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A Provincial Survey of the Contemporary Management of Autosomal Dominant Polycystic Kidney Disease

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Abstract

Background: Recent years have witnessed an encouraging expansion of knowledge and management tools in the care of patients with autosomal dominant polycystic kidney disease (ADPKD), including measurement of total kidney volume as a biomarker of disease progression, stringent blood pressure targets to slow cyst growth, and targeted treatments such as tolvaptan.

Objectives: We sought to evaluate clinicians' familiarity with, and usage of, novel evidence-based management tools for ADPKD.

Design: On-line survey.

Setting: British Columbia, Canada.

Participants: Nephrologists in academic and community practice (excluding clinicians who practice exclusively in transplantation).

Measurements: Participants answered multiple-choice questions in 6 domains: sources of information, self-identified needs for optimal care delivery, prognostication, imaging tests, blood pressure targets, and use of tolvaptan.

Methods: An online survey was developed and disseminated via email to 65 nephrologists engaged in current clinical practice in British Columbia.

Results: A total of 29 nephrologists (45%) completed the questionnaire. The most popular source of information was the primary literature (83% of respondents). While 86% of respondents reported assessing the risk of disease progression before the onset of kidney function decline, most were using traditional metrics such as blood pressure and proteinuria rather than validated prediction tools such as the Mayo Classification. Although 90% of respondents obtained additional imaging after diagnosis in some or all of their ADPKD patients, only 1 in 5 reported being confident in their ability to interpret kidney size. The recommended blood pressure (BP) target of $<$110/75 mmHg was sought by 17% of respondents. All respondents reported being familiar with the literature regarding tolvaptan; however, only half were confident in their ability to identify suitable patients for treatment. The top 3 needs identified by clinicians were better access to medications (69%), clear management protocols (66%), and easier access to imaging tests (59%).

Limitations: Funding mechanisms for tolvaptan can vary; therefore, clinicians' experience with the drug may not be generalizable. Although the response rate was acceptable, the survey is nonetheless subject to responder bias.

Conclusion: This survey indicates that there is substantial variability in the usage of, and familiarity with, evidence-based ADPKD management tools among contemporary nephrologists, contributing to incomplete translation of evidence into clinical practice. Providing greater access to tolvaptan or imaging tests is unlikely to improve patient care without enhancing knowledge translation and education.

Trial Registration: Not applicable as this was a survey.

Abrégé

Contexte: On a assisté au cours des dernières années à un élargissement prometteur des connaissances et des outils de gestion dans le domaine des soins prodigués aux patients atteints de maladie polykystique rénale autosomale dominante (MPRAD). On pense notamment à la mesure du volume rénal total comme biomarqueur de l'évolution de la maladie, à des cibles strictes en matière de pression artérielle visant à ralentir la croissance des kystes et à des traitements ciblés comme le tolvaptan.

Objectifs: Nous souhaitions évaluer la connaissance des cliniciens à l'égard de ces nouveaux outils fondés sur des données probantes et mesurer leur usage en contexte de MPRAD.

Type d'étude: Sondage en ligne
Cadre: Colombie-Britannique, Canada.
Participants: Les néphrologues pratiquant en milieu hospitalier universitaire et communautaire (à l'exception des médecins pratiquant exclusivement en transplantation).
Mesures: Les participants ont répondu à un questionnaire à choix multiples touchant six domaines précis: les sources d'information, les besoins autodéclarés pour une prestation de soins optimaux, le pronostic, les tests d'imagerie, les cibles de pression artérielle et l'utilization du tolvaptan.
Méthodologie: Un sondage en ligne a été élaboré et distribué par courriel à 65 néphrologues pratiquant actuellement en Colombie-Britannique.
Résultats: En tout, 29 néphrologues (45 %) ont répondu au questionnaire. La principale source d'information était la littérature (83 % des répondants). Bien que 86 % des répondants mentionnaient évaluer le risque de progression de la maladie avant les premières manifestations d'un déclin de la fonction rénale, la plupart recouraient à des indicateurs traditionnels comme la pression artérielle et la protéinurie plutôt qu'à des outils validés comme la classification de la clinique Mayo. Et bien que 90 % des répondants aient pu faire des tests d'imagerie supplémentaires après le diagnostic, chez certains ou chez tous leurs patients atteints de MPRAD, seul un médecin sur cinq s'est déclaré confiant en sa capacité d'interpréter la taille du rein. La cible recommandée de pression artérielle, soit moins de 110/75 mmHg, était recherchée par seulement 17 % des répondants. Tous les médecins ont mentionné être familiers avec la littérature portant sur le tolvaptan, mais la moitié des répondants doutaient de leur capacité à bien cerner les patients pour qui ce traitement est adéquat. Les cliniciens ont nommé trois principaux besoins: un meilleur accès aux médicaments (69 %), des protocoles de prise en charge clairs (66 %) et un accès plus facile aux tests d'imagerie (59 %).
Limites: Les mécanismes de financement du tolvaptan sont variables et ainsi, l'expérience des cliniciens avec ce médicament pourrait ne pas être généralisable. Bien que le taux de réponse ait été jugé acceptable, le sondage demeure sujet à des biais de la part des répondants.
Conclusion: Ce sondage indique qu'il existe une variabilité substantielle dans l'usage et la connaissance des outils de gestion de la MPRAD fondés sur les données probantes parmi les néphrologues. Cette situation contribue à l'application incomplète des résultats dans la pratique clinique. Offrir un accès accru au tolvaptan ou aux tests d'imagerie est peu susceptible d'améliorer les soins si l'application des connaissances et l'éducation ne sont pas améliorées.
Enregistrement de l'essai: Sans objet puisqu'il s'agit d'une étude sous forme de sondage.

Keywords
autosomal dominant polycystic kidney disease, evidence-based medicine, knowledge translation, survey, tolvaptan

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What was known before

New clinical and therapeutic management strategies have emerged in recent years for the treatment of ADPKD.

What this adds

This provincial survey demonstrated substantial heterogeneity in the utilization of, and familiarity with, novel evidence-based ADPKD management tools amongst clinical nephrologists, emphasizing the need for education and knowledge translation.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, occurring in approximately 1 in 1000 to 1 in 400 live births and is the fourth leading cause of end-stage kidney disease (ESKD) in Canada.[1] Historically, care for patients with ADPKD was limited to supportive measures due to an incomplete understanding of disease mechanisms and a lack of targeted treatments. As such, the majority of physicians in current clinical practice received their core nephrology training in an era where the management of ADPKD was primarily focused on preparing patients for renal replacement therapy, and managing symptoms and complications of ADPKD as the disease progressed unabated.[2-4]

Recent years have witnessed intensive research efforts to improve our understanding of the pathogenesis of ADPKD, inform clinical management strategies, and investigate novel therapeutic approaches.[5,6] For example, total kidney volume (TKV), measured via magnetic resonance imaging or computed tomography, has been identified as a clinically useful biomarker of disease severity and a measurable prognostic

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marker for disease progression.[7] The HALT-PKD randomized controlled clinical trial demonstrated the importance of stringent blood pressure control in ADPKD. Individuals with a blood pressure target of less than 110/75 mmHg experienced a slower increase in TKV and a greater reduction in albuminuria, compared to individuals with a blood pressure target of less than 130/80 mmHg.[8] A series of landmark clinical trials have demonstrated that the vasopressin V2 receptor antagonist tolvaptan can slow disease progression in patients with ADPKD and both preserved and reduced kidney function.[9,10] The TEMPO 3:4 trial demonstrated a slower decline in estimated glomerular filtration rate (eGFR) and a reduction in rate of TKV growth among patients who received tolvaptan. Similarly, the REPRISE trial demonstrated a significant reduction in the rate of eGFR decline at the 1 year mark in patients who received tolvaptan versus placebo.[9,10]

These studies have greatly advanced the literature and offered hope to patients with ADPKD. They have also dramatically changed the treatment paradigm of ADPKD from a reactive model of care centered on monitoring, identifying complications and preparing for organ replacement therapy, to a proactive model underpinned by accurate risk stratification and the identification of suitable patients for therapies to slow down disease progression. It is not known how well these novel management tools have been incorporated into contemporary clinical practice. In this provincial survey, we sought to evaluate the extent to which clinicians have translated this new knowledge and understanding into the care of patients with ADPKD in British Columbia, Canada.

Methods

Sample

The target sample included all practicing nephrologists in the 6 health authorities of British Columbia, Canada: Vancouver Coastal/Providence Health, Fraser Health, Interior Health, Northern Health, BC Children's, and Vancouver Island Health. Participants were identified using the current roster for practicing nephrologists in British Columbia. Nephrologists who exclusively practice in transplantation and those who were retired from practice were excluded. The survey link was initially sent to 65 nephrologists in the province in April 2018. Reminder emails were sent in June and July 2018. The survey was locked for analysis in August 2018.

Survey Design

The choice of questions for the survey was informed by a previous survey disseminated to members of the Canadian Society of Nephrology (CSN).[11] We included 20 questions which assessed the following 6 domains: sources of information regarding clinical management of patients with ADPKD, self-identified needs for optimal care delivery, renal prognostication tools, imaging tests and frequency of follow-up imaging, blood pressure targets, and understanding of tolvaptan indications and safety profile. Survey length was kept to a minimum of 10 minutes as there is evidence that shorter length improves online survey response rate, quality, and attentiveness to the responses.[12] The responses were also kept anonymous as this is associated with a greater willingness to disclose sensitive information.[13] The survey was hosted online on the platform Qualtrics (SAP, Seattle, Washington) supported by University of British Columbia. This online platform was chosen as it could be accessed on both mobile and desktop platforms, which has been shown to improve response quality as compared to mobile device only.[14] The responses were recorded in Microsoft Excel and exported into Stata version 14.1 (StataCorp, College Station, TX) for descriptive analysis. For the response rate calculation, only responses with at least 80% completion were considered.

Results

Response Rate and Demographics of Respondents

Out of 65 clinicians who were actively engaged in nephrology practice, a total of 32 completed the questionnaire for a response rate of 49%. A further 3 surveys were excluded due to incomplete data (less than 80% of questions completed). Therefore, the final response rate was 45% (29 out of 65). All 6 health authorities of British Columbia were represented by at least one nephrologist. The respondents had a broad range of clinical experience in nephrology: 11 (38%) were in practice for 5 to 10 years, 6 (21%) for 10 to 15 years, 6 (21%) for 15 to 20 years, and 6 (21%) for more than 20 years. The majority of respondents (n = 21, 72%) had less than 25 ADPKD patients in their practice.

Sources of Information

The most frequent source of information regarding ADPKD was from the primary literature (n = 24, 83%), followed by international guidelines (n = 23, 79%), conferences (n = 21, 72%), and local educational rounds (n = 21, 72%). A minority (n = 7, 24%) of clinicians stated that they get their information from industry sources. The most commonly used guideline was from the Canadian expert consensus group (96%).[11] A minority of clinicians reported using the Kidney Disease Improving Global Outcomes (KDIGO) guidelines (25%) or European guidelines (21%).[15,16]

Needs Assessment

The top 3 needs identified by clinicians to assist in the delivery of care to patients with ADPKD were (1) better access to medications such as tolvaptan, (2) clear treatment algorithms and protocols, and (3) improved access to imaging tests (Figure 1).

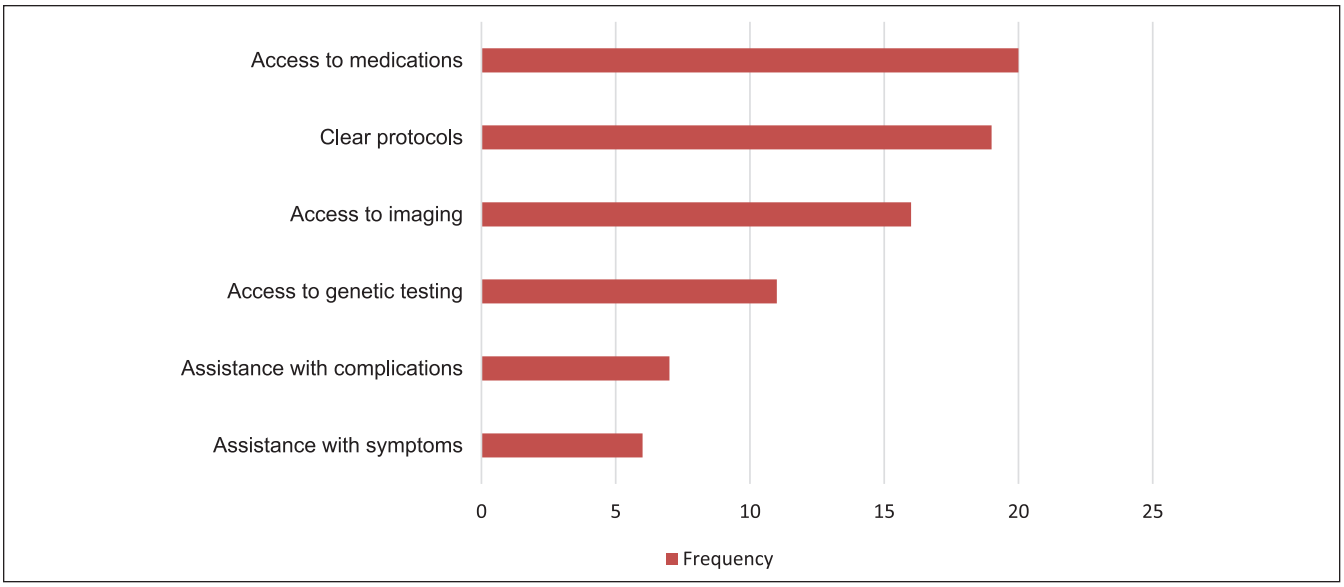

Figure 1. Needs identified by clinicians.

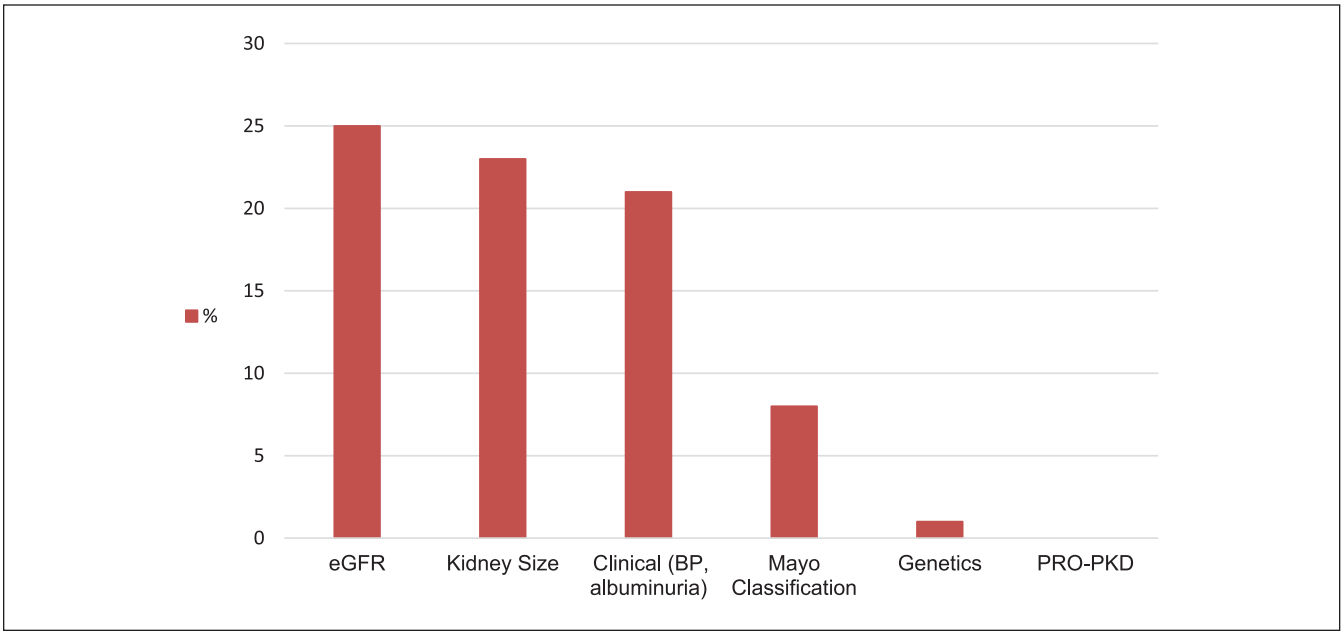

Figure 2. Tools used to determine risk of disease progression in patients with autosomal dominant polycystic kidney disease.
Note. eGFR = estimated glomerular filtration rate; BP = blood pressure.

Risk of Disease Progression

The majority of respondents (86%) reported that they assess the risk of disease progression before the onset of kidney function decline in some (18%) or most (68%) patients. However, there was substantial heterogeneity in the tools used to assess prognosis (Figure 2). The majority of clinicians reported using individual clinical parameters such as hypertension, eGFR, and albuminuria to determine the risk of disease progression. In contrast, a much smaller proportion used validated models such as the Mayo Classification, a tool used to prognosticate and risk stratify patients according to TKV, or the PRO-PKD score, which combines clinical parameters and genetic information to predict outcomes.[7,17]

Imaging

The vast majority of clinicians (90%) reported that they order repeat kidney imaging in their patients with large variability in the frequency of repeat imaging, from 7% who order annual imaging tests to 34% who order additional imaging when indicated by a change in clinical status. The

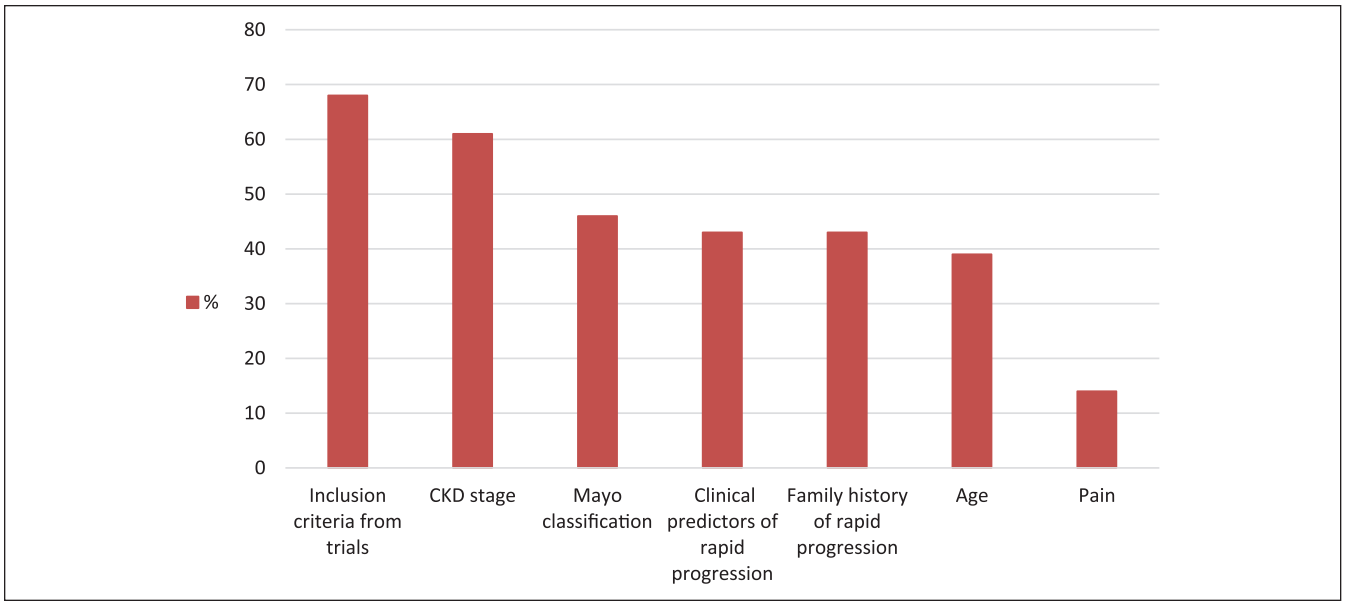

Figure 3. Criteria used for identifying candidates for treatment with tolvaptan.
Note. CKD = chronic kidney disease.

criteria for repeat imaging were also variable: 61% of respondents order additional imaging based on a change in symptoms, 54% based on a change in kidney function, 29% based on patient age, and 18% to monitor response to treatment. More than half of the clinicians (57%) order additional imaging as a "routine" periodic assessment, and 18% of respondents reported having no specific criteria. Among those who reported using kidney size to assess the risk of disease progression, 13% were not confident and 65% were only "somewhat confident" in response to the question "How confident are you in your ability to assess/interpret metrics of kidney size in ADPKD such as TKV or kidney length?"

Blood Pressure Targets

Approximately one-third of respondents (31%) reported a target blood pressure of <140/90 mmHg. Half of the respondents (52%) targeted a blood pressure of <120/80 mmHg and 17% of respondents sought a lower target of <110/75 mmHg. Among clinicians in practice for 5 to 10 years (n = 11), 36% reported a blood pressure target of <140/90 mmHg and no respondent reported a target of <110/75 mmHg. Among respondents who reported going to the primary literature for information, 21% sought the HALT-PKD target of <110/75 mmHg.

Tolvaptan

A total of 12 respondents (41%) had prescribed tolvaptan previously. Among those who had not prescribed tolvaptan, 59% had been approached by patients seeking information about the drug. All respondents reported being familiar with the evidence regarding tolvaptan use in ADPKD: 45% were "very familiar" and 55% were "somewhat familiar." The majority of respondents were not confident in adjusting the dose of tolvaptan, with 79% concerned about the risk of hepatotoxicity. One-third of respondents (31%) reported being "very confident" in identifying patients who are suitable for tolvaptan, and 10% of respondents were not confident in their ability to identify suitable candidates for treatment. The criteria used to identify patients for treatment were highly variable (Figure 3).

Discussion

In this provincial survey of nephrologists with varying durations of clinical practice, we observed a substantial mismatch between the evidence-based care that is recommended from clinical trials in ADPKD and the self-reported, real-world management that is delivered to patients with ADPKD in contemporary nephrology practice. Despite a decade of significant advances in risk stratification, blood pressure management, and novel repurposing of therapeutic agents, respondents did not appear to be well-versed in all of these domains. This survey also identified a lack of confidence in using novel management tools and a self-identified need for clearer protocols, indicating that the observed gap in knowledge translation could be bridged through enhanced education and standardization of care.

The vast majority of respondents cited the Canadian Expert Consensus recommendations as their primary source of information regarding the management of ADPKD. Published in 2017, the scope of these recommendations was informed by a national survey of nephrologists who were

members of the CSN.[11] The survey was limited to 4 questions about preferred guidelines, methods of screening, level of experience with different treatments, and what respondents perceived as their top needs in the management of ADPKD.[11] Despite the availability of Canadian guidelines, many respondents in the present survey were not following the recommendations. Furthermore, they identified similar challenges to those captured by the CSN survey, including a lack of care pathways, lack of consensus on the optimal approach for prognostication, and lack of clarity on subgroups of patients that may benefit from specific treatments. This indicates that there is uncertainty about how to apply guideline recommendations to the care of individual patients. Our findings suggest that this may stem from a lack of confidence in specific aspects of care such as interpreting TKV, using prognostication tools, and appropriate prescribing of tolvaptan. The underlying reasons for this are unknown and were not explored in this survey, although one might hypothesize that a lack of direct experience played a role. Given the consistent themes in the needs identified by clinicians in this survey and the previous CSN survey, the next step may be to develop educational opportunities at a national level to enhance the knowledge and understanding of these more nuanced aspects of ADPKD management.

We observed significant variability in the self-reported use of kidney imaging in the management of patients with ADPKD. Although clinicians frequently order imaging tests, only a minority were very confident in their ability to interpret the results. This finding was consistent among those who reported using kidney size to assess the risk of disease progression. At the same time, easier access to imaging tests was identified as one of the top 3 needs identified by clinicians. This suggests that resources would be better used by improving the interpretation of imaging test results and standardizing the indications and frequency of imaging in patients with ADPKD, rather than simply increasing the number of imaging tests performed. The blood pressure values targeted by most clinicians in this sample were lower than the target of $<$140/90 mmHg recommended by Hypertension Canada for patients with chronic kidney disease (CKD), but higher than the HALT-PKD target of $<$110/75 mmHg.[8,18] This finding was consistent among nephrologists who were in clinical practice for 5 to 10 years, none of whom targeted a blood pressure $<$110/75 mmHg. The survey asked about blood pressure targets only, and not specifically about awareness of clinical trial data. It is conceivable that respondents were aware of the lower blood pressure target from the HALT-PKD trial but may not necessarily believe that aggressive blood pressure control is justified, or that it provides incremental benefit to patients who are already receiving tolvaptan. Only one respondent reported using genetics as a method of prognostication, and no one reported using the PRO-PKD score which incorporates genetic information. At the time of this survey, genetic testing in the province could only be arranged through a referral to medical genetics and was therefore not part of routine ADPKD care, outside of very specific situations. This, along with the emergence of TKV as a prognostic tool, may explain the apparent shift away from genetic testing. With respect to tolvaptan, all respondents claimed to be at least somewhat familiar with the evidence for treatment; however, the majority were not confident in adjusting the dose of the drug. Furthermore, some 60% of respondents had been approached by patients regarding tolvaptan but only a third of respondents reported being very confident in identifying patients who were suitable for the therapy.

The time lag between accrual of evidence from clinical trials and its incorporation into clinical practice is well recognized. The discrepancy between evidence-based care and what actually occurs in clinical, day-to-day practice can be incredibly vast.[19,20] In 1981, the Beta-blocker Heart Attack Trial demonstrated a 26% relative reduction in the risk of myocardial infarction in those treated with Propranolol, with a corresponding number needed to treat of 40.[21] However, more than a decade after the publication of this trial, only 50% of Medicare patients hospitalized from 1994 to 1995 with acute myocardial infarction were prescribed a beta-blocker.[22] In the same time frame, despite aspirin being shown to be a cornerstone in the management of coronary artery disease and acute myocardial infarction, early administration of aspirin in patients with acute myocardial infarction was only 76%.[22,23] A literature review of health care delivery in the United States demonstrated a consistent failure to translate research into clinical practice, whereby only 50% of patients received recommended preventative care, 70% of patients received recommended care in the acute setting and 60% received recommended care for chronic disease management.[24] Despite physicians' recognition of the importance of slowing down progression of chronic conditions such as diabetes and heart failure, only 12.5% to 38.5% make use of published protocols and guidelines to achieve this.[25] There is often slow uptake of evidence and translation of knowledge into clinical practice. Understanding behavior change has led to multiple interventions to close this gap.[26-28] However, the time lag in translational research has been estimated at 17 years.[29]

The responses from this survey identified specific areas for improvement and thus provide opportunities at an organizational level for education and standardization of practice. For example, the availability of clear algorithms and protocols was clearly identified as an important factor for clinicians. There are examples from other domains in nephrology where an integrated approach to care can be advantageous. For example, individuals in British Columbia with glomerular disease have access to a multi-disciplinary clinic with provincial oversight of immunosuppression treatment protocols.[30] A recent systematic review concluded that models of integrated care may enhance patient satisfaction, increase perceived quality of care, and enable access to services.[31] ADPKD care is well suited to this model of care; modern ADPKD care is a multifaceted endeavor that

involves disease-specific interdisciplinary management strategies over and above routine CKD clinic services.[32] Moreover, as the landscape of ADPKD assessment and management continues to evolve, ongoing efforts to translate these research findings into clinical care will be crucial.[33] For this reason, leaders in ADPKD care have advocated for the development of dedicated ADPKD-specific clinical services within interdisciplinary renal care settings, which have the potential to provide the exposure and familiarity of these novel treatment options and therefore facilitate incorporation of evidence-based management into clinic practice.[15,16] Specific services for individuals with ADPKD could be delivered within existing CKD care networks, provided that clinicians are supported with the necessary tools to enhance their knowledge and experience with this condition. Having a harmonized approach to care could benefit patients by streamlining investigations, providing clear protocols for treatments, and facilitating access to clinical trials.

Our study has some limitations. Despite a reasonably robust response rate, the survey is nonetheless subject to responder bias. In particular, findings within subgroups should be interpreted with caution given the small sample sizes involved. For the same reason, we were unable to reliably interrogate potential regional variability in practice patterns. Treatment algorithms for tolvaptan and funding mechanisms to access the drug are variable across provinces, therefore respondents' prescribing experience and level of comfort with tolvaptan may not be generalizable. The survey did not capture nephrologists who were less than 5 years into independent practice. Given the timeframe of recent advances in ADPKD, it would have been informative to obtain the perspectives of this group of clinicians. Strengths of our survey include the diversity of respondents in terms of clinical experience and location of practice within a provincial health care system, the breadth of clinical domains addressed in the survey, and a response rate that was higher than the average response rate (35.7%) reported in academic journals.[34]

In conclusion, this provincial survey of practicing general nephrologists in British Columbia identified substantial gaps in knowledge translation regarding the optimal care of patients with ADPKD, including risk stratification, prognostication, blood pressure management, and the identification of patients who are suitable for tolvaptan. Importantly, respondents recognized the need for guidance in implementing recent clinical trial data into their everyday practice, including the availability of clearer protocols. We observed marked heterogeneity in the use of resources such as longitudinal kidney imaging and genetic testing, emphasizing the need for increased standardization in the work-up, risk stratification and treatment of patients with ADPKD as part of an integrated model of care.

Disclosures

A.L. has received travel support from Otsuka to attend scientific meetings, unrelated to this work. M.B. has received honoraria and grants from Otsuka, unrelated to this work. T.Y. and M.C. have no disclosures.

Ethics Approval and Consent to Participate

A research ethics board review was not required for implementation of the survey as participation in the survey was considered implied consent for reporting of the findings.

Consent for Publication

All authors provided their consent for publication of the manuscript.

Availability of Data and Materials

Available on request from corresponding author.

Declaration of Conflicting Interests

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