Early Diagnosis of Rare Diseases with a Focus on Pulmonary Arterial Hypertension: A Narrative Review

by

Russell Bonaguro

M.P.H., Simon Fraser University, 2015
Master's Project; Capstone

Health Sciences / Simon Fraser University/ Population Health

Faculty of Health Sciences

© Russell Bonaguro 2015

SIMON FRASER UNIVERSITY

Summer 2015

All rights reserved.
However, in accordance with the *Copyright Act of Canada*, this work may be reproduced, without authorization, under the conditions for "Fair Dealing." Therefore, limited reproduction of this work for the purposes of private study, research, criticism, review and news reporting is likely to be in accordance with the law, particularly if cited appropriately.

Approval

Name:	**Russell Bonaguro**
Degree:	**Masters of Public Health**
Title:	***Early Diagnosis of Rare Diseases with a Focus on Pulmonary Arterial Hypertension: A Narrative Review***

Examining Committee:

Kitty Corbett
Senior Supervisor
Professor

Michel Joffres
Second Reader
Professor

Date Defended/Approved: July 29, 2015

Abstract

Health outcomes for rare diseases can be greatly affected by timely diagnosis. This paper presents a narrative review of current literature on rare diseases, with a focus on Pulmonary Arterial Hypertension (PAH), to identify needs for early diagnosis initiatives. The review assessed: what needs to be done, what is currently being done, and what are the approaches or change theories that underlie these initiatives. Literature from online key-word searches included academic articles pertaining to diagnostic methods and physician surveys, and reports from advocacy groups and health authorities. Findings centred on the needs for: physician awareness/education, public awareness/education, research needs, consolidation of disease information, and the need for system-wide early diagnosis strategies. Recommendations highlighted steps to promote awareness and education among physicians and the public, investigate theories of behaviour change, and develop and diffuse evaluation criteria of early diagnosis initiatives.

Keywords: rare disease; pulmonary hypertension; pulmonary arterial hypertension; early diagnosis; early detection

Acknowledgements

This Capstone would not have been possible without the support and help of many individuals. I would like to extend my sincere thanks to all of them.

I am highly indebted to Kitty Corbett for her supervision and guidance including helping me to refine this project topic over many months, and for working to help me focus my ideas and the overall structure of this report.

I would like to express my gratitude towards the staff at the Pulmonary Hypertension Association of Canada, where they took me in for my practicum placement and continued to offer support long after it was over. Thank you to Angie Knott, Bronwyn McBride, and Shirley Wong. Also a very special thank you to Tarya Laviolette for supervising me during my practicum, and for feedback and support during the generation of this capstone.

Many thanks to Kate Carty for her tireless work helping to find a practicum position for myself (and countless others) and to Michel Joffres for being a second reader for this capstone. Also thank you to Malcolm Steinberg for thoughtful discussions regarding all things MPH throughout the course of my degree.

I'd also like to thank the HSCI graduate student administrative staff: Jen Van Rassel, Margaret van Soest, Linda Hegland, Rehana Bacchus, Marion Cardenas and others for their positive energy and encouraging help along the way. They truly helped create an amazing environment to be a student in.

Table of Contents

List of Tables

List of Figures

List of Acronyms

ACCF	American College of Cardiology Foundation
AHA	American Heart Association
CME	Continuing Medical Education
CORD	Canadian Organization for Rare Disorders
EURORDIS	European Organisation for Rare Diseases
IRDiRC	International Rare Disease Research Consortium
PAH	Pulmonary Arterial Hypertension
PH	Pulmonary Hypertension
PHA	Pulmonary Hypertension Association
PKU	Phenylketonuria
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
SFU	Simon Fraser University
UK	United Kingdom
USA	United States of America

Introduction

Rare diseases affect millions of Canadians and many more worldwide (Canadian Organization for Rare Disorders [CORD], 2015a). Due to their rarity they are often difficult to diagnose in a timely manner, which can result in a wide range of health implications. Pulmonary Arterial Hypertension (PAH), a lung disease, is one such rare disease whose patients suffer greatly from delayed diagnosis. Due to the slow progression of symptoms, PAH often goes undiagnosed until the patient is in an advanced state of the disease. Promoting early diagnosis of such diseases is crucial for recognition and subsequent early treatment options leading to improved health outcomes.

The current status and usefulness of what initiatives have been done, or are in progress, to help improve the time to diagnosis for such diseases is dependent on circumstance, and varies based on a wide range of factors, such as current methods of diagnosis, public and physician awareness, and system-wide infrastructure. This paper uses a narrative review method to analyze the current literature on rare diseases, with a focus on PAH, to identify current needs for early diagnosis initiatives. The questions explicitly asked are, for rare diseases and PAH early diagnosis, what needs to be done, what is currently being done, and what are the approaches or change theories that underlie these initiatives. The paper ends with research need recommendations based on the analysis of the literature found.

Rare Diseases: An Overview

At present approximately 7000 rare diseases have been identified, and it is estimated that almost five percent of the world's population suffers from a rare disease (Shire, 2015a). Depending on the country or region, the definition of a rare disease, also referred to as 'orphan diseases', varies. In Europe it is defined as a disease that affects fewer than 5 in 10,000 people, while the United States defines it as having a prevalence of fewer than 200,000 people (Shire, 2015a; Syed, Camp, Mischorr-Boch, Houyez &

Aro, 2015). Canada has no formal definition, however Health Canada has informally used the following definition: "A life-threatening, seriously debilitating, or serious chronic condition that only affects a very small number of patients (typically less than 5 in 10,000 persons)" (CORD, 2015a, p. 4). Due to the large number of rare diseases, it is estimated that 1 in 12 Canadians are affected, which translates to almost 3 million people in Canada (CORD, 2015a). Table 1 highlights some examples of rare diseases and their respective estimated prevalence.

Table 1: Examples of Rare Diseases

Name	Description of Disease	Prevalence (per 100,000 individuals)
Cystic Fibrosis	Multi-system disorder	12.6
Phenylketonuria (PKU)	Metabolic deficiency	6
Huntington's Disease	Neurodegenerative	7
Mucopolysaccharidosis type 2 (MPS 2)	Lysosomal storage	1.5
Pulmonary Arterial Hypertension (PAH)	Excessive cell proliferation or scarring in lung arteries	0.5 - 5

[a] Orphanet Report Series, 2014; [b] CORD, 2009; [c] (Lau, Humbert, & Celermajer, 2015; Pulmonary Hypertension Association, 2011; Rich & Rich, 2014),

Approximately 80 percent of rare diseases are thought to have a genetic cause (CORD, 2015b). Mutations in the genetic code affecting a variety of developmental and physiological pathways can lead to severe impairments and possibly death. Over half of rare diseases present during childhood, with 30 percent of patients dying before the age of five (CORD, 2015b; Shire, 2015a). Many of the more well-known and serious genetic-based rare diseases are screened for at birth, as many of the genetic causes of these diseases are now known. For example phenylketonuria (PKU), a genetic-based metabolic disease, can be screened for at birth and treatment can begin immediately. Other genetics-based rare diseases that develop slowly, and thus present later in childhood or beyond, can also be tested for, resulting in specific and early treatment options.

The diagnosis of rare diseases that are not routinely screened for is often just that: rare. Due to the rarity of these diseases many doctors may not see a single case in

their career (UK Department of Health, 2013). As each rare disease only affects a small number of people, the ability of a physician to consider a specific rare disease is often unrealistic. Due to the often-complex nature of symptoms for rare diseases, a physician must often be competent in many fields of medicine to understand and decipher the nature of a specific rare disease (Rare Diseases Europe [EURORDIS], 2009). This characteristic of a rare disease to hide behind an array of symptoms, often common, makes a diagnosis extremely challenging and demonstrates how misdiagnoses could occur (Shire, 2015a). Additionally, symptoms of a specific rare disease may differ between individuals with the same disease, further complicating the diagnostic process (CORD, 2015b). It is often the lack of research available on a specific rare disease that makes it more difficult to diagnose compared to more frequently occurring, and more frequently studied, diseases (EURORDIS, 2009). This lack of knowledge, including the natural course and epidemiological data for many rare diseases, significantly hinders both diagnosis and treatment (World Health Organization, 2013).

Physicians are trained to diagnose conditions by following a process that starts with the common causes of presented symptoms. During medical school an analogy presented is that when a physician hears hoof beats, i.e., symptoms, they should think of horses, the common cause, rather than zebras, the rare cause. This analogy transfers to practice as when symptoms are present physicians should look for the common diagnosis first, and only after those diagnoses fail to hold should they move on to less common explanations. While this methodology intuitively makes sense for physicians, at what point should rare explanations realistically be investigated? What would be the subsequent implications for progressive diseases that slowly become worse over time, such as PAH? Furthermore, at what point should rare diseases then be introduced into the diagnostic pathway?

While expertise is available in Canada for many rare diseases, structural and geographic factors often create barriers to access this expertise. Clinical expertise is often spread out across Canada, resulting in a limited and fragmented awareness, knowledge, and treatment base (CORD, 2015a; CORD, 2015b). This context can result in a long diagnostic journey for patients, often including delays in access to needed treatment or care resulting in additional health concerns and costs to patients and the

health care system (CORD, 2015b). An expert in one rare disease may not be knowledgeable in others, thus if one disease is ruled out the patient often has to start the diagnostic process over with other experts.

The wait to exclude common explanations and the delay to provide a conclusive diagnosis of rare diseases pose a significant challenge to timely access to appropriate treatment (UK Department of Health, 2013). For those diseases where timely treatment could improve health outcomes, a diagnosis delay is a serious matter. According to an international online survey conducted by Engel, Bagal, Broback, and Boice (2013), approximately 40 percent of rare disease patients received a misdiagnosis at least once, and the average time to an accurate diagnosis after symptoms have appeared is approximately 4.8 years. While this survey was able to draw upon a wide range of quantitative and qualitative date, approximately 90 percent of the physician and patient responses were from either the USA or Canada, so any inferences outside of those countries should be tempered. Wherever it occurs, as a result of the severity of the disease and the delay to diagnosis, patients often experience high levels of disability and a low quality of life (Limb, Nutt, & Sen, 2010). Additionally, individuals often experience negative economic and social burdens during the path to an accurate diagnosis (Engel et al., 2013).

Treatments for rare diseases are often much farther behind those of common diseases. While we know of 7000 rare diseases, the causes are only understood for half (Lougheed, 2013). Additionally, while many symptoms can be effectively managed, only approximately 200 rare diseases, less than 3 percent of the total, can be definitively treated (Lougheed, 2013). As cohort sizes for clinical trials for rare disease treatments are often very small, the ability to test new or existing therapies and the resulting power of these trials are often unable to adequately inform the evidence base for evidence-based medicine to incorporate new therapies into practice.

In Canada there are numerous specific rare disease organizations, and a few broad rare disease groups that are working toward improved awareness, research, and care for those suffering from rare diseases. Of note, the Canadian Organization for Rare Disorders (CORD) and the Rare Disease Foundation work to provide support and

resources to those affected by rare diseases, and also work to promote research and awareness across Canada and internationally. While public awareness of rare diseases may lead to a broader knowledge of them, the extent that this affects the ability of a physician to accurately diagnose a rare disease is not known.

Pulmonary Arterial Hypertension: an Overview

Pulmonary Hypertension (PH) is a rare disease that is characterized by abnormally high blood pressure (hypertension) in the lungs due to the thickening or scarring of the arteries, sometimes completely cutting off blood flow to areas of the lungs (Pulmonary Hypertension Association of Canada [PHA Canada], 2014). Pulmonary Arterial Hypertension (PAH) is a sub-category of PH that is characterized by the presence of PH without such causes as: chronic thromboembolic PH, lung disease, or other rare conditions (Preston, 2013). PAH is a progressive disorder defined by hypertension of the pulmonary artery, which delivers blood to the lungs from the right ventricle (National Organization for Rare Disorders [NORD], 2011). Over time the right ventricle of the heart must pump harder and will become enlarged to help meet the oxygen needs of the body and, if left untreated, will strain the heart until eventual failure resulting in disability or death (Pulmonary Hypertension Association, 2011; PHA Canada, 2014). Symptoms of PAH include shortness of breath (especially during activity), chest pain, fatigue, dizziness, and fainting (McLaughlin et al., 2009; NORD, 2011; Pulmonary Hypertension Association, 2011). PAH can either be idiopathic, meaning that there have been no aetiological factors identified as causing the disease, or can be induced via certain drugs or toxins, be familial (i.e., genetic), or be associated with conditions such as connective tissue disease, portal hypertension, congenital heart disease, or HIV infection (Armstrong, Rochnia, Harries, Bundock, & Yorke, 2012; Lau et al., 2015). While there are many therapies available to treat PAH, there is no known cure (NORD, 2011).

In Canada, PAH is estimated to affect between 300 to 800 adults (Canadian Agency for Drugs and Technologies in Health [CADTH], 2015). As there is no nation-wide registry or database for PH patients in Canada, the exact prevalence and incidence

is not accurately known. However, there are estimates that PAH has an international prevalence of between 5-50 cases per million (Lau et al., 2015; Pulmonary Hypertension Association, 2011; Rich & Rich, 2014). PH can affect anyone across all geographies regardless of age, sex, social, or ethnic background, however international registries have shown that PAH occurs two to four times more frequently in women (Matura & Carroll, 2010; Pulmonary Hypertension Association, 2011). Recent data from the USA based REVEAL project (Registry to Evaluate Early and Long-term PAH Disease Management) showed that the mean age at diagnosis of PAH was 48 years, and that 80 percent of the patients were female (Brown et al., 2011; Matura & Carroll, 2010). The REVEAL study also defined delayed diagnosis as greater than two years elapsed between symptom onset and PAH diagnosis, which occurred in roughly 20 percent of patients (Brown et al., 2011).

There is a current need in Canada for earlier diagnosis of PAH, as the median survival time for patients with PAH without treatment is estimated to be 2.8 years, which is also the estimated average current time between symptom onset and accurate diagnosis (PHA Canada, 2014). Even with access to high-quality care and treatment, approximately 50 percent of patients die within five to seven years (Pulmonary Hypertension Association, 2011; Wryobeck, Lippo, McLaughlin, Riba, & Rubenfire, 2007). However, due to the range and lack of severity of initial symptoms, early diagnosis of PH is difficult and often overlooked until symptoms increase in severity (McGoon et al., 2004). Accordingly, approximately ¾ of patients have advanced PH by time they are diagnosed (Pulmonary Hypertension Association, 2011), and diagnosis of PAH at a late stage of progression is correlated with a poor survival prognosis (Brown et al., 2011). As PAH is rapidly progressive without treatment, the faster a diagnosis is reached the sooner therapy can be started to potentially halt, or reverse, the level of severity.

While PAH has been shown to have a genetic component, it is not considered a solely “genetic” disease, as a clear link for all PAH cases has not been found. Approximately 15-20 percent of PAH diagnoses have heritable genetic roots (NORD, 2011). For example, mutations in the BMPR2 gene, which helps regulate the growth of cells on artery walls in the lungs, are one of the prominent genetic determinants of PAH

(NORD, 2011; Pulmonary Hypertension Association, 2011). While BMPR2 mutations can be tested for, just as many other rare diseases can be screened for, unless there is a suspected familial pattern these tests are currently not endorsed on a systemic or institutional level.

Regardless of familial history, suspected PAH must be confirmed through a variety of tests, including echocardiograms, blood tests, chest X-rays, physical exertion tests, and a right heart catheterization (NORD, 2011). However, although an echocardiogram can show signs of PH, which needs to be correctly interpreted by a physician, only a right heart catheterization test, the current PH gold standard test, can confer an accurate PAH diagnosis. As PAH is often a diagnosis of exclusion, without straightforward genetic or physiologic tests available, confirmation of the disease may take much longer than more common diseases (Matura & Carroll, 2010).

The usual pathway to diagnosis of PAH in Canada typically involves the increasing severity of the symptoms listed previously, without relief due to common solutions to common conditions that are prescribed by family physicians (Domenighetti, 2007). Common pathways to diagnosis include initial misdiagnoses of asthma, anxiety, chronic obstructive pulmonary disorder (COPD), and lack of fitness or being overweight (Pulmonary Hypertension Association, 2011). At some point specialists become involved who then look to increasingly rare explanations. However, the time delay to referral to a specialist can vary widely depending on the physician. Once specialists are involved, it is up to their own differential diagnosis methods, either based on best practices or their own experience, to narrow down to considering PAH as a diagnosis. Once a diagnosis is either confirmed or strongly suspected, patients are then referred again to one of the fifteen Canadian PH specialized treatment centres. Thus a delay at any of these steps towards a final diagnosis and appropriate treatment can have significant time to diagnosis implications and associated health repercussions.

In Canada there are currently 8 approved drugs for the treatment of PAH (CADTH, 2015). Thus, while treatment availability may be a concern from an access standpoint, specifically cost, there are options for patients once PAH has been diagnosed. The economic cost of PH to the health care system results from care such

as physician visits or medical tests, in addition to the costs of treatments, which can be very expensive. For example, the common drug for the highest severity of PH, Epoprostenol (brand name: Flolan), can cost from $45,000 to $100,000 per year (CADTH, 2015). No studies indicated that earlier diagnosis of PH leads to a reduction of long-term health care usage or drug costs to the health care system. Investigation of these questions will help to inform the relationship between earlier diagnosis and health care costs to both the patient and the system.

The key concern in this process is that diagnosis is not happening as quickly as needed from the time of initial symptoms until diagnosis is confirmed. Findings noted but not cited within PHA's 2011 white paper state that patients often see three physicians over a three-year period and often received misdiagnoses before an accurate PH diagnosis is made. Earlier diagnosis can benefit the health care system by decreasing time and cost burdens, and more importantly can improve health outcomes in those affected by PAH.

Methods

For the topics rare diseases (in general) and PAH, literature was sought and reviewed to address the following questions:

- What needs to be done to improve early diagnosis?
- What is currently being done to address these needs?
- What approaches or change theories underlie initiatives focused on improving time to diagnosis?

Literature on PAH early diagnosis needs and theories is very limited and, to my knowledge, there are no published systematic or other reviews of the topic, so a narrative review of multiple types of sources (e.g., published articles, grey literature, online discussions), using broad search terms, is appropriate.

After gathering and reviewing the literature, it was coded for cross-cutting themes regarding what needs to be done to improve early diagnosis. Themes were given more weight if the literature contained significant detail or were mentioned in multiple references.

Narrative reviews use available literature and information to describe a current state of affairs for a given topic, and while similar in some aspects to a systematic review, they are different in a few important ways. Narrative reviews focus on a subset of information and, although they attempt to be as comprehensive as possible, they are often built around information used to tell a purposeful story by the author (Uman, 2011). In this way articles are often chosen based on author selection or availability. Information is thus gathered to tell a story, not just state what the current literature tells us.

A narrative review is subjective insofar as it explicitly tells a specific ‘story’ and the author can take the reader in the direction they desire. The lack of systematicity and transparency in selection of sources, and the lack of any requirement for a methods section that delineates clear inclusion and exclusion criteria or analytic processes, may decrease the perceived value of the conclusions of the article (Uman, 2011). That said, a

narrative review is useful as an educational article as it brings together many resources of information into a cohesive and clear product (Green, Johnson, & Adam, 2006). Additionally, as narrative reviews often discuss the theory and context of a topic, it can function as a tool to spur new thoughts and address controversy (Green et al., 2006).

An alternative description for a similar kind of review is a "scoping review". A scoping review consists of a systematic review of the literature with the goal of mapping the key concepts of a specific research area, including the types of evidence available and the main sources thereof (Mays, Roberts, & Popay, 2001). Scoping reviews are often undertaken to determine the depth of research available for a topic, which could then inform further, more intensive, systematic reviews (Arksey & O'Malley, 2005). Scoping reviews are also valuable to identify research gaps in the literature, with the goal of informing future planning and implementation of new research initiatives (Arksey & O'Malley, 2005).

I have elected to use the term "narrative review" because much of the literature known to the author is not based on published literature that is readily found in a typical systematic review, but rather via a wide range of sources. Rather than attempting a rigid systematic review to determine the breadth and methodological quality of literature for rare disease and PAH early diagnosis, I hope to use this review to discuss the current context and needs for early diagnosis based on the current knowledge base. A "narrative review" is the most appropriate description for the framework of this review.

Search method

Databases searched initially started with PubMed and the SFU library website to identify academic literature, and was broadened to larger Google searches for grey literature, organizational publications, informational websites, and any other material that was considered peer reviewed publications. Some material that was previously made available to the author but that was not available online, such as internal PHA and PHA Canada documents, were also included.

Search terms were employed such as: “rare diseases”, “pulmonary hypertension”, “pulmonary arterial hypertension”, and were used in combination with terms such as “diagnosis”, “early detection”, “early diagnosis”. The first 50 results for each combination of search terms (E.g. “pulmonary hypertension” + “early diagnosis”) on each of the described sites were reviewed for inclusion criteria. Additionally, if any material was referenced in items obtained from the search results and was found to be useful, it was included in this review. Once a large enough body of literature was found to describe the issue, as deemed by the author, further searching was concluded.

The inclusion criteria for search results were very broad. To be included in this review material must describe or mention diagnosis or early diagnosis of rare diseases / PH, but not solely treatment options. The material was not required to be published in a peer-reviewed journal, but could for example be web-based or published by a private organization.

Types of resources and information found

Most literature obtained for rare diseases were reports produced by national health organizations, national and international advocacy organizations, and industry groups. A smaller proportion of the literature was from published peer-reviewed journals and websites. In total 21 references were found to be useful for this review based on the search criteria outlined above.

PH and PAH related searches returned primarily (>90 percent) academic literature, which was then scanned for relevance to early diagnosis, as most only focused on diagnosis protocol aspects of the disease. Material obtained from advocacy organizations (E.g., The Pulmonary Hypertension Association (PHA), and PHA Canada) was both external, such as a white paper (Pulmonary Hypertension Association, 2011), Burden of Illness survey results (PHA Canada, 2014), and website information, and internal, from internal documents obtained directly from previous contact with said organizations. In total 23 references were found to be useful for this review based on the search criteria outlined above.

The Big Picture: Early Diagnosis of Rare Diseases

The academic literature for rare diseases is primarily concerned with the biological pathways and treatments for specific rare diseases and making that information available to the medical community. However, some of the academic literature also focuses on evaluating outcomes regarding rare disease awareness, knowledge, and needs.

Non-profit advocacy groups primarily supply current perspectives on what needs to be done for the earlier diagnosis of rare diseases. In Canada, groups such as the Canadian Organization of Rare Disorders (CORD) and the Rare Disease Foundation work towards a wide variety of goals including education, awareness, and advocacy, for clinicians, researches, and those affected by rare diseases. There are also large groups in Europe and the United Kingdom (UK) that focus on the same goals, such as EURORDIS (the European Organisation for Rare Diseases) and the UK Department of Health.

Overall, there was limited literature regarding early diagnosis of rare diseases, and even more limited literature investigating the steps taken to move recommendations into action.

What needs to be done to improve early diagnosis?

Five themes regarding areas of need were shown in the literature: physician education/awareness; public education/awareness; improved research; consolidation of rare disease information; and system-wide early diagnosis strategies. Table 2, at the end of this section, summarizes of the challenges and suggested action items for rare disease early diagnosis.

1. Physician Education/Awareness

A common theme found was that the education and training of physicians on rare diseases are lacking. In health care systems around the world, there are few health care professionals who have experience with rare diseases (CORD, 2015b; Syed et al., 2015). While primary care physicians realize that early diagnosis of rare diseases is important, the training of family physicians or general practitioners for the recognition of rare diseases is not sufficient (Engel et al., 2013). It has been suggested that this lack of training spans from medical school education to continued education of practicing healthcare professionals (EURORDIS, 2009). For example, while rare diseases are covered in the UK during medical school, it is unrealistic for this training to prepare general physicians for encountering rare diseases in the clinic (UK Department of Health, 2013). Currently, training for rare disease is not mandatory for most practicing physicians, but there are recommendations that it become so, possibly via Continued Medical Education (CME) modules (Syed et al., 2015). Additional training could be addressed via programs that are designed to educate physicians on how to diagnose rare diseases or, at the very least, realize the need to refer a patient to an expert who could then make a diagnosis (Engel et al., 2013). However this may be an uphill battle as general physicians generally do not want to get involved with rare disease diagnoses, primarily due to the large number of possible rare diseases (Engel et al., 2013). As expertise is needed to correctly recognize and diagnose a rare disease, proper and effective education is important (UK Department of Health, 2013).

2. Public Education/Awareness

While patients are ill equipped for accurate self-diagnoses, they and their social communities are important elements in the diagnostic pathways for rare diseases. Patients can go through a wide-range of experiences until a diagnosis is reached, often including multiple misdiagnoses, specialists, and years waiting (CORD, 2015b). As such, the public does not believe that physicians are well informed when it comes to rare diseases (CORD, 2015b). Indeed, most patients must provide their own physician with information about their rare disease (Engel et al., 2013). Delays to diagnosis and subsequent inappropriate care given to many patients further erode the trust that they have in the medical community (EURORDIS, 2009). It is this trust that needs to be nurtured to ease the inequality that is present between rare disease patients and

patients who have more common diseases (EURORDIS, 2009). CORD has recognized that public awareness towards broader recognition and understanding of rare diseases is important, and has made this a part of their proposed Canadian Rare Disease Strategy (CORD, 2015b).

3. Improved Research

As most rare diseases have a genetic component, if not direct cause, there is a need for increased genetic research. Initiatives focused on identifying unknown genetic links and on identifying the natural progressions of rare diseases are needed (CORD, 2015b). Without knowing this information, screening and early detection is very difficult (CORD, 2015b). For the 20 percent of rare diseases that do not have a direct genetic cause, research on the natural progression of the disease is very important so that earlier signs of the disease may be discovered which may lead to improved diagnosis and therapies (CORD, 2015b).

Once a genetic cause has been found for a rare disease, there is then a need to distribute and implement the appropriate test for use by the medical community. Thus there is a need to promote awareness of the genetic test, encourage healthcare institutions to integrate the test into common practice, possibly via screening at birth, and to lobby for governments to fund these tests as part of standard practice (Shire, 2015a).

Most descriptions of rare diseases describe an advanced stage of the disease, often due to a lack of effective intervention (EURORDIS, 2009). This implies that physicians may unintentionally wait until the hallmarks of a rare disease are present before a diagnosis is even considered. This is perpetuated due to ever-increasing clinical data and descriptions of rare diseases that uniquely describe the later stages, where treatment may have limited impact on health outcomes. Thus waiting for ‘classic’ hallmarks of a rare disease is not an effective strategy, and increased research for earlier indications of the disease, followed by educational initiatives, is needed to promote the consideration of rare diseases at earlier time points. In this way innovative diagnostic tests can enable early diagnosis and intervention (World Health Organization, 2013).

4. Consolidation of Rare Disease Information

As diagnostic tools improve for rare disease diagnosis, so does the opportunity for improved outcomes. As such, improved diagnosis may come from the ability to better link the current knowledge base of symptoms and the progression of rare diseases. The medical community at large can hold the needed knowledge and experience to properly identify rare diseases; however, this breadth of knowledge is not realistic to expect of the average physician (Dragusin et al., 2013). Current tools such as PubMed and Google are currently used for such searches, however there is a need to develop specific online tools for rare diseases (Dragusin et al., 2013). While there are online resources available specifically designed for narrowing down rare disease possibilities in patients, such as 'orphaned', 'MIM', 'GARD', and 'NORD', they do not offer a consolidated database (Dragusin et al., 2013). However, some online programs, such as FindZebra (http://findzebra.compute.dtu.dk/), have developed database searches that match symptoms to potential rare diseases, and are designed for use by both physicians and patients. While websites such as FindZebra are slowly being taken-up in practice, widespread use and validation are still in process (Dragusin et al., 2013).

5. System-Wide Early Diagnosis Strategies

The need for improved diagnosis tools highlights the last theme identified: system-wide strategies. Certain factors not present in individual diagnosis methods may be causing delays. For example, gender, the presence and nature of misdiagnoses, and the ability of a patient or family to approach a physician with their own views on diagnosis may create delays to diagnosis (EURORDIS, 2009). This indicates that a different perspective or process may be required by the medical community to properly address diagnosis needs.

Each country or region needs to have its own rare disease national plan (Shire, 2015a). There have been general, yet vague, recommendations for countries to take action by prioritizing rare disease health policies to improve funding and education initiatives (Shire, 2015a). Such policies may address needs including the networking of knowledge and infrastructure, and coordination of services (CORD, 2015b). In this manner, current resources could be used to enhance collaborations, capabilities, initiatives, and programs (CORD, 2015b).

Syed et al. (2015) summarize the current need for system transformation by emphasizing the notion that the classic healthcare system is not built to effectively deal with rare disease diagnosis, but rather non-rare diseases. This situation results in rare disease patients experiencing diminished access to timely, high-quality services (Syed et al., 2015).

Table 2: Challenges and Suggested Steps to Address Rare Disease Early Diagnosis

Challenges to Early Diagnosis	Suggested Actions
Lack of Physician Education/Awareness	- Improve CME opportunities - Increased training in medical school - Targeted messaging (e.g. general physicians vs. specialists) - Creation of an inventory of educational programs - Targeted advocacy group campaigns
Lack of Public Education/Awareness	- Advocacy group campaigns centred on communicating balanced information - Establish a Rare Disease definition
Research Needs	- Increased funding via national and international agencies - Improved incorporation of genetic sequencing technologies - Implementation of disease registries
Non-Centralized Disease Information	- Creation of consolidated online resources regarding symptoms, treatments, and other resources.
Lack of System-Wide Early Diagnosis Strategies	- Creation and implementation of national strategies

What is currently being done to address these needs?

In Canada, CORD, acting as an over-arching organization for rare disease patients and patient organizations, has recently unveiled a framework for a 2015 Canadian Strategy for Rare Diseases (CORD, 2015a; CORD, 2015b). This national strategy outlines eight goals that involve many different stakeholders, including governments, and is aimed at improving the lives of patients and families of those affected by rare diseases (Figure 1). Of those eight goals, four can be categorized as including action items pertaining to the early diagnosis needs detailed in the previous section.

Figure 1: Eight Goals of the Canadian Strategy for Rare Diseases (2015)

1. **Public awareness**: Enhancement of public awareness of rare diseases and their public health impact
2. **Recognition**: Canada offers an environment that recognizes the diversity of rare diseases and is responsive to the wide-ranging needs of those living with them
3. **Prevention and Early Detection**: Prevention and early detection of rare diseases are regarded as important goals of public health
4. **Community Resources**: Communities are resourced to provide support to individuals with rare diseases and their families
5. **Timely, Equitable Care**: Timely and equitable access to seamless care for all individuals with rare diseases, regardless of where they live
6. **Informed Decisions**: All decisions informed by the best available evidence, generated throughout the course of disease
7. **Sustainable Access**: Sustainable mechanisms for providing access to promising therapies for rare diseases
8. **Innovative Research**: Canada is a world leader in enabling and fostering innovative research around the prevention, diagnosis and management of rare diseases

Note: Underlined goals have applicable early diagnosis themes (CORD, 2015b)

The first stated goal of the strategy is to improve public awareness of rare diseases. This includes establishing a specific Canadian definition of what a rare disease is, but also focuses on improving efforts to communicate balanced information to the public (CORD, 2015b). CORD also currently spearheads communication initiatives such as the Annual Rare Disease Day (February 28th).

The third stated goal of the strategy, and the one that is most applicable for early diagnosis needs, is directly concerned with prevention and early detection of rare diseases (CORD, 2015b). This goal had three action items centred on: 1) improved genetic and metabolic screening in newborns and children, 2) preventative genetic screening, and 3) system-wide initiatives including improved rare disease registries, engagement of healthcare professionals, and decision making guidelines. While the first two action items are primarily genetic screening-based and are increasingly centering on next-generation genetic testing, the third touches on many different aspects such as awareness, education, research (in the case of registries to better understand disease epidemiology), and system-wide changes to focus on early detection, including policy changes (Critchley, n.d.; Wong-Rieger, n.d.). For diseases that lack a clear genetic link, focuses on research of the cause and natural progression of a disease are very important to improve early diagnosis (CORD, 2015b).

The fifth stated goal is to provide "timely and equitable access to seamless care for all Canadians with rare diseases" (CORD, 2015b, p. 30). While this goal has many sub-points to act on, only one, to "improve education and capacity of healthcare providers related to rare diseases" (CORD, 2015a, p. 2) touches on the need for greater education for the medical community to recognize and diagnose rare diseases. For example, they indicate a need to create an inventory of educational programs and to integrate case studies into training (Critchley, n.d.). The strategy also suggests that professional associations and medical colleges need to incorporate new training and education into their continuing education and curriculum, respectively (Wong-Rieger, n.d.).

The eighth stated goal focuses on research initiatives to determine the pathology and aetiologies of rare diseases, as well as improving on, and developing new, screening and diagnostic tools towards earlier and more accurate diagnoses (CORD, 2015b). Through the development of a Rare Disease Research program research can be prioritized to include these needs, as well as focusing on more general epidemiological needs such as the incidence, prevalence, and natural history of rare diseases. Better understanding of rare diseases, it is hoped, will also improve the

understanding of more common diseases, thus leading to more diagnostic and treatment resources that go beyond just rare diseases (CORD, 2015b).

Much of the set of goals for the Canadian Strategy for Rare Diseases is focused on dealing with rare diseases after they have been diagnosed. While this immediate need is very important, proper identification of rare diseases and subsequent early intervention may result in improved health outcomes, and thus is an integral component to decrease this need.

CORD has stated that they want Canada to follow the examples set by France and the UK in implementing their initiatives (Critchley, n.d.). While these healthcare systems have their differences, the national plans may be very useful models for improving our own strategies.

France completed a national plan from 2005-2008 that was structured around ten strategic priorities, including developing information for patients, health professionals, and the general public concerning rare diseases, and training health professionals to better identify rare diseases (French National Plan for Rare Diseases 2005-2008, 2004). This strategy had clearly laid out goals, such as objectives, measures, and costs. However, while the overall campaign was viewed as a success, the objectives that centered on epidemiology, screening and diagnostic programs, and professional training were viewed as lacking (Rodwell & Aymé, 2014). They are currently building off of their successes and opportunities for improvement to work towards a more comprehensive national plan.

The UK has also developed a rare disease strategy. Their goal is to “deliver evidence-based diagnosis and treatment of rare diseases, developed through the best use of regional and national resources that are easily accessible by patients and professionals” (UK Department of Health, 2013, p. 9). In regards to earlier diagnosis, they have recommended programs centred on education and training of healthcare professionals, as well as improved screening of newborns (UK Department of Health, 2013). Of particular note is a focus on ensuring that doctors are aware of the possibility of rare diseases as a possible diagnosis, both via university courses and professional development opportunities, even if they are unable to identify the specific disease (UK

Department of Health, 2013). However, much like CORD's national strategy for Canada, there is little mention (only recommendations) of what actual initiatives are to be implemented to address these focuses.

International organizations are also working on initiatives to address rare disease needs. EURORDIS is a non-governmental organization that is working towards patient welfare and policy reforms over 49 European countries (European Commission, 2013; EURORDIS, 2009). By combining the voices of rare disease patient organizations they hope to gain the necessary power to create change at national levels in Europe (European Commission, 2013). However, much of the literature regarding EURORDIS is based on what the current state of rare disease care is in Europe, not what is being done to create change (EURORDIS, 2009).

The International Rare Disease Research Consortium ("IRDiRC"), established in 2011 as a joint venture between the USA National Institute of Health and the European Commission, is focused on the identification of the genetic mechanisms of rare diseases, working towards new genetic screening methods and thus earlier diagnosis of genetically-based rare diseases (European Commission, 2013; World Health Organization, 2013). Funding via the IRDiRC will thus help to simplify diagnostic methods and reduce diagnostic delay (European Commission, 2013).

Industry is also playing a role in addressing early diagnosis needs. Shire, a global biotech company, focuses on "developing and delivering innovative medicines for patients with rare diseases and other specialty conditions" (Shire, 2015b, para. 1). They are leading an initiative called "Diagnosis Doesn't Have to be Rare" that highlights rare disease diagnosis challenges and calls for improved genetic testing to improve diagnosis pathways (Shire, 2015a). Shire's platform for this campaign focuses on rare disease awareness, as well as education of medical professionals towards improved usage of genetic testing. While they do have a stake in increased genetic testing, this kind of campaign is not uncommon for private companies who benefit from uptake of this message.

Bringing together collective knowledge has also emerged as a method to address limitations on individual physician or patient ability to reach a rare disease

diagnosis. FindZebra is one such internet-based search tool that has been proposed to be useful for physicians and medical students to use symptoms to narrow down possible rare diseases (Nuwer, 2013). CrowdMed is another application that utilizes user suggestions to narrow down disease possibilities, although this method may be prone to bias and lack of medical expertise (Nuwer, 2013). Orphanet is another open access online resource that contains information for over 6000 rare diseases and is highly searchable for a wide variety of diseases, treatments, and other resources (European Commission, 2015).

What approaches or change theories underlie initiatives focused on improving time to diagnosis?

While CORD has done good work outlining a strategy to address the rare disease needs in Canada, specific responsibilities and accountability to turn these needs into concrete action are lacking. While they state that they are engaging with stakeholders, including government, and have a goal to have support from all stakeholders by fall 2015, they do not explicitly state how they expect these groups to support proposed initiatives (Wong-Rieger, n.d.). CORD states that they will be "monitoring progress" against the goals in Figure 1, but do not list what progress is expected, or how to judge success or failure (CORD, 2015a). While the goals are sound, how and when change will actually occur is not clear and was not found in the resources found in this review. However, if explicit support can be gained from government and appropriate stakeholders, specific goals can be set and stakeholders can then be held accountable for actions, or lack thereof, towards realizing those goals.

One of the challenges that CORD faces is that, as rare diseases have a wide range of aetiologies, focusing on early diagnosis, as a general concept, is very difficult (CORD, 2015b). They recognize that early diagnosis communication might best be served by individual disease advocacy organizations (CORD, 2015b). However, coordination between groups is also needed for efficient knowledge integration of rare disease needs. Unfortunately, they do not offer action items for this, only recommendations (CORD, 2015b).

The French national strategy took a step beyond the Canadian strategy and explicitly stated their objectives and associated costs. These measureable goals allowed for direct evaluation of their plan. Indeed they were able to show which aspects of their plan were working when their initial five year plan was completed. Although unfortunately those goals that were associated with early diagnosis were not met, it allowed them to re-evaluate for future strategies based on what they learned (Rodwell & Aymé, 2014).

The UK national strategy is based on the belief that education and training will improve the ability of physicians to identify rare diseases, thereby decreasing time to diagnosis. Training does not need to be all encompassing, but does need to give an appreciation that rare diseases are possible and should be considered. This model may lead to education that does not actually inform on any specific diseases, but rather to emphasize the fact that rare diseases need to be considered during diagnosis, even if only in a general manner. One difficulty is that evaluating this method may prove challenging and was not discussed.

As a whole, improved education for both the public and the medical community is highlighted as very important to early diagnosis. Engel et al. (2013) suggest programs centred on rare disease knowledge, and processes to identify rare diseases, may improve diagnosis but no methods of how to best do this are suggested. Educational seminars for physicians on rare diseases are not uncommon, but best practices on evaluating the effectiveness of these educational opportunities have rarely been discussed (Anekwe, n.d.). Additionally, different targeting needs for educational initiatives are required for general practitioners compared to specialists, indicating that specific programs and theories of change need to be explicit for each group (Engel et al., 2013).

Finally, the simplification and optimization of search tools for rare diseases should remove barriers to early diagnosis, but ultimately remain contingent on accuracy and uptake by the public and medical community. Proper marketing of these tools is underway, but is still considered to be in the early stage (Dragusin et al., 2013).

The Case of Pulmonary Arterial Hypertension

The majority of the literature found for PAH early diagnosis was academic articles that focused on diagnostic methods and biological pathway descriptions of the disease, with only minimal mentioning of early diagnosis. This portion of the literature primarily informed on aspects of the 'need' for early diagnosis. The smaller proportion of material found was generated by advocacy groups, such as PHA and PHA Canada, and was primarily in the form of reports and online campaigns. Overall, literature directly related to the early diagnosis of PAH was extremely limited.

What needs to be done to improve early diagnosis?

Early diagnosis is challenging for PAH. As the mean time from symptoms to diagnosis (approximately two years) did not improve between the NIH registry in the 1980's and the REVEAL registry in the early 2000's, this demonstrates a clear need for early diagnosis improvement (Palevsky, 2011). While recognition of PH may have improved in that time due to factors such as improved diagnostic tools and the availability of new PH–specific drugs, these factors do not seem to be improving the time from symptoms to diagnosis (Rich & Rich, 2014). However, while early diagnosis has been shown to be associated with a lower severity at diagnosis and thus improved long-term survival, there are many barriers concerning early diagnosis (Humbert, Coghlan, & Khanna, 2012). Five themes regarding PAH early diagnosis need were identified in the literature: physician education/awareness (including two sub themes); public education/awareness; early screening initiatives; improved research; and system-wide early diagnosis strategies. Table 3, at the end of this section, summarizes of the challenges and suggested action items for PAH early diagnosis.

1. Physician Education/Awareness
    a. Awareness of PAH in the Medical Community:

The primary need identified for early diagnosis is improved physician awareness of PAH (Armstrong et al., 2012; Haddad & Mielniczuk, 2015; McGoon & Kane, 2009; Pulmonary Hypertension Association, 2011; Rich & Rich, 2014). Because the symptoms of PAH are non-specific, common conditions need to be investigated first, but once these conditions fail to be validated, PAH should be considered (Armstrong et al., 2012; McGoon et al., 2004; McLaughlin, Shah, Souza, & Humbert, 2015). Without prompt recognition by physicians there is little chance that PAH will be diagnosed in the early stages (McGoon & Kane, 2009). However, waiting for the presence of severe symptoms, indicating an advanced stage of PAH, is not a valid alternative (Haddad & Mielniczuk, 2015; Lau et al., 2015).

As no medical subspecialty has been linked with a delayed recognition of PAH, broad education and awareness is needed (Brown et al., 2011). This includes, but is not limited to: primary care physicians, immunologists, cardiologists, rheumatologists, and obstetrician-gynaecologists (Pulmonary Hypertension Association, 2011). Canada has only approximately 30 PH treating doctors ('PH specialists') across the country, but as this is not a true medical subspecialty, most treating doctors have different specialties, such as respirologists, rheumatologists, and internists, for example (Tarya Laviolette, PHA Canada Ambassador, personal communications). It is, however, recognized that due to PAH's rarity it is difficult for physicians outside of specialty centres to develop the necessary expertise and experience to diagnosis PAH early (Armstrong et al., 2012; Rich & Rich, 2014). This inexperience with PH has not gone unnoticed in the patient population, as 51 percent of patients stated that their family physician was not able to initially recognize PH symptoms and thus delayed referral to a specialist (PHA Canada, 2014). Thus clinicians must be suspicious of PAH even when symptoms and small indicators are present (Domenighetti, 2007). Finally, if PAH is considered, referral to a specialty centre should take place as soon as possible to optimize patient outcomes (Armstrong et al., 2012).

b. Identification of High-Risk Populations:

Physicians should have greater education about who are at high-risk for developing PAH. Those with high-risk conditions should be screened regularly, and PAH should be considered earlier when symptoms are present (Haddad & Mielniczuk, 2015).

Individuals with genetic markers, such as PAH-associated mutations in the BMPR2 gene, are at high-risk of developing PAH (Lau et al., 2015). As genetic research on PAH is ongoing, newly found genetic markers should also be incorporated into genetic testing, and any asymptomatic family members of PAH patients should also be screened (Haddad & Mielniczuk, 2015). Additional populations who are at a higher risk of developing PAH, for example populations with sickle cell disease, HIV, or scleroderma, have been recommended as part of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) screening guidelines (Humbert et al., 2012). As PAH can also be induced by certain drugs or toxins (such as fenfluarmaine and aminorex), screening should also include populations who have had past exposure to them (McLaughlin et al., 2015). New research has also suggested that younger patients (those under 36 years old) and those diagnosed with a common respiratory illness are at a higher risk of delayed recognition of PAH (Brown et al., 2011). Thus there is a need to develop ways to identify these high-risk populations and have their physicians be made aware that PAH is a possibility when progression or responses to therapies do no fit the current diagnosis (Brown et al., 2011).

2. Public Education/Awareness

While physicians are the gate-keepers of a PAH diagnosis, an educated and aware public also improves the early detection of PAH (Lau et al., 2015). Numerous articles and groups emphasize that increased public disease awareness is vital to early PAH diagnosis (Armstrong et al., 2012; Lau et al., 2015; Pulmonary Hypertension Association, 2011). A study conducted by PHA Canada on the burden of PH showed that patients down-played major symptoms and suffered for an extended period before approaching a doctor (PHA Canada, 2014). While this may be a broader social issue regarding a reluctance to seek general medical treatment, even in the presence of symptoms, unfamiliarity with PAH can delay the initial suspicion of the disease

(Armstrong et al., 2012). In order to improve the public's knowledge of PAH, volunteer organizations should be using a variety of methods to spread awareness and use both qualitative and quantitative focuses (Armstrong et al., 2012). In this way many of the educational elements needed for physicians can also be directed at the public.

3. Early Screening Initiatives

As earlier recognition of PAH is associated with improved survival, improving screening to identify pre- or early symptomatic individuals is recommended (Lau et al., 2015). While high-risk populations may fall into this category, and should be screened more frequently than other populations, the challenges are the sporadic cases that do not have identifiable risk factors to warn physicians of potential disease (Humbert et al., 2012; Lau et al., 2015).

In order to have buy-in for screening programs in the medical community, some requirements need to be met. Screening must be able to alter the progression of the disease and improve the prognosis (Lau et al., 2015). If early screening does nothing to improve outcomes, then it can be argued that such screening is a waste of resources. Registry evidence has shown that earlier diagnosis and intervention, even when symptoms are mild, can lead to improved health outcomes in PAH (Lau et al., 2015). Screening tools must be easily obtainable by the medical community, simple, non-invasive, and should be acceptable to patients (Lau et al., 2015). Finally, such tools must be shown to have high standards of accuracy (e.g. sensitivity, specificity, reliability) against current gold-standard approaches (Lau et al., 2015).

In order to improve the accuracy of these screening initiatives, there must be improved research towards more accurate risk and diagnosis measures.

4. Improved Research

The ability to identify early cases of PAH are generally centred on the development of biomarkers, new genetic markers, and registries that track the natural progression of symptoms and characteristics that may predict outcomes (McGoon et al., 2004; McLaughlin et al., 2015). While there has been considerable progress in understanding the mechanisms of PAH and subsequent development of therapies, this has not yet translated into any measurable earlier diagnosis (Palevsky, 2011).

Certain biomarkers, such as Brain Natriuretic Peptide, have been correlated with the progression of PAH and may warrant follow-up for the presence of PAH (Badesch et al., 2009; Haddad & Mielniczuk, 2015).

5. System-Wide Early Diagnosis Strategy

The development of guidelines or a strategy for PAH early diagnosis should be a priority. This should include a discovery strategy for at-risk populations, including any risk factors, unexplained and worsening symptoms, and genetic markers (McLaughlin et al., 2009). For example, a national guideline is recommended regarding the diagnostic pathway for unexplained dyspnea, which would include PAH as a possible cause to consider (Armstrong et al., 2012).

Table 3: Challenges and Suggested Steps to Address PAH Early Diagnosis

Challenges to Early Diagnosis	Suggested Actions
Lack of Physician Education/Awareness	- Improve CME opportunities and medical training to focus on PAH - Targeted messaging (e.g. general physicians vs. specialists) - Targeted advocacy group campaigns
Identification of High Risk Populations by Physicians	- Targeted messaging to physicians who deal with high-risk populations
Lack of Public Education/Awareness	- Advocacy group awareness campaigns
Early Screening needs	- Develop improved screening methods/tools
Research needs	- Increased funding via national and international agencies - Implementation of disease registries - Develop accurate biomarkers
Lack of System-Wide Early Diagnosis Strategies	- Discovery strategy and screening guidelines for at-risk populations

What is currently being done to address these needs?

Many of the procedures and initiatives surrounding PAH care take place after diagnosis is either considered or confirmed. Once suspected, there are diagnostic algorithms that guide the evaluation of PAH (McGoon et al., 2004). However, if the limiting step for diagnosis is suspecting PAH, then all the medical information regarding subsequent diagnostic steps is moot, no matter how reasoned the approach and evidence base.

The need for advanced screening of high-risk populations is not debated as part of best practice guidelines. Recommendations have been made, but exactly which sub-populations should be screened, how often, via which tools, and how to interpret the accuracy of the results, are questions that remain in the medical community (Brown et al., 2011; Humbert et al., 2012; Lau et al., 2015). Such initiatives can also become difficult, as they must involve both informed patients and physicians. Thus even as there are many "at-risk" populations that can be screened for PAH, the logistics of implementing such a screening initiative, no matter the scale, has many roadblocks to overcome. Based on the literature there were no such explicit initiatives described.

Biomarkers are part of a growing field of PAH diagnosis. While research is ongoing for validation of current markers and development of new ones, current tests are not sufficiently accurate for widespread use (Humbert et al., 2012). While biomarkers may improve over time, this will not help patients unless these tests can become standard practice in a healthcare setting.

In the case of sporadic PAH, in the absence of risk factors there is no indication of pre- or early symptomatic screening needs (Lau et al., 2015). Aside from population wide systematic screening for PAH, which is not feasible due to the combination of the rarity of PAH and available resources, and potential false positive results, it is unclear if there have been any early screening initiatives proposed.

Even if early screening initiatives were available, they do have their downsides. Due to the low prevalence of PAH, the ability to find true PAH patients via early screening is very unlikely in both sporadic (i.e., with no family history of PAH) and at-risk

populations. Indeed, for any screening initiative, it is inevitable that there will be some false positives, which could lead to anxiety and retesting (Collier, 2012). There is also the concern that test results will not be clear enough to give a positive result, leaving patients unsure of what the future holds (Collier, 2012). Even if patients were identified, there have been no randomized trials to test if early screening confers improved health outcomes compared to no screening.

While screening could be confined to high-risk populations (e.g., those with familial genetic markers or diseases associated with PAH), exactly what benefit and what harm could result from such screening is unknown for PAH. For example, subsequent medical procedures, such as a right heart catheterization, are invasive and could put the patient's health at risk.

Additionally, It is difficult to know which patient will have a slow or fast progression of PAH. A slowly progressing patient may undergo many invasive tests and start medication long before a clear benefit of treatment has been established. Those who remain asymptomatic may have undergone tests or treatments that create stress to the patient, both physically and psychologically. The cost of screening also needs to be evaluated, when resources and money are considered against the possible improved health outcomes achieved.

Academic or medical education efforts regarding PAH directed at the medical community rarely focus on early diagnosis. While there are CME resources for physicians that highlight PAH diagnosis and care, the amount of material that is dedicated to early diagnosis is minimal (Traill, 2011).

As early diagnosis has a strong need based on awareness and education, national and international PH advocacy groups represent a driving force for this. The Pulmonary Hypertension Association (PHA) is based in the United States and is a patient-initiated organization that consists of clinicians, scientists, patients, and pharmaceutical companies (McGoon & Kane, 2009). PHA works to advance the understanding and care of PH via activities such as spearheading educational initiatives for both the public and medical community, funding research projects, organizing conferences, and supporting patients and caregivers (McGoon & Kane, 2009).

Over the last few PHA has developed and refined an early diagnosis campaign named “Sometimes It’s PH” with the goal of reducing the time to diagnosis for PH. This campaign is focused on three aims: 1) providing educational tools and resources, 2) encouraging healthcare providers to consider PH when the symptoms warrant, and 3) urging referrals to specialists when PH may be a possibility (Pulmonary Hypertension Association, n.d.).

While initially the Sometimes It’s PH campaign was focused on public awareness, Jessica Armstrong, the PHA early diagnosis campaign manager, stated during a conference call in 2014 that, after a year of successful PH community outreach, the campaign committee consulted with their medical advisory board who confirmed that the medical outreach piece of the campaign was insufficient to achieve the desired early diagnosis change (personal communication, 2014). After re-evaluating their aims, they then shifted emphasis to sequentially focus on primary care providers, then specialty physicians, and later, potential PH patients. The current status of this campaign is not publicly available.

Aspects of this campaign are striving to meet the needs discussed earlier. By collaborating with volunteer medical professionals to publish awareness articles, forming partnerships with medical organizations and the health community, and encouraging collaboration of general physicians with PH specialty centres, they hope to improve the awareness and ultimately the time to diagnosis of PH in the USA (Pulmonary Hypertension Association, n.d.). They also are working on the qualitative side of PH by working with patients, families, and caregivers to share experiences and promote public advocacy for PH awareness. Again, it should be noted that most of the information presented by PHA only goes as far as stating what ‘needs’ to happen, but does little to lay out steps that show how they expect ‘change’ to occur.

PHA Canada works in much the same manner as their American counterpart, but at a smaller scale. They are currently spearheading their own early diagnosis initiative, and are primarily focusing on physician awareness and education initiatives, targeted at both general practitioners and specialists (PHA Canada internal documents). This campaign is in its early stages and plans to piggy back on the USA’s Sometimes It’s PH

theme. By forming partnerships with national physician and health awareness groups, and by promoting educational and awareness events and multimedia campaigns, they hope to increase the knowledge base of physicians so that PH is considered sooner during the diagnostic journey of a patient with unexplained symptoms.

Overall, while the needs have been stated to improve system wide awareness and education of PAH, there have been no explicit responsibilities discussed; rather change is expected based on the fact that need is present (Brown et al., 2011). Aside from advocacy groups, the extent of efforts of the medical community to create change is difficult to know.

What approaches or change theories underlie initiatives focused on improving time to diagnosis?

Most research articles on PH contain a variation of the phrase 'in patients with suspected PH' (McGoon et al., 2004; McGoon & Kane, 2009; McLaughlin et al., 2009). While this concept is emphasized in most diagnosis related literature and focuses on diagnostic algorithms, it is primarily helpful only for physicians who have already considered PAH. While these approaches may improve the time to a final concrete diagnosis, they do little to help those physicians at the pre-consideration stage, when symptoms may not warrant consideration of a rare disease, let alone PAH. For example, while ACCF has a "diagnostic strategy", it is only laid out for high-risk patients and does not seek methods to determine how to best identify those who are not yet at high risk, such as those whose symptoms are mild to moderate.

Thus the main theory of change proposed in the literature is that further educating both the public and the medical community about PAH will drive earlier recognition of symptoms that may indicate PAH. Knowledge gained could range from simple awareness of the existence of the disease, to an understanding of the early symptoms.

While the medical community should not wait for patients to present with advanced stages of PAH, neither can the public expect the physician to catch this rare

disease right away. Current initiatives seem to bring these two ideas forward together to focus on change by reaching out to physicians, who are the ultimate gate-keepers of diagnosis, and the public, who have a right to be educated and aware of what may be the cause of their symptoms.

The PHA's current theory of change is that by providing education tools and resources to physicians, they will better be able to recognize or consider PH in patients. Additionally, by partnering with physician organizations, this will allow PHA to reach more of the medical community with their material.

Conclusion

Early diagnosis for rare diseases is separated into two distinct sets of needs. The first are for those diseases that have a defined genetic cause that requires utilization of genetic tests to confirm a diagnosis. Diagnosis of these diseases requires knowledge of, and access to, these tests on a large scale. If access to these tests is widespread, then it is conceivable that all of those rare diseases that have an accurate genetic test associated with them could be screened for at birth. Thus early diagnosis could occur at one of the earliest time points possible and treatment, if available, could begin before symptoms even present themselves.

The second need is for those diseases, such as PAH, that do not have a defined genetic cause. Without a simple screening tool, such as a definitive biomarker, these diseases will not present themselves until symptoms escalate to the point that a rare disease is ultimately considered. As early screening initiatives have not been undertaken to investigate if they result in improved health outcomes for patients, early screening initiatives may not even be appropriate for PAH. Regardless, as more and more focus is being put on genetic testing, diseases such as PAH are being left behind in the discussions and initiatives addressing the early diagnosis of rare diseases.

In the case of PAH, there is a known lack of awareness in both the medical and public populations about not only what it is, but about what symptoms are signs to consider PAH. The PHA has been working to improve education of PH in the medical community, and PHA Canada is now following suit to address this need. The most applicable action area is to identify and educate physicians for individuals in high-risk groups, however exactly what action is being taken is not known. While research and registries may elucidate causative mechanisms and natural progressions of PAH, without physicians and the public better able to recognize the disease, early diagnosis will still suffer, even when treatment options improve. While research may result in new diagnostic tools that could be used to screen for a variety of conditions, we are not sufficiently capable of this yet.

A silence in one of the main theories of change for PAH is that while awareness can be promoted, it is very difficult to evaluate whether earlier diagnosis is actually occurring. In the absence of a national database (in Canada or the USA), exact prevalence and incidence of PAH is unknown and thus improvement in time to diagnosis is very difficult to measure. This emphasizes the need for a Canada-wide registry to help address both epidemiology statistics, but to also allow for the ability to inform about changes to early diagnosis and health outcomes over time.

While the need is present, overall there is no evidence that current educational efforts towards improving early diagnosis are creating meaningful change (Deano et al., 2013). Part of the issue may be the message to physicians and the public, while part of the issue may be the lack of concrete implementation of recommendations, of which there are many.

This current lack of effective communication about and uptake of early diagnosis needs, i.e., knowledge translation (KT), that separates promoting need and the effective uptake of messages in the medical and public community, indicates that proper communication strategies and theories need to be investigated. The incorporation of theories of change that underlie early diagnosis campaigns will help to focus KT initiatives, and modeling activities off of similar successful campaigns could also be useful. In the case of PAH there is a limited evidence base on what is effective for proper KT, which means that this process may need to be iterative and continually evaluated to ensure that proposed communication goals and objectives are being met.

Overall there is ample literature about “what” needs to be done in practice, but not how this can actually be achieved. How should doctors effectively incorporate these recommendations into their practice? Is there an organization, government or otherwise, that could or should be responsible for this?

Based on the current literature and initiatives undertaken for the early diagnosis of PAH, the most pertinent area to focus on seems to be the ‘need to establish the need’ for awareness and education of PAH. While educating physicians about PAH could be effective on a small scale, without an atmosphere that is promoting the ‘need’ that they know more, then there will be little uptake on a large scale. With this in mind the

'Sometimes It's PH' campaign may help to create this atmosphere, but specific evaluation criteria needs to be tracked so that success and failures can be incorporated into future planning. Exactly how to accomplish the evaluation of these campaigns is unfortunately not discussed in the current literature.

Research Needs

The primary area identified that requires research is how to best promote awareness and education among health professionals and the public in general. One possible avenue for this research is formative research / assessment with key stakeholders, such as general physicians, specialists, health authorities, advocacy groups, and active members of the public. Information gathered could be used to generate a SWOT analysis (Strengths, Weakness, Opportunities, and Threats) that may inform ideas about what initiatives may be undertaken next.

Another area to investigate would be the usage of theories of behaviour change to improve physician-targeted educational and awareness campaigns or material for rare diseases and PAH early diagnosis. For example, the Health Belief Model contains many components that could apply here. Behaviour change of physicians could be analyzed for rare diseases and PAH based on components such as the perceived susceptibility and perceived severity of missing an early diagnosis, the perceived benefits of being able to recognize the early signs of disease, and the self-efficacy belief to increase confidence in the ability to better identify rare diseases (Janz, Champion, & Strecher, 2008).

To complement these research needs, there must be a way to evaluate the effect of any such campaign or strategy. As this was observed as a silence in the literature, establishing a logic model and a program theory model that explicitly states the underlying rationale for campaigns is important to evaluating outcomes. Deliberate discussions with all stakeholders should discuss methods on how to best do this, and assign responsibilities for follow-up such that programs can be properly evaluated and lessons can be learned to inform future initiatives. One avenue that merits specific

follow up for this need is the development and implementation of a national registry for PAH.

Future research should also analyze how Canada's healthcare system's infrastructure affects early diagnosis initiatives. As the National, Provincial, and local levels of healthcare governance will each affect the ability for the discussed research needs to be addressed, a comprehensive review investigating barriers and resources towards early diagnosis is warranted.

Limitations

As this was a narrative review, a systematic analysis of the literature was not done and some information may have been missed. However, due to the literature rarity of the topic, without more extensive search methods, obtaining more pertinent data was very difficult. The subjective nature of the review also limits its validity. For example more attention may have unintentionally been spent on organizations that the author was more familiar with.

This report would have benefited from real-world discussions with stakeholders involved with early diagnosis of rare diseases, specifically PAH. As many of the campaigns are not academic in nature, the literature surrounding these initiatives is not as available, or at least as searchable, as academic research results.

As mentioned as part of research needs, this report also lacks an analysis of how the healthcare system's infrastructure affects early diagnosis initiatives. This context may have been important to fully understanding the progress, or lack thereof, of early diagnosis initiatives.

References

Anekwe, L. (n.d.). Training a future generation of doctors to diagnose rare diseases. Retrieved from http://www.rarediseases.co.uk/research/training-a-future-generation-of-doctors-to-diagnose-rare-diseases#.VZhaNqY6NYU

Arksey, H., & O'Malley, L. (2005). Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology*, *8*(1), 19-32. DOI: 10.1080/1364557032000119616

Armstrong, I., Rochnia, N., Harries, C., Bundock, S., & Yorke, J. (2012). The trajectory to diagnosis with pulmonary arterial hypertension: a qualitative study. *BMJ Open, 2*(2). doi:10.1136/bmjopen-2011-000806

Badesch, D.B., Champion, H.C., Sanchez, M.A., Hoeper, M.M., Loyd, J.E., Manes, A., McGoon, M., Naeije, R., Olschewski, H., Oudiz, R. J., & Torbicki, A. (2009). Diagnosis and assessment of pulmonary arterial hypertension. *Journal of the American College of Cardiology, 54*(1 Suppl), S55-66.

Brown, L.M., Chen, H., Halpern, S., Taichman, D., McGoon, M.D., Farber, H.W., Frost, A.E., Liou, T.G., Turner, M., Feldkircher, K., Miller, D.P., & Elliott, C.G. (2011). Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL Registry. *Chest, 140*(1), 19-26.

Canadian Agency for Drugs and Technologies in Health. (2015). CADTH Therapeutic Review Report: Drugs for Pulmonary Arterial Hypertension: Comparative Efficacy, Safety, and Cost-Effectiveness – Recommendations Report. Retrieved from https://www.cadth.ca/sites/default/files/pdf/TR0006_PAH_Recs_Report.pdf

Canadian Organization for Rare Disorders. (2009). Profiles of Rare Diseases. Retrieved from http://www.raredisorders.ca/documents/Rare_Disease_Profiles.pdf

Canadian Organization for Rare Disorders. (2015a). Now is the Time: A Strategy for Rare Diseases is a Strategy for all Canadians. Retrieved from http://www.raredisorders.ca/documents/CORD_Canada_RD_Strategy_22May15.pdf

Canadian Organization for Rare Disorders. (2015b). Strategy for Rare Diseases in Canada. Retrieved from http://raredisorders.ca/documents/CORD_RD-Strategy_16APR15_COMPLETE.pdf

Collier, R. (2012). The downside of genetic screening. *Canadian Medical Association Journal 184*(8): 862-864.

Critchley, W. (n.d.). Strategy for Rare Diseases in Canada. Where are we now? What else is needed? Retrieved from http://www.slideshare.net/raredisorders/wayne-critchley-strategy-for-rare-diseases-in-canada-present

Deano, R.C., Glassner-Kolmin, C., Rubenfire, M., Frost, A., Visovatti, S., McLaughlin, V.V., & Gomberg-Maitland, M. (2013). Referral of patients with pulmonary hypertension diagnoses to tertiary pulmonary hypertension centers: the multicenter RePHerral study. *JAMA internal medicine, 173*(10), 887-893.

Domenighetti, G. (2007). Prognosis, screening, early detection and differentiation of arterial pulmonary hypertension. *Swiss medical weekly, 137*(23-24), 331-336.

Dragusin, R., Petcu P., Lioma C., Larsen B., Jørgensen H.L., Cox I.J., Hansen L.K., Ingwersen P., & Winther O. (2013). Specialized tools are needed when searching the web for rare disease diagnoses. *Rare diseases* 1: e25001-1 – e25001-4.

Educational Initiatives for Physicians. *Journal of Rare Disorders 1*(2), 1-15. Retrieved from http://www.journalofraredisorders.com/

Engel, P., Bagal, S., Broback, M., and Boice, N. (2013). Physician and Patient Perceptions Regarding Physician Training in Rare Diseases: The Need for Stronger Educational Initiatives for Physicians. *Journal of Rare Disorders 1*(2), 1-15. Retrieved from http://www.journalofraredisorders.com/

European Commission. (2013). Rare diseases: How Europe is meeting the challenges. Retrieved from http://ec.europa.eu/research/health/pdf/rare-diseases-how-europe-meeting-challenges_en.pdf

European Commission (2015). ORPHANET portal. Retrieved from http://ec.europa.eu/health/rare_diseases/orphanet/identification/index_en.htm

French National Plan for Rare Diseases 2005-2008. (2004). Retrieved from http://www.orpha.net/actor/EuropaNews/2006/doc/French_National_Plan.pdf

Green, B.N., Johnson, C.D., & Adam, A. (2006). Writing narrative literature reviews for peer-reviewed journals: secrets of the trade. *Journal of chiropractic medicine, 5*(3), 101-117.

Haddad, R.N. & Mielniczuk, L.M. (2015). An evidence-based approach to screening and diagnosis of pulmonary hypertension. *The Canadian journal of cardiology, 31*(4), 382-390.

Humbert, M., Coghlan, G.J., & Khanna, D. (2012). Early detection and management of pulmonary arterial hypertension. *European respiratory review : an official journal of the European Respiratory Society, 21*(126), 306-312.

Janz., N.K., Champion, V.L., Strecher, V.J. (2008) Chapter 3: The Health Belief Model. In K. Glanz, B. Rimer, & F.M. Lewis (Eds.), *Health Behaviour, Health Education; Theory, Research and Practice* (pp. 45-66). San Francisco: Jossey-Bass.

Wong-Rieger, D. (n.d.). Who Needs A 'Canadian Rare Disease Strategy'? Retrieved from http://www.rarediseaseawareness.ca/canadian-plan/who-needs-a-canadian-rare-disease-strategy

Lau, E.M., Humbert, M., Celermajer, D.S. (2015). Early detection of pulmonary arterial hypertension. *Nature reviews. Cardiology, 12*(3), 143-155.

Limb, L., Nutt, S., & Sen, A. (2010). Experiences of Rare Diseases: An Insight from Patients and Families. Retrieved from http://www.raredisease.org.uk/documents/RDUK-Family-Report.pdf

Lougheed, T. (2013). Rare diseases reconsidered. *Canadian Medical Association Journal, 185*(8), E315-E316. doi:10.1503/cmaj.109-4456

Matura, L.A. & Carroll, D.L. (2010). Human responses to pulmonary arterial hypertension: review of the literature. *The Journal of cardiovascular nursing, 25*(5), 420-427.

Mays, N., Roberts, E., & Popay, J. (2001). Synthesising research evidence. In N. Fulop, P. Allen, A. Clarke, & N. Black (Eds.), *Methods for studying the delivery and organisation of health services*. London: Routledge

McGoon, M.D. & Kane, G.C. (2009). Pulmonary hypertension: diagnosis and management. *Mayo Clinic proceedings, 84*(2), 191-207.

McGoon, M., Gutterman, D., Steen, V., Barst, R., McCrory, D.C., Fortin, T.A., & Loyd, J.E. (2004). Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest, 126*(1 Suppl), 14S-34S.

McLaughlin, V.V., Archer, S.L., Badesch, D.B., Barst, R.J., Farber, H.W., Lindner, J.R., Mathier, M.A., McGoon, M.D., Park, M.H., Rosenson, R.S., Rubin, L.J., Tapson, V.F., & Varga, J. (2009). ACCF/AHA 2009 Expert Consensus Document on Pulmonary HypertensionA Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration With the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *Journal of the American College of Cardiology, 53(*17), 1573-1619.

McLaughlin, V.V., Shah, S.J., Souza, R., & Humbert, M. (2015). Management of Pulmonary Arterial Hypertension. *Journal of the American College of Cardiology, 65*(18), 1976-1997.

National Organization for Rare Disorders. (2011). Pulmonary Arterial Hypertension. Retrieved from http///www.rarediseases.org/rare-disease-information/rare-diseases/byID/706/printFullReport

Nuwer, R. (2013, April 16). Crowd diagnosis could spot rare diseases doctors miss. *NewScientist*. Retrieved from http://www.newscientist.com/article/dn23392-crowd-diagnosis-could-spot-rare-diseases-doctors-miss.html#.VZhdSKY6NYU

Orphanet Report Series. (2014, May). Prevalence of rare diseases: Bibliographic data. *Rare Disease collection*. Number 1: alphabetical order of disease or group of diseases. Retrieved from http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

Palevsky, H.I. (2011). The early diagnosis of pulmonary arterial hypertension: can we do better? *Chest, 140*(1), 4.

Preston, I. R. (2013). Properly diagnosing pulmonary arterial hypertension. *The American journal of cardiology, 111*(8 Suppl), 2C-9C.

Pulmonary Hypertension Association. (n.d.). Frequently Asked Questions. The Early Diagnosis Campaign: Sometimes It's PH. Retrieved from http://www.phassociation.org/SometimesItsPH/FAQ

Pulmonary Hypertension Association. (2011). Recommendations for Improving Patient Outcomes. Retrieved from http://www.phaonlineuniv.org/files/pha_white_paper_final.pdf

Pulmonary Hypertension Association of Canada. (2014). The Impact of Pulmonary Hypertension on Canadians: Burden of Illness Survey Summary Report. Retrieved from http://www.phacanada.ca/en/about-ph/boi-report/

Rare Diseases Europe [EURORDIS]. (2009). The Voice of 12,000 Patients. Retrieved from http://www.eurordis.org/IMG/pdf/voice_12000_patients/EURORDISCARE_FULLBOOKr.pdf

Rich, J.D. & Rich, S. (2014). Clinical diagnosis of pulmonary hypertension. *Circulation, 130*(20), 1820-1830.

Rodwell C. & Aymé S., eds. (2014). 2014 Report on the State of the Art of Rare Disease Activities in Europe. Retrieved from http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivitiesFR.pdf

Shire. (2015a). The Global Challenge of Rare Disease Diagnosis: A Policy Briefing. Retrieved from https://www.shire.com/~/media/shire/shireglobal/shirecom/pdffiles/patient/therapeutic%20areas/2015-feb-shire-rarediseaseday-globalchallenge.pdf

Shire. (2015b). Who We Are. Retrieved from https://www.shire.com/who-we-are

Syed, A. M., Camp, R., Mischorr-Boch, C., Houyez, F., & Aro, A.R. (2015). Policy recommendations for rare disease centres of expertise. *Evaluation and program planning* 52: 78-84.

Traill, E.M. (2011). CME Pulmonary arterial hypertension Pulmonary arterial hypertension: An early diagnosis makes a difference. *Journal of the American Academy of Physician Assistants, 24*(5), 30-34.

UK Department of Health. (2013). The UK Strategy for Rare Diseases. Retrieved from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/260562/UK_Strategy_for_Rare_Diseases.pdf

Uman, L.S. (2011). Systematic reviews and meta-analyses. *Journal of the Canadian Academy of Child and Adolescent Psychiatry, 20*(1), 57-59.

World Health Organization. (2013). Priority diseases and reasons for inclusion: Rare diseases. Retrieved from http://www.who.int/medicines/areas/priority_medicines/Ch6_19Rare.pdf?ua=1

Wryobeck, J.M., Lippo, G., McLaughlin, V., Riba, M., & Rubenfire, M. (2007). Psychosocial aspects of pulmonary hypertension: a review. *Psychosomatics, 48*(6), 467-475.

Appendix

Post-Reflection

I found my practicum and capstone experience both motivating and frustrating. The people I interacted with were fantastic, and the goals being worked towards hold real-world implications that give a strong value to the work I've done. However the dynamics of working to create change across stakeholders proved more difficult than I had initially envisioned.

I was not familiar with the PH community when I first started my practicum, but I quickly found that in the community was very passionate about creating meaningful change towards improved health outcomes. This energy allowed me to find value in almost all the work I did, including side projects not directly related to my practicum or capstone. I believe I helped significantly contribute to an atmosphere of creativity and problem solving towards meeting the goals of PHA Canada, even though I had minimal experience with PH.

Working with a small organization allowed for significant feedback and collaboration on projects, but it also meant that there were limited resources to draw on. Of particular frustration was the difficulty encountered to involve the medical community in early diagnosis program planning. Feedback was very difficult to obtain from the medical community, even by those who are heavily involved in the care of PH. While this is not necessarily surprising, as physicians and nurses are very busy professionals, the extent of the difficulty to get them involved was almost stifling at times. This difficulty to communicate with the medical community, especially in the short time frame of my practicum, emphasized the need for prolonged relationship building when a goal is behaviour or policy change.

The development of this capstone evolved through many different possible topics. Through discussions with my supervisor, Kitty Corbett, she helped me to understand how to approach a problem such as early diagnosis from the perspective of theories of change and how to establish what the real 'needs' of such a problem are.

This capstone also highlights the need for knowledge translation between different stakeholders. There is a distinct separation between basic researchers, medical professionals, advocacy groups, and policy makers. Each has their own goals, and often work independently towards those goals. They also offer recommendations to other stakeholder groups, but without the appropriate understanding of what those other groups need or respond to. For example if advocacy groups want the Canadian government to help raise the awareness of PH, they need to appeal to what the government holds as a priority (e.g. budget concerns), not necessarily what they feel is the priority (e.g. quality of life of PH patients). This framework of knowledge translation will be a part of my professional mentality going forward.

Overall I feel that this experience has broadened my awareness regarding how to approach a large, multi-stakeholder problem, and how to critically evaluate perceptions surrounding such a problem, including my own.