures in order to improve care. Epidemic outbreaks in the past centuries have urged authorities to publish guidelines for the diagnostics and treatment of patients with cholera, yellow fever, TBC and sexually transmitted diseases.

Before the 20th century physicians worked solitary, while cooperation between medical profession emerged around 1900. Reason for this change is that in the beginning of the 20th century physicians started to specialize in medical areas which required cooperation. Also, public health programs were developed and requiring standardization of diagnosis and treatment. Standardisation of physical and psychological measurements made it possible to compare and discuss cases (e.g., visual acuity, weight, height, and IQ).

Another advantage was that insurance companies could evaluate cost effectiveness and scientists could perform studies based on the data. Many guidelines nowadays are available for different diseases and a wide variety of medical procedures. They enhanced cooperation between healthcare professionals and standardization of care.

Accessible healthcare and the role of primary care(12)

Until the 19th century healthcare was only accessible for a small group of people. In 1883, Germany introduced the first European Social Health Insurance (SHI) that was state mandated and covered the total population. SHI's expanded over Europe and at the end of the 20th century healthcare was accessible for most Europeans.

In September 1978, during the International Primary Healthcare Conference in Alma-Ata (Kazakhstan) delegates from all over the world agreed upon urgent action to promote health for all world citizens. The delegates were of the opinion that health should be, and therefore become a fundamental human right. To achieve this, primary healthcare has to be an integral part of the healthcare system. The general practitioner should be the first contact person for individuals seeking healthcare support. According to the delegates, primary healthcare was seen as the key to health for all(13) and this was written down in the Alma-Ata declaration. The aim for the year 2000 was to achieve primary healthcare *"based on practical, scientifically sound and socially acceptable methods and technology made universally accessible through people's full participation and at a cost that the community and country can afford"*(14).

Nowadays, primary healthcare is nowadays well implemented in some parts of the world. Unfortunately, worldwide healthcare access for everyone worldwide has not been established yet. Primary healthcare provides patient centred care(15) and is also functioning as gatekeeper for specialist care, resulting in more efficient healthcare use(16). This gatekeeper function makes

that the general practitioner is often the first to diagnose patients and cooperates with other healthcare professionals. Patients with diseases that require specialist treatment are referred to secondary or tertiary care.

Asthma and COPD are examples of common illnesses that are mostly treated in primary care. Both are chronic diseases requiring ongoing management by patient and GP. The focus of this thesis is on the patient centered management of asthma and COPD in primary care.

The history of asthma and COPD(17)

The word asthma originates from the Greek word "aazein" which means "breathing out with open mouth." Asthma is first described in the Georg Ebers papyrus dated around 1550 BC. The Swiss physician Bonet was the first to describe emphysema in 1679. Chronic bronchitis was first presented by Badham. He described it as a disabling illness caused by chronic cough and mucus hypersecretion. Laënnec was the first physician who recognised that emphysema lungs were not empty but hyper inflated (1821). Diagnoses were solely based on history taking. This changed in 1846, when the first spirometer was invented by Hutchinson. Hutchington's spirometer however only measured vital capacity. Tiffeneau added in 1947 the timed vital capacity that is still currently being used. This improved the assessment of patients with an obstructive pulmonary disease tremendously. Hence spirometry is still the cornerstone of asthma and COPD diagnostics. Current asthma and COPD guidelines recommend assessment of patients using the spirometer. Early diagnosis is important because timely treatment can reduce symptoms and in COPD reduce deteriorating of the lungs(18,19).

Current asthma and COPD prevalence

Asthma and COPD are common chronic respiratory diseases. The 2015 worldwide prevalence of asthma was 358.2 million and the world prevalence of COPD was 174,5 million(20). COPD was the 4th leading cause of death in 2015(4) and is expected to be the third leading cause of death in 2030(21). The estimated annual costs for asthma and COPD in Europe are 82 billion euros(22). It is therefore important to optimize the management of Asthma and COPD.

COPD consists of chronic bronchitis and lung emphysema and is primarily caused by tobacco smoke (including second hand smoke) but can also be caused by indoor air pollution like biomass fuel for indoor cooking or heating(23). COPD patients experience a variety of symptoms like cough, phlegm, dyspnoea and mental problems. Asthma patients have symptoms of wheezing, cough, dyspnoea and these symptoms can be triggered by allergens. Both asthma and COPD can impair physical, mental and social functioning. Patients can suffer from exacerbations which are short periods with an increase in symptoms that need medical attention and can lead to hospitalisation. Symptoms and severity of asthma and COPD vary between patients.

The Dutch hypothesis

Diagnosing asthma and COPD can be complicated because some patients have symptoms and signs of both diseases. For example, some asthma patients have a fixed obstruction, whereas

COPD patients sometimes have a positive bronchodilator response (increase in FEV_1 of more than 12%). Patients with features from asthma and COPD are overlap syndrome patients (ACOS). It is important to bear this in mind because patients with symptoms of both asthma and COPD are more likely to have severe disease and are more at risk for exacerbations. In contrast to mild to moderate COPD patients, overlap patients may need to use anti-inflammatory treatment to reduce the inflammation in their lungs.

In 1961 Prof. D. Orie from the University of Groningen suggested that all obstructive airway diseases like asthma emphysema or chronic bronchitis are one single disease with different manifestations. Expression was supposed to be influenced by smoking, allergens, infection, environmental factors and innate mechanisms. Allergies and bronchial hyperresponsiveness were seen as hereditary risk factors. Treatment therefore needed to be tailored to the patient specific manifestation of the obstructive airway disease resembling the current trend towards tailored management. Unfortunately, Prof. D. Orie was ahead of his time and his Dutch hypothesis was criticized and widely discussed by his international colleagues(24,25). In 1965 prof. Reid proposed the British hypothesis in which he states that asthma and COPD are distinct diseases generated by different mechanisms. Chronic obstruction was supposed to be caused by an infection which caused respiratory tract stenosis(26).

In the past decade, the Dutch hypotheses has received more attention and in 2015 the GINA and GOLD guidelines introduced a new report called: *"Diagnosis of diseases of chronic airflow limitation: asthma, COPD and asthma or COPD overlap syndrome(ACOS)"*. Aim of this document is to support physicians in diagnosing and treating patients with symptoms of asthma ánd COPD(27). This is important because the prevalence of overlap in COPD patients is 27%(28). However, there is still no consensus about how to label patients with symptoms from asthma and COPD. The GINA and GOLD report leaves room for interpretation.

A brief history of respiratory treatment

The earliest treatment for asthma was described in the *"Georg Ebers papyrus"* and consisted of inhalation therapy with herbal vapour, enemas and application of excreta from animals(29). The Chinese treated asthma patients 100 years BC with the Ephedra Sinica which contains ephedrine, causing widening of the bronchi.

Antibiotic penicillin, discovered by A. Fleming in 1928, can be used to treat respectively inflammations and infections. John Mudge developed the first inhaler in 1778 which was used to inhale opium to treat cough. Alfred Newton developed the first dry power inhaler in 1864. These inhalers were only used with bronchodilators. Not until 1950 the first inhaler with inhaled corticosteroids was invented by Reeder and Mackay. After its introduction in the 7ties, inhalated corticosteroids became the recommended treatment for asthma.

Treatment of COPD in the mid-20th century consisted of antibiotics, potassium iodide to reduce mucus and ephedrine in combination with theophylline. Inhaled isoproterenol was used from the 1960s. Remarkable was that oxygen was contra-indicated for COPD in the mid-20s. Smoking cessation, bronchodilators and corticosteroids became common treatment from

the 1990s(29). Relatively new is the treatment of severe asthma with biologicals. Pulmonologist can treat a specific group of asthma patients with anti IL5 or anti IgE. These treatments require specialist care and are not available in primary care.

It can be a challenge to match the best pharmaceutical component and inhaler to each patient because there are many different inhaled treatments on the market. Above that, the efficacy of the treatment depends on the respiratory disease, the symptoms, the severity and patients' preferences.

Involving the patients

The communication between patient and physician shifted in the past 100 years from a paternalistic form of communication towards shared decision making. In the early 20th century the physician was always right and patients fully trusted their GP. In that time healthcare was not accessible for everyone. Above that, most patients were poorly educated, and many were not able to read. Nowadays almost every patient in Europa has access to primary care. Patients are better educated and better informed compared to patients at the time of the Spanish flu. GPs are more openly discussing medical decisions with patients and they can make treatment decisions together with their patients, also referred to as shared decision making. Patients are more involved in their treatments, and one of the benefits is that this might improve the way they manage their disease. This is called self-management. This is important because an increasing number of patients suffer from one or more chronic diseases that affect their daily functioning.

THE INTRODUCTION OF INTERNET IN HEALTHCARE

Technology changes in the past 20 years

In the past 20 years Internet became widely available. Sharing information became easier because data was no longer stored on paper but digitally on the computer. This improved information sharing e.g., between GPs and hospitals. Furthermore, patients can now easily gather information about their disease and contact peer patients. This can lead to a change in the relationship between patients and physicians.

The application of internet in healthcare is called eHealth. Several eHealth applications are available to support patients in their self-management. For example, medication applications on smartphones, communication with healthcare providers trough video calling or patient web portals were developed by healthcare providers. Unfortunately, it is not always clear to what extent these tools are effective in improving patients' lives. Involving patients in the development procedure can improve the implementation and effectiveness(30). An advantage of eHealth is the development of large anonymous databases with healthcare data. Large numbers of clinical data can easily be collected and stored. These can be used to evaluate relationships between patients' characteristics and treatments effects or disease outcomes. Results can be used to facilitate tailored patient care.

An example of a mixed technology based and careful patient centered diagnostic support system

The Asthma/COPD-service in the North of the Netherlands

The important role of the GP in diagnosing and treating patients with respiratory diseases have led to the development of the Asthma/COPD-service. The service supports GPs in diagnosis and management of patient with respiratory complaints. The Asthma/COPD-service plays an important role in this thesis. Data from this service were used to evaluate its feasibility and effectiveness. Additionally, options for improvement were examined.

The development of the Asthma/COPD-service

In 2007 the service was initiated by general practitioners and pulmonologists in the region. The guiding principles of this service were as follows:

1. The service should optimise the diagnosis, treatment and management of asthma and COPD
2. The general practitioner is in lead
3. The service should be easy accessible for both patients as well as healthcare providers in primary and secondary care
4. The cooperation between primary and secondary care must be clear.

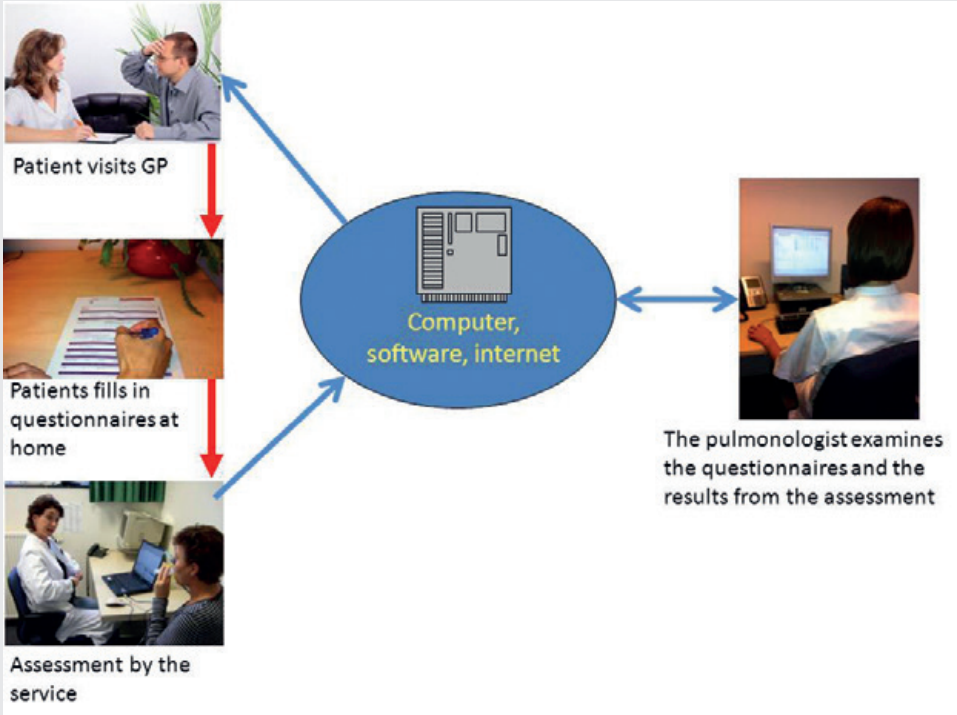
Meetings were organised before the implementation. Related healthcare providers were involved in the developmental procedure by giving them the opportunity to give feedback during these meetings. In 2007 the service started in a small rural area in the Netherlands and

has now expanded to other areas in Groningen and extended to parts of Friesland and Drenthe. Principles of this service are also used in other primary care support services in some other parts of the Netherlands.

The working procedure of the Asthma/COPD-service

General practitioners can refer patients with respiratory complaints to the service. Patients are assessed close to their homes in healthcare centers using a strict diagnostic protocol. Since questionnaire data play an important role in this procedure, patients have to fill in questionnaires at home: [1] a history questionnaire with questions regarding family history, smoking habits, allergies, reaction on irritating gases in air, occupation, previous diagnosis, and medication use. [2] The Clinical COPD Questionnaire (CCQ) to assess health status and [3] the Asthma Control Questionnaire (ACQ) to assess asthma control. During their assessment in the laboratory weight, height and inhaler technique are evaluated. Lung function is measured with spirometry by well-trained laboratory assistants using proper and up-to-date equipment. All information from the spirometry, the assessment and the questionnaires is inserted by the laboratory assistant in the electronic database. A local pulmonologist evaluates the data through the Internet, without seeing the patient. Using a predefined algorithm, the conclusion of the pulmonologist is shared with the GP using Internet. For an overview of the service see figure 1.

Figure 1: overview of the Asthma/COPD-service



Feasibility and effectiveness of the Asthma/COPD-service

The service has proven to be successfully implemented in the region and expands rapidly. The service includes approximately 2000 new patients each year and all data are stored according to strict protocol in a digital database. This provides unique possibilities for scientists to evaluate real-life primary care data from respiratory patients. At this moment the asthma COPD service has assessed more than 15,000 individual patients with respiratory problems. Cross-sectional and longitudinal data is stored anonymously and can be used for research. This is very important because in this way researchers can study treatment efficiency in real-life patients instead of selective populations. All included patients are comparable with regular primary care patients which enhances the generalisability of results of these studies. Data from these patients were used in several publications of this thesis.

Real–life databases

Large digital real-life databases give researchers information about the variation in patient populations. Patients can differ in many areas like for example age, gender, severity, symptoms or comorbidities. One size does not fit all. Real-life studies enhance the generalisability of the results to the common clinical population(31). Several scientists have divided large real-life databases with respiratory patients into clusters based on symptoms and characteristics(32,33). These clusters can be important for a more accurate prognosis of the disease and to predict the effectiveness of treatment so that patients can receive tailored treatment.

PATIENT CENTRED MANAGEMENT OF ASTHMA AND COPD PATIENTS

Aim of this thesis

Respiratory illnesses are common in primary care. Patients differ in symptoms, disease severity and prognoses. It can therefore be difficult to match the best treatment with each patient. The Asthma/COPD-service can support GPs in diagnosing and treating their respiratory patients. The feasibility and effectiveness of this service was assessed.

Aim of this thesis is to explore how patient centred disease management of asthma and COPD can be achieved in primary care. The main focus is on the Asthma/COPD-service which is a well implemented service for GPs and patients in the northern part of the Netherlands. This thesis shows how this service can be optimized by expanding patient centred disease management options. Results from this thesis can be used to develop other patient catered disease management services. The experiences and data provide unique opportunities to elaborate on two aspects:

Part 1: How to provide patient centred disease management in primary care respiratory patients?

The feasibility and effectiveness of the Asthma/COPD-service is evaluated. Data collected during regular Asthma/COPD-service assessments is used to build a model to predict diagnosis in primary care respiratory patients. Finally, data from another Dutch, primary care population was used to evaluate the prevalence and relevance of comorbidities in COPD patients.

Chapter 2

This publication describes the feasibility and effectiveness of the Asthma/COPD-service in the North of the Netherlands. A cross-sectional baseline population description is presented along with longitudinal results regarding asthma control, COPD health status and exacerbation rate.
Metting EI, Riemersma RA, Kocks JWH, Piersma-Wichers MG, Sanderman R,
van der Molen T
NPJ Primary Care Respiratory Medicine. 2015 Jan 8;25:14101

Supplement to Chapter 2

The publication from chapter 2 was also published in a Dutch journal for healthcare providers. The first paper was published in 2015 and the Dutch paper was published in 2016. Between these publications, new patients were included in the asthma COPD database. Therefore we have added new data to the Dutch publication, and this makes it of interest for this thesis.
Metting EI, Riemersma RA, Kocks JW, Piersma-Wichers MG, Sanderman R, van der Molen T
Nederlands Tijdschrift voor Geneeskunde. 2016;160(0):D281

Chapter 3

The large anonymous database from the Asthma/COPD-service was used to develop a diagnostic decision tree for obstructive pulmonary diseases. The database consists of real-life patients which enhances the generalizability to general practice. The tool can be used as an algorithm in a digital diagnostic system and a simplified version of the tool can be used as desktop tool in clinical practice.

Metting EI, In 't Veen JC, Dekhuijzen PN, van Heijst E, Kocks JW, Muilwijk-Kroes JB, Chavannes NH, van der Molen T

European Respiratory Journal Open Research. 2016 Jan 22;2(1)

Supplement to chapter 3

The simplified decision tree from chapter three is used by the International Primary Care Respiratory Society (IPCRG) to develop a desktop tool for GPs around the word. This tool can support them in diagnosing their patients with respiratory complaints.

Available from: www.theipcrg.org

Chapter 4

COPD often coexists with chronic conditions that may influence disease prognosis. We investigated associations between chronic (co)morbidities and exacerbations in primary care COPD patients. This study was based on data from 179 Dutch general practices in the South of the Netherlands. Chronic comorbidities are highly prevalent in primary care COPD patients. Several chronic comorbidities were associated with having frequent exacerbations and increased exacerbation risk.

Westerik JA, Metting EI, van Boven JF, Tiersma W, Kocks JW, Schermer TR.

Respiratory Research. 2017 Feb 6;18(1):31

Part II: How to involve patients?

To explore whether patients' involvement can be improved by adding a patient web portal to the Asthma/COPD-service focus groups were executed. We spoke with patients about their preferences regarding eHealth and patient web portals. During these focus group meetings patients mentioned the social implications of asthma and COPD. These findings were compared with scientific publications about this topic.

Chapter 5

An increasing number of healthcare professionals and organizations develop patient web portals. We have evaluated the opinions, emotions and needs of 29 asthma and COPD patients towards a hypothetical patient web portal using focus group meetings. The results can be used to develop a patient web portal according to the wishes and needs of asthma and COPD patients.

Metting EI, Schrage AJ, Kocks JW, Sanderman R, van der Molen T

Submitted to: Journal of Medical Internet Research. Status: in pre-print

Chapter 6

During the focus group meetings emotional discussions emerged because patients were affected by the social implications of asthma and COPD. This publication aims to draw attention to this problem and the results from our focus group meetings were expanded with results from literature regarding this topic. Moreover, recommendations from patients and literature are provided to reduce and prevent the social implications of asthma and COPD.

Metting EI, Schrage AJ, Kocks JW, Sanderman R, van der Molen T

Submitted to: NPJ Primary Care Respiratory Medicine. Status: Under consideration

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PART 1

How to provide patient centered disease management in primary care respiratory patients?

The strength of the study is the large population of primary care obstructive airway disease patients in real-life and the strict protocol used to assess these patients.

Page 38