

RESPIPLUS™ PRESENTS

AUGUST 2021

# CANADIAN CHRONIC COUGH INITIATIVE





RESPIPLUS

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**AUGUST 2021**

*The content of this report are not to be used as guidelines and should not influence any patient treatment plans. The following is based on the opinions of the expert panel members who have in interest in chronic cough. It is for informational purposes only. It is not intended to provide medical or professional advice. Medical advice should be sought-after from a qualified health care professional for any questions. Reliance on any information disclaimed in this report is solely at your own risk. We do not assume any responsibility or legal liability for the accuracy, completeness, timeliness or quality of any information in this report.*

*In order to maintain anonymity and protect the privacy of individuals interviewed during this process, some names and identifying details have been changed.*

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This report is available on the website [www.chroniclungdiseases.com](http://www.chroniclungdiseases.com)

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# ABOUT THE CHRONIC COUGH REPORT



## A LITTLE BIT ABOUT OUR PROJECT

The Chronic Cough Report, is a report overseen by a panel of clinicians, academics and patients in the field of respiratory medicine and chronic cough. The report has been prepared and published by RESPIPLUS, a non-profit organization with more than 20 years expertise in developing self-management programs for patients in the field of respiratory medicine. The report was funded by a non-restrictive educational grant from Merck.

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# PANEL & RESPIPLUS TEAM MEMBERS

## STEERING COMMITTEE

**Jacky Smith**, MB, ChB, FRCP, PhD | Respiriologist | Panel Lead

**Louis-Philippe Boulet**, MD, FRCPC | Respiriologist

**Jean Bourbeau**, MD, MSc, FRCPC | Respiriologist

**Imran Satia**, M.A MB BChir (cantab) MRCP PhD | Respiriologist

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**Cheryl Connors** | Executive Director, CNRC

**Gail Attara** | President & CEO, Gastrointestinal Society

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## RESPIPLUS TEAM

**Maria Sedeno** | Executive Director

**Becky Zucco** | Program Director

**Emily Horvat** | Senior Project Manager

**Patrick Rich** | Medical Writer

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# EXECUTIVE SUMMARY

Cough is the most common presenting symptom in the offices of both primary care physicians and respiratory specialists and is often a common presenting symptom for other specialists and health care professionals. Chronic cough – cough that lasts for 8 weeks or more – is one of the more challenging medical conditions to screen for and to treat because it often has multiple differential diagnoses and is occasionally due to more than one condition. For patients, chronic cough can be frustrating or even disabling and have a major impact on their quality of life.

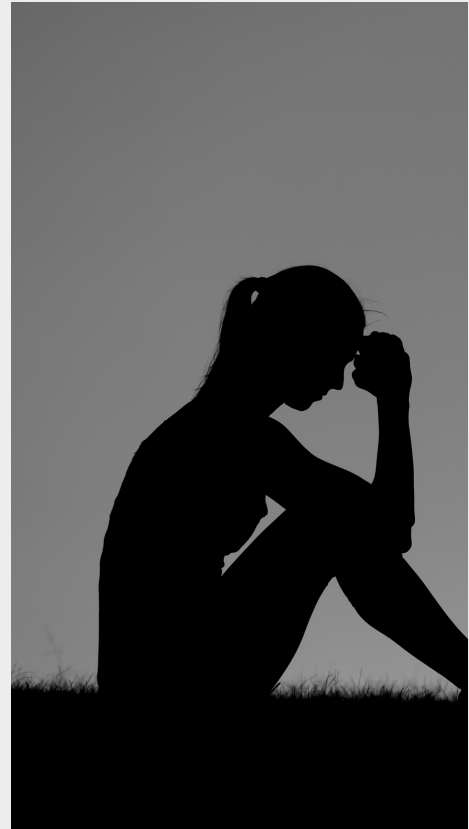
This report has been prepared by RESPIPLUS. Under the direction of leading clinicians and academics in the field of chronic cough and input from patients, RESPIPLUS has developed this report to raise awareness about this common but underdiagnosed and often improperly managed condition.

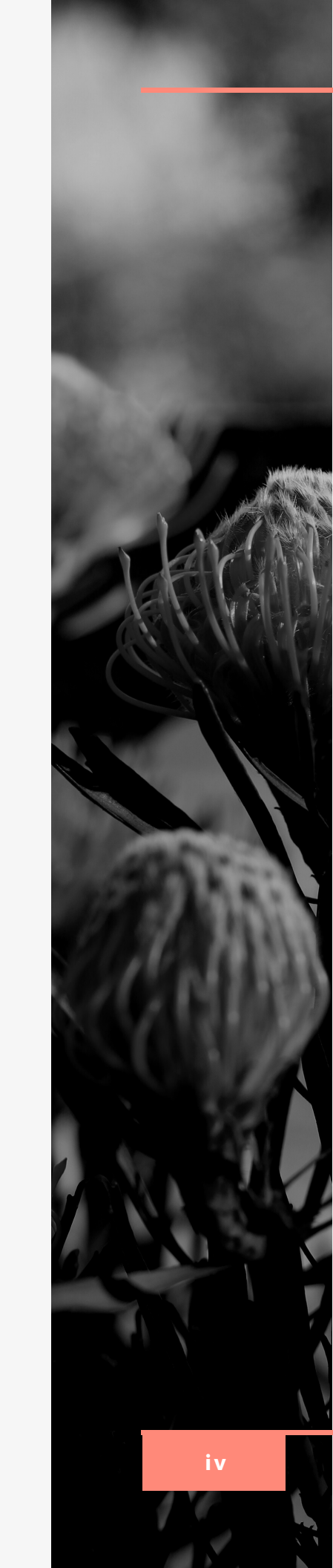
Various estimates for the global prevalence of chronic cough place the percentage from 5% to as high as 12%. Age- and gender-related differences in the incidence of chronic cough have also been noted with the condition being more common in females and in older populations.

## THE IMPACT OF CHRONIC COUGH HAS BEEN ELOQUENTLY EXPRESSED BY SOME PATIENTS INTERVIEWED FOR THIS REPORT.

*"I don't remember ever not coughing. I also wake up choking in my sleep. It's really, really hard to be in public, during COVID, when you could have a cough attack. I've been in places and having to run out of the store just so I can have my cough attack, because everybody looks at you like you're infectious and have COVID."*

- Cathy, 53





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Chronic cough places a burden on the health care system as a whole as patients often have to seek repeated visits with family physicians and various specialists. In a recent survey performed in 1,120 people with chronic cough, more than 70% of the subjects had sought more than 3 consultations in connection with their chronic cough.

At its most severe, chronic cough can lead to depression, anxiety, urinary incontinence, syncope, rib fractures, and dysphonia. Chronic cough has also been associated with sleep disorders and voice disorders.

For health care professionals responsible for screening, diagnosing and treating chronic cough there are a number of challenges, not the least of which is in properly defining the condition. Clinicians, researchers and guidelines have adopted a definition of chronic cough as one that has lasted 8 weeks or more in adults and 4 weeks or more in children. European Respiratory Society guidelines state: "The failure to recognize that the patient is suffering from the syndrome of chronic cough may lead to misdiagnosis with the patient labelled as suffering from recurrent chest infections, treatment resistant asthma or exacerbations of chronic obstructive pulmonary disease (COPD)."

Chronic cough can be caused by exposure to noxious stimuli such as cigarette smoke or air pollution or be caused by excessive stimulation of a normal cough reflex which can take place following inhalation of a

foreign body. It is also a symptom of several well-recognized chronic conditions.

1. Asthma
2. Non-asthmatic eosinophilic bronchitis (NAEB)
3. Gastroesophageal Reflux Disease (GERD)
4. Postnasal drip syndrome/ upper airways cough syndrome (UACS)

It is when the cough cannot be adequately explained by these conditions that issues become more complicated. A proportion of patients with chronic cough, particularly among adults, have persistent cough despite undergoing numerous tests and various treatments according to clinical practice guidelines. This condition has been described using a number of terms including idiopathic chronic cough, unexplained chronic cough and chronic refractory cough. One found 42% of patients presenting to a UK cough clinic have unexplained cough.

A growing understanding of the etiology of chronic cough is helping provide new approaches for therapy and defining targets for medications which could help treat the condition. The concept of cough hypersensitivity syndrome is now used to explain many cases of chronic cough and was first articulated by the European Respiratory Society (ERS) in 2011. Cough hypersensitivity syndrome is associated with hypersensitivity of the larynx and upper airways.

For family physicians, nurse practitioners, respiratory

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therapists, respirologists and other specialists who deal with chronic cough in Canada, the challenges of properly diagnosing and treating chronic cough are many. Canadian family physicians report the frustrations felt by both themselves and patients when chronic cough is not properly investigated or treated. Even specialists in managing respiratory health report many patients are not properly diagnosed and end up being told that they will have to live with their condition.

Recent review articles propose a stepwise approach to assessing and managing chronic cough as follows:

1. Exclude and treat obvious causes
2. Investigate and treat common triggers of chronic cough
3. Exclude and treat rarer triggers of chronic cough
4. Manage unexplained chronic cough with speech therapy and/or neuromodulatory treatments

With no approved medications for uncontrolled chronic cough most specialist clinics management relies on using interventions with evidence of efficacy in clinical trials. In the UK, low dose morphine sulphate (MST) is often used, however, concerns about dependency have limited this use in Canada. Gabapentin or pregabalin have also been shown to be effective but can have significant side effects. Amitriptyline has also been used. Some patients may select speech and language therapy instead of medication. This intervention involves a multi-modality approach of education, reducing laryngeal irritation with relaxation exercises, cough suppression techniques and counselling. Those that benefit often have speech and language therapy as an adjunct to medication.

New therapies under investigation for treatment of chronic cough target specific receptors or channels in the peripheral sensory neurons.

The drug holding the most promise to be

the first therapy licensed for chronic refractory cough is gefapixant (MK-7264/AF-219) a selective antagonist of the P2X3 receptor. Phase 1 and 2 clinical trials evaluated more than 300 patients and demonstrated positive results for decreased mean daytime cough frequency, 24-hour cough frequency, and awake cough frequency.

Following the positive results from phase 1 and 2 trials, investigation of the drug continued with phase 3 clinical trials. Two parallel, double-blind, randomized, placebo-controlled trials (COUGH-1 and COUGH-2) were conducted to assess the efficacy and safety of gefapixant (15 mg or 45 mg twice daily) in patients with chronic cough. Results of COUGH-1 and COUGH-2 showed a statistically significant reduction in 24-hour cough frequency versus placebo at 12 weeks and 24 weeks in patients treated with gefapixant 45 mg twice daily. AEs reported were consistent with previous trials (dysgeusia occurring at a higher incidence with gefapixant 45 mg twice daily), and discontinuations of study drugs due to AEs were more frequent in the gefapixant 45 mg treatment arms.

In Canada, the ideal model of care for chronic cough involves appropriate and timely access to:

- Primary care - primary care physicians or nurse practitioners and pharmacists (screening)
- Secondary care - specialists (usually respirologists but also allergists, gastroenterologists and otolaryngologists)
- Tertiary care - cough clinics
- Other health care professionals - speech and language therapists, respiratory therapists, and specialized respiratory educators

Initial workup, diagnosis and treatment would be performed by primary care providers with referral to specialists when necessary. Patients with unexplained chronic cough or other more complex or





severe cases would be referred to interdisciplinary cough clinics. In addition to providing care, these clinics would also have a role in setting practice standards, conducting research, and training future respiratory specialists.

A consensus that patients with chronic cough should only wait two weeks to see a primary care provider and four months to see a specialist once referred for chronic cough are tempered with the recognition that wait times are currently often far longer due to the COVID-19 pandemic and the regional shortages of both general practitioners and specialists.

Given the complex and multifactorial nature of managing chronic cough it would be important that patients be fully engaged in their own care and have the knowledge and information to make important decisions about treatment. Physicians and all other professionals involved in providing care similarly would require the necessary education and training to provide the necessary care.

Patient education is seen as a critically important factor in better managing chronic cough in Canada.

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**“I THINK WE HAVE TO MAKE THEM AWARE THAT THEY'VE GOT A CONDITION AND THAT THERE'S SOMETHING THAT CAN BE DONE ABOUT IT, RATHER THAN JUST SUFFERING WITH IT,”**

**- Dr. Alan Kaplan (Family Physician)**

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Reference has also been made to the need to educate patients about non-pharmacologic approaches to managing chronic cough as well as drug therapies.

**FOR THE PUBLIC AND PATIENTS A VARIETY OF INFORMATIONAL AND EDUCATIONAL TOOLS SHOULD BE CONSIDERED INCLUDING THE FOLLOWING:**

- Self-help tools
- Online information modules
- Printed information sheets
- Podcasts and videos
- Webinars provided by experts

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# INTRODUCTION

**COUGH IS THE MOST COMMON PRESENTING SYMPTOM IN THE OFFICES OF BOTH PRIMARY CARE PHYSICIANS AND RESPIRATORY SPECIALISTS.<sup>1,2</sup>**



Chronic cough – cough that lasts for 8 weeks or more – is one of the more challenging medical conditions to screen for and treat because it often has multiple differential diagnoses and is occasionally due to more than one condition. For patients, chronic cough can be frustrating or even disabling and have a major impact on their quality of life.

As Dr. Jacklyn Smith, professor of respiratory medicine at the University of Manchester, UK and an authority on chronic cough and her colleague Dr. Ashley Woodcock write:

**“The disabling effects of chronic cough are understandable, given that patients with the condition cough hundreds or even thousands of times per day; this is similar to the frequency of coughing that occurs in acute viral cough, but chronic cough can persist for months or years.”<sup>3</sup>**

Various estimates exist for the global prevalence of chronic cough place the percentage from 5% to as high as 12%. A systematic review and meta-analysis of 90 articles published in 2015 showed an overall prevalence of chronic cough of 9.6%.<sup>4</sup> That analysis showed the prevalence to be higher in Oceania, Europe and the US than in Asia and Africa. Data from Canada are limited but an as-yet unpublished analysis conducted using the Canadian Longitudinal Study of Aging with a cohort of about 30,000 patients placed the prevalence of chronic cough at about 14.5%-15% among Caucasians but 7% of non-Caucasians.<sup>5</sup>

Age- and gender-related differences in the incidence of chronic cough have also been noted. A 2014 review of the age and sex of 10,032 unselected referrals to 11 cough clinics located at various locations around the world found the most common age of presentation was 60-69 years.<sup>6</sup> Two-thirds of the patients attending the clinics were females and this female

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preponderance was consistent in each individual cough clinic. The authors stated that the age and sex distribution in this large group of patients across three continents “was strikingly uniform. The over representation of females in the patient population presenting with a primary complaint of chronic cough has been long recognized and is perhaps the most striking example of sex-related differences in respiratory pathophysiology. Whilst often mentioned in the discussion of papers concerned with cough, it is frequently ignored in reviews dealing with the structure and function of the male and female respiratory tract.”

Chronic cough places a burden on the health care system as a whole as patients often have to seek repeated visits with family physicians and various specialists. In a recent survey performed in 1,120 people with chronic cough, more than 70% of the subjects had more than 3 consultations in connection with their chronic cough; a diagnosis was given in only 53% of the cases. In addition, only 30% of the subjects felt that “their doctor had dealt with their cough thoroughly” and the medication was judged as having limited (57%) or no effectiveness (36%).<sup>7</sup>

Dr. Peter Dicpinigaitis, professor of medicine at Albert Einstein College of Medicine, and director of the Montefiore Cough Center Montefiore Medical Center Bronx, New York noted that in the US alone, there were 21 million outpatient consultations for cough in 2015.<sup>8</sup> “The impact of chronic cough on the healthcare system is

multifactorial,” he writes. “Patients are often referred to several specialists and occasionally obtain multiple opinions from physicians within the same specialty. This can lead to unnecessary repeat testing, increased costs to both payers and patients, less time for patients with other symptoms, and exposure to polypharmacy as well as possible adverse events (AEs) of these medications. Because there can be potentially life-threatening etiologies to explain the chronic cough, it is also not a symptom that should be easily dismissed.” In the US, it is estimated that more than \$7 billion is spent each year on over-the-counter cough and cold medications, most of which contain dextromethorphan, which has very limited if any clinical effectiveness in controlling chronic cough.<sup>9</sup>

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# PATIENT EXPERIENCE

As noted above, chronic cough can have a significant impact on daily living for individuals and be disabling in nature. "Patients are embarrassed socially and in the workplace. They are physically exhausted by the frequent prolonged coughing bouts," writes Dr. Imran Satia, assistant professor at McMaster University, Hamilton and an expert in cough and his colleagues.<sup>10</sup> At its most severe, chronic cough can lead to depression, anxiety, urinary incontinence, syncope, rib fractures, and dysphonia.<sup>11</sup>

Chronic cough has also been associated with sleep disorders and speech disorders. And as Dr. Dicipinigaitis notes "the impact of chronic cough on a patient's quality of life (QoL) is frequently underappreciated by healthcare professionals."<sup>12</sup>

The following direct quotes from Canadians reflect the views and experiences of those with chronic cough and its impact:<sup>13</sup>

*"I'm from a wonderful tropical country called Trinidad. At age 18 I saw snow for the first time in my life and I ended up getting bronchitis and started coughing and I have been coughing and getting coughing fits ever since. I've seen tons of family doctors and it went through to the stage where we did everything and then we finally just gave up. The strange thing is, every summer, I'm fine. When it gets hot outside, and wonderful, I don't cough at all. For two months of the year, I can be normal. And that's when I actually live and I go, I go away, I do family vacations, I do anything that I want to do. I squeeze it in those two months, because the rest of the year, coughing, it's not nice to go away or to do anything. I've been through SARS, swine flu and you go out in public and you cough and the public freaks out on you. I've been called some really disgusting names. With COVID it is pretty bad. I've been stuck at home for a year, and I very rarely go out. I work at home. I really don't want that reaction when I go out and have that coughing fit in the middle of a store or the supermarket or whatever."*

*- Shania, 47 years old*

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## "I DON'T REMEMBER EVER NOT COUGHING."

*"Certainly cold is a huge trigger for me. For me, it's really hard to be outside when it's cold and be able to breathe. I also wake up choking from my sleep. I don't leave home without lots of cough drops and I have to have water with me. It's really, really hard to be in public, during COVID, when you could have a cough attack. I've been places where, I'm paying at the grocery store, and I can't talk because I'm trying so hard not to cough so that I don't breathe, and I'm having to run out of the store just so I can have my cough attack, because everybody looks at you like of course you're infectious and have COVID. It's embarrassing. I'll be on a call and a meeting, and I've had to throw a phone down and say, I'm sorry, because you can't breathe, and you're choking. There's a lot of emotional stigma to all of that. For women who cough, particularly if you've had a baby, there is an additional layer to what coughing will cause that no amount of kegels will stop from happening. So it's all embarrassing, and it gets minimized by and you feel like 'I really don't have anything wrong with me'. But you do. It really impacts your quality of life."*

- Cathy, 53

*"As a young girl, I had some breathing issues and back then you didn't have a nebulizer at home, you had to go to the hospital for treatment. They decided I had asthma. There was no actual testing done but I was on corticosteroids and salbutamol for probably about 30 years. Then I started to have the cough getting worse and worse. I was lucky enough to start working in a spirometry clinic with a respirologist. During one of our clinic days, I went into a coughing fit or attack. And he was like, 'Oh my god, what is that?' So we did the spirometry testing and lo and behold, I have no asthma. We did a methacholine challenge. That was normal. So we did CT scans, we did spirometry, allergy testing, we did immunoglobulin testing, we checked for an autoimmune disorder. I was sent to an ENT specialist, an immunotherapy specialist, as well as an allergist. Everything came back absolutely fine. I am absolutely fine, except that when I get into the coughing fit, I can't stop. At a specialized clinic they did sputum induction, as well as more blood work. And long story short, the final diagnosis was a neuropathic cough with an increase in epithelial cells in the sputum. Every single day, I will have at least one to two coughing attacks at our office. Now the staff knows just to leave me alone. As long as I've got water, I'm good to go. I still don't have really anything to fix it. I use cough drops, I use my water."*

- Jo-Anne, 45

*"I've had asthma for many, many years and I've been well controlled and a runner. About five years ago, I started a dry cough and it went on for a couple months. Fortunately, I work in a clinic with respirology and I was under the care of a respirologist. He did all the bloodwork, all the inflammatory markers, CAT scans, bronchoscopy and he diagnosed me with Allergic bronchopulmonary aspergillosis. After months of treatment of antibiotics and prednisone it resolved. But it took a full year of treatment before the cough really resolved and it really impacted my life in that I wasn't able to do the things that I wanted to do because of this cough. I couldn't run because of all the medications they had me on. So it certainly impacted my quality of life and it affected my work life. When you're coughing like that and you're at work, people think that you're dying."*

- Rachel, 56

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# DEFINING CHRONIC COUGH

For health care professionals responsible for diagnosing and treating chronic cough there are a number of challenges, not the least of which is in properly defining the condition.

As the European Respiratory Society (ERS) clinical practice guidelines state: “to define a chronic cough on the basis of longevity is clearly an arbitrary paradigm.”<sup>14</sup> However clinicians, researchers and guidelines have adopted a definition of chronic cough as one that has lasted 8 weeks or more in adults and 4 weeks or more in children.

The ERS guidelines note “while some patients cough on a daily basis over many years, for others the disease has a relapsing and remitting course, making a definition based purely on a temporal basis difficult to sustain. The failure to recognize that the patient is suffering from the syndrome of chronic cough may lead to misdiagnosis with the patient labelled as suffering from recurrent chest infections, treatment resistant asthma or exacerbations of chronic obstructive pulmonary disease (COPD).”

Chronic cough can be caused by exposure to noxious stimuli such as cigarette smoke or air pollution or be caused by excessive stimulation of a normal cough reflex such as from a cold or following inhalation of a foreign body. It is also a symptom of several well-recognized chronic conditions.

- Asthma
- Non-asthmatic eosinophilic bronchitis (NAEB)
- Gastroesophageal Reflux Disease (GERD)
- Postnasal drip syndrome/upper airways cough syndrome (UACS)

The concept of UACS has evolved in recent years from the earlier categorization of postnasal drip syndrome. A 2018 BMJ Best Practice review, notes that within a population of patients with chronic cough it is estimated that approximately 10% to 70% of cases are associated with upper airway abnormalities that fulfill the criteria for upper airway cough syndrome.<sup>15</sup> However the authors of that review also wrote that “it is important to be aware that some physicians with an interest in chronic cough have challenged the existence of UACS as a distinct clinical entity. The diagnostic precision of clinical assessment for this syndrome has also been challenged. Expert opinion is moving towards a description of many of the features of UACS as being part of a general cough hypersensitivity syndrome.”

Chronic cough is also known to be a common side-effect of taking angiotensin-converting enzyme (ACE) inhibitors.

In addition, chronic cough can be associated with a number of other respiratory or other diseases including cystic fibrosis, congestive heart failure and lung cancer. Chronic cough can also develop after an infection or is associated with the use of certain medications.

It is when the cough cannot be adequately explained by these conditions that issues become more complicated. A proportion of patients with chronic cough, particularly among adults, have persistent cough despite undergoing number tests and various treatments according to clinical practice guidelines. This condition has been

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described using a number of terms including idiopathic chronic cough, unexplained chronic cough and chronic refractory cough. A 2005 study found 42% of patients presenting to a UK cough clinic have unexplained cough<sup>16</sup> although Dr. Smith notes the frequency is unclear among patients seen in primary care practices.

The linguistic challenges involved in defining unexplained chronic cough (UCC) are well demonstrated in this statement contained in the clinical practice guidelines published by the American College of Chest Physicians (ACCP) in 2016.<sup>17</sup>

“Patients can be assessed, investigated, and identified as having conditions that are known to be associated with chronic cough.

but the cough persists after treatment of these conditions, indicating refractory chronic cough. When patients with chronic cough undergo investigation and the results of these investigations do not identify a cause of their cough, this condition is termed UCC. Some patients may not have investigations for chronic cough due to lack of resources and undergo empiric trials of therapy based on a history of associated symptoms only. This can be challenging because without objective investigations/evidence it is unclear if chronic cough is refractory to treatment or if it is truly unexplained chronic cough. Despite these descriptive semantics, there are so many shared clinical features of RCC/UCC that many consider this to be the same condition because they have a shared underlying pathology, i.e., neuronal dysregulation.”

### DR. IMRAN SATIA EXPLAINS THAT PROPERLY DEFINING UNEXPLAINED CHRONIC COUGH CAN OFTEN DEPEND ON AVAILABLE RESOURCES:

There's a lot of debate going on about the nomenclature. Some people are saying, “Well, let's just keep it simple and call it chronic cough, which is more than eight weeks”. That's a good way of spreading the fishing net and catching these people and then hopefully, being able to work out what it is that's causing the cough. The first problem with terms such as refractory or unexplained chronic cough is it depends on what resources you have available to make a diagnosis. For example, in certain situations or certain hospitals, you might have all the tests available, to be able to say “Well, I found a cause and I think this is eosinophilic bronchitis, and therefore this cough is refractory to treatment for eosinophilic bronchitis”. Whereas that same patient, had you not had access to sputum eosinophilia would have been labelled not as a refractory chronic cough but as unexplained chronic cough because the test was not available. The second problem is that many patients with refractory and unexplained chronic cough have a mainly dry cough which is irritating and it's often triggered by changes in temperature, chemical irritants or low levels of mechanical stimulation. We've tried to label these features as cough hypersensitivity syndrome, that is, a neuronal hyperresponsiveness or sensitivity. So when somebody says someone has an ‘unexplained’ chronic cough, it's very difficult to say, ‘well, we're not saying it's unexplained we're saying it's chronic cough. But you have a sensory neuronal problem.’ Does that mean it's truly unexplained, because we've just explained it?

Dr. Satia said the issue of unexplained chronic cough can also be unsettling for patients. “If I tell them you've got unexplained chronic cough, this can be interpreted as ‘no reason’ for cough, it's a bit of an anticlimax. Yet, we do know that there is an underlying patho-biological reason most likely due to neuronal hypersensitivity either in the peripheral nervous system, or the central nervous system. So this is a bit of a CATCH-22 situation where although we have these terminologies such as unexplained chronic cough, from the patient's perspective it can be quite counterintuitive or problematic to understand.”

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# ETIOLOGY & PATHOPHYSIOLOGY

## **A GROWING UNDERSTANDING OF THE ETIOLOGY OF CHRONIC COUGH IS HELPING PROVIDE NEW APPROACHES FOR THERAPY AND DEFINING TARGETS FOR MEDICATIONS WHICH COULD HELP TREAT THE CONDITION.**

As noted in the European Respiratory Society guidelines, cough is a vagal reflex evoked by stimulation of afferents carried by the tenth cranial nerve, with their receptive fields primarily in the larynx and conducting airways. Noxious stimuli (e.g. gastric fluid, protons, cigarette smoke) are detected through receptors and ion channels (e.g. TRPV1, TRPA1, TRPV4, ASIC, P2X3) localized to vagal afferent nerve terminations in the airway's mucosa. The vagal afferent nerves regulating cough are polymodal and respond to a variety of different chemical and mechanical stimuli.

The cough reflex is thought to involve two main subtypes of sensory vagal afferent nerves. The first subtype is c-fibres; these form networks of unmyelinated nerves throughout the airways and are characteristically sensitive to capsaicin (chili pepper extract) through activation of the transient receptor potential vanilloid type 1 (TRPV1) receptor and other irritant chemicals. They can also respond to other stimuli such as heat, acidity and inflammatory mediators. The second type, myelinated sub-epithelial A $\delta$  fibres, are found in the proximal airways and respond to mechanical stimuli, osmolarity and acidity but do not typically express TRPV1, and are normally insensitive to capsaicin and inflammatory mediators.

The concept of cough hypersensitivity syndrome is now used to explain many cases of chronic cough and was first articulated by the European Respiratory Society (ERS) in 2011 based on a literature

review and input from 44 key opinion leaders in respiratory medicine. Cough hypersensitivity syndrome is associated with hypersensitivity of the larynx and upper airways. It is described as a disorder of sensory airway nerves caused by hypersensitivity to innocuous irritants linked to an upregulation of mucosal cough receptors, including the receptor channel transient receptor potential vanilloid (TRPV) type 1, a cough receptor triggering afferent nerve activity in response to cough-provoking stimuli. To quote the 2020 ERS guidelines on chronic cough: "The cough hypersensitivity syndrome has been adopted as an overarching diagnosis with the different phenotypes dependent on the type and location of the inflammation seen. Both central and peripheral mechanisms have been postulated for cough reflex hypersensitivity." However, in a 2016 review article, Dr. Satia and colleagues write that "evidence from experimentally evoked cough suggests that the neuronal pathways exhibit hyper-responsiveness rather than hypersensitivity."

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# DIAGNOSIS & TREATMENT

For family physicians, nurse practitioners, respiratory therapists, respirologists and other specialists who deal with chronic cough in Canada, the challenges of properly diagnosing and treating chronic cough go far beyond definitional issues. A sample of recent comments follows from Canadian physicians and other providers follows here:

*We see chronic cough and we try our little bag of tricks. Then when we run out of tricks we don't even refer patients. We just sort of give up in primary care, because we figured there's nothing else. We've tried PPIs (proton pump inhibitors), we've tried the asthma route, and then we're just exhausted. By that time the patient has given up as well because nothing is working. It becomes a dead end and they know not to come to me anymore. But unfortunately, they also have nowhere to turn.*

- Dr. Peter Lin, family physician

*In the real world of pharmacy in Quebec I see chronic cough patients each and every day but with no solution.*

- Denis Villeneuve, pharmacist

*I have worked in both urban and rural clinics, with this type of complaint of chronic cough, and it's very frustrating when you can't seem to help them. I think of one patient in particular. She had a diagnosis of asthma and she had maxed out on treatment but the cough continued. It was chalked up as a mental health issue but no other treatment was offered. And I felt that she wasn't heard, because she knew that it was not her asthma causing this cough, it was something beyond her asthma causing the cough. And not having any resolution, that really impacted me.*

- Angela Taylor, respiratory therapist

*Very often there is a huge care gap in regard to the diagnosis of the cause of cough. Some primary care physicians sometimes have difficulty investigating the cough. Even specialists sometimes do a baseline evaluation and say "Well, unfortunately, you tried everything and I can't do anything for your cough. You just have to keep coughing and you have to live with it."*

- Dr. Louis-Philippe Boulet, respirologist



*I've heard this kind of story (of a patient with an unresolved chronic cough) so many times that the initial shock of hearing this kind of things has almost numbed in me. I just finished my clinic and I had 10 patients with similar stories. Many of our patients with chronic cough have spent years in the wilderness because nobody wants to take ownership to solve the problem. I often find my own colleagues and friends who are respiratory physicians don't want to, in the long term, look after and manage patients with chronic cough, because they find it difficult and don't know what to do sometimes. That is quite common for conditions which are poorly understood and no licensed treatments. The treatments we offer are 'off-label' and have significant side effects and burden. I'm trying to tell people that this is a real problem. Chronic cough is a pathological disorder, it's not just in people's head. There is neurophysiological evidence, there's research backing, and we can show you the evidence.*

- Dr. Imran Satia, respirologist

*It (chronic cough) is a very common clinical problem that we all face and I obviously see a fair bit of cough in my general respirology clinic. Unfortunately, I see many of the same patients over and over again, when they get re-referred by family doctors two and three years later with the same problem they had when I first saw them, with none of the things I recommended having been done in the interim.*

- Dr. Paul Hernandez, respirologist

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# CHRONIC COUGH MANAGEMENT

RECENT REVIEW ARTICLES PROPOSE A STEPWISE APPROACH TO ASSESSING AND MANAGING CHRONIC COUGH. THE INFORMATION BELOW IS BASED ON A SUMMARY OF INFORMATION FROM A 2016 ARTICLE BY DR. SATIA AND COLLEAGUES FROM THE UNIVERSITY OF MANCHESTER AND MANCHESTER ACADEMIC HEALTH SCIENCES CENTRE.<sup>20</sup>

1. Exclude and treat obvious causes
2. Investigate and treat common triggers of chronic cough
3. Exclude and treat rarer triggers of chronic cough
4. Manage unexplained chronic cough with neuromodulatory treatments

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# 1. EXCLUDE & TREAT OBVIOUS CAUSES



A detailed history and examination should be undertaken to identify obvious causes and exclude serious pathologies, such as lung cancer. Smoking, even in otherwise healthy subjects, has now been shown to be associated with an increased frequency of chronic cough.

**About 15% of patients on an angiotensin-converting enzyme inhibitor may develop a chronic cough and changing to the alternative angiotensin receptor blocker would be appropriate.**

For patients with chronic cough, an initial evaluation should also include a chest radiograph and spirometry.

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## 2. INVESTIGATE & TREAT COMMON TRIGGERS OF CHRONIC COUGH

If the chest radiograph, spirometry and clinical examination are normal, then investigations for asthma, GERD and rhinosinusitis should be considered. Although most patients with asthma have a history of wheeze and shortness of breath as the predominant feature, some patients have cough as the key feature and have been previously coined 'cough-variant asthma'. Objective evidence of asthma requires evidence of variable airflow obstruction and bronchial hyper-responsiveness (BHR) may be required using either methacholine or histamine inhalational challenge. These tests are not always available in a secondary care setting, hence a treatment trial of inhaled corticosteroids for 6 weeks is often a more pragmatic approach.

### A NOTE ON TRIALS

As a trial of inhaler therapy can be limited by the patient's technique and compliance an alternative is to prescribe 14 days of oral steroids, prednisone 30 mg daily is our preference. However, a dramatic improvement in cough still leaves some diagnostic uncertainty; a response to inhaled therapy suggests either asthma or eosinophilic bronchitis (EB) and a response to oral steroids could also indicate allergic nasal disease or interstitial lung diseases. Elevated eosinophils (>3%) in the airways in the absence of BHR suggests EB, which has been reported in up to 13% of patients attending cough clinics. This can be evaluated in samples of induced sputum or from broncho-alveolar lavage (BAL) performed at bronchoscopy.

Overall, the key recommendation is that inhaled steroids be trialed in patients who have evidence of BHR or airway eosinophilia in sputum, BAL or exhaled nitric oxide. Objectively investigating GERD is a challenge and previous guidelines advised empirical acid suppression treatment with proton pump inhibitors (PPIs). However, a Cochrane review<sup>21</sup> of PPIs for managing chronic cough in adults, said there is insufficient evidence to conclude definitely that GERD treatment with PPI is universally beneficial for cough associated with GERD'. Those with objective evidence of increased esophageal acid exposure on pH monitoring or complained of heartburn were most likely to benefit from proton pump inhibitor (PPI) therapy in a retrospective review of the PPI studies. Patients with chronic cough also often report sensations of post-nasal drip, so guidelines recommend nasal corticosteroids and anti-histamines for those thought to have underlying allergic rhinitis and antibiotics/decongestants for sinusitis. Many patients with chronic cough are often assessed by ENT specialists and, upon inspection, their larynxes are found to be red and inflamed; this is often attributed to laryngopharyngeal reflux (LPR) secondary to gastric refluxate reaching the larynx. However, evidence of gastric reflux reaching the larynx is lacking and patients who are often coughing hundreds of times may show signs of trauma to the larynx.

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### 3. EXCLUDE & TREAT RARER TRIGGERS OF CHRONIC COUGH

For those without a clear diagnosis or chronic cough that is refractory to treatment of associated conditions, it is important to exclude rarer conditions by performing a high-resolution computerized tomography scan of the chest. This can reveal interstitial lung diseases not easily visible on chest radiograph, e.g. pulmonary fibrosis, sarcoidosis and bronchiectasis. When other

investigations are normal, bronchoscopy can be performed to assess vocal cord movements, identify tracheobronchomalacia or tracheopathia osteochondroplastica and take BAL and biopsies to evaluate eosinophils. Bronchoscopy can also reveal naso-pharyngeal pathologies such rhinitis, polyps and large tonsils, which the patient may benefit from having removed.



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## 4. MANAGE UNCONTROLLED CHRONIC COUGH WITH NEUROMODULATORY TREATMENTS

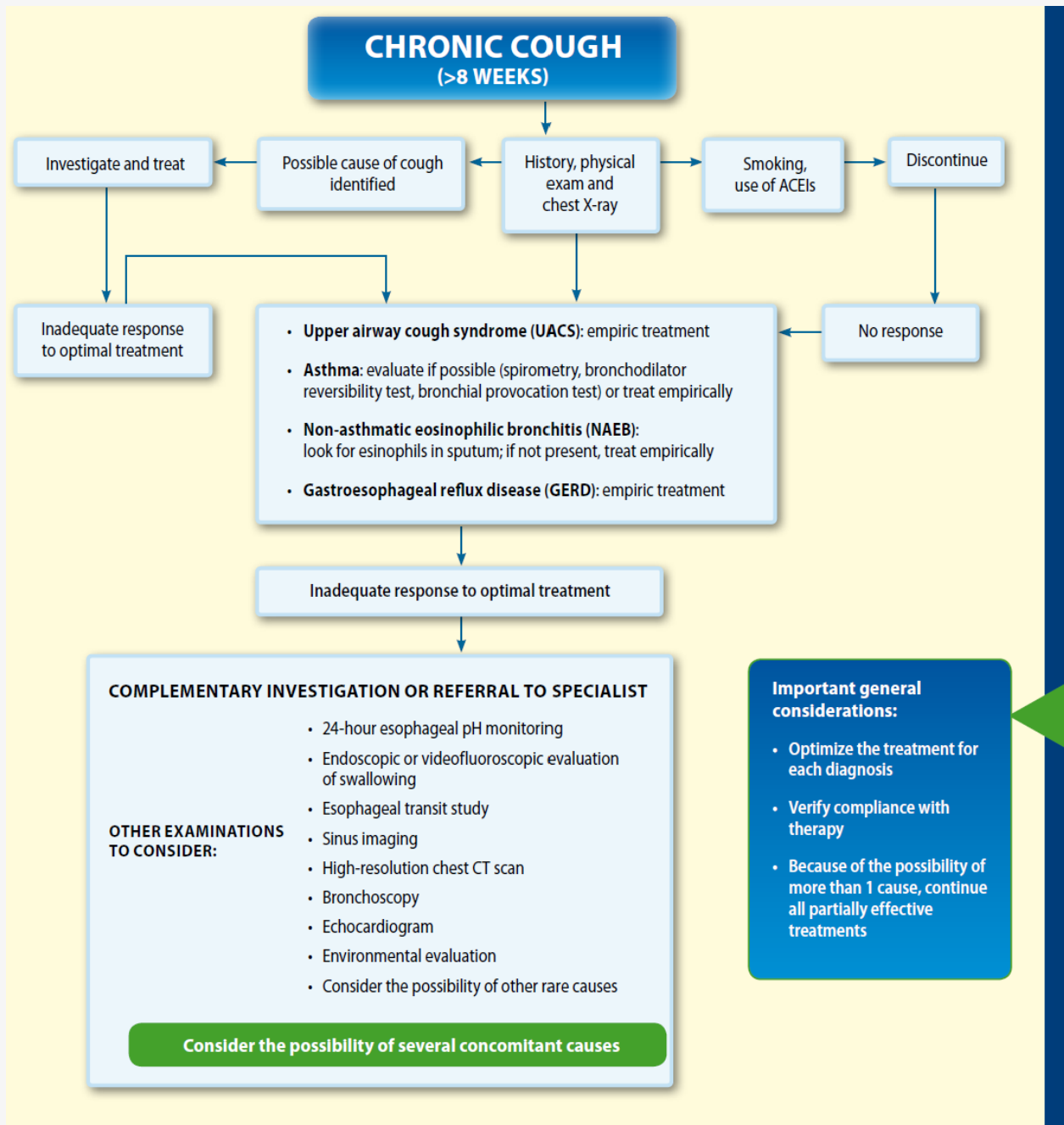


With no approved medications for uncontrolled chronic cough most specialist clinics management relies on using interventions with evidence of efficacy in clinical trials. In the UK, low release morphine sulphate (MST) is often used. If MST is ineffective then a discussion of the potential risks and benefits of trialing gabapentin or pregabalin is crucial. These medications can cause unsteadiness, drowsiness, severe depression, hallucinations and, occasionally, suicidal ideation<sup>22</sup> Like MST, the benefits in cough have been reported by subjective improvements in the cough-specific quality of life questionnaire or a 100 mm visual analogue score. Low dose gabapentin has also been shown to be effective in cough syncope. Amitriptyline has also been used. Some patients may select speech and language therapy instead of medication. This intervention involves a multi-modality approach of education, reducing laryngeal irritation with relaxation exercises, cough suppression techniques and counselling.

Those that benefit often have speech and language therapy as an adjunct to medication and this was assessed in a 2016 trial with placebo or pregabalin. The study showed that combining pregabalin with speech and language therapy improved cough-specific quality of life and visual analogue score, but showed no additional improvement in actual objective cough frequency.<sup>23</sup>

**For clinicians, definitive advice is not always available on what treatments to use in managing chronic cough. For example, while the 2020 European Respiratory Society (ERS) guidelines endorse the use of morphine and inhaled corticosteroids for management of chronic cough these are not recommended in the 2016 American Society of Chest Physicians guidelines.**

BASED ON GUIDELINES FROM THE AMERICAN COLLEGE OF CHEST PHYSICIANS, THE CANADIAN THORACIC SOCIETY IN 2012 PRODUCED THE FOLLOWING FLOWCHART FOR ASSESSING AND MANAGING PATIENTS WITH CHRONIC COUGH WHICH ENCAPSULATES MUCH OF THE MATERIAL DESCRIBED EARLIER.<sup>24</sup>



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# PRIMARY CARE PROVIDERS

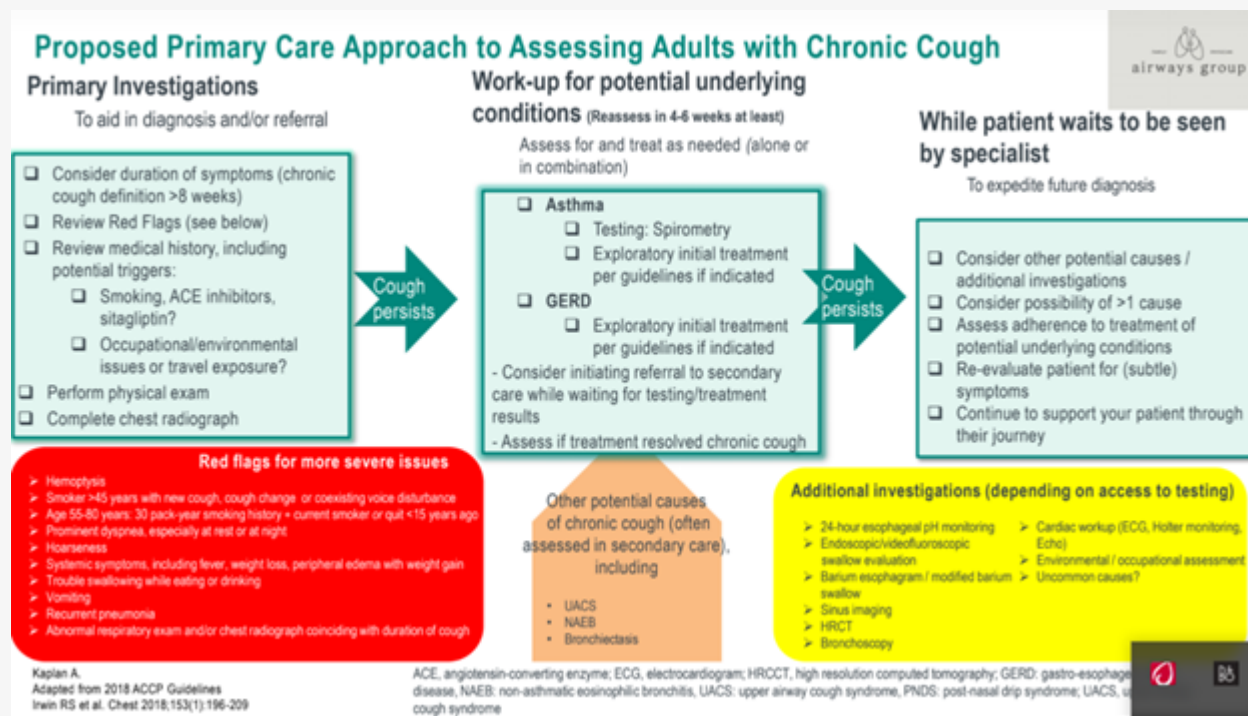
As noted earlier, cough is one of the most frequent reasons for patient visits to a primary care practitioner and chronic cough is often seen by both family physicians and nurse practitioners.

A 2017 article in American Family Physician outlines two key recommendations for family physicians in managing chronic cough:

- In adults with chronic cough, initial evaluation should focus on the most common causes: upper airway cough syndrome, gastroesophageal or laryngopharyngeal reflux disease, asthma, and non-asthmatic eosinophilic bronchitis. Other causes to consider include angiotensin-converting enzyme inhibitor use, environmental triggers, tobacco use, and chronic obstructive pulmonary disease.
- In patients with refractory chronic cough, referral to a pulmonologist or otolaryngologist should be considered, as well as a trial of gabapentin, pregabalin, or speech therapy.

The article also proposes a workflow for managing patients with chronic cough that involves initially evaluating the patient for red flags, considering doing a chest x-ray and excluding common causes mentioned above. If no potential cause of the cough is identified or if symptoms continue despite treating a specific cause, the family doctor is urged to initiate sequential or empiric treatment. If the cough remains refractory, the workflow then recommends specialist referral, further testing or a trial with gabapentin/pregabalin/speech therapy.

More recently the Family Physicians Airway Group of Canada (FPAGC) has also published a chart detailing an approach to assessing patients with chronic cough in primary care.



With permission from Kaplan. A, Chair | FPAGC

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## IN CANADA THERE ARE CHALLENGES AND FRUSTRATIONS INVOLVING THE AVAILABILITY OF RESOURCES FOR PRIMARY CARE PROVIDERS MANAGING CHRONIC COUGH IN THE COMMUNITY

"I can't get a speech pathologist at all. They don't exist for me at all in the community. You have to pay for them privately and the ones you get privately are only interested in kids. Accessing a hospital resource from the community is actually very difficult. In terms of gastroenterologists there's only one of them who will do a pH monitor. In terms of ENT as well, maybe you're going to get one to look in and say, 'Well, that looks like reflux to me'. Sometimes it's based on good findings and sometimes it's just because they figure that they're giving you an answer. I have a little bit of expertise (in chronic cough) as a family doctor, and I still don't have those abilities to find the resources. If I have to send someone for a bronchoscopy then I'll send someone for a bronchoscopy, but ultimately, it just doesn't happen in the community. I know a little bit about respiratory medicine yet, my RTs will not do a methacholine challenge for me in the hospital, because it has to be done by one of the respirologists."

- Dr. Alan Kaplan

Dr. Kaplan also noted that in some jurisdictions such as Ontario, family physicians cannot receive remuneration for ordering spirometry testing, or sometimes are unable to even avail spirometry testing for their patients in a timely manner.

unaware or only minimally aware of clinical practice guidelines for the management of chronic cough. Only half of those responding to the survey said they had received training or education about chronic cough. Full results of the survey can be found in Appendix I.

**Despite these resourcing constraints in the Canadian system patients with chronic cough almost always see a primary care physician or nurse practitioner and a referral from a family physician or general practitioner is nearly always needed in order to receive specialist care.**

A small survey of non-physician health care providers who deal with chronic cough (primarily respiratory therapist or certified respiratory educators) conducted by RESPIPLUS found about three-quarters felt chronic cough was a major health problem. More than half of these providers reported they were

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# SPEECH AND LANGUAGE THERAPY

Speech and language therapy for chronic cough aim to improve voluntary control over the cough by teaching patients to identify sensations that precipitate the cough, to substitute the cough with another response (breathing or swallowing exercise), and to modify behaviors that contribute to laryngeal irritation. In Canada this approach is usually undertaken by speech and language therapists and includes pathophysiological assessment (cough characteristics, urge to cough evaluation, laryngeal assessment and voice symptoms), followed by a program using several tools including education, cough suppression strategies, vocal hygiene training and psycho-educational counseling.

Both US and European guidelines suggest there is moderate evidence to support using multimodality speech pathology therapy to treat unexplained chronic cough. The approach involves two to four sessions of education, cough suppression techniques, breathing exercises, and counseling and has no associated adverse effects. A systematic review of nonpharmacologic approaches to managing refractory cough quoted by the American Thoracic Society guidelines<sup>28</sup> found this approach resulted in a reduction in cough frequency (three studies), an improvement in cough severity (two studies), and a beneficial effect on cough-related quality of

life (four studies). “Although the review found support for nonpharmacologic therapy for UCC, it also noted the paucity of high-quality evidence and the need for additional studies,” the guideline adds. The ERS guidelines give conditional support to using cough control therapy noting “this is a complex intervention that requires further study to determine which components are of value. Experienced practitioners should undertake cough-directed physiotherapy and speech and language therapy interventions.”

A Cochrane Review published in 2019 assessed the value of speech and language therapy for managing chronic cough.<sup>29</sup> The authors based their assessment on two randomized, controlled trials involving 162 adults that met their inclusion criteria. The duration of treatment and length of sessions varied between studies from four sessions delivered weekly, to four sessions over two months. The length of sessions varied slightly from one 60-minute session and three 45-minute sessions to four 30-minute sessions. The control interventions were healthy lifestyle advice in both studies. A significant difference favoring speech and language therapy was seen objective cough count, symptom score and clinical improvement as defined by trialists. There was no significant difference between therapy and control regarding subjective measures of cough and



cough reflex sensitivity. The authors noted that while a large number of studies of the therapy were found only two high quality studies met the criteria for inclusion.

**“Because of the paucity of data, we can draw no robust conclusions regarding the efficacy of speech and language therapy interventions for improving outcomes in unexplained chronic cough.”<sup>29</sup>**

Most reviews assessing the management of unexplained chronic cough include speech and language therapy as a potential therapeutic approach. A review specifically updating knowledge about speech and language therapy and published in 2019<sup>30</sup> states that “the efficacy of speech pathology treatment for chronic refractory cough is well established. However the article notes that there are no good evidence-based criteria for determining when to use this approach rather than other therapeutic approaches and that “little is known or understood regarding optimal delivery of care.” Selection of appropriate patients is important, the reviewers add, noting that patient input is important in considering who is a good candidate for this approach. “Patients who are looking for a quick fix, are not easily able to attend therapy sessions, or are unlikely to follow through with recommendations outside of therapy are not good candidates,” they write. Research into the optimal delivery of speech pathology therapy for chronic cough is ongoing and continues to clarify the important role speech pathology plays in the treatment of chronic cough.

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# FOR PATIENTS

## INFORMATION ON CHRONIC COUGH FOR THE PUBLIC HAS BEEN PREPARED BY A NUMBER OF ORGANIZATIONS WITH DIFFERING LEVELS OF LITERACY REQUIRED TO UNDERSTAND THE INFORMATION.

The Lung Health Foundation section on chronic cough states that chronic cough is not a disease but a sign of something wrong.<sup>31</sup> The Foundation notes it is important to “see your doctor” to diagnose the cause of chronic cough. The National Health Service in the UK section on cough does not distinguish between acute and chronic cough and says cough is usually self-limiting and clears up within 3-4 weeks.

For causes of chronic cough, healthcare organizations list the following:

- Post-nasal drip syndrome described by the NHS as “mucus dripping down the throat from the back of the nose.”
- Something at home or work that is irritating your nose or airway
- Allergies such as hay fever
- Asthma or pulmonary fibrosis
- Smoking
- COPD
- Heartburn or Acid reflux (sometimes referred to as gastro-esophageal reflux disease or GERD)
- Some high blood pressure medications
- Infections like bronchitis
- Serious conditions such as lung cancer

UpToDate, a very popular commercial online clinical support tool, has sections specifically for patients. For chronic cough it states:

**“The most common causes of chronic cough are postnasal drip, asthma, and acid reflux from the stomach. These three causes are responsible for up to 90 percent of all cases of chronic cough.”**

The American Lung Association acknowledges the challenges of diagnosing chronic cough and its impact on patients.<sup>33</sup>

**“Although cough is a common symptom of many lung diseases, chronic cough can't always be linked to another disease or condition and it often doesn't respond to treatment. If you have chronic cough it can feel like a burden on your daily life, with lack of sleep, mental and physical exhaustion and social stigma impacting your quality of life.”**

The organization adds “it is important to understand that a chronic cough can also be a sign of a disease not related to the lung at all. Your healthcare provider may have you be evaluated by other specialists besides a lung doctor. This could include an allergist, an ear, nose and throat specialist (ENT) or an esophagus/stomach specialist.”

The Canadian Lung Association states that “in rare cases, chronic cough can be caused by serious diseases like tuberculosis (TB), lung cancer. Your doctor may want to order a chest x-ray to determine whether you have a serious condition.” To find the cause of the cough, the NHS says the GP may:

- Take a sample of any mucus you might be coughing up
- Order an x-ray allergy test, or a test to see how well your lungs work
- Refer you to hospital to see a specialist but this is rare

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## UPTODATE LISTS COMMONLY PERFORMED TESTS FOR CHRONIC COUGH AS:

**Lung imaging** – If you are a current or former cigarette smoker, or if you have other medical conditions that can affect the lung, a chest X-ray or even a chest CT scan may be done.

**Lung function tests** – If asthma is suspected but cannot be confirmed, the clinician may perform lung function tests that measure the pattern of air flow into and out of the lungs.

**Acid reflux testing** – To confirm a diagnosis of acid reflux, a test may be done to measure the acid level of fluid in the esophagus. This test is called a pH probe. In some people, a test called upper endoscopy will be done to look for irritation of the esophagus and to obtain a biopsy of the esophagus.

**For diagnosis UpToDate says:** "Your healthcare provider will ask about your symptoms and perform a physical examination. Based upon your symptoms and examination, your clinician may recommend a trial of treatment before other testing is performed."

## THE AMERICAN LUNG ASSOCIATION (ALA) LISTS TESTS THAT CAN BE PERFORMED AS FOLLOWS:

- Chest X-ray: Quick and easy chest picture
- Blood sample: To see if your body is fighting an infection or if there are signs of allergies
- CT scan of the chest: A better-quality picture of the chest
- Throat swab: Usually done with a long cotton swab
- Phlegm or sputum sample: Collected after a deep cough
- Spirometry: You will be asked to breathe out hard and fast into a small plastic device to measure how well you breathe out air
- Methacholine challenge test: A breathing test often used to diagnose or rule out asthma

In many instances, patients are advised to make lifestyle changes such as quitting smoking or taking steps to control reflux if these are believed to be factors causing the chronic cough. Patients can also be advised to seek support from online communities of patients facing the same challenges.<sup>34</sup>

**For treatment the UpToDate states:** "Treatment of chronic cough aims to eliminate the underlying cause. Most of the time, each type of treatment is tried separately, one after another, instead of all at the same time. Seeing which one works best helps to figure out the underlying cause. On the other hand, a number of patients have more than one cause for their chronic cough. In such cases cough only resolves when all causes are successfully treated at the same time. Thus, if your clinician believes there is more than one cause of your cough, or if your cough is particularly disabling, treatment or evaluation of the likely causes may be pursued simultaneously."

Information for the public often does not include information on uncontrolled chronic cough or the option of speech or language therapy to manage this condition.

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## FOR MANAGEMENT OF UNCONTROLLED CHRONIC COUGH THE DOCUMENT LISTS THE FOLLOWING TREATMENT OPTIONS:

- Non-prescription cough medicines that contain dextromethorphan may help suppress the cough reflex.
- Benzonatate is a prescription medication that may be recommended if dextromethorphan is not helpful.
- Codeine and hydrocodone are prescription narcotic medications that can be added to cough syrup; these may be tried if other treatments have not been effective. However, both medications can cause you to feel sleepy and should not be used while working or driving.
- Gabapentin or pregabalin, which are drugs more commonly used to ameliorate chronic pain by blocking nerve impulses, may be helpful in some patients with chronic cough. Both medications may have side effects, such as nausea and fatigue (with gabapentin) or dizziness, confusion, or difficulty concentrating (with pregabalin), and so they should be started at a low dose and the dose gradually increased only if needed and tolerated.

A small survey of patients conducted by RESPIPLUS among a population of predominately of those with respiratory conditions showed some had been dealing with chronic cough for more than 20 years and more than a quarter of those polled waited more than 3 months to seek medical care. The survey confirmed that the family physician was the initial point of care for three-quarters of those polled and almost 60% were not referred onwards to a specialist. Of those who did see a specialist the majority were treated by a respirologist although a small number had seen more than five specialists for their chronic cough.

In this survey population the cause of the chronic cough was identified in 70% of cases. Patients responding to the poll reported being prescribed a wide range of medications for their cough including oral and systemic

corticosteroids, proton-pump inhibitors and antibiotics.

However this population reported their treatment was only somewhat or not at all successful in controlling the cough.

About three-quarters of those who answered the question said chronic cough was a major health problem and the majority responded that the cough had an impact on a number of aspects of their life. A wide-range of ill effects were reported as a result of the chronic cough including anxiety, depression, fatigue and incontinence. Full results of the survey can be found in appendix I.

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# NEW TREATMENTS

## NEW THERAPIES UNDER INVESTIGATION FOR TREATMENT OF CHRONIC COUGH TARGET SPECIFIC RECEPTORS OR CHANNELS IN THE PERIPHERAL SENSORY NEURONS.

The Transient Receptor Vannilloid-1 (TRPV1) channel was one of the first therapeutic targets evaluated for chronic cough.<sup>35</sup> C fiber sensory neurons, including those in the airways, typically express TRPV1 channels through which they respond to heat, acidity, and capsaicin (chili pepper extract). In a review of new therapies, Dr. Smith and Dr. Huda Badri (PhD) noted that “as inhaling capsaicin readily evokes cough, and patients with chronic cough exhibit heightened responses to capsaicin, the testing of compounds antagonizing this receptor was an obvious step in the search for novel antitussive therapies.”<sup>36</sup> However trials in patients with chronic cough did not demonstrate that TRPV1 antagonists showed clinical benefit. SB-705498, a highly selective and potent competitive antagonist for TRPV1 receptors, has shown to significantly affect the capsaicin cough reflex but had almost no effect on objective cough frequency. XEN-D0501, which is more potent than SB-705498 in vivo, exhibited similar results and failed to significantly reduce cough frequency in patients with chronic cough compared with placebo.

P2X3 receptors play an important role in the activation of sensory neurons integral to the cough reflex (A $\delta$ -fibres and C-fibres) and P2X3 receptor antagonists are being investigated as a potential therapeutic option.

Gefapixant (MK-7264/AF-219) is a selective antagonist of the P2X3 receptor currently in clinical trials evaluating its safety and efficacy for treatment of chronic cough. Phase 1 and 2 clinical trials evaluated more than 300 patients and demonstrated positive results for decreased mean

daytime cough frequency, 24-hour cough frequency, and awake cough frequency. Phase 1 trials used a significantly higher dose of gefapixant (600 mg), resulting in major taste disturbances due to inhibition of the P2X2/3 channels. Subsequent dose-finding studies found an optimal dose of 30 mg to 50 mg twice daily.<sup>43</sup> Gefapixant was generally well tolerated in all phase 2 trials with no major safety concerns. Dose-dependent dysgeusia (change of perception of taste) was the most common AE and subsided when the drug was stopped.

Following the positive results from phase 1 and 2 trials, investigation of the drug continued with phase 3 clinical trials. Two parallel, double-blind, randomized, placebo-controlled trials (COUGH-1 and COUGH-2) were conducted to assess the efficacy and safety of gefapixant (15 mg or 45 mg twice daily) in patients with chronic cough. The primary efficacy outcomes included 24-hour cough frequency (at week 24), percentage of at least 1 AE during treatment and follow-up (up to 54 weeks), and percentage of participants who discontinued due to an AE (up to 52 weeks). Results of COUGH-1 and COUGH-2 showed a statistically significant reduction in 24-hour cough frequency versus placebo at 12 weeks and 24 weeks in patients treated with gefapixant 45 mg twice daily. AEs reported were consistent with previous trials (dysgeusia occurring at a higher incidence with gefapixant 45 mg twice daily), and discontinuations of study drugs due to AEs were more frequent in the gefapixant 45 mg treatment arms compared to the gefapixant 15 mg and placebo arms.<sup>37</sup>



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**Three additional P2X3 antagonists, BAY1817080, BLU-5937 and S-600918, are newer agents under investigation which are seen as being more selective and potentially not causing dysgeusia.**

Therapies are also being investigated that target NK-1 and substance P which are suspected of playing an important role in the induction and maintenance of cough reflex hypersensitivity. Evidence for the utility of NK-1 receptor antagonists has come from studies evaluating aprepitant in patients with lung cancer-associated cough. A recent randomized, controlled trial with 20 patients showed improvements in cough frequency, with reductions over placebo of 22% during awaking hours and 30% over the whole 24-hour period, "were sufficient to be appreciated by study participants, who recorded significant improvements on all patient-reported outcomes."<sup>38</sup> The study documented that aprepitant also inhibited substance P activation of vagal tissue. Recently, a phase 2, open-label, pilot study (VOLCANO-1) was conducted to evaluate efficacy and safety of orvepitant, a selective, centrally acting NK-1 receptor antagonist, in 13 patients with RCC. Orvepitant showed clinically relevant and sustained improvements in objective cough frequency and subjective measures, including QoL, in patients with intractable chronic cough. It was also safe and well-tolerated. VOLCANO-2 was a phase 2b, placebo-controlled trial conducted over 12 weeks in patients with RCC and a baseline awake cough frequency of at least 10 coughs/hour. The primary cough frequency end point was not significant but a trend towards improved efficacy was observed among patients taking 30 mg orvepitant and a higher cough frequency compared with placebo. The most common AEs included headache, dizziness, fatigue, and somnolence. Authors of the trial<sup>o</sup> assessing aprepitant in patients with lung cancer note "it should not be assumed that treatments targeting specific neuronal mechanisms will implicitly be effective for cough across a range of respiratory diseases. Recent evidence suggests changes in airway nerve function are likely to be disease specific, and therefore treatments may need to be tailored to particular neurophenotypes in respiratory disorders."

Many other therapies are in various stages of investigation for their use in the treatment of chronic cough, including TRPV4 antagonists, voltage-gated sodium channel blockers,  $\gamma$ -aminobutyric acid (GABA) B receptor agonists, nicotinic acetylcholine receptor  $\alpha 7$ -subunit agonists, and inhaled sodium cromoglycate.

### **IN THEIR REVIEW, DRS. SMITH AND BADRI CONCLUDED:**

"There has been a very significant growth in the development of therapeutic agents to treat cough, especially refractory chronic cough (RCC). The P2X3 antagonist, Gefapixant currently holds the most promise to be the first therapy licensed for the treatment of RCC, but as further programs yield data, other new therapies may emerge. Such therapies have the potential to change the way refractory cough is managed and reduce the prolonged suffering patients with this condition currently withstand. Unraveling of the underlying mechanisms and the identification of markers of these will ultimately be needed to characterize patients and match them to the most appropriate treatments".

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# MODEL OF CARE

Canadian physicians have access to a number of relatively timely guidelines on managing chronic cough, but as Dr. Paul Hernandez says “most of the guidelines emphasize pathophysiology, diagnosis and treatment, but they don't really talk about models of care.”

## DR. HERNANDEZ AND OTHERS OUTLINE AN IDEAL MODEL FOR MANAGING PATIENTS WITH CHRONIC COUGH THAT WOULD INVOLVE APPROPRIATE AND TIMELY ACCESS TO:

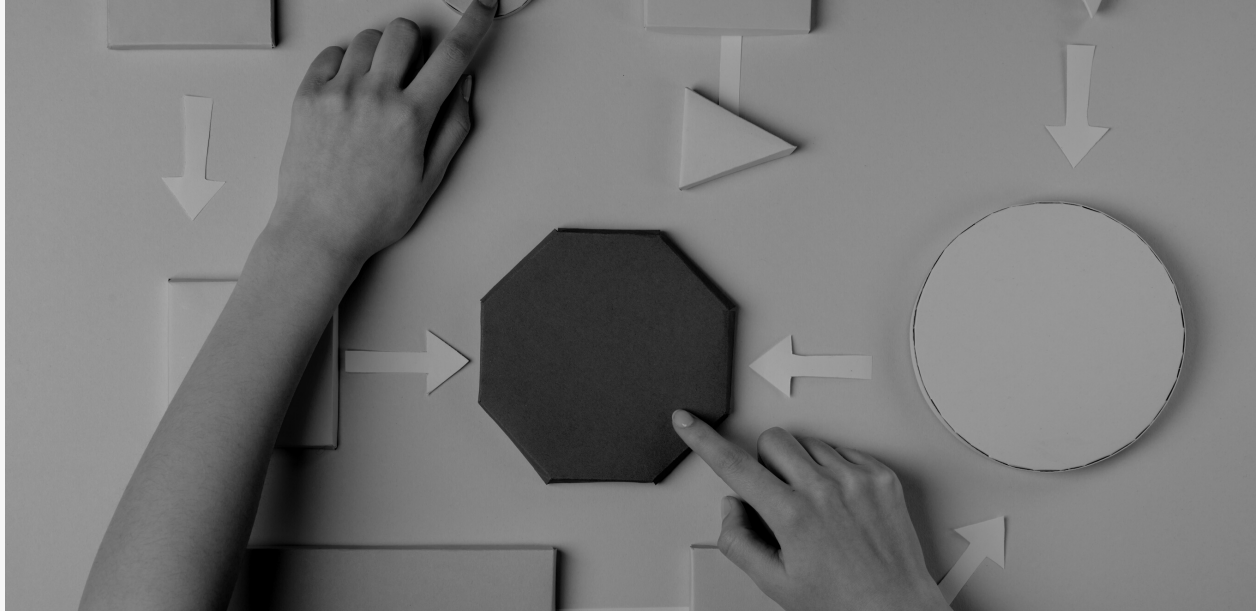
- Primary care - primary care physicians or nurse practitioners
- Secondary care - specialists (usually respirologists but also allergists, gastroenterologists and otolaryngologists)
- Tertiary care - cough clinics
- Other health care professionals - speech and language therapists, respiratory therapists, and specialized respiratory educators

Initial workup, diagnosis and treatment would be performed by primary care providers with referral as appropriate to specialists when necessary. Patients with unexplained chronic cough or other more complex or severe cases would be referred to interdisciplinary cough clinics. In addition to providing care, these clinics would also have a role in setting practice standards, conducting research, and training future respiratory specialists.

In Canada, the cough clinic founded and overseen by Dr. Stephen Field in Calgary is often held up as an ideal model for a cough clinic. This clinic relies on specialized respiratory educators (SREs) to assess patients and coordinate treatment. The clinic focuses on speech pathology therapy and psychoeducational counseling and makes limited use

of neuromodulatory medications to manage patients with uncontrolled chronic cough. Because of the lack of availability and lengthy wait times to access speech and language therapists, this therapy is provided by CREs.

For such a model to work effectively, care would have to be accessible and provided in a timely fashion at each level. Referrals between levels of care would also have to be made in an effective and timely manner. A consensus that patients with chronic cough should only wait two weeks to see a primary care provider and four months to see a specialist once referred for chronic cough are tempered with the recognition that wait times are currently often far longer due to the pandemic and the regional shortages of both general practitioners and specialists.



Human resources would need to be available and distributed in an equitable manner across the country. Diagnostic tests would also need to be available as appropriate.

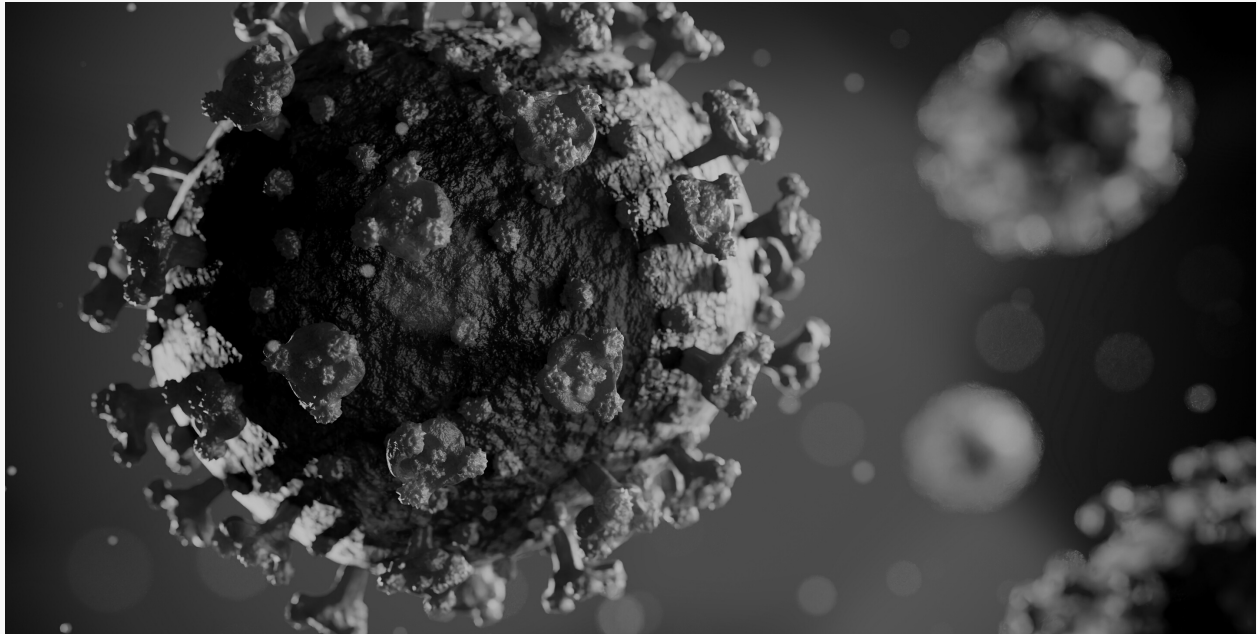
**Given the complex and multifactorial nature of managing chronic cough it would be important to patients be fully engaged in their own care and have the knowledge and information to make important decisions about treatment. Physicians and all other professionals involved in providing care similarly would require the necessary education and training to provide the necessary care.**

A proposed model of care developed by the RESPIPLUS Scientific Panel is outlined in Appendix III.

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# COVID-19

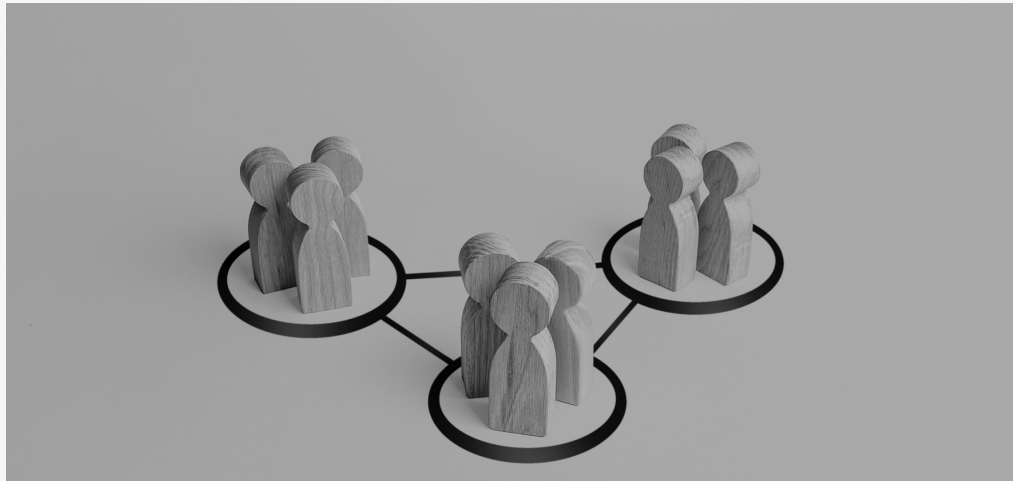


The COVID-19 pandemic has had a significant impact on patients with chronic cough. In addition to having to face increased stigma because cough is a common symptom of COVID-19, resources that would traditionally be allocated to helping patients with chronic cough have often been diverted to manage patients with COVID-19 who have been hospitalized and may be seriously ill. The presence of the SARS-CoV-2 virus also creates more diagnostic and treatment headaches for primary care physicians and specialists who are assessing chronic cough.

The pandemic has also resulted in a wholesale shift in care delivery to virtual models such as the telephone in order to avoid potential infection between physicians and patients. However, virtual care can be a challenge when it comes to chronic cough.

"I think it's really hard to make a diagnosis of cough virtually, it's really, really difficult," says Dr. Alan Kaplan. "At the end of the day, there's just certain tests, you just have to do. You can't live without them. I don't think you can make a diagnosis of a cough virtually although I think you can start the process."

"I've had a few patients who are referred to me for chronic cough and the first visit was over the phone," Dr. Maxine Cormier adds. "Sometimes it's clearly obvious that they just saw someone at a walk-in clinic who didn't do any primary investigations. Sometimes it's very obvious it is just reflux or postnasal drip. And it's an easy fix. But for most people who are going to be referred to tertiary care center because of a diagnosis of cough. I think you really need an in-person visit."



One of the most concerning aspects of the relationship between chronic cough and COVID-19 is the fact that chronic cough is a common symptom in patients who have suffered an initial infection with COVID-19 but continue to have a variety of symptoms related to the virus many months later - what is known as post-COVID syndrome or "Long COVID".

A review of COVID-19 associated cough published in the *The Lancet Respiratory Medicine* by Dr. Woo-Jung Song and colleagues noted that cough is one of the most common symptoms of COVID-19 and that "chronic cough after SARS-CoV-2 infections occurs less frequently but is common in the so-called post-COVID syndrome (long COVID) in which it is usually associated with other symptoms...".<sup>41</sup> In their pooled analysis of 14 studies of hospitalized patients who had COVID-19 and had been followed-up for between 6 weeks to 4 months, the estimated prevalence of persistent cough was 18%.

The study authors speculate that COVID-19 cough might result from invasion of vagal sensory neurons by SARS-CoV-2 or a neuroinflammatory response, or both, leading to peripheral and central hypersensitivity of cough pathways.

### MANAGING CHRONIC COUGH IN POST-COVID 19 SYNDROME:

The study authors state that while "neuromodulators such as gabapentin or opioids might be considered for COVID-19 cough, new anti-inflammatories or neuromodulators could be considered to treat not only cough, but also the post-COVID syndrome."

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# EDUCATION

**THE NEED FOR MORE OR BETTER INFORMATION ABOUT CHRONIC COUGH HAS BEEN IDENTIFIED AS ONE OF THE BIGGEST CHALLENGES CURRENTLY FACING THOSE TRYING TO DEVELOP A BETTER APPROACH TO CHRONIC COUGH IN CANADA.**



Such education needs to be tailored to the public and each type of healthcare provider specifically given their unique roles within the healthcare system. Given the absence of any dedicated training on chronic cough within the medical education system, it is felt there would be value in developing a case study that could be used at various levels to help inform medical students, residents and physicians in practice. Especially at the primary care level, physicians also seek

point-of-care tools such as checklists to help synthesize best practice information contained in the detailed guidelines.

“I think we have to get them aware that they've got a condition and that there's something that can be done about it, rather than just suffering with it,” said Dr. Kaplan. Reference has also been made to the need to educate patients about non-pharmacologic approaches to managing chronic cough as well as drug therapies.

## **FOR THE PUBLIC AND PATIENTS A VARIETY OF INFORMATIONAL AND EDUCATIONAL TOOLS SHOULD BE CONSIDERED INCLUDING THE FOLLOWING:**

- Self-help tools
- Online information modules
- Printed information sheets
- Podcasts and videos
- Webinars provided by experts

## **SURVEY DATA OF CANADIAN PATIENTS WITH CHRONIC COUGH SHOWED SUPPORT FOR RECEIVING INFORMATION ON THE FOLLOWING TOPICS:**

- Guidance on treatment options
- Advice on dealing with cough that is getting worse
- Maintaining a healthy lifestyle with chronic cough
- How to exercise and stay active with chronic cough

---

# ONGOING CHALLENGES

**A NUMBER OF GAPS OR CHALLENGES REMAIN IN PROPERLY ADDRESSING THE SIGNIFICANT ISSUES MANY PATIENTS FACE AS A RESULT OF CHRONIC COUGH BEING POORLY UNDERSTOOD AND MANAGED IN THE CANADIAN HEALTH CARE SYSTEM.**

## CHALLENGES INCLUDE THE FOLLOWING:

- Lack of knowledge of chronic cough among patients, primary care physicians, specialists, therapists and pharmacists.
- Inappropriate use of over-the-counter cough medications to treat chronic cough
- Lack of access to necessary diagnostic tools and tests for primary care physicians
- Lack of validated tools or scales to assess cough severity
- Unacceptably long wait times to see primary care physicians and specialists to obtain a proper diagnosis of chronic cough and receive appropriate treatment.
- Inadequate numbers of respirologists, respiratory therapists, certified respiratory educators, and speech-language pathologists with knowledge in chronic cough to meet demand.
- Poor distribution and/or lack of specialized cough clinics across Canada.
- Maldistribution of respiratory health care professionals and clinics across Canada
- Lack of approved medications to successfully treat cases of unexplained chronic cough.

Some proposed solutions to many of these challenges have been spelled out by the RESPIPLUS Scientific Panel (see Appendix II).

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# CHRONIC COUGH MANAGEMENT TOOLS AND RESOURCES

## **GUIDELINES**

Canadian Thoracic Society - Cough Etiology, Evaluation and Treatments (2012)  
[https://drive.google.com/drive/folders/1ri2mlj2gKFqySs8AUrU3YCpP\\_HH\\_m4mH](https://drive.google.com/drive/folders/1ri2mlj2gKFqySs8AUrU3YCpP_HH_m4mH)

Treatment of Unexplained Chronic Cough (2016)

American College of Chest Physicians Clinical Practice Guideline  
<https://pubmed.ncbi.nlm.nih.gov/26426314/>

Managing Chronic Cough Due to Asthma and NAEB in Adults and Adolescents (2020)

American College of Chest Physicians Clinical Practice Guideline  
<https://pubmed.ncbi.nlm.nih.gov/31972181/>

European Respiratory Society Guidelines on the diagnosis and treatment of chronic cough in adults and children  
<https://erj.ersjournals.com/content/55/1/1901136>





# APPENDIX

33

Appendix I - Patient and Provider Survey results

51

Appendix II - Barriers/Gaps and Solutions

53

Appendix III - Stepwise approach to the diagnosis and management of chronic cough in primary & secondary care.

# APPENDIX I

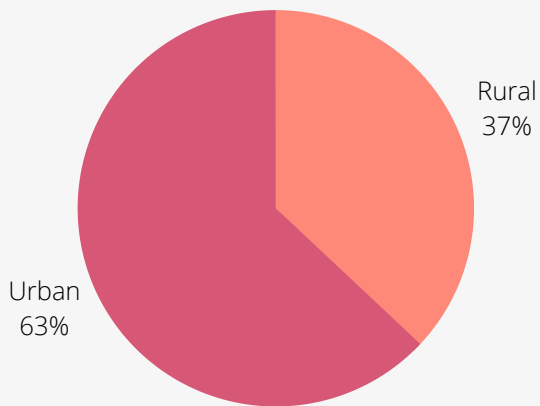
## PATIENT AND PROVIDER SURVEY RESULTS CHRONIC COUGH SURVEY RESULTS - HEALTHCARE PROFESSIONALS (NON-PHYSICIAN)

DATA COLLECTION: APRIL 13 - JUNE 7, 2021

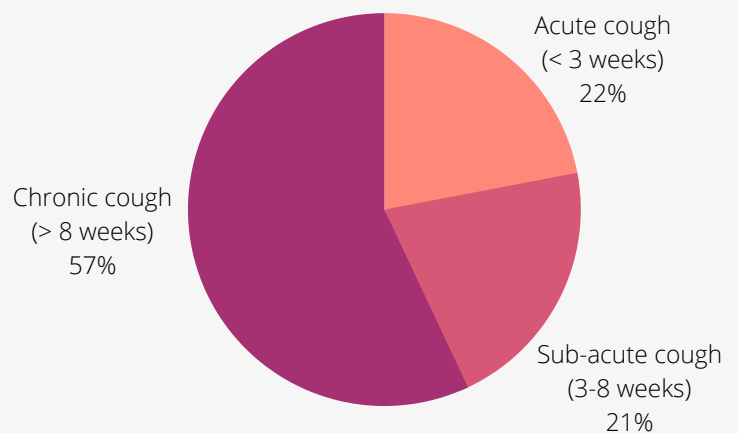
TOTAL RESPONSES: 264

Respiplus would like to give thanks to Louis-Philippe Boulet and Laval University Chair in Education, Prevention and Knowledge translation in Respiratory and Cardiovascular Health. This group will be publishing a survey of medical practice in primary care. This will be made available through a link on [www.chroniclungdiseases.com](http://www.chroniclungdiseases.com).

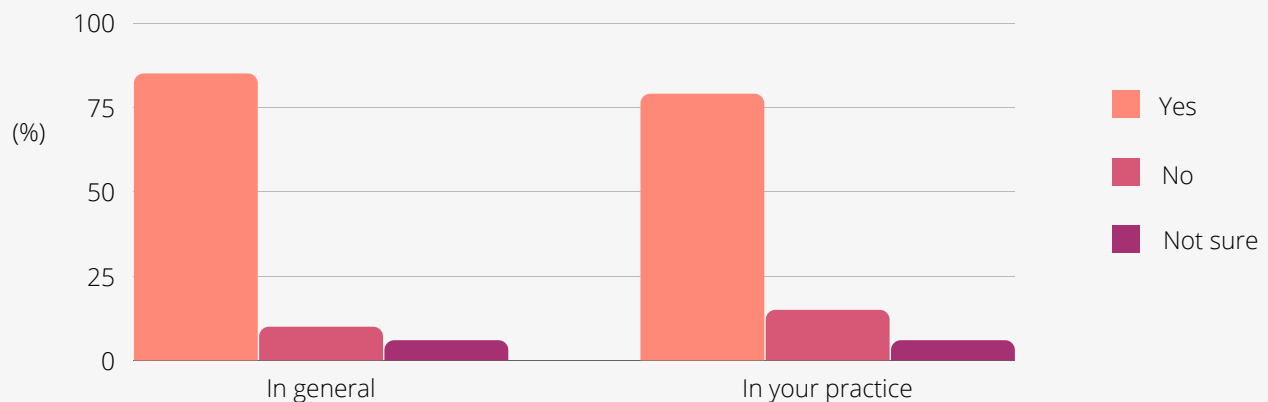
### PRACTICE SETTING



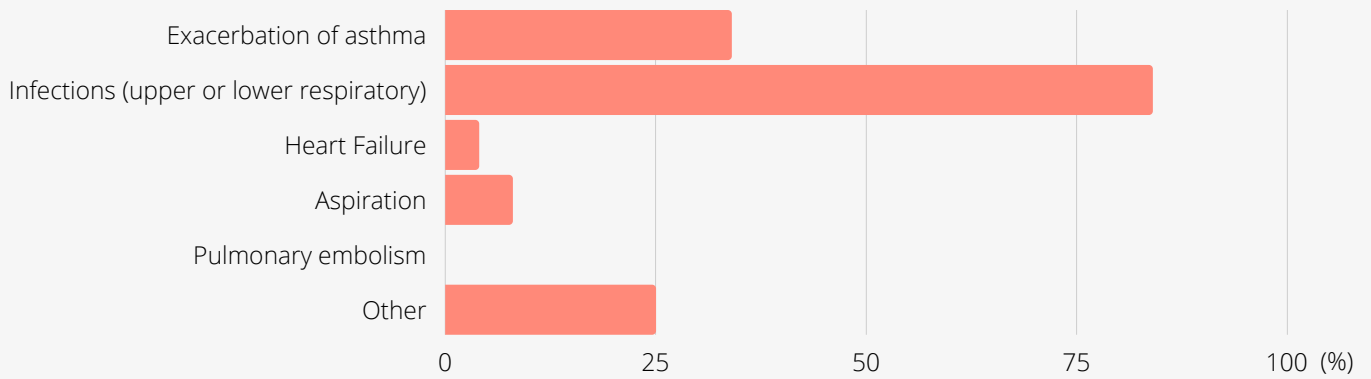
### WHAT IS THE PERCENTAGE OF PATIENTS IN YOUR PRACTICE SEEN FOR COUGH AS A PRIMARY SYMPTOM, UNRELATED TO COVID-19?



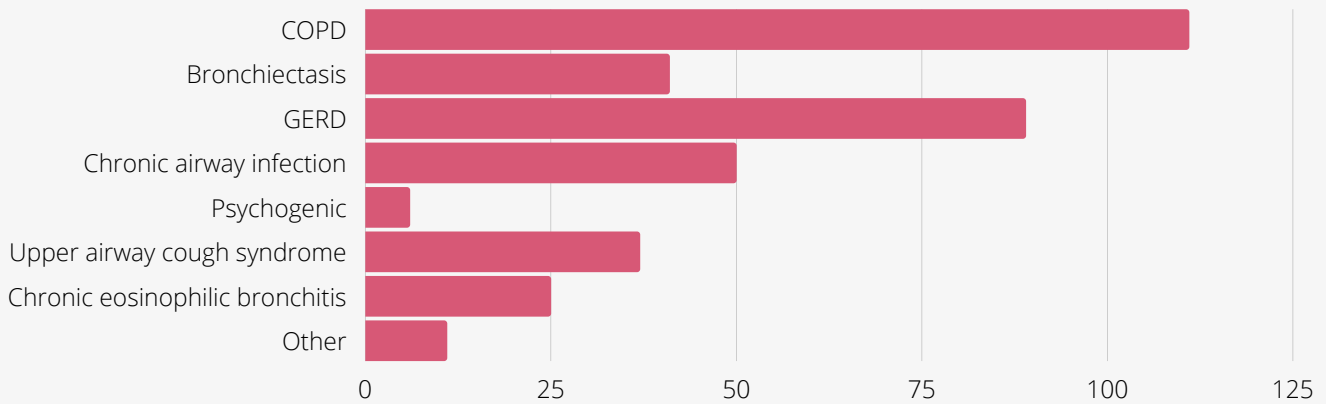
### DO YOU BELIEVE THAT CHRONIC COUGH IS A MAJOR (FREQUENT/TROUBLESOME) HEALTH PROBLEM IN GENERAL OR IN YOUR PRACTICE?



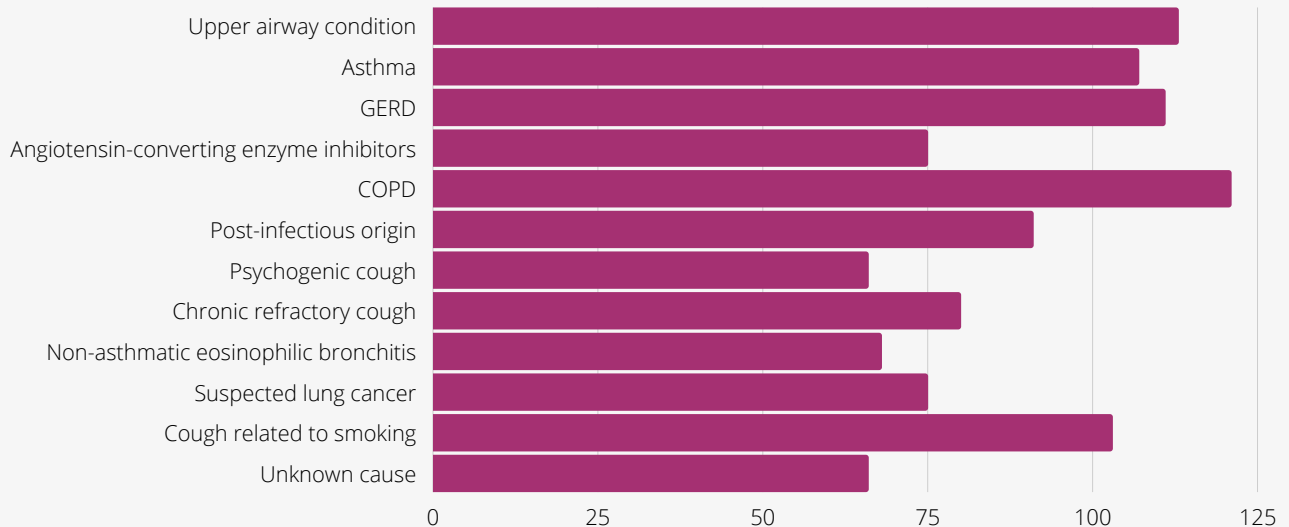
**IN YOUR OPINION, WHAT IS THE MOST COMMON CAUSE OF ACUTE COUGH?**



**IN YOUR OPINION, WHAT ARE THE 3 MOST COMMON CAUSES OF CHRONIC COUGH (IF WE EXCLUDE SMOKING AND DRUGS)?**

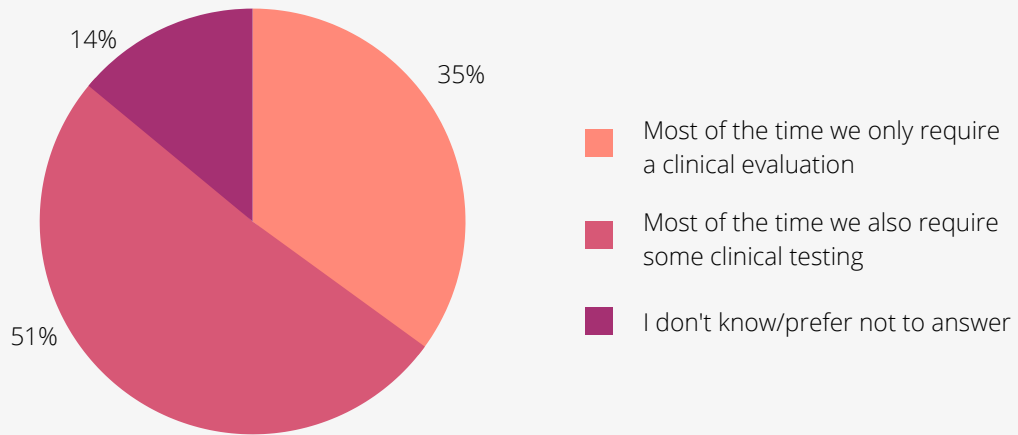


**AMONG YOUR PATIENTS WITH CHRONIC COUGH (LASTING +8 WEEKS), ACCORDING TO YOUR ESTIMATE, WHAT PROPORTION IS DUE TO:**

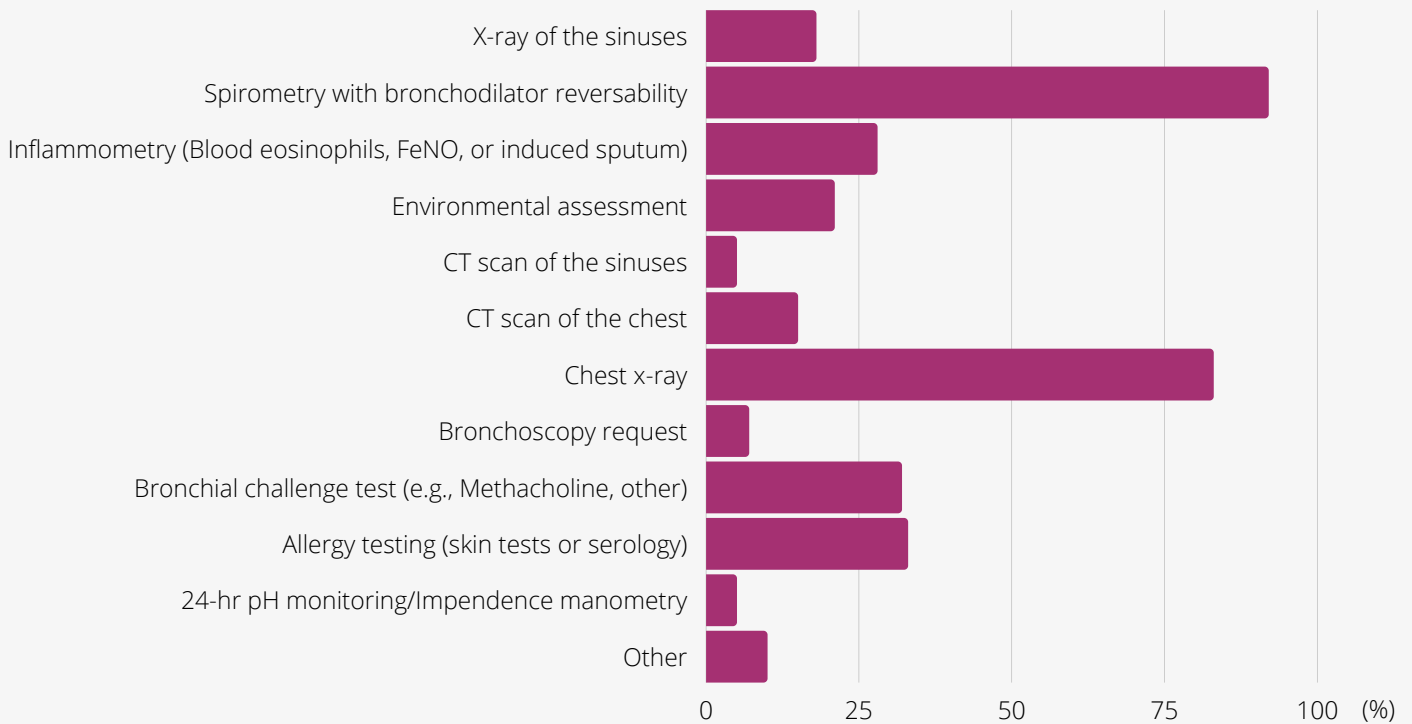


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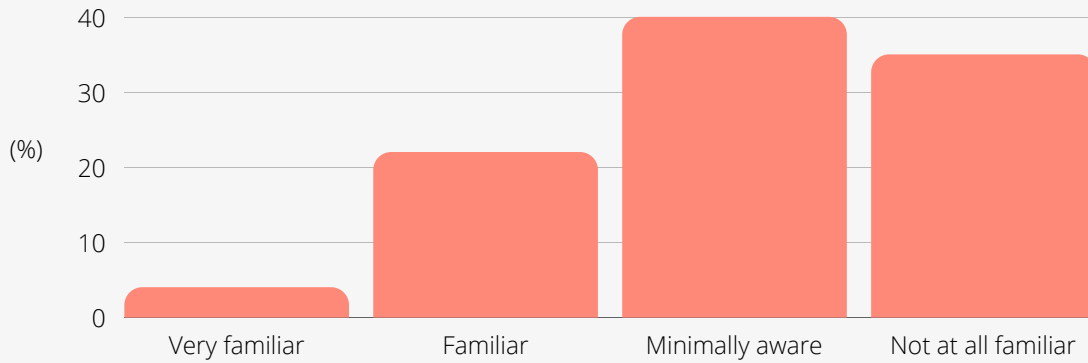
**IS IT PART OF YOUR COMMON PRACTICE (TREATING TEAM) TO ORDER ANY CLINICAL TESTS OR SIMPLY CONDUCT A CLINICAL EVALUATION?**



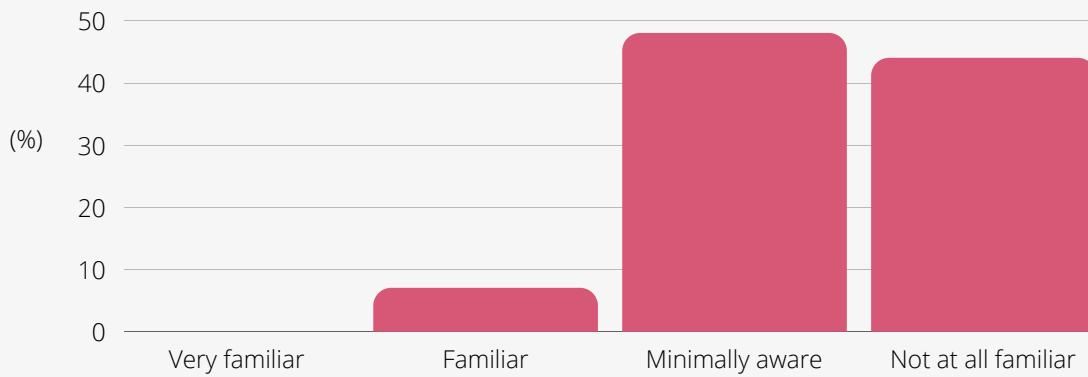
**IF CLINICAL TESTS ARE COMMONLY ORDERED, WHICH ONE(S)?**



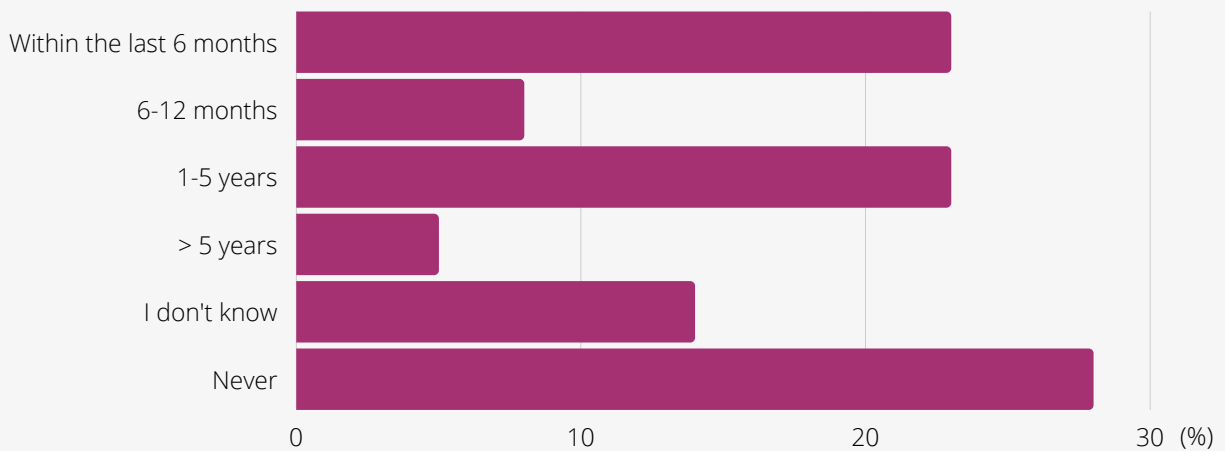
**HOW FAMILIAR ARE YOU WITH THE AMERICAN COLLEGE OF CHEST PHYSICIANS (ACCP) GUIDELINES/RECOMMENDATIONS FOR THE MANAGEMENT OF CHRONIC COUGH?**



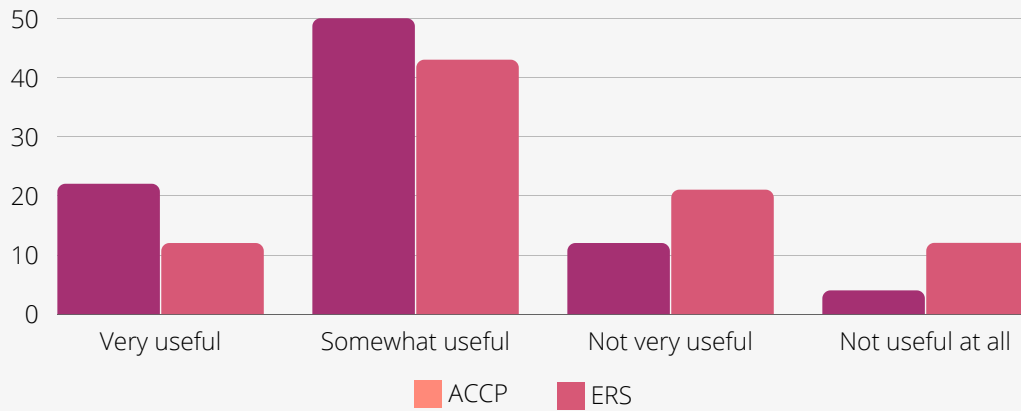
**DO YOU KNOW THE EUROPEAN RESPIRATORY SOCIETY (ERS) GUIDELINES/RECOMMENDATIONS FOR THE MANAGEMENT OF CHRONIC COUGH?**



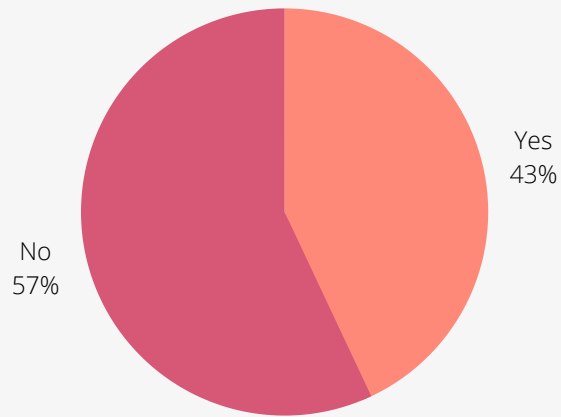
**WHEN IS THE LAST TIME YOU CONSULTED A COUGH GUIDELINE?**



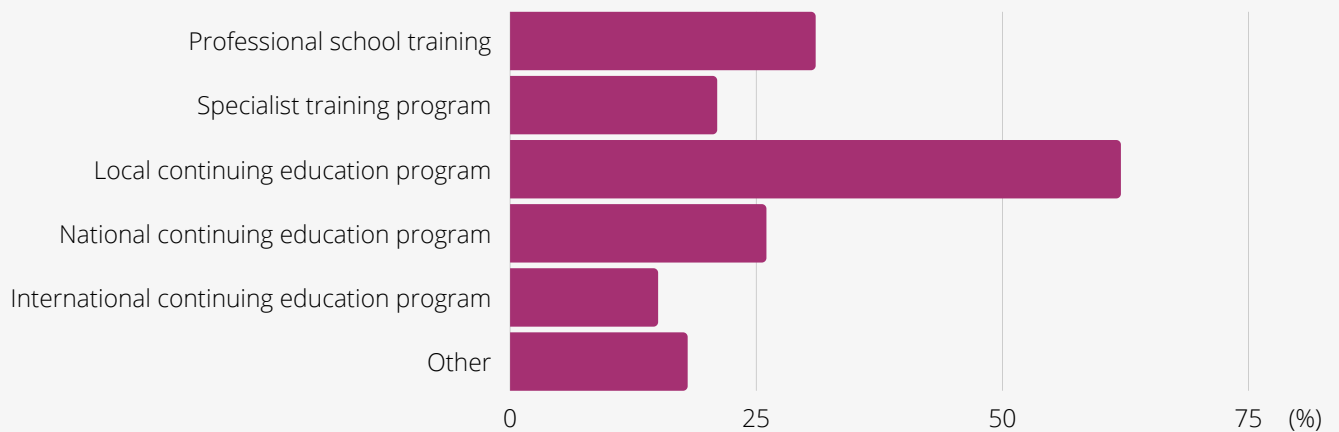
**WHICH CURRENT GUIDELINES ARE MOST USEFUL FOR YOU IN YOUR MANAGEMENT OF CHRONIC COUGH?**



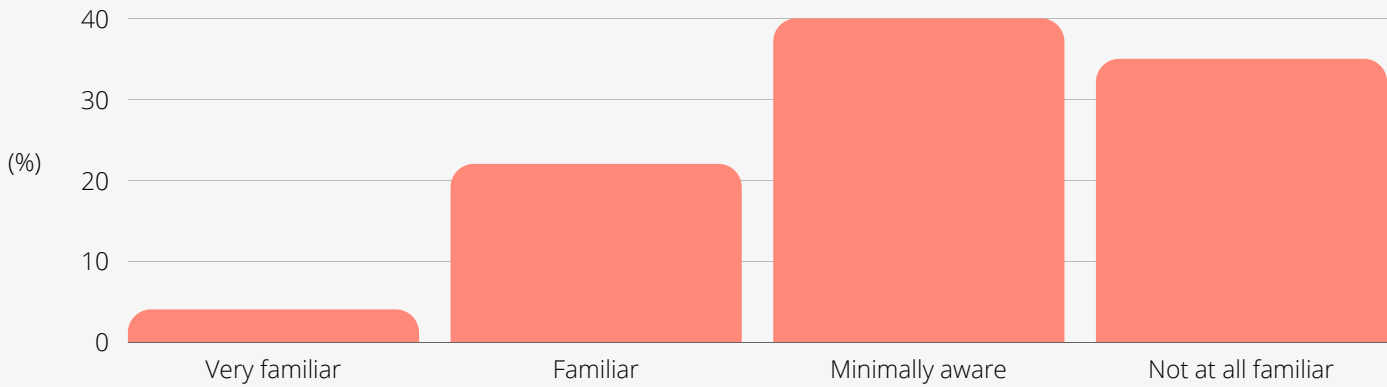
**HAVE YOU HAD TRAINING OR EDUCATION ABOUT CHRONIC COUGH PREVIOUSLY?**



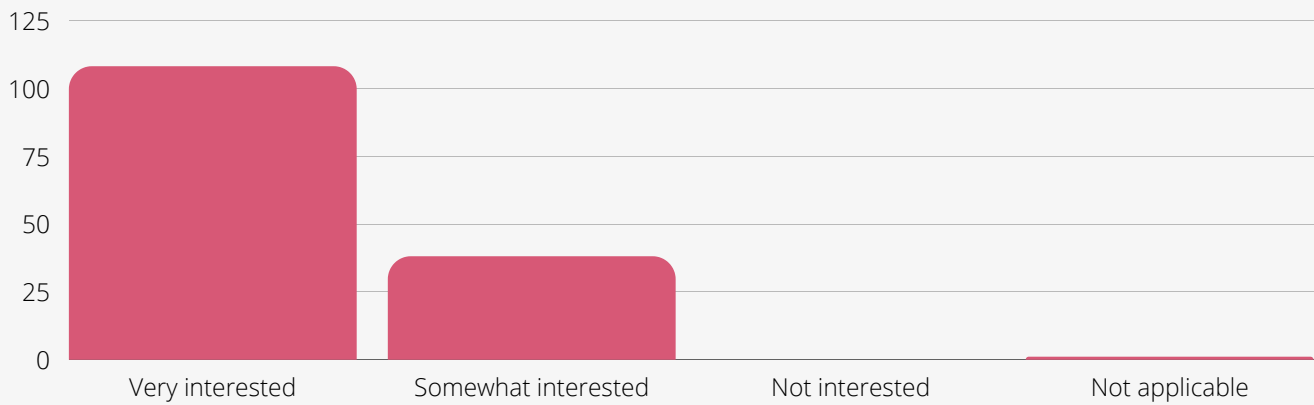
**WHERE DID YOU RECEIVE THIS TRAINING?**



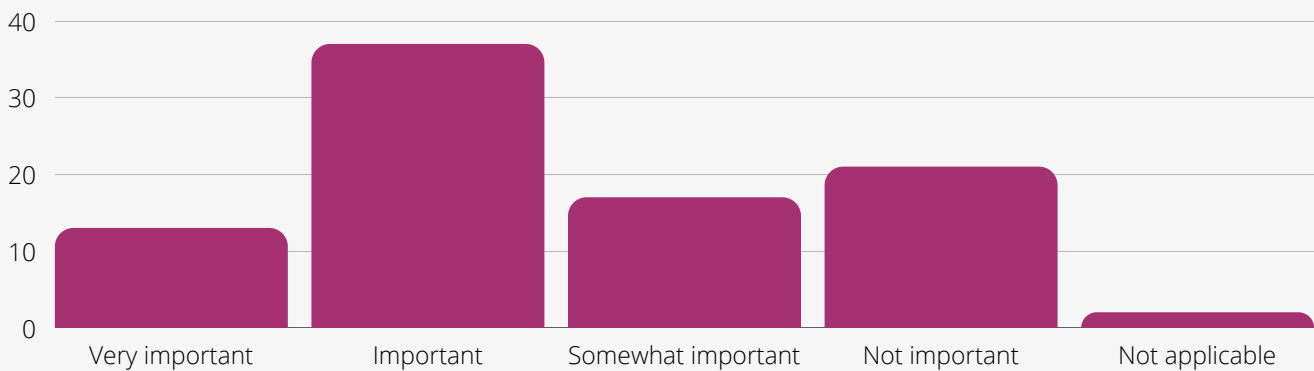
**WHICH AREAS/ELEMENTS WOULD BE MOST USEFUL FOR YOU TO USE WITH YOUR CHRONIC COUGH PATIENTS?**



**IF WEB-BASED PROFESSIONAL TRAINING FOR COUGH MANAGEMENT IN PRIMARY CARE WERE AVAILABLE, WOULD YOU BE INTERESTED IN TAKING SUCH A COURSE?**

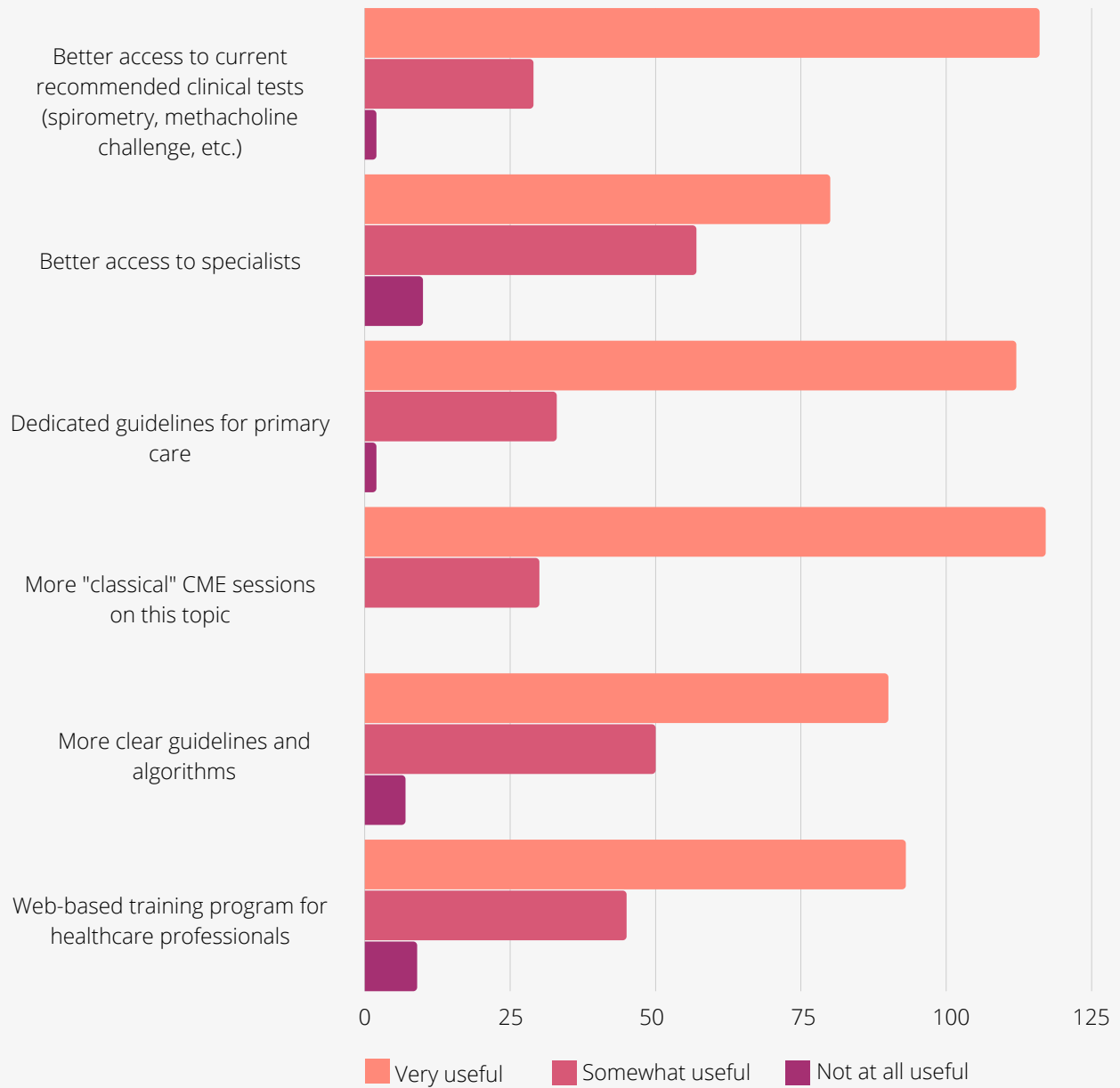


**HOW IMPORTANT WOULD IT BE FOR YOU TO RECEIVE PROFESSIONAL CREDITS IN ORDER TO PARTICIPATE IN THIS TRAINING PROGRAM?**



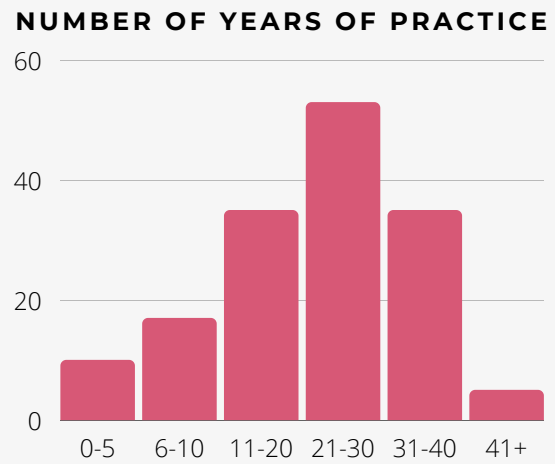
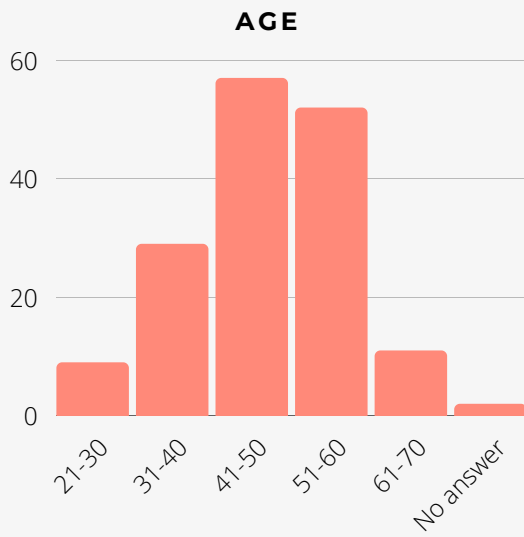
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**WHICH OF THE FOLLOWING WOULD YOU CONSIDER MOST USEFUL TO HELP YOU MANAGE PATIENTS WITH CHRONIC COUGH?**

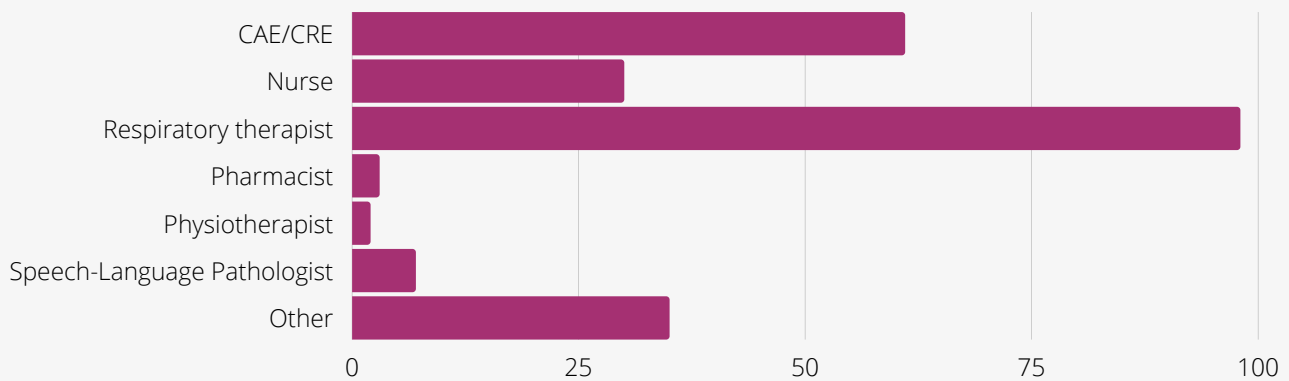




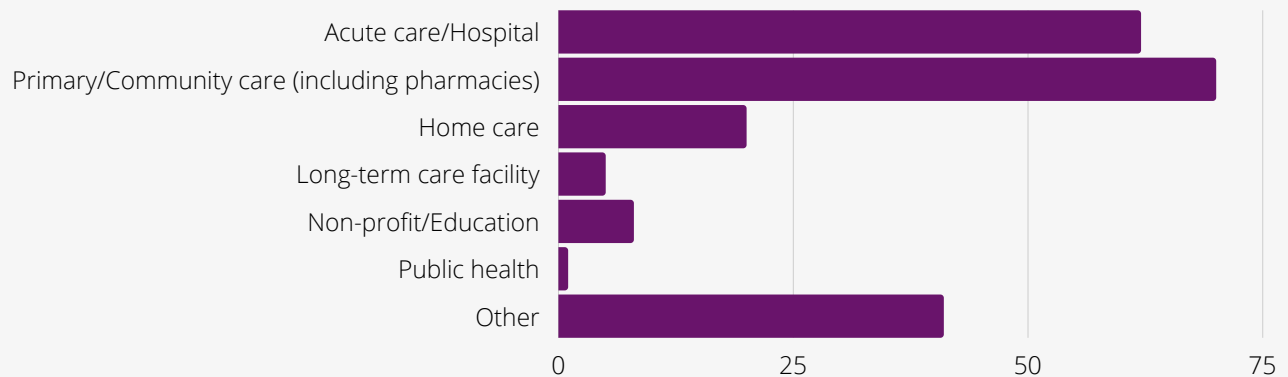
## DEMOGRAPHICS



## WHAT IS YOUR PROFESSION? (SELECT ALL THAT APPLY)



## PLEASE INDICATE WHERE YOU ARE CURRENTLY WORKING. (SELECT ALL THAT APPLY)

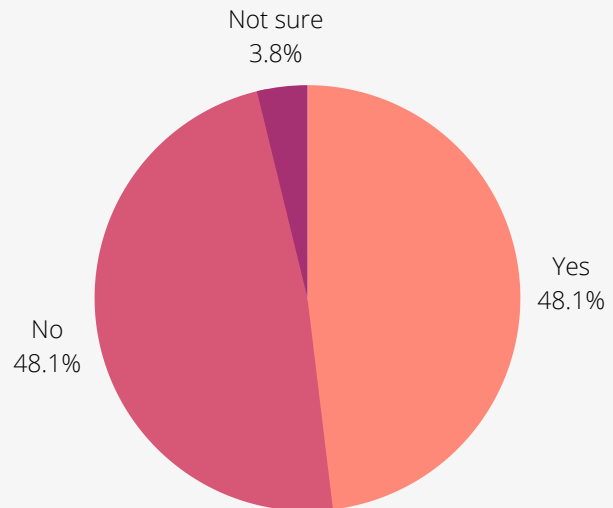


## CHRONIC COUGH SURVEY RESULTS - PATIENT

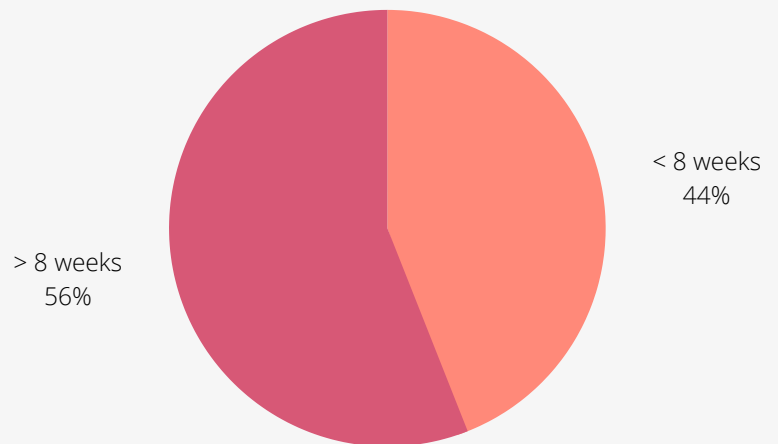
DATA COLLECTION: APRIL 13 - JUNE 7, 2021

TOTAL RESPONSES: 112

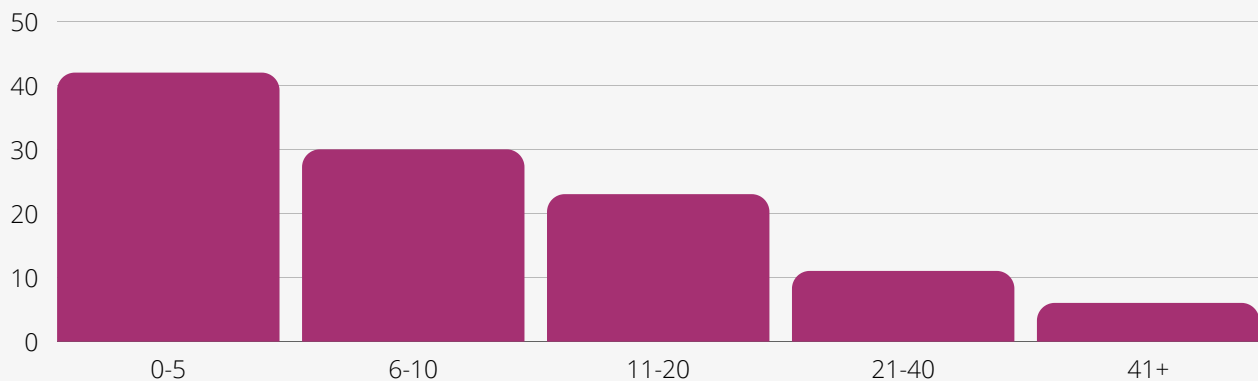
**HAVE YOU EVER HAD A LONG-LASTING COUGH FOR WHICH YOU SOUGHT MEDICAL CARE?**



**THINKING ABOUT THE LONGEST OR MOST BOTHERSOME COUGH YOU HAVE HAD, HOW LONG DID IT LAST FOR?**

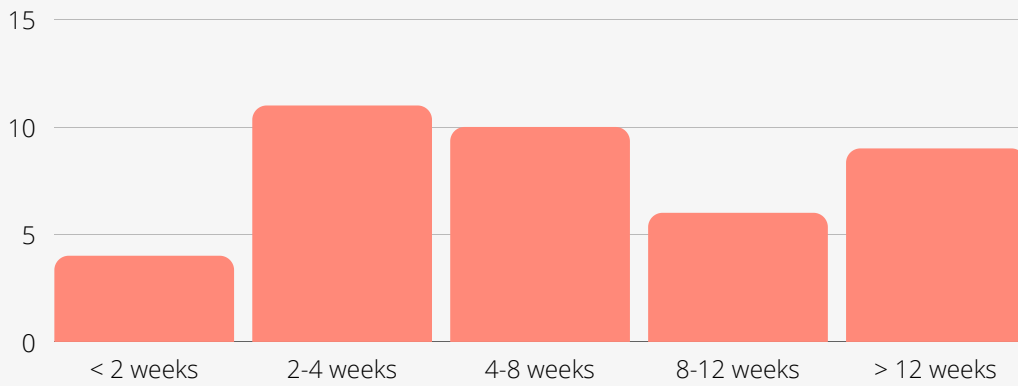


**NUMBER OF YEARS LIVING, (OR CARING FOR SOMEONE), WITH CHRONIC COUGH?**

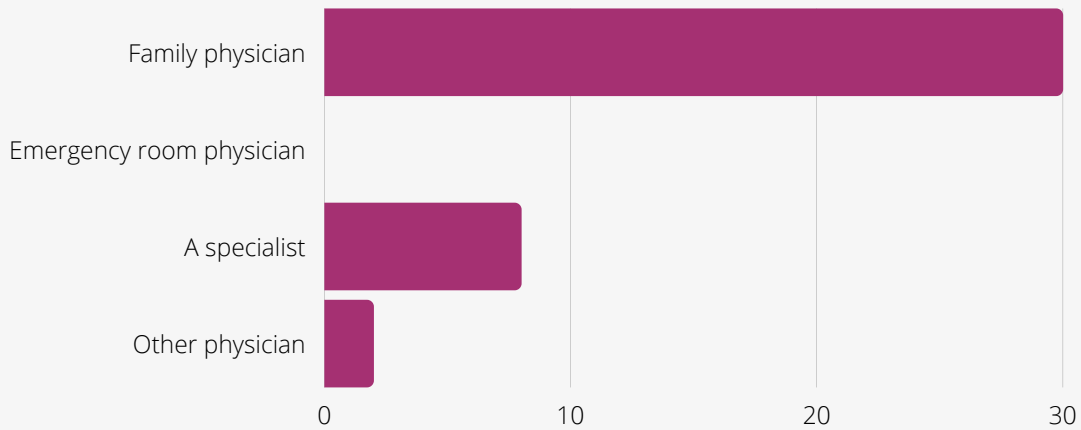


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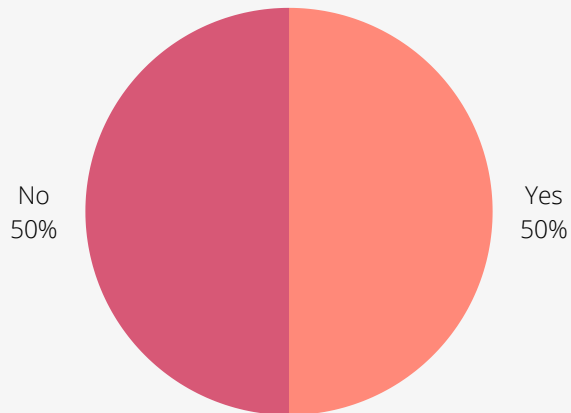
**HOW LONG HAD YOU HAD THE COUGH BEFORE SEEKING A MEDICAL APPOINTMENT?**



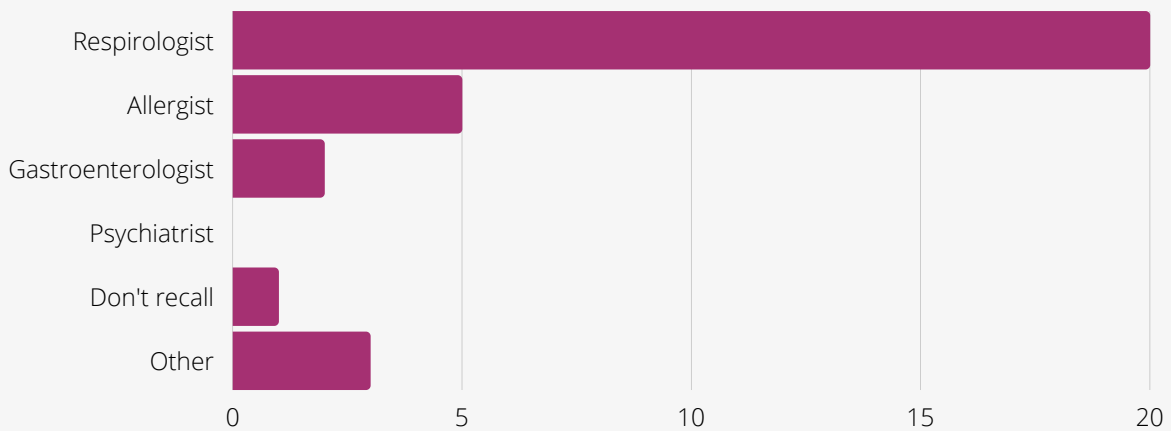
**WHO DID YOU SEE ABOUT YOUR COUGH?**



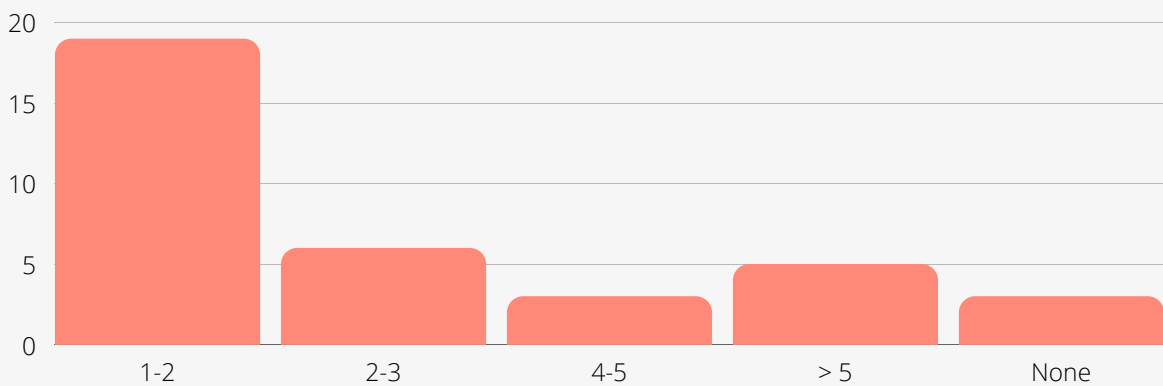
**DID THE PHYSICIAN IDENTIFIED IN THE PREVIOUS QUESTION REFER YOU TO A SPECIALIST FOR YOUR COUGH?**



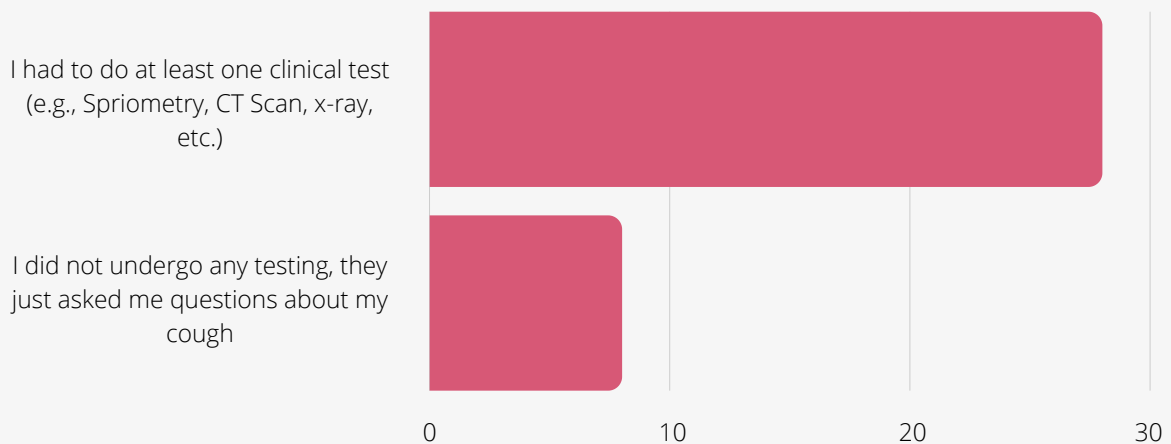
**WHAT TYPE OF SPECIALIST WERE YOU REFERRED TO? YOU CAN SELECT MORE THAN ONE**



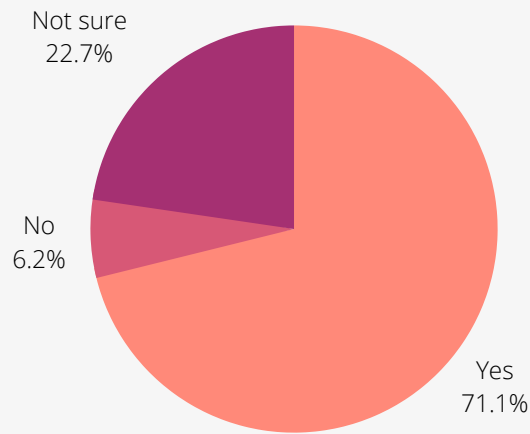
**HOW MANY SPECIALISTS HAVE YOU SEEN (EVER) REGARDING YOUR CHRONIC COUGH?**



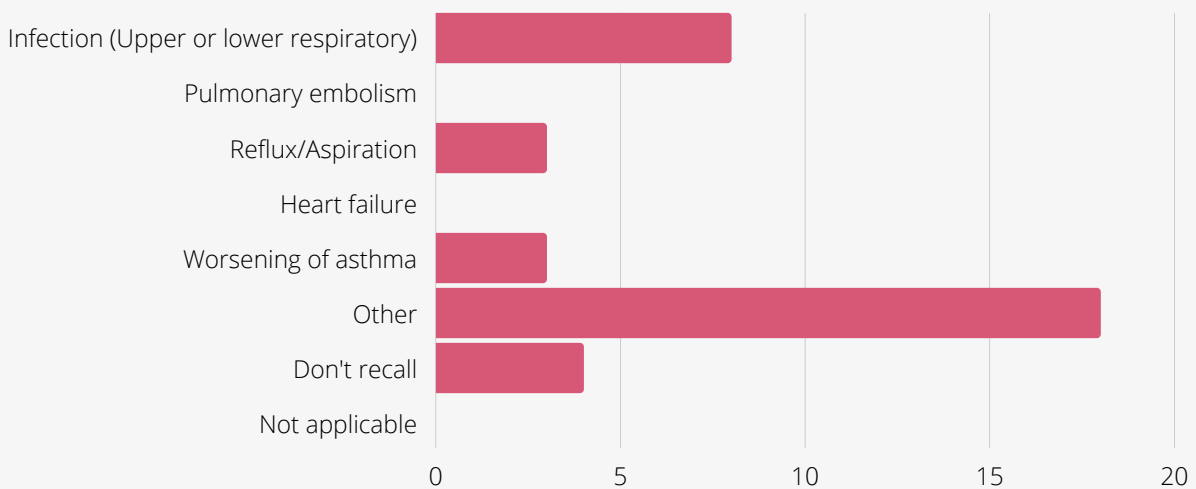
**DID YOUR TREATING TEAM ORDER ANY CLINICAL TESTS OR SIMPLY CONDUCT A CLINICAL EVALUATION (IE. HISTORY AND PHYSICAL EXAM)**



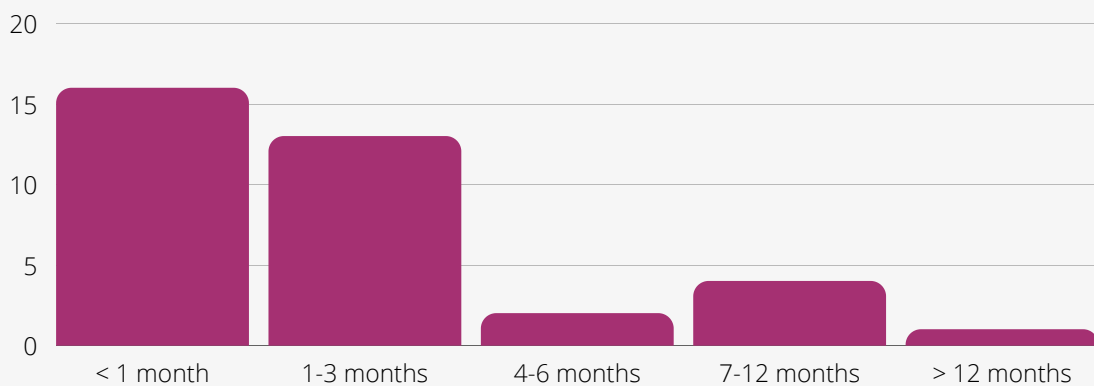
## WAS THE CAUSE OF YOUR COUGH DETERMINED?



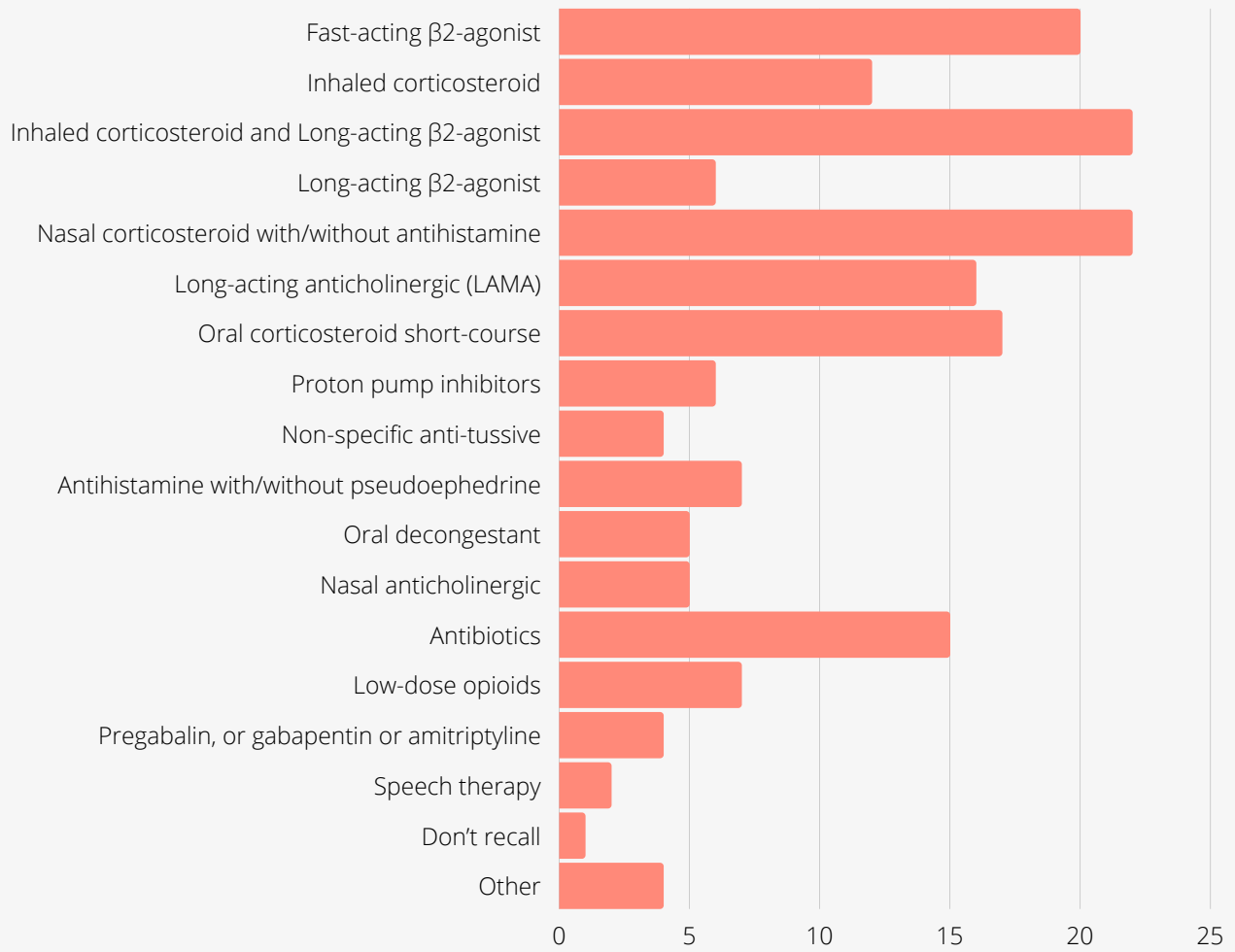
## IF YOU WERE GIVEN A DIAGNOSIS, OR AN EXPLANATION OF THE MAIN CAUSE FOR YOUR COUGH, WHAT WAS IT?



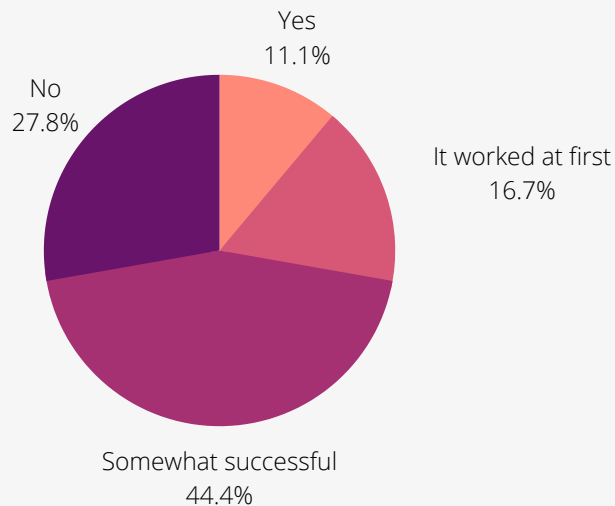
## HOW LONG DID YOU HAVE TO WAIT TO SEE A SPECIALIST FOR YOUR CHRONIC COUGH AND/OR TO RECEIVE A DIAGNOSIS?



**HAVE YOU EVER BEEN PRESCRIBED ANY OF THE FOLLOWING TREATMENTS/ THERAPIES FOR YOUR COUGH? YOU MAY SELECT MORE THAN ONE.**

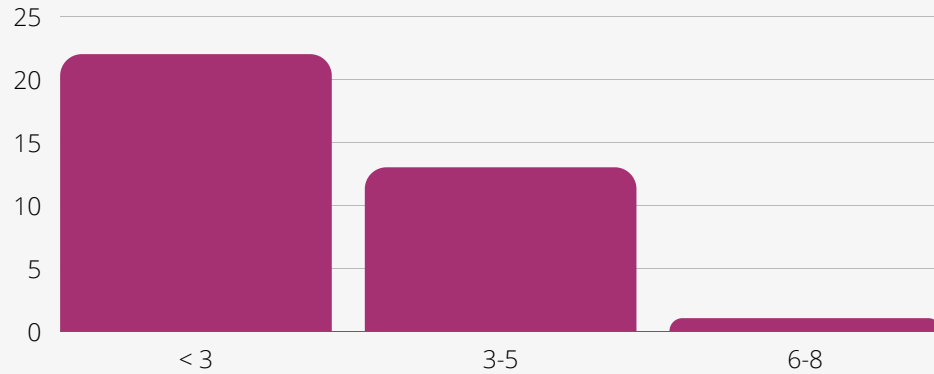


**WAS THE TREATMENT SUCCESSFUL?**

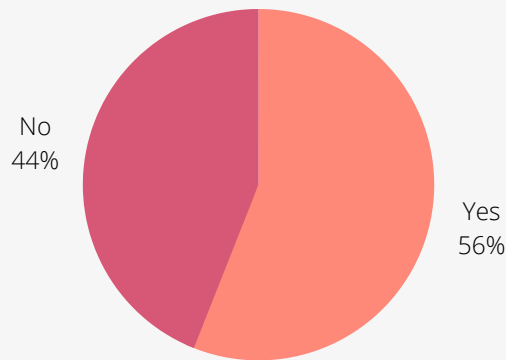


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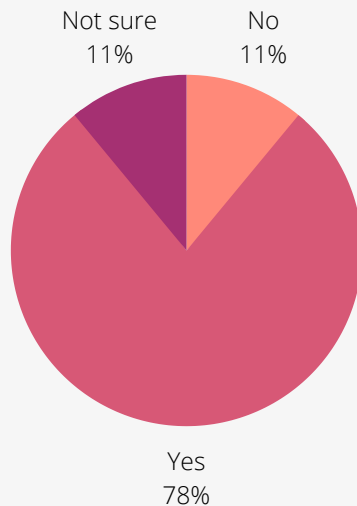
**HOW MANY TIMES PER YEAR DO YOU VISIT A CLINIC, FAMILY PHYSICIAN, OR HOSPITAL FOR COUGH AS A PRIMARY SYMPTOM?**



**HAVE YOU HAD A COUGH OF MORE THAN 8 WEEKS DURATION FOR WHICH YOU DID NOT SEEK MEDICAL CARE AND/OR SELF-MEDICATED?**

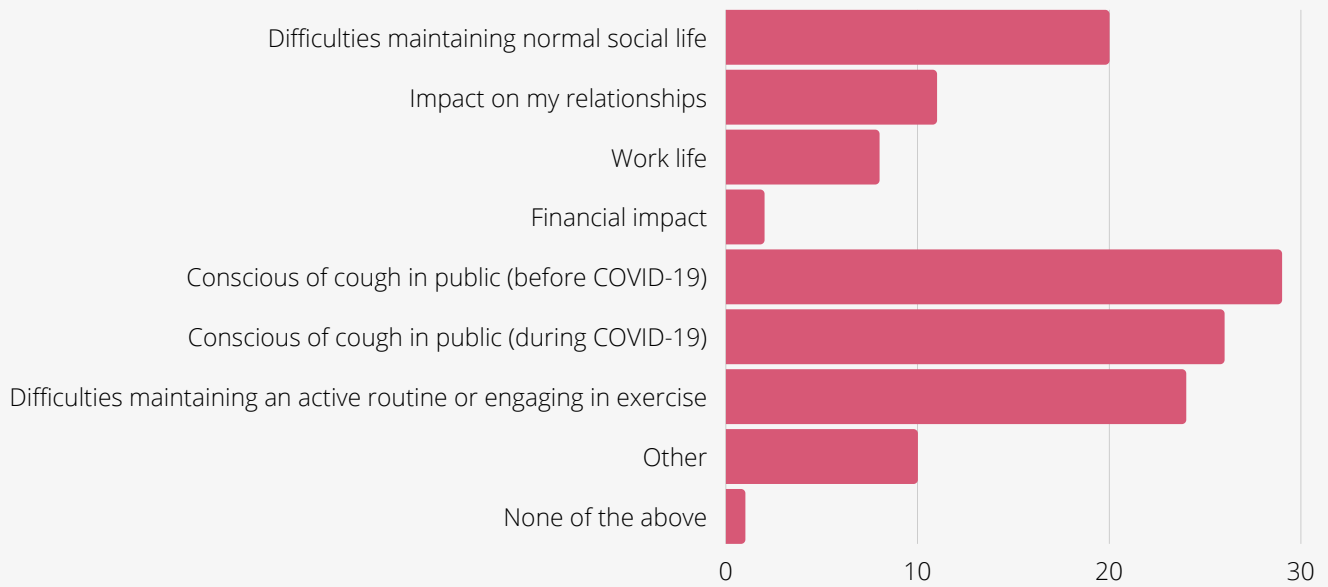


**DO YOU BELIEVE THAT CHRONIC COUGH IS A MAJOR (FREQUENT/TROUBLESOME) HEALTH PROBLEM FOR YOU?**

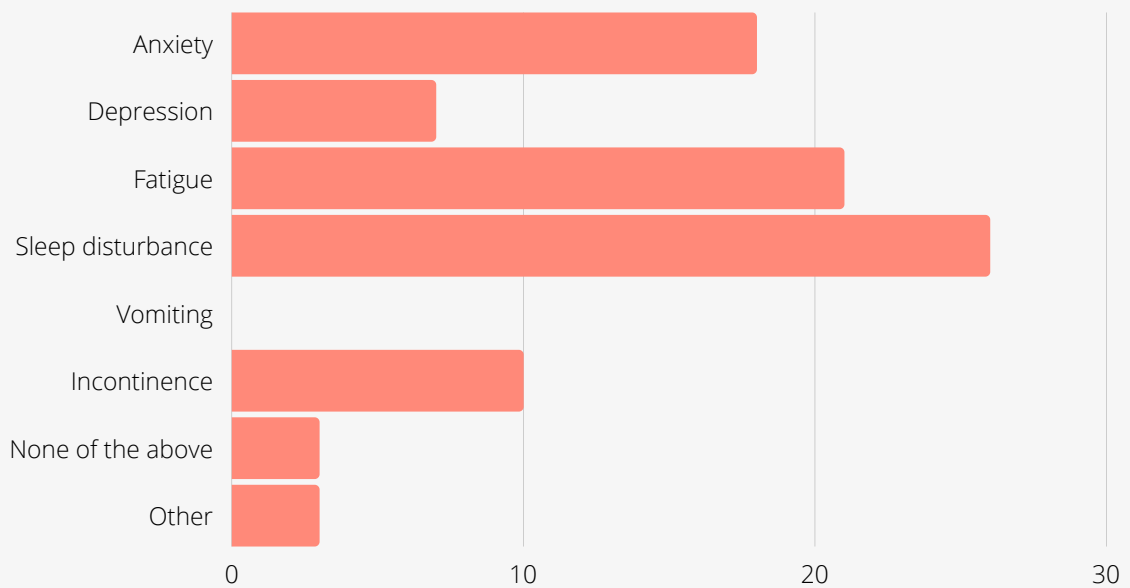


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**WHICH AREAS/ELEMENTS OF YOUR LIFE HAVE BEEN IMPACTED DUE TO YOUR CHRONIC COUGH? PLEASE SELECT ALL THAT APPLY.**

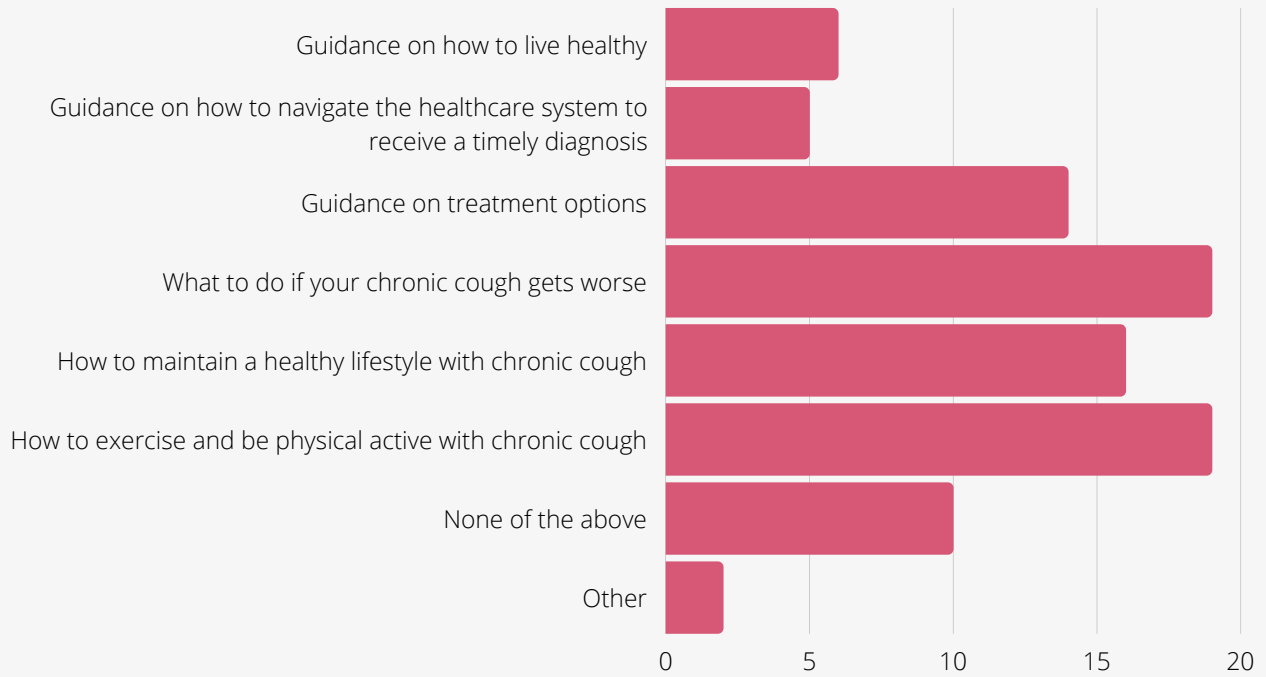


**HAVE YOU SUFFERED ANY OTHER ILL EFFECTS AS A RESULT OF YOUR CHRONIC COUGH? IF YES, PLEASE CHECK ALL THAT APPLY:**

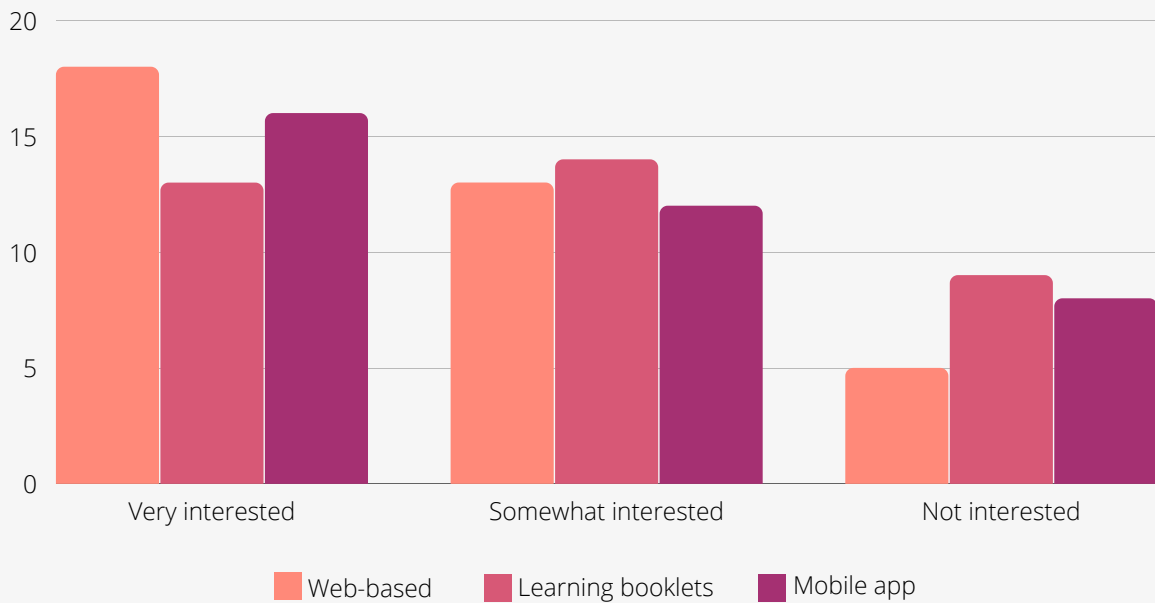




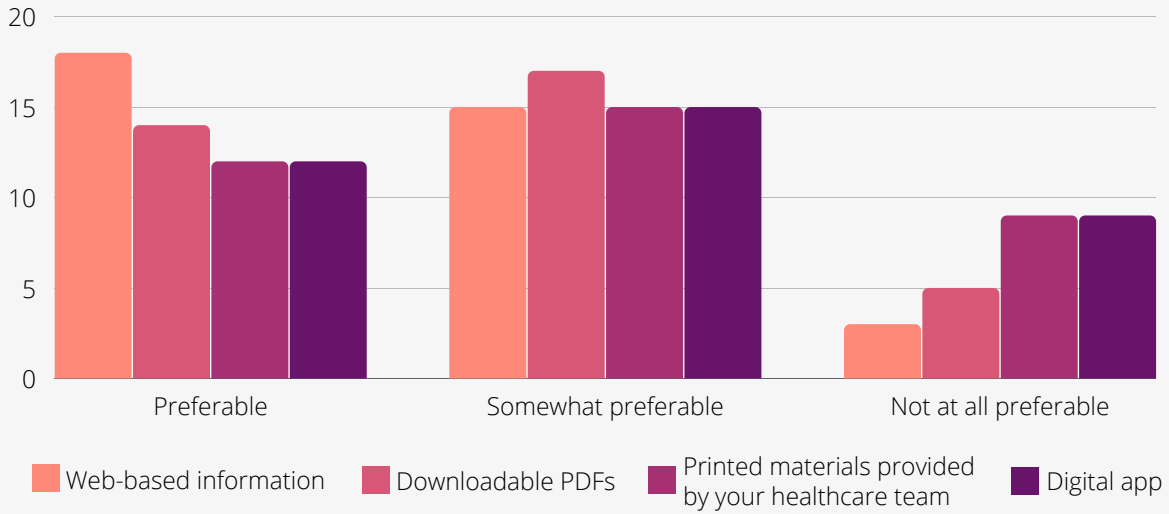
**ARE THERE ANY ELEMENTS REGARDING CHRONIC COUGH FOR WHICH YOU NEED MORE INFORMATION? PLEASE CHECK ALL THAT APPLY:**



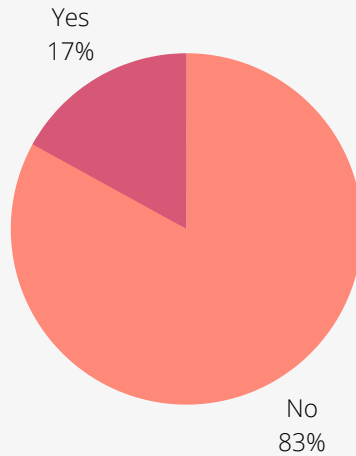
**IF AN APP, WEB-BASED OR PRINTED MODULE-BASED TOOL FOR COUGH MANAGEMENT WERE AVAILABLE, WOULD YOU BE INTERESTED IN CONSULTING SUCH A TOOL?**



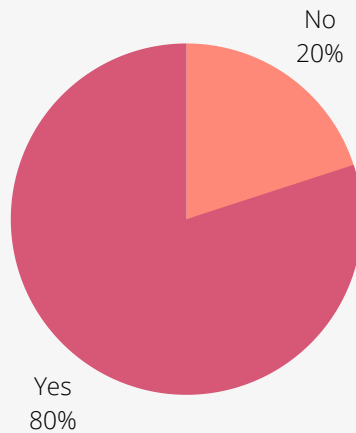
**HOW WOULD YOU PREFER TO READ THIS GUIDANCE TO HELP YOU MANAGE CHRONIC COUGH?**



**ARE YOU AWARE OF ANY SPECIALIST COUGH CLINICS?**

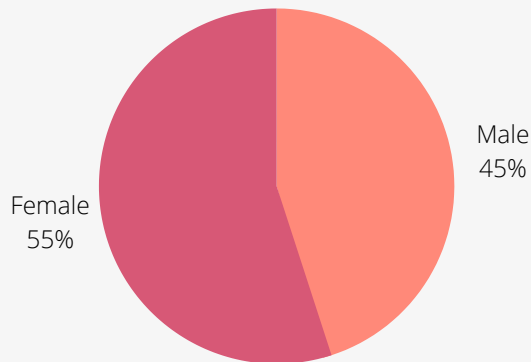


**DO YOU THINK A DEDICATED COUGH CLINIC WOULD BE BENEFICIAL FOR YOU?**

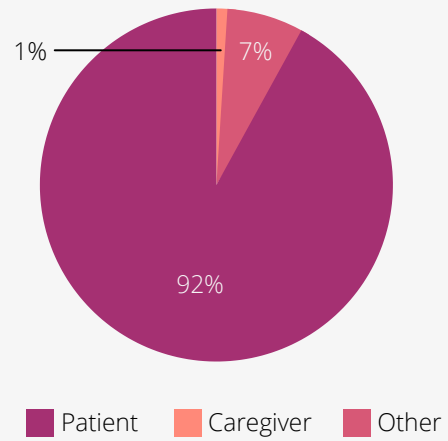


## DEMOGRAPHICS

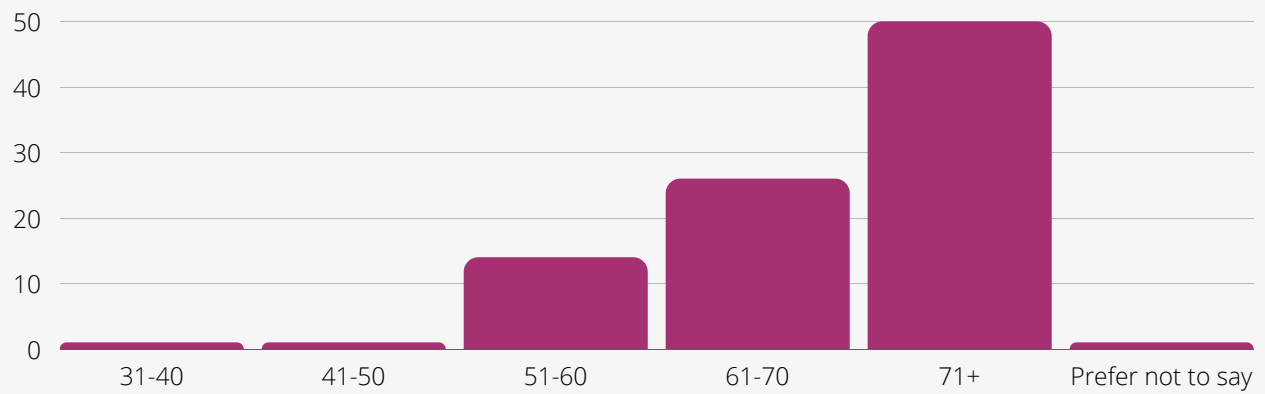
### GENDER



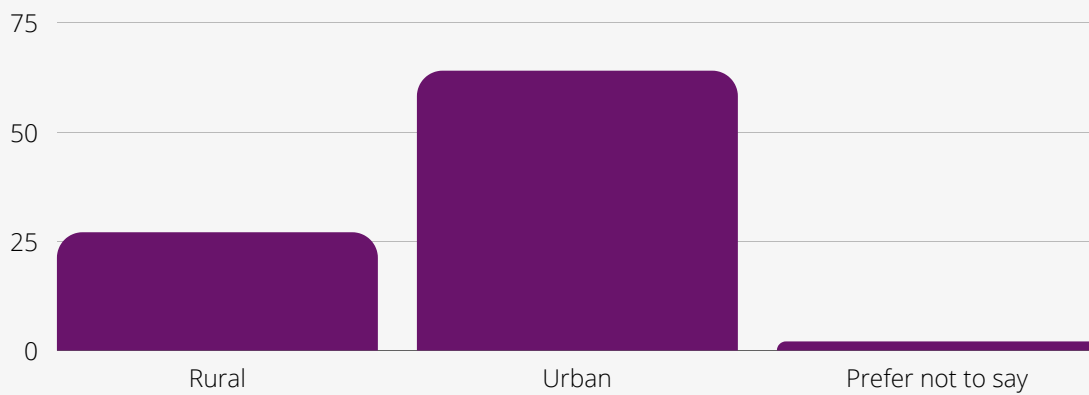
### WHICH OF THE FOLLOWING BEST DESCRIBES YOU?



### AGE



### PLACE OF RESIDENCE



# APPENDIX II

## BARRIERS/GAPS AND SOLUTIONS

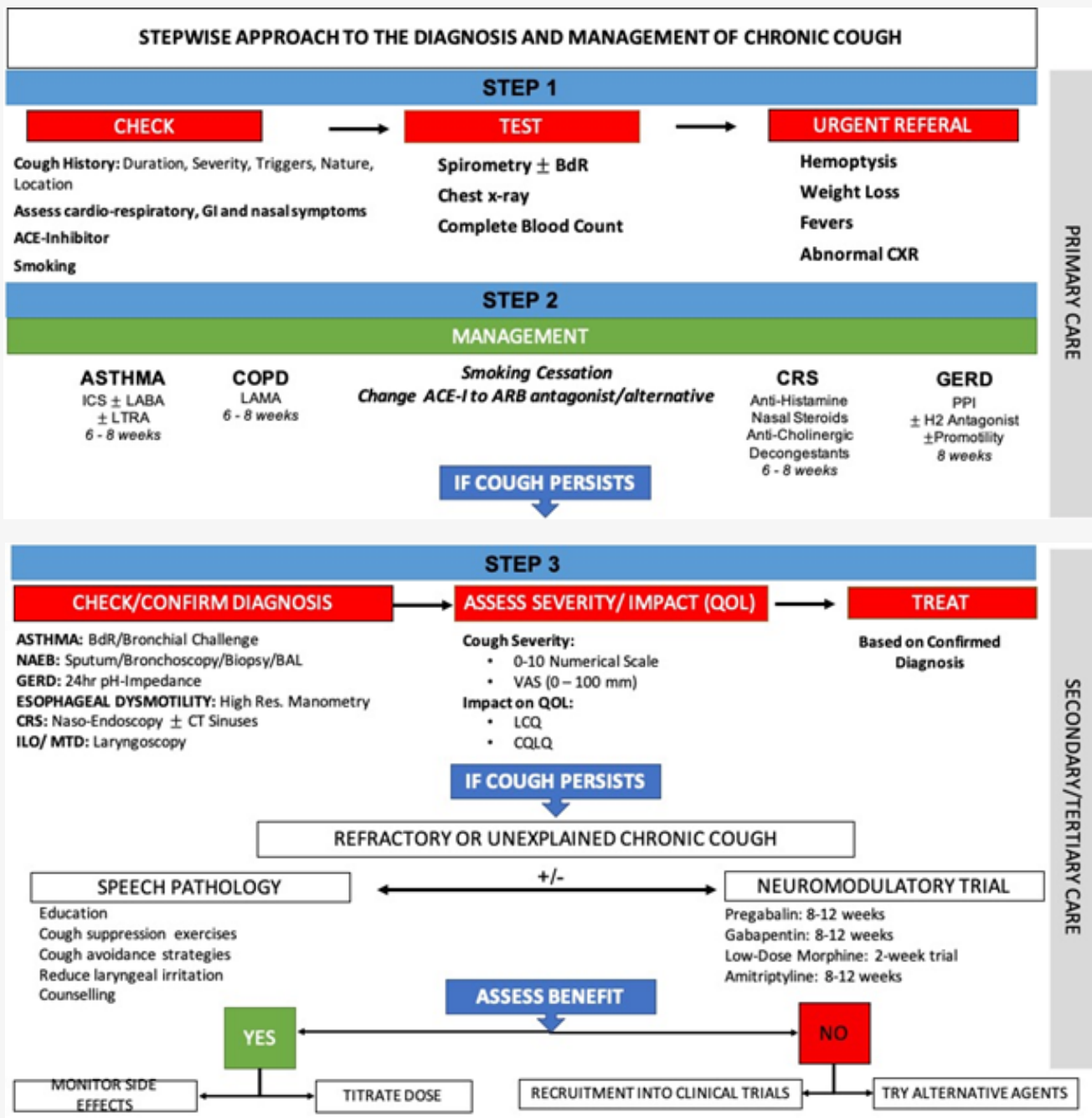
CHART DEVELOPED BY RESPIPLUS SCIENTIFIC PANEL

BARRIERS/GAPS	POSSIBLE SOLUTIONS
<b>DIAGNOSIS</b>	
Lack of patient understanding of the multiple etiologies and comorbidities associated with chronic cough	Patient education <ul style="list-style-type: none"> <li>• Access to credible information (website, webinars, pamphlets, etc.)</li> </ul>
Lack of knowledge among primary care providers of proper diagnosis of chronic cough	Primary care physician education <ul style="list-style-type: none"> <li>• Focused undergraduate medical education about chronic cough</li> </ul>
<b>REFERRAL</b>	
Excessive wait times to see providers for diagnosis and management of chronic cough	Resource planning to ensure adequate numbers of primary care providers, specialists and allies respiratory health professionals  Identification of local champions with chronic cough expertise in each region  Listing of Canadian cough clinics  Establishment of ideal referral times <ul style="list-style-type: none"> <li>• To see primary care physician about chronic cough</li> <li>• To see specialist after referral from primary care physician</li> <li>• To chronic cough clinic after referral</li> </ul>
<b>MANAGEMENT/INVESTIGATION</b>	
Excessive and inappropriate use of OTC cough medications	Pharmacist education: <ul style="list-style-type: none"> <li>• Brief interactive intervention for pharmacists</li> <li>• Article(s) in pharmacist publication</li> <li>• Better monitoring of cough medications of potential abuse</li> <li>• Acknowledgement and action on potential pharmacist conflict of interest in selling cough medications</li> <li>• Choosing Wisely initiative to education and change behavior related to inappropriate prescribing and selling of cough suppressant medications</li> </ul>

<b>BARRIERS/GAPS</b>	<b>POSSIBLE SOLUTIONS</b>
<b>MANAGEMENT/INVESTIGATIONS</b>	
Lack of knowledge among primary care provider of proper management of chronic cough	Primary care physician education <ul style="list-style-type: none"> <li>• Focused undergraduate medical education about chronic cough</li> </ul>
Lack of access by primary care provider to appropriate diagnostic tools for assessing cough	Identification of key tests primary care providers can do and have access to for assessing chronic cough (spirometry, chest x-ray and CBC)
Lack of good, validated tools or scales to assess chronic cough	Development and validation of cough assessment tools Development of reliable self-assessment tools for patients (e.g. apps)
Lack of paradigm or model for proper management of chronic cough	Develop paradigm (see Appendix II)
Lack of approved treatment for undefined chronic cough	Develop and approve new drugs. Encourage cough clinics to participate in research
Lack of awareness of role of certified respirator educators and speech and language pathologists in managing chronic cough	Encourage more interest in chronic cough among allied respiratory health professionals and provide appropriate education
<b>MONITORING AND FOLLOW-UP</b>	
Lack of knowledge of incidence and clinical implications of cough as a symptom of Long COVID	Publication and dissemination of observational data and clinical studies

# APPENDIX III

## STEPWISE APPROACH TO THE DIAGNOSIS AND MANAGEMENT OF CHRONIC COUGH IN PRIMARY AND SECONDARY CARE



With permission from corresponding author Satia, I.

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# END NOTES

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