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Review

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How Will a Treatable Traits Approach Reshape Clinical Practice in Chronic Cough?

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ABSTRACT

Chronic cough, which affects 5%–18% of adults, has traditionally been considered a symptom defined by its duration. However, recent advances in understanding the pathophysiology of chronic cough have prompted the concept that chronic cough may exist as a distinct clinical entity driven by neuronal dysregulation and cough hypersensitivity. This evolving perspective recognizes various treatable traits and clinical characteristics which support the notion of cough as a disease entity and beyond that of a symptom-based classification. Initially developed for asthma and chronic obstructive pulmonary disease, the treatable traits approach has now been extended to chronic cough management, offering a more personalized treatment model. It focuses on identifying modifiable traits that significantly impact patient outcomes. However, challenges remain in implementing this model, including the need for trait validation, biomarker development, staff training, and the integration of new therapies. Despite these challenges, the treatable traits approach provides a promising framework for refining chronic cough management strategies and improving patient care.

Keywords: Cough; chronic cough; chronic care model; biomarkers; precision medicine

INTRODUCTION

Over the past decade, the understanding of chronic cough has shifted from a symptom-based model to a distinct disease entity characterized by neuronal dysregulation[1,2] and cough hypersensitivity.[3] While it was traditionally defined by duration (≥ 8 weeks in adults), recent insight emphasize the importance of underlying pathophysiological mechanisms and identifiable treatable traits that contribute to the persistence and treatment response of cough.

Chronic cough affects 5%–18% of the adult population[4-8] and impairs quality of life, leading to physical complications, psychological distress, and social isolation.[9,11] Patients frequently

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report abnormal throat sensations and irresistible coughing triggered by trivial stimuli, distinguishing pathological cough from protective or voluntary cough responses.[12-14] These hypersensitivity features represent a deviation from normal protective functions and support the concept of chronic cough as a distinct clinical entity.[15]

Evidence suggests that 10%–50% of chronic cough patients seeking specialist care may have refractory or unexplained cough, with most experiencing cough for 5–10 years before receiving appropriate diagnosis and treatment.[16-18] During this prolonged period, many patients encounter significant challenges in the healthcare journeys, where their condition is often neglected or misattributed to psychological factors.[19] They are also exposed to various empirical treatments and investigations, such as computed tomography scans, antibiotics, oral corticosteroids, or narcotic drugs.[18,20-24]

The change in perspective of chronic cough parallels developments in pain research, where chronic pain, once considered purely a symptom, is now recognized as a disease requiring targeted management.[25] Recognizing chronic cough as a disease in its own right provides a stronger foundation for developing targeted therapies that address its root causes rather than merely treating associated conditions.[3,26] This disease concept is accompanied by advances in evaluation and intervention strategies tailored to treatable traits.

THE TREATABLE TRAITS APPROACH TO CHRONIC COUGH

The treatable traits approach, initially developed for severe asthma and chronic obstructive pulmonary disease (COPD),[27] has now been extended to chronic cough.[28,29] This approach emphasizes identifying and targeting specific, measurable, and modifiable traits, rather than adhering to rigid etiological classifications in managing chronic complex conditions that are not adequately addressed by traditional disease-based frameworks. This is a patient-centered rather than a disease-centered approach, making it particularly relevant to complex medical conditions. Therefore, we believe that the underlying principles can be similarly applied across chronic airway disorders, including chronic cough, severe asthma, and COPD, although the relevance of each trait may vary.

According to expert consensus, treatable traits should meet 3 key criteria: 1) the trait must significantly impact patient outcomes and overall disease burden; 2) it should be assessable through validated tools such as biomarkers or structured questionnaires; and 3) it must have evidence-based interventions that can improve patient outcomes.[30]

The British Thoracic Society (BTS) guidelines now recommend this approach for chronic cough management in adults.[29] The BTS guidelines have proposed several potential treatable traits in chronic cough, including smoking, angiotensin converting enzyme (ACE) inhibitor use, airway eosinophilia (or type 2 [T2] airway inflammation), productive cough, chronic rhinosinusitis, inducible laryngeal obstruction, reflux, obesity, obstructive sleep apnea (OSA), anxiety, and cough hypersensitivity.[29] However, the strength of evidence supporting these traits varies considerably, necessitating a careful approach to their implementation in clinical practice and further studies for confirming key treatable traits. Although strong evidence for certain treatable traits remains limited, we recommend early identification and management of the following key treatable traits, when chest X-rays are normal and red flag signs are absent (**Fig. 1**).

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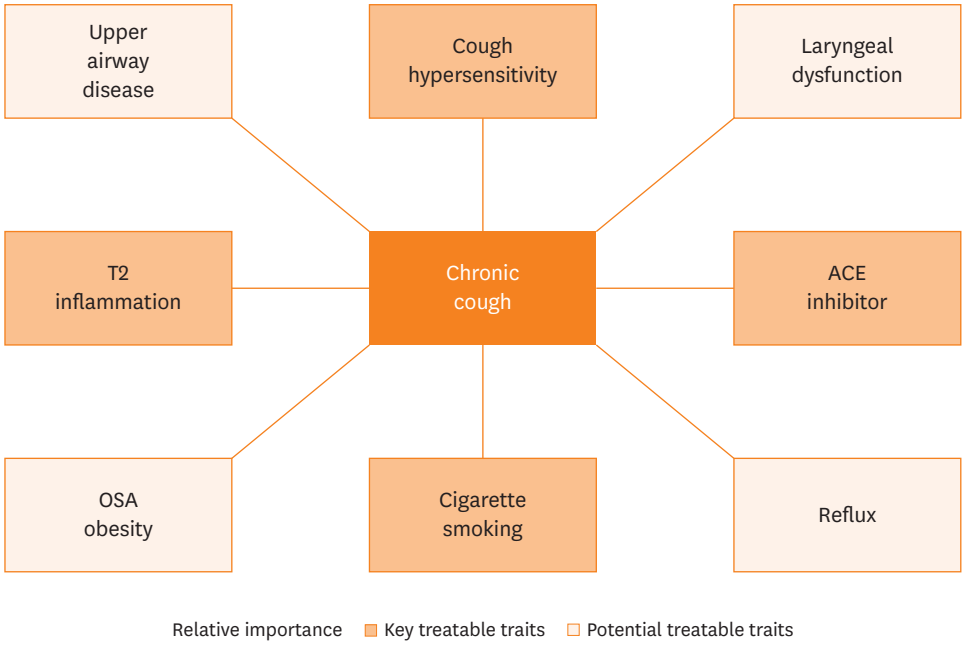

Fig. 1. The treatable traits framework in adult chronic cough. This diagram illustrates the treatable traits approach to chronic cough management in adults, highlighting key modifiable traits that contribute to disease burden. The model emphasizes an individualized, precision medicine approach by targeting these traits through validated assessments and evidence-based interventions. The classification of traits (key and potential traits) is based on current guidelines and available clinical evidence,[28,29] recognizing that their clinical relevance and therapeutic potential may evolve with ongoing research.
T2, type 2; ACE, angiotensin converting enzyme; OSA, obstructive sleep apnea.

KEY TREATABLE TRAITS AND THEIR MANAGEMENT

Cigarette smoking

The causal relationship between cigarette smoking and chronic cough has been long documented through epidemiological and observational studies.[31-33] While ethical considerations preclude randomized clinical trials (RCTs) on smoking cessation, substantial evidence supports smoking cessation as a fundamental intervention in chronic cough management.[34] Beyond its direct impact on cough, smoking cessation provides broad health benefits that make it an essential component of treatment.[35,36] However, clinicians should note that the immediate post-cessation period may paradoxically worsen cough symptoms due to enhanced cough sensitivity from nicotine withdrawal.[37] In such cases, nicotine replacement therapy may help reduce this rebound effect.[29]

ACE inhibitor use

The use of ACE inhibitors represents a clearly defined and easily modifiable treatable trait, as it is a sensitizer of the cough reflex.[38] When identified, ACE inhibitors should be discontinued in all patients with chronic cough. Alternative medications, such as angiotensin receptor blockers, can be substituted to maintain cardiovascular disease management while eliminating this contributor to cough.[39]

T2 inflammation

Airway T2 inflammation is a key treatable trait in chronic cough, particularly in patients with eosinophilic airway diseases such as cough variant asthma or eosinophilic bronchitis. The underlying mechanism involves the activation of T2 cytokines, specifically interleukin (IL)-4, IL-5, and IL-13, which play crucial roles in driving airway eosinophilia and airway hyperresponsiveness.[40]

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Assessing T2 inflammation can be accomplished through several complementary approaches in clinical practice. Sputum eosinophilia, defined as an eosinophil count exceeding 3%, has been the gold standard as it provides direct evidence of airway T2 inflammation. However, the widespread implementation of sputum analysis faces practical limitations due to the technical expertise required and processing time constraints, making it impractical in many clinical settings. Alternative biomarkers have emerged as more practical options for routine clinical use. These include fractional exhaled nitric oxide (FeNO) levels ≥ 25 ppb and peripheral blood eosinophil count ≥ 0.3×10^9/L.[29] These surrogate markers have demonstrated good correlation with airway eosinophilia and offer significant advantages in terms of accessibility and rapid results.[41] Among these markers, FeNO can be more useful as it directly reflects T2 inflammation in the lower airways and provides results more rapidly and less invasively than blood tests.[41] In chronic cough evaluation, FeNO demonstrates high specificity (85%) for predicting cough variant asthma or eosinophilic bronchitis in adults.[42] FeNO measurement may help avoid unnecessary empirical inhaled corticosteroid (ICS) trials by identifying patients most likely to benefit from targeted therapy.

The management of T2 inflammation typically begins with a therapeutic trial of ICS for an initial duration of 2–4 weeks. The choice of the specific ICS medication and the delivery device should be individualized, considering factors such as patient preference, coordination ability, and economic considerations. However, a high-dose ICS regimen may be more beneficial as the initial treatment.[43]

Cough response to the ICS treatment response can be gradual in patients with chronic cough and T2 inflammation.[44] Therefore, a short-course of oral corticosteroids may be considered a treatment option for patients with severe cough and high T2 inflammation levels; however, it may be also useful as a diagnostic testing to identify corticosteroid-responsive cough.[45] Empirical trials with ICS could be considered in primary care settings where T2 inflammation tests are not accessible. However, distinguishing between pharmacological and placebo effects can be challenging in such cases.[43]

When patients with T2 inflammation show insufficient response to initial ICS therapy, several treatment escalation strategies should be considered. A common first step involves increasing the ICS dose to achieve better control of T2 airway inflammation and associated symptoms, guided by repeated FeNO measurements, as recommended in previous guidelines for symptomatic patients with asthma.[46] However, clear guidance on the use of repeated FeNO measurements, including timing, intervals, and cutoff values, and ICS dose adjustments in the context of chronic cough is currently lacking. In patients where airway hyperresponsiveness or airflow obstruction is documented, the addition of a long-acting bronchodilator may provide additional benefit.[1] In patients with severe refractory disease, T2-targeted biological therapies may be considered[47]; however, further studies are needed to determine their effects on cough related to T2 inflammation.

Cough hypersensitivity

Over the past decade, cough hypersensitivity has been recognized as both a treatable trait and a core mechanism defining a disease entity, termed Cough Hypersensitivity Syndrome.[48-50] While previous guidelines positioned anti-tussive or cough-modulating medications as a last resort in clinical pathways (only after extensive etiology-targeted therapies had failed),[1,51] we propose that addressing cough hypersensitivity should be considered earlier in the evaluation pathways for treatable traits.

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In medicine, all treatment decisions should be guided by a thorough evaluation of the risk-benefit balance. In our view, just as the appropriate use of antipyretics may not interfere with the treatment of infectious diseases,[52,53] the judicious use of cough suppressants in the management of chronic cough, when red flag signs, treatable traits, infections, aspiration, and malignancy have been carefully considered, may not only help reduce symptom burden but also lead to a more rapid improvement in patient quality of life.

Cough hypersensitivity can be assessed through several methods. A thorough clinical history should focus on identifying specific cough-triggering factors and characterizing throat symptoms.[54] Validated questionnaires provide structured assessment tools, including the Hull Airway Reflux Questionnaire,[55] Newcastle Laryngeal Hypersensitivity Questionnaire,[56] and Cough Hypersensitivity Questionnaire.[57,58] Objective measures can be used through cough challenge tests using capsaicin, citric acid, or adenosine triphosphate inhalation[59,60]; however, these are usually reserved for research purposes. It is a major challenge that these subjective and objective tools have not been validated for clinical utility; therefore, their validation is likely to be a key issue in advancing the management of cough hypersensitivity.

Although the exact mechanisms underlying cough hypersensitivity remain unclear, recent evidence suggests that dysregulated sensory processing in the brainstem, particularly in the medulla and midbrain, plays a crucial role.[61] This shifts the focus from peripheral vagal hypersensitivity to central sensitization as a major contributing mechanism. The therapeutic benefit of centrally acting drugs, such as opiates and gabapentinoids reported by some chronic cough patients, may be through modulation of disordered central neuronal processing and reinforces the concept of distinct treatable traits of central sensitization in refractory chronic cough.

Management of cough hypersensitivity encompasses both pharmacological and non-pharmacological approaches. The pharmacological arsenal includes low-dose opioids (as alluded to above), typically administered as slow-release morphine at 5–10 mg twice daily, which has shown efficacy in controlled trials.[62,63] However, morphine is not allowed as an anti-tussive in many countries including Korea, and codeine is being used as an alternative.[23] In a recent registry study of Korean adults with chronic cough attending referral clinics, 16.7% were classified as codeine treatment responders (showing a rapid and clear response), and 18.7% were partial responders.[16] In the case of responders, the antitussive effects of opioids may be rapid, strong, and usually apparent within 1 weeks after initiation of therapy.[64] Also, the dose of codeine may be reduced in those excellent responders, for example, from 60 mg to 20 mg per day or less. Older women with chronic dry cough may respond well to codeine treatment.[16] Adverse reactions, including nausea and constipation, are generally mild in adults but can occur in up to 50% of patients.

Gabapentinoids (gabapentin and pregabalin) are another medication class for managing cough hypersensitivity.[65,66] However, their treatment response is less evident than that of opioids, and they frequently cause neurological adverse effects.[1,65,66]

Novel P2X3 antagonists, particularly gefapixant, have demonstrated promising results in clinical trials and represent an important advancement in targeted therapy.[67,68] Gefapixant, the first-in-class P2X3 antagonist, is now available in Japan and European countries. Recent real-world data from Japan[69] suggests that more than 50% of patients show clinically significant improvement, with some patients being “super responders.” Treatment response

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is typically rapid, occurring within 2–4 weeks, and effects can persist for several months even after discontinuation in responsive patients. Notably, patients with asthmatic cough and significant laryngeal symptoms showed particularly good responses to gefapixant treatment in Japanese patients, suggesting potential predictive factors for treatment success.[69] Other emerging pharmacological options include TRM8 agonists and NK1 receptor antagonists, which are currently under investigation.[70]

Non-pharmacological cough control interventions play an important role in management and typically involve multimodal approaches, including breathing strategies, laryngeal hygiene, and psychosocial support by speech pathologists.[71] The treatment has demonstrated significant benefits in reducing cough frequency and improving quality of life in RCTs.[72,73] Despite growing endorsement in international guidelines,[1,29,51] access to specialized services and trained professionals remains limited in many regions, highlighting the need for broader implementation strategies.

Other potential treatable traits

Various traits, including reflux, esophageal dysmotility, upper airway diseases, OSA, obesity, and laryngeal dysfunction are associated with chronic cough and its clinical outcomes. However, in this review, we classify them as potential treatable traits, as their treatability or causal relationships with chronic cough have not been confirmed through RCTs.

The relationship between acid reflux and chronic cough has been extensively studied, though the evidence supporting its treatment remains limited and controversial.[1] In patients with proven acid reflux confirmed by 24-hour pH monitoring or with positive dyspeptic symptoms, proton pump inhibitors may be effective; however, response rates to acid suppression remain relatively low.[74] Indiscriminate use of acid suppressant drugs should be avoided due to limited evidence from RCTs, particularly in the absence of peptic symptoms or objective evidence of acid reflux.[1,51,75]

The role of airway reflux, such as micro-aspiration of non-acids and esophageal dysmotility, likely plays an important role in refractory chronic cough. Approximately two-thirds of refractory cough patients exhibited esophageal dysmotility on high resolution manometry.[76] However, establishing this diagnosis remains challenging outside of specialist centers.

Nasal symptoms frequently occur in patients with chronic cough. However, direct evidence supporting the effectiveness of rhinosinusitis-targeted local treatments in improving chronic cough is lacking. While non-sedating H1-antihistamines are commonly prescribed for chronic cough associated with nasal symptoms, their specific benefit for cough outcomes remains unproven,[77] although their effectiveness for nasal allergic symptoms is well-established. Roles of intranasal corticosteroids or nasal irrigation remain controversial in relation to cough.

Obesity is another potentially modifiable trait in chronic cough. Mechanical factors associated with obesity, such as increased abdominal pressure, gastroesophageal reflux, and altered breathing patterns, may trigger and perpetuate chronic cough.[78] While weight reduction is likely to be beneficial in alleviating cough, its effectiveness warrants confirmation through RCTs.

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OSA is a potentially overlooked comorbidity and treatable trait in chronic cough, especially among patients presenting with risk factors including snoring, excessive daytime sleepiness, or obesity. Although continuous positive airway pressure therapy has demonstrated promising improvements in cough-related quality of life, definitive conclusions await larger multicenter trials with objective cough assessment.[79]

Laryngeal dysfunction is a frequent comorbidity in both chronic cough and severe asthma, is often misdiagnosed as severe asthma alone, leading to unnecessary treatments such as the administration of oral corticosteroids.[80,81] Diagnosis requires laryngoscopy with provocation, performed during quiet respiration and phonation, and may include additional assessment during trigger exposure when appropriate.[82] Management primarily involves comprehensive speech and language therapy.[83]

HOW IT WILL RESHAPE OUR CLINICAL PRACTICE

The treatable traits approach offers several advantages over traditional anatomic diagnostic protocols by shifting the focus from broad disease labels to specific, measurable, and modifiable characteristics that directly guide treatment. Conventional diagnostic categories such as asthma, upper airway diseases, or gastroesophageal reflux disease (GERD) fail to capture the heterogeneity within these conditions, leading to suboptimal treatment selection. For instance, asthma is not always eosinophilic, and GERD is not necessarily acidic. Additionally, in cases without clear etiologies, empirical trials have been often recommended, but distinguishing true treatment effects from placebo responses or regression to the mean remains challenging. Thus, within the treatable traits' framework, management based on measurable traits is preferred over stepwise empirical treatments and unfocused diagnostic testing.

History-taking, physical examination, and chest X-ray remain important foundational elements, and patients with evident lung parenchymal disorders or red flag signs such as fever, weight loss, hemoptysis, or aspiration should be promptly referred to appropriate specialists or investigated further as indicated.

In patients without apparent underlying diseases or red flag signs, the initial evaluation of patients with chronic cough must include systematic screening for potential treatable traits. This includes careful evaluation of modifiable environmental and medication factors, such as smoking and ACE inhibitor use, alongside measurement of key inflammatory markers such as blood eosinophils and FeNO. Cough hypersensitivity is one of the major treatable traits and it can be effectively managed with anti-tussive therapies in selected patients. In patients with relevant symptoms or risk factors, the assessment should also include screening for other potential treatable traits, such as GERD, upper airway diseases, or OSA (**Fig. 2**).

Treatment decisions should be guided by the strength of evidence supporting each intervention, the likelihood of trait reversibility, and considerations of both risk and cost-effectiveness. Monitoring and treatment adjustments take on new importance under the treatable traits approach. Each identified trait may require specific outcome measures and appropriate timelines for assessment. Clinicians must regularly evaluate cough severity and impact, using structured tools,[54] while monitoring relevant inflammatory markers where appropriate. Treatment plans should undergo regular reviews and adjustments based on

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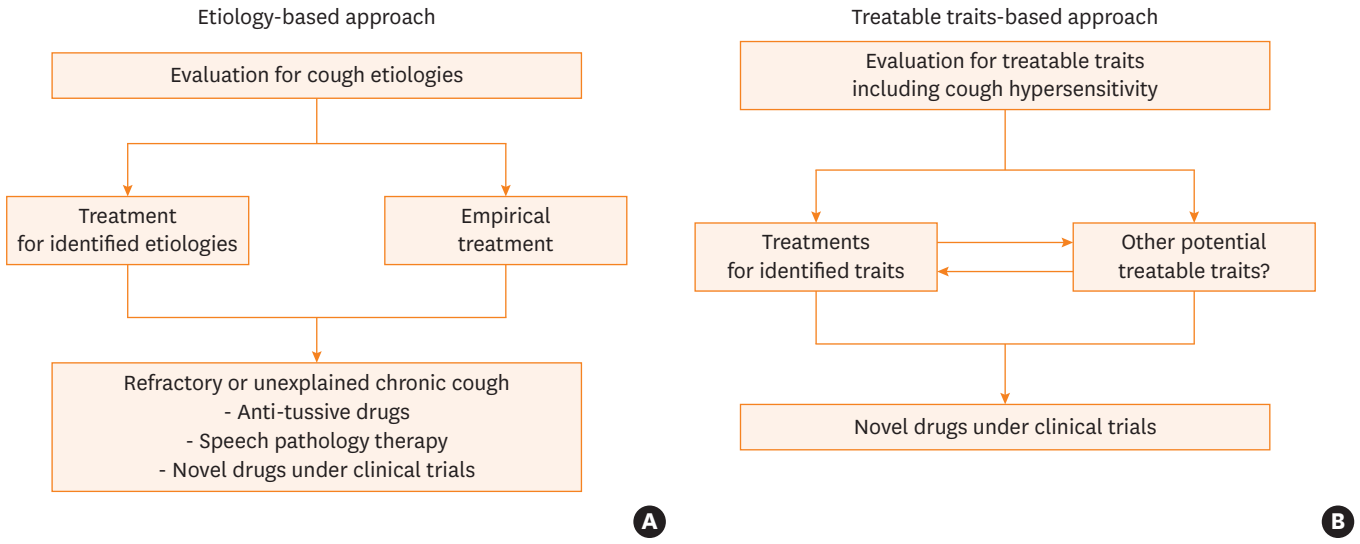

Fig. 2. Comparison of etiology-based and treatable traits-based approaches in chronic cough management. This schematic diagram contrasts 2 paradigms in chronic cough evaluation and treatment. (A) The etiology-based approach follows a traditional diagnostic framework, where evaluation focuses on identifying underlying cough etiologies, leading to either specific treatment for diagnosed conditions or empirical therapies. If the cough remains refractory or unexplained, anti-tussive medications, speech pathology therapy, or novel drugs under clinical trials may be considered. (B) The treatable traits-based approach shifts the focus toward identifying modifiable traits, including cough reflex hypersensitivity. Following evaluation, targeted treatments are applied to identified traits, with continuous reassessment for additional or emerging treatable traits until achieving control of cough. Reliance on empirical trials without evidence of biomarkers is not recommended. Novel drugs under clinical trials may be incorporated for cases of persistent cough that do not respond to currently available treatments.

observed responses to trait-targeted interventions, rather than trying empiric therapies without clear evidence of benefit. In cases of persistent cough unresponsive to current treatments, novel drugs under clinical trials may be considered (**Fig. 2**).

Implementation challenges include developing structured assessment protocols, training staff in assessment techniques, and establishing systems to monitor multiple interventions simultaneously. Healthcare providers must also consider cost implications and resource allocation to ensure sustainable implementation. Given these challenges, treatable trait-based care may be more effectively implemented for the management of refractory chronic cough in specialist cough clinics.[54] However, the fundamental principles of identifying key treatable traits can be uniformly applied as a standard in all practice settings.

Looking to the future, several key developments in clinical practice and research are needed to successfully implement the treatable traits approach. Clear clinical pathways must be established for the assessment and management of each trait, including well-defined criteria for therapy escalation and tapering. Given the comprehensive nature of trait assessment and management, efficient systems for coordinating care among different specialists are essential.

These developments in clinical practice must be supported by continued research into biomarker development, treatment response patterns, and disease mechanisms. Investigations are warranted to confirm truly relevant traits and develop clinical strategies to evaluate and manage them. In this review, we proposed several key traits based on the currently available literature and our clinical experience. However, we acknowledge that our proposal was not derived from a systematic review and should be updated as new evidence emerges.

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The integration of new targeted therapies for cough hypersensitivity, such as P2X3 antagonists,[67-69] into clinical practice provides opportunities to better understand treatment response patterns and potentially identify new treatable traits. This ongoing evolution requires sustained commitment to research and development, alongside practical considerations of implementation in diverse clinical settings.

CONCLUSIONS

The treatable traits approach represents a paradigm shift in chronic cough management, moving beyond the traditional symptom-based classification toward a precision medicine model. This approach will reshape clinical practice guidelines for chronic cough management, by prioritizing key treatable traits over sequential empirical therapeutic trials for possible etiologies.

While it offers the potential for more personalized and effective treatment, it also demands significant structural and procedural changes in clinical practice, as well as advances in the measurement and monitoring. Its future success will depend on our ability to continuously refine treatable traits while developing practical tools for their assessment and management in routine care. Despite implementation challenges, the treatable traits approach offers a promising framework to transform chronic cough management to targeted therapy addressing underlying mechanisms. This evolution aligns with broader trends toward precision medicine and has the potential to significantly improve outcomes for patients affected by this often-debilitating condition.

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