



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

## Diabetes &amp; Metabolic Syndrome: Clinical Research &amp; Reviews

journal homepage: [www.elsevier.com/locate/dsx](http://www.elsevier.com/locate/dsx)

# Adapting to telemedicine in the COVID-19 era: Feasibility of dried blood spot testing for hemoglobin A1c



Alissa J. Roberts <sup>a, b, \*</sup>, Faisal Malik <sup>a, b</sup>, Catherine Pihoker <sup>a, b</sup>, Jane A. Dickerson <sup>c, d</sup>

<sup>a</sup> Department of Pediatrics, University of Washington, Seattle, WA, USA

<sup>b</sup> Seattle Children's Research Institute, Seattle, WA, USA

<sup>c</sup> Department of Laboratory Medicine and Pathology, University of Washington School of Medicine, Seattle, WA, USA

<sup>d</sup> Department of Laboratories, Seattle Children's Hospital, Seattle, WA, USA

## ARTICLE INFO

### Article history:

Received 23 December 2020

Received in revised form

28 January 2021

Accepted 3 February 2021

### Keywords:

Telemedicine

Diabetes mellitus

COVID-19

## ABSTRACT

**Background and aims:** The COVID-19 pandemic has led to a rapid growth in the use of telemedicine for delivery of ambulatory diabetes care. This study evaluated the feasibility of remote HbA1c monitoring via dried blood spot (DBS) testing to support assessment of glycemic control for telemedicine visits and examined clinical and demographic characteristics associated with patient completion of DBS testing.

**Methods:** Providers could place orders for DBS HbA1c 3 weeks prior to telemedicine visits. Feasibility was assessed by examining DBS completion rates, time to completion, and availability of DBS results prior to telemedicine visits. Chi-square tests and Mann Whitney tests were used to assess whether completion rates were associated with participant characteristics.

**Results:** Of 303 DBS orders placed for telemedicine visits in June 2020, 162 patients completed the DBS test for a completion rate of (53.4%). Average time from collection at home to result being reported was 6.9 (3.8) days. The DBS result was available in 67.6% of patients who completed successful DBS, before the telemedicine clinic visit. HbA1c was lower in the DBS completion group as compared to the non-completion group (8.2% vs. 8.9%,  $p = 0.01$ ). No other clinical or demographic characteristics were significantly different between the two groups.

**Conclusion:** Remote HbA1c monitoring via DBS is feasible and offers an avenue to support assessment of glycemic control for patients seen via telemedicine. Future work should focus on improving clinic and laboratory processes to support remote DBS collection.

© 2021 Diabetes India. Published by Elsevier Ltd. All rights reserved.

## 1. Introduction

With the recent global pandemic due to the novel coronavirus (COVID-19), outpatient care for patients with diabetes has transformed rapidly with the increased use of telemedicine to deliver routine ambulatory care [1,2]. Telemedicine is not new to the diabetes care landscape. When utilized in type 1 diabetes (T1D) care, it has been shown to be cost-effective, increase appointment adherence, and improve patient satisfaction [3,4]. According to two recent meta-analyses, the use of telemedicine in diabetes care can also improve clinical outcomes such as hemoglobin A1c (HbA1c), blood pressure, and hypoglycemia event rate [5,6].

While telemedicine technology and its use are not new,

widespread adoption among diabetes centers has been slow. Barriers to implementation of telemedicine have included staff-related challenges both around the comfort and use of technology, as well as costs for healthcare organizations to purchase equipment and strict reimbursement criteria [7]. However, in the COVID-19 pandemic era, some of these barriers have been removed in the United States, as Medicare expanded reimbursement for telemedicine services and penalties for HIPAA-noncompliance with communications technologies have been modified [8].

As diabetes clinics have incorporated increased use of telemedicine, teams have struggled to meet current standards of care around assessment of overall glycemic control. For youth and adolescents using continuous glucose monitoring (CGM) systems, glycemic control can be remotely assessed by reviewing standardized metrics such as time in range and glucose management indicator [9,10]. However, CGM technology is only utilized in approximately 30% of youth with diabetes[11]. International

\* Corresponding author. M/5 OC.7.820, PO Box 5371, Seattle, WA, 98145, USA.  
E-mail address: [Alissa.Roberts@seattlechildrens.org](mailto:Alissa.Roberts@seattlechildrens.org) (A.J. Roberts).

consensus guidelines recommend using a HbA1c target of <7.0–7.5% in children, adolescents, and young adults with diabetes, with HbA1c measurements performed every 3 months, as a standard of care to assess glycemic control and guide clinical management[12]. The American Diabetes Association recommends HbA1c assessment at least twice a year, often more frequently, with a target HbA1c <7.5% in children and adolescents or <7.0% in children if able to do so without hypoglycemia[13,14]. Thus, with a transition to telemedicine, the inability to measure HbA1c, particularly for those patients not using a CGM system, has emerged as a barrier to providing optimal ambulatory diabetes care.

HbA1c evaluation via dried blood spot (DBS) collected on filter paper at home by patients offers a means to measure HbA1c levels remotely. Historically, DBS has primarily been utilized in the research setting, as a method of obtaining information on glycemic control without requiring an in-person study encounter. There are many published reports assessing testing parameters of self-collected samples with DBS[15–18], including a large-scale investigation with samples collected in 78 countries to assess reliability for multinational studies [19]. This study evaluated the feasibility of remote HbA1c monitoring via dried blood spot (DBS) testing to support assessment of glycemic control for telemedicine visits and examined clinical and demographic characteristics associated with patient completion of DBS testing.

## 2. Methods

### 2.1. Setting

Seattle Children's Hospital is a tertiary care, stand-alone pediatric hospital that serves a large geographic region in the Pacific Northwest of the United States. The diabetes program follows over 2200 youth and young adults with diabetes. In March 2020, due to the COVID-19 pandemic most quarterly visit encounters were transitioned to telemedicine encounters. The study included all telemedicine (phone or video) visits from June 2020 when DBS testing was available, who had a DBS order placed. This study was approved by the Seattle Children's IRB.

### 2.2. Process

Beginning in May 2020, diabetes providers could place orders for DBS testing at least 3 weeks prior to their scheduled telemedicine encounter. An order placed by a diabetes provider in the electronic medical record would prompt laboratory personnel to mail the patient a DBS collection kit. The DBS kit included collection instructions, filter paper card, lancet, a laboratory requisition, and pre-addressed/postage paid envelopes (Fig. 1). Once received by the laboratory, the DBS was processed and results were made available in the patient's electronic medical record for provider review at the telemedicine encounter.

Patients collected a fingerprick capillary sample directly on the filter paper at home, air-dried for at least 3 hours, and mailed them to the laboratory. Using a method previously described, two 3-mm discs were punched and were placed in a 2 mL rounded bullet tube. Hemolysate reagent was added (500 mL) and soaked for 3 hours, gently vortexing every 30 minutes. Analysis was performed directly from the test tube[20]. DBS extract was analyzed using the same method as routine whole blood HbA1c. DBS HbA1c was measured in the clinical lab by an automated immunoturbidimetric inhibition assay on the VITROS 4600 (Ortho-Clinical Diagnostics). Blood is hemolyzed and mixed with anti-HbA1c antibody to form a soluble antigen-antibody complex; the resulting hematin derivative is measured at two wavelengths, 340 and 700 nm. Unbound anti-HbA1c antibody reacts with polyhapten to form an insoluble

complex, which is measured turbidimetrically at 340 nm. The % HbA1c is calculated based on the measurements of hemoglobin and HbA1c.

To validate the assay, 20 inter-day replicates from two patient pools (5% and 7% HbA1c) were analyzed to determine assay imprecision. The intra assay variation coefficient of variation was found to be <3%. We evaluated the assay's linearity by analyzing CAP (College of American Pathology) linearity samples in triplicate. Patient comparisons of spotted venous blood (n = 29) were used to correlate the method with the whole blood assay (R = 0.996, slope = 0.975). Stability at room temperature was evaluated by testing two patient pools (5% and 7% HbA1c) over 2 weeks and 5 individual patient samples tested over 35 days.

### 2.3. Analysis

Participant demographic and clinical characteristics including age, sex, ethnicity, health insurance, insulin regimen, diabetes technology use, diabetes duration and HbA1c were abstracted from the medical record. For those who did not complete DBS testing, the most recent point-of-care HbA1c measurement from their clinic visit was also obtained.

Descriptive statistics were used to summarize patient characteristics. Chi-square (or Fisher's exact) tests and Mann Whitney tests were used to evaluate associations between two groups (DBS completion vs. DBS non-completion) and patient demographic/clinical characteristics. Analysis was conducted in RStudio (RStudio Team, 2019).

## 3. Results

In June 2020, 303 orders for DBS testing were placed by diabetes providers for upcoming telemedicine visits. A total of 162 patients returned the DBS for lab processing for a completion rate of 53.4%. For those that completed the DBS, 20 were not able to be processed due to insufficient sample collected. The average time from patient collection at home to when the HbA1c was available for review in the EMR was  $6.9 \pm 3.8$  days. The DBS result was available on average 0.73 days before the clinic visit with 67.6% of DBS tests available at the time of the telemedicine visit.

There were no significant differences observed across most demographic and clinical characteristics for those who completed the DBS testing and those who did not (Table 1). Patients in the DBS completion group had a lower HbA1c compared to the non-completion group (8.2% vs. 8.9%,  $p = 0.01$ ).

## 4. Discussion

The American Diabetes Association recommends measuring HbA1c at least two times a year in patients who are meeting treatment goals and quarterly in patients whose therapy has changed or who are not meeting glycemic control given its strong predictive value for diabetes complications[13]. With the need for immediate transition to remote delivery of ambulatory diabetes care in the setting of the COVID-19 pandemic, DBS testing proved to be a feasible method to support assessment of glycemic control in pediatric diabetes patients seen via telemedicine. Given the recent explosion in telemedicine services and a growing body of evidence suggesting that telemedicine modalities may be effective at reducing HbA1c in patients with diabetes [21,22], the use of DBS testing offers a promising strategy to meet the recommended standards of care for individuals with diabetes [12,13].

There are many published studies that have compared HbA1c in DBS and venous blood. One such study demonstrated that DBS testing for HbA1c correlated well with venous blood samples

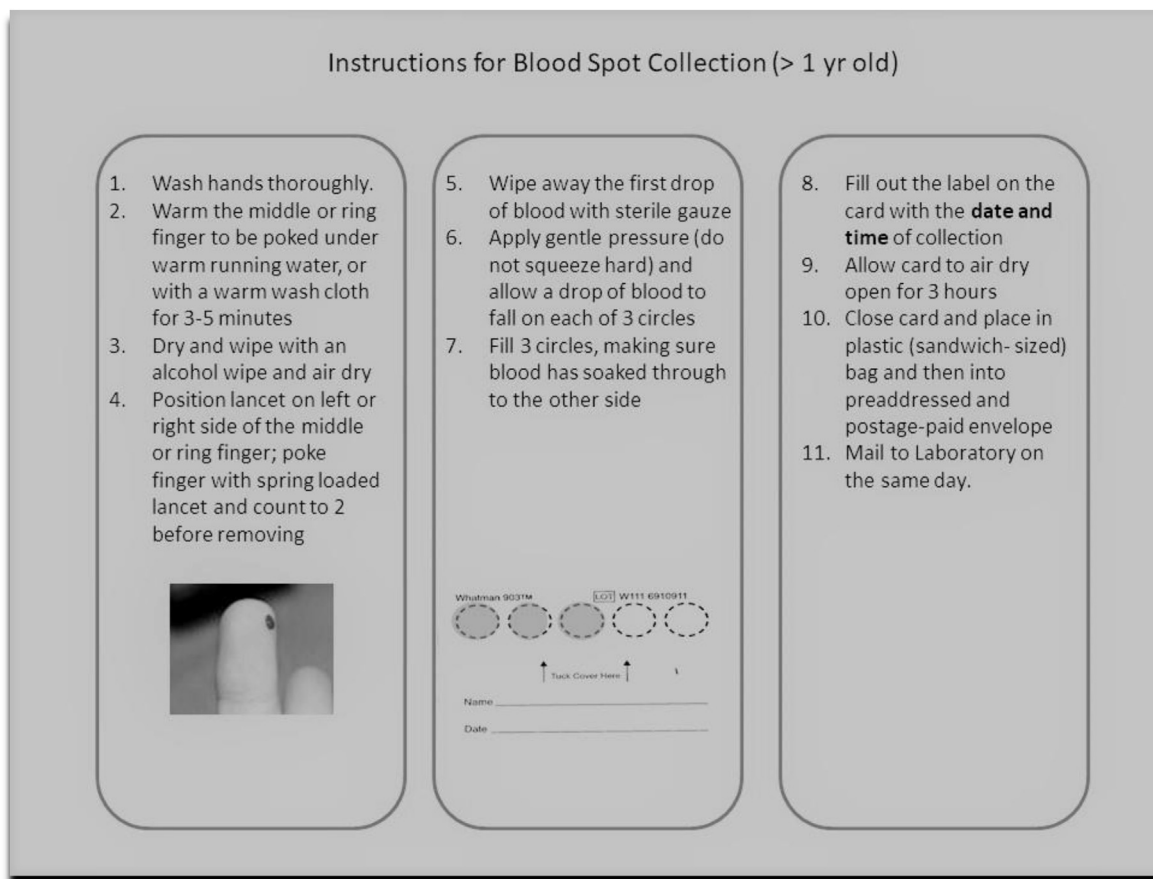


Fig. 1. Patient instructions for blood spot collection.

Table 1  
Differences in patient characteristics in completion of dried blood spot (DBS) HbA1c testing.

	Total N = 303	Completed DBS Test n = 162	Did not Complete DBS Test n = 141	P-value
Age at screening (years), Mean (SD)	13.9 (4.0)	13.8 (4.0)	13.9 (4.0)	0.88
Diabetes duration (years), Mean (SD)	5.1 (4.2)	5.1 (4.2)	5.2 (3.9)	0.70
Sex, n (%)				0.69
Female	154 (50.8)	84 (51.9)	69 (48.9)	
Male	151 (49.2)	78 (48.1)	72 (51.0)	
Race/Ethnicity, n (%)				0.11
Non-Hispanic White	190 (62.7)	110 (67.9)	79 (56.0)	
Non-Hispanic Black	26 (8.6)	9 (5.6)	17 (12.1)	
Hispanic	41 (13.5)	18 (11.1)	22 (15.6)	
Other	48 (15.8)	25 (15.4)	23 (16.3)	
Insurance, n (%) <sup>a</sup>				0.24
Private	211 (69.6%)	117 (72.2%)	92 (65.2)	
Medicaid/Medicare	87 (28.7%)	42 (25.9)	45 (31.9)	
Diabetes Regimen, n (%)				0.34
Insulin Pump	163 (53.8)	92 (56.8)	71 (50.4)	
Insulin MDI	118 (38.9)	57 (35.2)	61 (43.3)	
No insulin	22 (7.3)	13 (8.0)	9 (6.4)	
Continuous Glucose Monitoring Use, n (%)				0.11
Yes	181 (59.7)	104 (64.2)	77 (54.6)	
No	122 (40.3)	58 (35.8)	64 (45.4)	
Diabetes Type				0.23
Type 1	269 (88.8)	144 (88.9)	125 (88.7)	
Type 2	22 (7.3)	14 (8.6)	8 (5.7)	
Other	14 (4.6)	4 (2.5)	8 (5.7)	
HbA1c, Mean (SD)	8.6 (1.8)	8.2 (1.4)	8.9 (1.5)	0.01

<sup>a</sup> 7 patients with insurance not classified.

( $R = 0.99$ ) and the samples were stable for 5–7 days at 20–21 °C, 10 days at 4–6 °C, and several months at –70° Celsius [15]. Other studies demonstrate similar accuracy, including a study evaluating a similar extraction and assay method as the one used in our laboratory for this study [20]. Internal test validation performed in our lab, as described in the results, showed similar accuracy ( $R = 0.996$ , slope = 0.975).

The availability and use of DBS testing in our clinic helped diabetes care team members better counsel patients around risk for complications when conducting telemedicine visits and anchor their treatment recommendations to glycemic control targets [12,14]. Further, the use of at-home testing offered patients an increased level of convenience by reducing the need to travel to a local laboratory or clinic setting to have a HbA1c measurement performed. The at-home testing approach was of particular importance in the setting of the COVID-19 pandemic as it helped patients and their caregivers better adhere to public health recommendations by eliminating the risk for potential exposure to community members and laboratory personnel that might be COVID-19 positive. Diabetes patients have a higher risk of COVID-19 related mortality and thus minimizing risk of exposure is of utmost importance [23].

While incorporating DBS testing for remote HbA1c monitoring was feasible in the context of telemedicine visits, it is worth highlighting that a substantial number of patients did not complete the DBS prior to their visit and 12% of specimens received by the lab could not be analyzed due to insufficient coverage of the filter paper. Possible explanations for not completing the DBS test include difficulty understanding instructions, competing demands at home, mail delays or misplacement of DBS kits. Previous work examining remote postal-based screening methods in other conditions has shown that low educational attainment and poor previous screening participation are associated with suboptimal completion rates, highlighting the important role health literacy plays in the implementation of successful at-home testing [24]. Quality improvement interventions aimed at addressing barriers related to health literacy should be considered, such as developing instructions with more visual cues and providing DBS kit instructions in languages other than English. The addition of both phone or electronic reminders could also potentially improve completion rates, as has been seen in other medical conditions requiring a mail-in specimen, such as with colorectal cancer screening [25,26]. Finally, given our finding that the results for approximately one-third of completed DBS tests were not available prior to telemedicine visits, quality improvement efforts focused on improving timely completion and processing of the DBS can help improve utility of DBS testing in the clinical setting.

We also found that pediatric patients who did not complete DBS testing had a higher HbA1c level than those who completed DBS testing. Past research has shown that poor glycemic control is associated with other behaviors that are indicative of less patient engagement with care, such as missed appointment frequency, and may partially explain the difference in HbA1c level seen between the two groups [27]. Given that diabetes patients with higher HbA1c are at higher risk for acute and chronic diabetes complications, these patients are particularly important to monitor and engage in diabetes care, including HbA1c monitoring, insulin regimen adjustment, and complications screening [28]. Future interventions should seek to target improving telemedicine care engagement and remote DBS completion in those with poor glycemic control.

A strength of this study is that it describes a clinical protocol that was developed and implemented in-vivo amidst the changing clinical landscape during the COVID-19 pandemic, as all clinics work to adapt and provide optimal care during this unprecedented time. We have a large pool of patients and thus were able to test this

protocol in a large number of participants. At this time, we do not have data from patients around satisfaction and barriers to DBS completion, which is a limitation in terms of informing future quality improvement efforts. We, however, hope to engage in a “Plan-Do-Study-Act” cycles to increase DBS completion rates, particularly in those with poorer glycemic control [27]. A limitation of this study is that the timing of when HbA1c levels were measured was different between groups given that the HbA1c level from the last in-person clinic visit was used for those that did not complete DBS testing.

## 5. Conclusion

Remote HbA1c monitoring via DBS is feasible and offers an avenue to support assessment of glycemic control for patients seen via telemedicine. This study describes the feasibility of this method of remote HbA1c monitoring and assesses our baseline completion characteristics. Future work should focus on improving clinic and laboratory processes to support remote DBS collection.

## Author contributions

A.J.R. and J.D. conceptualized and designed the study, coordinated and supervised data collection, and drafted the initial manuscript. J.D. performed data analysis. F.M. and C.P. conceptualized and designed the study and contributed to data interpretation. All authors reviewed, revised, and approved the final manuscript. All authors agree to be accountable for all aspects of the work.

## Guarantor statement

Dr. Alissa Roberts is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of data and the accuracy of data analysis.

## Funding

Dr. Malik’s time was supported in part by a K23 Career Development Award from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (DK119465).

## Declaration of competing interest

The authors have no conflicts of interest to disclose.

## Acknowledgements

We acknowledge Alya Nguyen and Miyako Bisacky for rapidly validating the assay for clinical use.

## References

- [1] Ranscombe P. How diabetes management is adapting amid the COVID-19 pandemic. *Lancet Diabetes Endocrinol* 2020 Jul;8(7):571.
- [2] Elbarbary NS, Dos Santos TJ, de Beaufort C, Agwu JC, Calliari LE, Scaramuzza AE. COVID-19 outbreak and pediatric diabetes: perceptions of health care professionals worldwide. *Pediatr Diabetes* 2020 Jul 20. Online ahead of print.
- [3] Xu T, Pujara S, Sutton S, Rhee M. Telemedicine in the management of type 1 diabetes. *Prev Chronic Dis* 2018;15:E13.
- [4] Lee JY, Lee SWH. Telemedicine cost-effectiveness for diabetes management: a systematic review. *Diabetes Technol Therapeut* 2018;20(7):492–500.
- [5] Wu C, Wu Z, Yang L, Zhu W, Zhang M, Zhu Q, et al. Evaluation of the clinical outcomes of telehealth for managing diabetes: a PRISMA-compliant meta-analysis. *Medicine (Baltim)* 2018;97(43):e12962.
- [6] Hu Y, Wen X, Wang F, Yang D, Liu S, Li P, et al. Effect of telemedicine

- intervention on hypoglycaemia in diabetes patients: a systematic review and meta-analysis of randomised controlled trials. *J Telemed Telecare* 2019;25(7):402–13.
- [7] Scott Kruse C, Karem P, Shifflett K, Vegi L, Ravi K, Brooks M. Evaluating barriers to adopting telemedicine worldwide: a systematic review. *J Telemed Telecare* 2018;24(1):4–12.
- [8] Keesara S, Jonas A, Schulman K. Covid-19 and health care's digital revolution. *N Engl J Med* 2020;382(23):e82.
- [9] Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019;42(8):1593–603.
- [10] Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017;40(12):1631–40.
- [11] Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016–2018. *Diabetes Technol Therapeut* 2019;21(2):66–72.
- [12] DiMeglio LA, Acerini CL, Codner E, Craig ME, Hofer SE, Pillay K, et al. ISPAD Clinical Practice Consensus Guidelines 2018: glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes. *Pediatr Diabetes* 2018;19(Suppl 27):105–14.
- [13] American Diabetes A. 6. Glycemic targets: standards of medical care in diabetes-2018. *Diabetes Care* 2018;41(Suppl 1):S55–64.
- [14] American Diabetes A. 13. Children and adolescents: standards of medical care in diabetes-2019. *Diabetes Care* 2019;42(Suppl 1):S148–64.
- [15] Jeppsson JO, Jerntorp P, Almer LO, Persson R, Ekberg G, Sundkvist G. Capillary blood on filter paper for determination of HbA1c by ion exchange chromatography. *Diabetes Care* 1996;19(2):142–5.
- [16] Anjali, Geethanjali FS, Kumar RS, Seshadri MS. Accuracy of filter paper method for measuring glycated hemoglobin. *J Assoc Phys India* 2007;55:115–9.
- [17] Parkes J, Ray R, Kerestan S, Davis H, Ginsberg B. Prospective evaluation of accuracy, precision, and reproducibility of an at-home hemoglobin A1c sampling kit. *Diabetes Technol Therapeut* 1999;1(4):411–9.
- [18] Fokkema MR, Bakker AJ, de Boer F, Kooistra J, de Vries S, Wolthuis A. HbA1c measurements from dried blood spots: validation and patient satisfaction. *Clin Chem Lab Med* 2009;47(10):1259–64.
- [19] Egier DA, Keys JL, Hall SK, McQueen MJ. Measurement of hemoglobin A1c from filter papers for population-based studies. *Clin Chem* 2011;57(4):577–85.
- [20] Jones TG, Warber KD, Roberts BD. Analysis of hemoglobin A1c from dried blood spot samples with the Tina-quantR II immunoturbidimetric method. *J Diabetes Sci Technol* 2010;4(2):244–9.
- [21] Lee SWH, Chan CKY, Chua SS, Chaiyakunapruk N. Comparative effectiveness of telemedicine strategies on type 2 diabetes management: a systematic review and network meta-analysis. *Sci Rep* 2017;7(1):12680.
- [22] Faruque LI, Wiebe N, Ehteshami-Afshar A, Liu Y, Dianati-Maleki N, Hemmelgarn BR, et al. Effect of telemedicine on glycated hemoglobin in diabetes: a systematic review and meta-analysis of randomized trials. *CMAJ (Can Med Assoc J)* 2017;189(9):E341–64.
- [23] Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020;8(10):813–22.
- [24] Hong S, Shin HY, Lee B, Hwang NR, Hwang SH, Jun JK. Increase in the colorectal cancer screening rate by a round-mailed fecal immunochemical testing kit and associated factors in underserved regions of Korea: a community-based intervention study. *Gut Liver* 2020;14(3):323–30.
- [25] Coronado GD, Rivelli JS, Fuoco MJ, Vollmer WM, Petrik AF, Keast E, et al. Effect of reminding patients to complete fecal immunochemical testing: a comparative effectiveness study of automated and live approaches. *J Gen Intern Med* 2018;33(1):72–8.
- [26] Muller D, Logan J, Dorr D, Mosen D. The effectiveness of a secure email reminder system for colorectal cancer screening. *AMIA Annu Symp Proc* 2009;2009:457–61.
- [27] Karter AJ, Parker MM, Moffet HH, Ahmed AT, Ferrara A, Liu JY, et al. Missed appointments and poor glycemic control: an opportunity to identify high-risk diabetic patients. *Med Care* 2004;42(2):110–5.
- [28] Diabetes C, Complications Trial/Epidemiology of Diabetes I, Complications Research G, Nathan DM, Zinman B, Cleary PA, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983–2005). *Arch Intern Med* 2009;169(14):1307–16.