Adult Asthma Diagnosis: Physician Reported Challenges in Alberta-Based Primary Care Practices

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Abstract

Introduction: An estimated 8.1% of Canadians adults have asthma. While there are challenges associated with the use of objective measurement of lung function in the diagnosis of asthma, we are uncertain of the barriers that impact the use of objective measures, and have limited understanding of the challenges experienced by primary care providers in diagnosis of asthma. The objectives of this quality improvement initiative were to identify primary care providers' methods of diagnosing asthma and to identify challenges with diagnosis.

Methods: An online survey was disseminated using a snowball methodology.

Setting: Primary care practices in Alberta, Canada.

Participants: A total of 84 primary care providers completed the survey.

Main Outcome Measures: Participants were asked their ideal and sufficient methods for diagnosing asthma and to identify challenges in their practice related to asthma diagnosis.

Results: They identified full pulmonary function testing (54%), pre- and postbronchodilator spirometry (54%), complete history and physical (42%), peak flow measurement overtime (26%), pulmonary consult (26%), and trial of asthma medication(s) (23%), as ideal methods of diagnosing asthma. The most significant barriers to diagnosis included episodic care—care provided typically during times of worsening symptoms without ongoing preventative/maintenance care (55%), patient follow-up (44%), conflict between clinical impression and pulmonary function results (43%), patient already on asthma medications (43%), and interpreting spirometry/pulmonary function results (39%).

Conclusion: The results of this survey indicate that the majority of primary care providers would choose full pulmonary function testing or pre- and postbronchodilator spirometry as the ideal methods of diagnosing asthma. However, barriers related to the nature of asthma care, patient factors, and challenges with diagnostic testing create challenges. This study also highlights that primary care providers have adapted to challenges in leveraging objective measurement and may rely upon other methods for diagnosis such as trials of medications.

Keywords
asthma, chronic illnesses, diagnostics, practice, primary care, pulmonary

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Asthma is an inflammatory disorder of the airways characterized by a combination of compatible clinical history, associated with variable airflow limitation and airway hyperresponsiveness to endogenous or exogenous stimuli (Lemiére et al., 2004; Lougheed et al., 2012). In 2014, Statistics Canada (2014) estimated that 8.1% of Canadians aged 12 and older had been diagnosed with asthma. Asthma in the community is often diagnosed empirically rather than through objective measurement (Aaron et al., 2017). An Ontario retrospective study found that only 42.7% of patients diagnosed with asthma receive objective measures of lung function within a year prior and 2.5 years postdiagnosis (Gershon et al., 2012). Aaron et al. (2017) recently found that one third of participants previously diagnosed with asthma by a physician did not have evidence of asthma when they were evaluated, consistent with previous research (Linden Smith et al., 2004; Lucas et al., 2008; Monténéry et al., 2002). The objectives of this quality improvement initiative were to identify primary care providers’ perceived ideal and sufficient methods of diagnosing adult asthma, to identify challenges with diagnosing asthma in primary health care, and to suggest tools that may facilitate adult asthma diagnosis.

Methods

An online survey was developed using Survey Select™ to identify the perceived barriers in primary care for establishing an appropriate diagnosis of asthma in adult patients. Survey questions were constructed by the Asthma Working Group (AWG) of the Respiratory Health Strategic Clinical Network™ (RHSCN) and the Primary Data Support Team, Analytics Department of Alberta Health Services. The Primary Data Support Team has extensive experience in survey design and evaluation and provided major input into the overall design of the survey including the specific wording of individual questions. AWG comprises multidisciplinary content experts aiming to address clinical challenges related to best practice management of asthma in the province. Through this understanding, the AWG would then be able to identify gaps to target for future quality improvement initiatives.

The survey collected only basic demographic data, to facilitate anonymous responses. Demographics included age group of participant, sex, years in practice and the location (city/town) of their practice. In addition to the demographic data, the survey included 11 multiple choice questions and 2 open-ended questions. The multiple choice questions focused on the diagnostic requirements the clinicians felt were ideal and sufficient to diagnose asthma, the tools available to the clinician and team (such as guidelines, care maps, and algorithms), the use of spirometry to diagnose asthma, self-management tools available to the clinical team, and factors that would better enable access to asthma education. The two open-ended questions invited participants to identify their wish list of tools they would like to have to assist with asthma diagnosis and to specify additional barriers to diagnosing asthma that they encounter in their practice. A copy of the survey has been provided in Appendix.

The survey was disseminated through several methods, using a snowball methodology. It was emailed to key contacts within three rural Primary Care Networks (PCNs) with a request to disseminate broadly. In Alberta, PCNs aim to improve access and primary care delivery for patients in the province through a coordinated approach of health-care providers. It was twice included in the provincial newsletter of the Alberta Medical Association and reminders were sent to PCNs. As this work was a quality improvement initiative, guided by the AWG of the RHSCN, ethical approval was not required, similarly, written consent was not requested from participants. The brief survey required approximately 15 minutes to complete and was electronically submitted through a secure server.

Demographic data were reported as frequencies and percentages for all dichotomous, categorical and ordinal data. For partially completed surveys, analysis was performed on the completed questions. Quantitative data were reported using descriptive statistics such as percentage of respondents. Open-ended questions that generated qualitative data were analyzed using a thematic approach. The questions were analyzed individually, and data with similar patterns were coded together to develop the initial themes. The themed data were shared with the AWG for their input as content experts, and the themes were linked to the quantitative questions. The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Results

A total of 54 responses were received. For the 2 optional open-ended questions, 24 respondents (28.6%) provided a wish list of tools for the diagnosis of asthma and 29 respondents (34.5%) identified additional barriers to asthma diagnosis. Given the dissemination methodology, it is not possible to ascertain how many received the survey notification. Respondents were predominantly females (58%) and 51.9% were under 50 years of age. Almost half (47%) had been in practice more than 20 years. The greatest number of responses (60%) came from Alberta’s two major urban centers, Edmonton and Calgary.
Diagnosing Asthma in Adults

Respondents were asked to identify what they considered to be the ideal and sufficient requirements of diagnosing asthma, from six choices and the option to provide other responses. They identified full pulmonary function testing (54%), pre- and postbronchodilator spirometry (54%), complete history and physical (42%), peak flow measurement overtime (26%), pulmonary consult (26%), and trial of asthma medication(s) (23%) as ideal methods of diagnosing asthma. Sufficient ways to diagnose asthma included trial of asthma medication(s) (43%), pre- and postbronchodilator spirometry (32%), complete history and physical (35%), peak flow measurement overtime (32%), pulmonary consult (20%), and full pulmonary function testing (17%). Figure 1 shows a comparison of respondent’s choices for ideal and sufficient factors to diagnosis.

Participants ranked the challenges they experience identifying adult asthma in primary health care from a list of nine options, and the choice to state that they experienced no challenges (Figure 2). In addition, 29 (34.5%) respondents provided qualitative data related to barriers to diagnosis. Four themes arose such as patient factors, process factors, clinical challenges, and access issues. Patient factors included patient buy-in and compliance as well as issues related to the cost of medication and transportation. One process issue was encouraging PCNs to identify respiratory illness as a priority area. Clinical issues demonstrated the challenges related to co-management and differential diagnosis as well as providing acceptable clinical management strategies. One respondent stated: “we are generalists and it would be helpful to learn the asthma stuff and concurrently the differences (or more similarities it seems now) between asthma and Chronic Obstructive Pulmonary Disease (COPD) management.” Figure 3 shows the respondents’ beliefs about the benefits of various mechanisms of diagnosing adult asthma.

Tools and Resources to Aid in Diagnosis

Participants self-selected a variety of tools and resources that they use to assist with the diagnosis of adult asthma including Canadian Thoracic Society guidelines (38%), asthma algorithm (30%), asthma care map (13%), American Thoracic Society guidelines (6%), and Global Initiative for Asthma guidelines (5%). Thirty two percent of the respondents declared that they do not use any particular guidelines for diagnosis of adult asthma and 29.8% of respondents use asthma algorithms, while another 13.1% use asthma care maps for diagnostic assistance. Confirming the diagnosis of asthma prior to initiating treatment was considered somewhat important by 60% of respondents, while only 18% considered it essential. Respondents indicated that spirometry is used to diagnose asthma in 75% or more of their adult patients 52% of the time, while 23% indicated they use spirometry for diagnosis less than 50% of the time. Seventy-two percent of respondents agreed that a clinical pathway would be beneficial to diagnose and treat adult asthma, despite evidence that the clinical pathways in national and international guidelines are infrequently used, for example, approximately 5% (Cabana et al., 1999).

A total of 24 (28.6%) respondents identified the tools that would be in their wish list to assist with adult asthma diagnosis. Respondents indicated that access to resources is critical such as spirometry/lung function testing, timely access to specialists, access to Certified Respiratory Educators, and in house spirometry. One respondent stated: “I currently do have an Asthma Educator in my office monthly – what a wonderful

Figure 1. Ideal and Sufficient Strategies for Diagnosing Adult Asthma.
thing! I truly would be devastated if I did not have that service. This is not under the auspices of my PCN.” Respondents stated they would like access to training for staff.

**Patient Education**

Over half of respondents indicated that they demonstrate and observe medication technique with patients (54%) and provide brief self-management education (individual or group session; 51%). Additional educational interventions included completing an asthma action plan with the patient, identified by 32% of respondents; to refer outside the PCN for education was selected by 29%; to refer to support groups selected by 8%; and to recommend websites by 5%. Most participants (58%) selected that they would like to have access to skilled educators. Patient resources were identified as important by 41% of respondents.

**Discussion**

**Current Practice**

While 77% of respondents order spirometry at least 50% of the time to assist in the diagnosis of asthma, and far more consider lung function testing important, research indicates lung testing remains underused. As such, our results on the frequency of the use of spirometry by primary care providers in Alberta may be an
overestimate (Tsuyuki et al., 2005). Primary care providers identified several barriers to objective measurement of lung function including access to spirometry and difficulties with interpretation. It is not surprising that physicians are relying on other methods of diagnosis such as trials of asthma medications.

The use of asthma medications as a diagnostic tool is an important finding. While little research has been published related to the trial of medication in adults, there is insight from the pediatric literature. Physicians have identified bronchodilator response as a diagnostic tool for asthma, second only to expiratory wheeze for diagnostic criteria (Werk et al., 2000). Bush (2007) advocated that in young children a therapeutic trial may be appropriate. However, Zuidegeest et al. (2008) determined that less than half the children in a study of over 70,000 that were taking asthma medications had a physician diagnosis of asthma. Asthma medication trial may lead to the misdiagnosis of asthma as noted by Aaron et al. (2017) and may result in patients being unnecessarily or over-medicated to treat symptoms. Therapeutic trials of asthma medication should be carefully weighed and should not replace objective lung function testing; further research is warranted.

Canadian Thoracic Society Guidelines were cited as the most common tool to help diagnose asthma, but a significant number of respondents (32%) do not use any guideline, and many rely on a clinical response to therapy. Notably, 72% of respondents felt that a clinical pathway would be beneficial in supporting diagnosis and treatment of adults with asthma, because there is heterogeneity in patient presentations and asthma is a variable disease. There is a discrepancy between the majority of respondents stating that a clinical pathway would be of value to their practice, and yet almost one third do not actively use any of the national or international guidelines. Moreover, a normal result on lung function testing does not rule out asthma—yet, an objective measure is an important component of an appropriate diagnosis. As identified by one respondent, there needs to be an “underlying philosophy that this can be done in the Medical Home and only the most severe or non-responders require referral.” We are working with our provincial primary care committees and individual primary care physicians to better understand how to present guidance in ways that are easily embedded within daily workflows.

**Challenges to Diagnosis**

Episodic care was identified by over half of respondents as a barrier to asthma diagnosis and can occur if the patient does not come back to the same practice for follow-up, so the primary care provider may treat the patient’s presenting symptoms instead of reviewing differential diagnosis (Tsuyuki et al., 2005). As noted by Aaron et al. (2017), the episodic nature of asthma is a challenge for diagnosing asthma, since there is inherent difficulty in diagnosing the disease based on a single encounter between the physician and the patient. In addition, 42.9% of physicians indicated that patients being on asthma medications (prior to confirming diagnosis) are a barrier.

Lack of patient follow-up was also noted as a significant challenge, with 44% of respondents indicating this as a barrier. Barriers associated with patients include (a) poor recognition of asthma symptoms (van Schayck et al., 2000), (b) poor recollection of symptoms (Montnémery et al., 2002), (c) denial that asthma is a chronic disease/serious (Dennis et al., 2010), (d) patient refusal to be referred because of lack of time and interest, and (e) lower socioeconomic status (Buffels et al., 2009; Marklund et al., 1999; Statistics Canada, 2014). Morrow et al. (2017) identified that patient attendance is a significant barrier to asthma self-management in primary care.

Incorrect diagnosis can occur because many diseases can present with similar symptoms to those of asthma including COPD, cardiac failure, pulmonary tumor, vocal cord dysfunction, and hyperventilation syndrome or functional breathing disorder (Marklund et al., 1999; Ringsberg et al., 1993). While some indicated they used various guidelines to aid in diagnosis of asthma, almost a third of respondents did not use any guidelines in their practice. The difficulty of dissemination and implementation of asthma guidelines by primary care providers have been linked to pressures of time, lack of awareness, lack of familiarity or agreement with professionals who developed the guidelines, lack of self-efficacy and outcome expectancy, complexity of the guidelines, and resistance to change (Boulet, 2013; Boulet et al., 2006; Laloo et al., 2011).

**Resources and Tools Used to Facilitate Care**

The most common self-management interventions currently offered by physicians and their teams are brief self-management education and demonstration of medication devices. Provision of self-management education could be limited by additional factors not mentioned including the lack of time or the perception that substantial time is required, the lack of confidence, uncertainty about what the patient needs to know, and the belief that patients will get appropriate guidance at the pharmacy or elsewhere. Regular access to a certified respiratory
educator was identified as a wish list item, in addition to having educational training support for staff.

**Strengths/Limitations**

This survey provided valuable insight to the practices and preferences of clinicians working primary care. The information will be used to better inform decision making for policy and practice of diagnosis of asthma in the community. In addition, it helps to identify avenues for educational interventions and possible future quality improvement projects to promote optimal use of diagnostic testing resources. This quality improvement project is limited by the potential for bias in the participants. It is likely that only primary care providers with an interest in the topic would have taken part, and may not be representative.

**Implications for Practice**

The results of this primary health-care survey indicate that a number of barriers deter the establishment of an appropriate diagnosis and management of asthma. In order of perceived importance these include dealing with episodic care, obtaining a useful interpretation of lung function tests to support other critical elements of a diagnostic work-up, having a reliable guidelines tool, and knowing how to access support for provision of self-management education. In addition, while respondents indicated that a clinical pathway would be of use in the diagnosis of asthma, almost one third did not use any of the national or international guidelines currently available. Cabana et al. (1999) identified several barriers to guideline adherence including awareness, agreement, familiarity, and self-efficacy. However, they also determined that barriers are likely setting specific and may not be generalizable. This study also highlights that primary care providers have adapted to challenges in leveraging objective measurement and may rely upon other methods for diagnosis such as trials of medications. Further work is necessary to explore the implications of this common empiric approach and address factors that contribute to overdiagnosis of asthma in the community.

**Conclusion**

This survey provided essential information to serve as a catalyst for development of user-friendly provincial guidelines for the management of asthma in primary health care and provincial quality improvements to lung function testing. Through the ongoing work of Airways Working Group and in collaboration with Alberta Medical Association, a new guideline for the management of chronic asthma for family medicine is now available at: https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/Chronic-Asthma-CPG.pdf.

**Appendix**

**Respiratory Health SCN–Physician Adult Asthma Survey**

We wish to collaborate with primary care physicians to better understand your priorities and challenges in the diagnosis and management of adult asthma. As the first step, we invite your insight through this short online survey. This voluntary survey should take less than 10 minutes to complete and your responses will remain anonymous.

**SECTION 1: A few questions about you**

1. What is your gender?
   - Male
   - Female

2. Please select your age-group.
   - Less than 40 years old
   - 41 to 50 years old
   - 51 to 60 years old
   - Greater than 60 years old

3. How many years have you been in practice?
   - 5 or less
   - 6 to 10
   - 11 to 15
   - 16 to 20
   - More than 20

**SECTION 2: Questions about your clinical practices**

4. What challenges do you face with confirming the diagnosis of asthma among adults?
   (please check all that apply)
   - Episodic care (patient seen by different primary care physicians); patient follow-up
   - Availability of spirometry/pulmonary function testing; arranging spirometry/pulmonary function testing; interpreting spirometry/pulmonary function test results
   - Conflict between your clinical impression and pulmonary function test results; lack of access to previous physicians’ documentation
   - Patient already on asthma medications; pediatric-to-adult clinical transition
   - I do not have any challenges regarding the diagnosis of adult asthma; I have challenges diagnosing asthma in the following populations:
5. What do you consider ideal and/or sufficient for an accurate diagnosis of asthma in adults? (please check all that apply for each column)

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<thead>
<tr>
<th></th>
<th>I consider the following IDEAL</th>
<th>I consider the following SUFFICIENT</th>
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</thead>
<tbody>
<tr>
<td>Peak flow measurement overtime (i.e., 1–2 weeks)</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Pre- and postbronchodilator spirometry</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Full pulmonary function testing</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Trial of asthma medication(s)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Pulmonary consult</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Other (please specify in next question if needed)</td>
<td>□</td>
<td>□</td>
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</tbody>
</table>

6. Please rate how much you agree which each of the following statements.

To accurately diagnose asthma in adults, I consider it beneficial to have:

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Neither disagree nor agree</th>
<th>Agree</th>
<th>Strongly agree</th>
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<tr>
<td>Complete history and physical</td>
<td>□</td>
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<td>Peak flow measurement over time (i.e., 1–2 weeks)</td>
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<td>Pre- and postbronchodilator peak flow measurement</td>
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<td>Full pulmonary function testing</td>
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<td>Methacholine challenge test</td>
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<td>Pulmonary consult</td>
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8. How important is a confirmed diagnosis of asthma prior to suggesting treatment or action plan among adults? (please select one answer)

- □ Not important at all
- □ Somewhat unimportant
- □ Neutral
- □ Somewhat important
- □ Essential

9. How often do you order spirometry to assist with the diagnosis of adult asthma? (please select one answer)

- □ Never (0% of time)
- □ Less than 25% of time
- □ 25% to 49% of time
- □ 50% to 75% of time
- □ 76% to 99% of time
- □ Always (100% of time)

10. When spirometry is ordered for diagnosis of adult asthma, what is your preference? (please select one answer)

- □ Perform my own spirometry in my clinic using my own device
- □ Ask clinic staff member to perform spirometry using clinic-owned device
- □ Refer to local certified respiratory educator (CRE) or asthma educator for spirometry
- □ Refer to nearest public (AHS) pulmonary function lab
- □ Refer to nearest private (independent) pulmonary function lab
- □ I do not order spirometry

11. What other tools do you often use to confirm the diagnosis of asthma among adults? (please check all that apply)

- □ Home peak flow monitoring
- □ Clinical response to therapy
- □ Methacholine challenge test
- □ Respiratory educator consultation
- □ Respirologist consultation
- □ Other specialist consultation
- □ No further testing/investigations
- □ Other, please specify:

12. Do you believe that a clinical pathway would be of benefit to the diagnosis and treatment of adult asthma?

- □ Yes
- □ No
13. If you responded “YES,” how do you believe that a clinical pathway would be beneficial? OR If you responded “NO,” why do you believe that a clinical pathway would not be beneficial?

14. What self-management interventions do you or your team most often use with your adult patients with asthma? (please check all that apply)

- Demonstrate and observe medication technique
- Complete the Alberta Asthma Action Plan or other written action plan for the patient
- Provide brief self-management education (individual or group session)
- Recommend MyHealthAlberta.ca or other website
- Refer outside PCN for comprehensive individual education (e.g., Respiratory Therapist, Pharmacist, or Certified Respiratory Educator)
- Refer to Alberta Health Services group programs such as Better Choices, Better Health Other, please specify:

15. What would enable you and your team to provide timely asthma education? (please check all that apply)

- Access to skilled educators such as Certified Respiratory Educators
- Staff training and resources
- Panel management and continuity of care
- Patient resources
- Clinic space
- Other, please specify

16. Please tell us about tools in your “wish list” that would be effective in assisting you with the diagnosis of asthma among adults.

17. Please tell us about any other barriers that should be addressed to better assist you with the diagnosis of asthma among adults.

18. The Respiratory Health Strategic Clinical Network would like to know if you would be willing to share your experiences and suggestions on improving asthma diagnosis in primary care through an online focus group.

Please indicate if you would be interested in participating in a future focus group:

- Yes
- No

19. Thank you for your interest. Please provide your name and email address, separated by a semicolon. A representative from the Respiratory Health Strategic Clinical Network will contact you in the future.

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Author contributions

H. Sharpe was primarily responsible for drafting the manuscript, assisting with data analysis, completing all revisions. F. C. Claveria-Gonzalez was responsible for the first draft of the manuscript, conducting data analysis, and developing data tables. Claveria-Gonzalez also participated in reviewing the final manuscript and providing feedback. W. Davidson developed survey and participated in evidence review and study design, and assisted with data analysis and ongoing feedback of manuscript preparation. AD Befus, co-chair of the Asthma Working Group, supervisor of Francisca Claveria (student), participated in conceptualization of the study, design of the questions, data analyses, and writing and editing of the manuscript. J. P. Leung, family physician, provided ongoing content expertise throughout the study design, implementation, and manuscript development. E. Young, Manager of the RHSCN, was involved in the study design, survey administration, and data collection. Young also provided ongoing feedback on the manuscript. B Walker, co-chair of the Asthma Working Group, was involved in study development, design, and interpretation of the results. Walker also provided ongoing suggestions for manuscript preparation.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: H. Sharpe—Advisory Board participant for Teva Pharmaceuticals. B. Walker—Speaker’s bureau/advisory board participant for Astra Zeneca, GSK, Novartis; Clinical Trials with AstraZeneca, Sanofi, GSK, Cephalon, Novartis, Genentech/Roche; Grant (summer studentship) from RHSCN. J. P. Leung—honoraria for moderating for pharmaceutical companies including Novartis, Shire, Eli-Lilly. W. Davidson—Grants/Research support: GSK, Novartis; Speakers Bureau/Honoraria: Astra-Zeneca, Boehringer Ingelheim, GSK, Merck, Novartis Pfizer. The rest of the authors declare no competing interests.

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References


