

### **Opportunistic pathology-based screening for diabetes**

Journal:	BMJ Open
Manuscript ID:	bmjopen-2013-003411
Article Type:	Research
Date Submitted by the Author:	15-Jun-2013
Complete List of Authors:	Simpson, Aaron; The Canberra Hospital, Chemical Pathology Krowka, Renata; The Canberra Hospital, Chemical Pathology Kerrigan, Jennifer; The Canberra Hospital, Chemical Pathology Southcott, Emma; The Canberra Hospital, Chemical Pathology Wilson, J; The Canberra Hospital, Endocrinology; Australian National University, Medical School Potter, Julia; The Canberra Hospital, Chemical Pathology; Australian National University, Medical School Nolan, Christopher; Australian National University, Medical School; The Canberra Hospital, Endocrinology Hickman, Peter; The Canberra Hospital, Chemical Pathology; Australian National University, Medical School
<b>Primary Subject Heading</b> :	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Pathology
Keywords:	Diabetes and Endocrinology, Diabetes screening, Chemical pathology, HbA1c

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## **Opportunistic pathology-based screening for diabetes**

Aaron J Simpson, Registrar<sup>1,2</sup> Renata Krowka, Registrar<sup>1</sup> Jennifer L Kerrigan, Research Assistant<sup>1</sup> Emma K Southcott, Research Assistant<sup>1,3</sup>, J Dennis Wilson, Director<sup>2,3</sup> Julia M Potter, Professor<sup>1,3</sup> Christopher J Nolan, Professor<sup>2,3</sup>, Peter E Hickman, Director<sup>1,3</sup>.

Departments of <sup>1</sup>Chemical Pathology and <sup>2</sup>Endocrinology, The Canberra Hospital, Canberra, ACT, 2605, Australia; <sup>3</sup>Australian National University Medical School, Canberra, ACT, 0200, Australia.

Corresponding author:

Prof Christopher J Nolan

Department of Endocrinology

The Canberra Hospital

Woden, ACT 2606, Australia

Tel +61 2 6244 2228

Email: christopher.nolan@anu.edu.au

### ABSTRACT

**OBJECTIVE:** To determine the potential of opportunistic glycated haemoglobin (HbA1c) testing of pathology samples to detect previously unknown diabetes.

**DESIGN:** Pathology samples from participants collected for other reasons and suitable for HbA1c testing were utilised for opportunistic diabetes screening. HbA1c was measured with a Biorad Variant II turbo analyser and HbA1c levels of ≥6.5% (48 mmol//mol) was considered diagnostic for diabetes. Confirmation of previously unknown diabetes status was obtained by review of hospital medical records and phone calls to general practititioners.

SETTING: Hospital pathology laboratory receiving samples from hospital and communitybased settings.

PARTICIPANTS: Participants were identified based on blood sample collection location into community-based (CB), emergency department (ED) and inpatient (IP) groups. Exclusions pre-testing were made based on electronic patient history of; age <18 years, previous diabetes diagnosis, query for diabetes status in the past 12 months, evidence of pregnancy, and sample collected post surgery or transfusion. Only one sample per individual participant was tested.

**RESULTS:** Of 22,396 blood samples collected, 4,505 (1,142 CB, 1,113 ED, 2,250 IP) were tested of which 327 (7.3%) had HbA1c levels ≥6.5% (48 mmol//mol). Of these 120 (2.7%)

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were determined to have previously unknown diabetes (11 [1.0%] CB, 21 [1.9%] ED, 88 [3.9%] IP). The prevalence of previously unknown diabetes was substantially higher (5.4%) in hospital-based (ED and IP) participants aged over 54 years.

**CONCLUSIONS:** Opportunistic testing of referred pathology samples can be an effective method of screening for diabetes especially in hospital-based and older persons.

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### ARTICLE SUMMARY

### Article focus

- Diabetes is a common condition with a high rate of undiagnosed persons.
- Opportunistic screening for diabetes using HbA1c in blood samples taken for other reasons could uncover undiagnosed persons.
- Blood samples from community-based, emergency department and inpatient patient groups were opportunistically tested for HbA1c ≥6.5%.

### Key messages

- Opportunistic diabetes screening using HbA1c showed previously unknown diabetes in 1.0%, 1.9% and 3.9% of community-based, emergency department, and inpatient persons, respectively.
- The prevalence of unknown diabetes was substantially higher in hospital-based persons older than 54 years.
- Opportunistic testing of referred pathology samples can be an effective method of screening for diabetes.

### INTRODUCTION

Diabetes is an important and common disease with significant morbidity and mortality<sup>1</sup>. Its worldwide prevalence in 2010 was estimated to be 285 million with this expected to increase to 439 million in  $2030^2$ . More than 90% of those affected have type 2 diabetes<sup>1</sup>. In 2000 in Australia, the prevalence of diabetes in persons  $\geq$  25 year olds was 7.5%, and importantly, half of those with diabetes had not been diagnosed prior to the survey<sup>3</sup>.

The high prevalence of undiagnosed type 2 diabetes is due to the insidious nature of its onset. The delay in clinical diagnosis of type 2 diabetes has been estimated to be at least 5-7 years<sup>4</sup>. This is of clinical relevance as both micro- and macro-vascular complications are often already present at the time of diagnosis<sup>4,5,6</sup>. As the association between hyperglycaemia and the development of retinopathy is very strong, the presence of this complication at the time of diabetes diagnosis is very likely a consequence of the prior undiagnosed diabetes<sup>7</sup>. Even though hyperglycaemia is associated with a greater risk of macrovascular disease events, the causative role of hyperglycaemia in these complications is less clear<sup>8,9</sup>. Nevertheless, the UK Prospective Diabetes Study showed that better glycaemic control in type 2 diabetes patients over 10 years reduced microvascular complication rates and, with longer term follow-up, macrovascular events and death from any cause<sup>10,11</sup>. Thus, early detection and treatment of type 2 diabetes has the potential to significantly reduce the morbidity and mortality associated with this disease. However there has been recent debate relating to the cost-benefit analysis of diabetes screening versus population-based health promotion approaches to reduce risk<sup>12,13</sup>.

Recently, the World Health Organisation (WHO) and the American Diabetes Association (ADA) endorsed the use of glycated haemoglobin (HbA1c) for the diagnosis of diabetes<sup>14,15</sup>, and more recently an Australasian working party has similarly recommended use of HbA1c for diagnostic purposes<sup>16</sup>. The recommendation is that diabetes is diagnosed by a HbA1c level of  $\geq 6.5\%$  (48 mmol/mol). The ADA also endorsed the use of HbA1c in the range of  $\geq 5.7\%$  and <6.5% ( $\geq 39$  and <48 mmol/mol)) for the diagnosis of pre-diabetes<sup>15</sup>. This allows for the development of new approaches to the screening for diabetes. A USA based study showed that HbA1c could be used to detect undiagnosed diabetes in hospitalised patients<sup>6</sup>. In a recent Australian study of hospitalised patients, using a diagnostic HbA1c cut off of  $\geq 6.5\%$ , undiagnosed diabetes was found in 11%<sup>17</sup>.

A major contributor to cost in screening programs is the organisation and collection of blood samples. In this study, we used blood samples already available to ACT Pathology from referral for unrelated tests to assess prevalence of undiagnosed diabetes using HbA1c. Three separate groups were assessed: community patients referred for pathology testing by family physicians, patients attending only the Emergency Department, and hospitalised inpatients.

### METHODS

### **Ethical considerations**

This study was approved by the ACT Health Human Research Ethics Committee. Approval without obtaining participant consent was based on the recommendations of Section 2.3.6 of the National Statement on Ethical Conduct in Human Research (2007), particularly part b *"the benefits of the research justify any risk or harm associated with not seeking consent"*, part c *"it is impracticable to obtain consent"* and part g *"in case the results have significance for participants' welfare there is, where practicable, a plan for making information arising from the research available to them"<sup>18</sup>.* 

### **Participants**

ACT Pathology (Canberra, ACT, Australia) is a certified laboratory with the National Glycohemoglobin Standardisation Program (NGSP) and provides pathology testing services to both acute hospital patients (inpatient and emergency) and community patients. HbA1c measurement requires a sample collected into an EDTA tube and this is the same sample required for a full blood count (FBC). We used samples referred to the laboratory for a FBC for our screening study. The ACT Pathology laboratory information system (LIS) was used to search for consecutive FBC samples from April 2010 - January 2011. There were some breaks in collection due to research assistant unavailability. A total of 22,396 FBC requests were identified and the pathology electronic history for the respective participants was exported into LabWizard (Pacific Knowledge Systems, Surry Hills, NSW, Australia). The participants were separated into three groups: community-based persons (CB), persons attending the emergency department without admission to hospital (ED), and hospital inpatients (IP). (Figure 1).

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Samples were excluded if they were duplicate samples from the same participant, if the participant was <18 years of age, if the participant was pregnant, or if the participant was post-surgery or had had a transfusion. Other exclusion criteria were any requests for HbA1c testing in the previous 12 months, evidence of diabetes screening by a glucose tolerance test or a glucose load test in the previous 12 months, and a previous diagnosis of diabetes identified from within the laboratory information system (LIS) from clinical notes, results indicative of diabetes, or requests for investigating diabetes. Samples from participants presenting to the Emergency Department who had a record of any pathology testing in the previous 12 months were also excluded (Figure 1).

### Sample collection and HbA1c assay

Samples were collected after completion of the FBC analysis and stored at -80°C prior to HbA1c testing. Samples that were not located, had insufficient volume or were visibly degraded were removed from the testing cohort (Figure 1). HbA1c was measured using a Biorad Variant II Turbo Analyser (Bio-Rad Laboratories Pty., Ltd., Gladesville, NSW, Australia). The interassay CV was 2.3% at an HbA1c of 5.15% and 1.7% at an HbA1c of 9.77%.

### **Diagnosis of unknown diabetes**

From the tested samples a diagnosis of diabetes was made if the HbA1c was  $\geq$ 6.5% (48 mmol/mol). To determine if this diagnosis was previously known or unknown for the respective individual, the hospital record (if available) was searched and the family practitioner was contacted (by phone) to determine prior history.

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### **Statistical analysis**

HbA1c data are dually reported in the traditional NGSP HbA1c % format and the new recommended International Federation of Clinical Chemistry HbA1c mmol/mol format. Descriptive statistics used include means ± SD, median, maximal and minimal as indicated.

An analysis of variance was conducted to investigate the variability in the measured HbA1C, with variation considered across the age in years, sex and the three patient groups. Age in years was included as a linear effect, rather than as specific age categories, because HbA1C was found to change in a smooth linear fashion with age. This linear effect was allowed to vary between males and females in the final model. More flexible non-linear age effects, and formulations that allowed differences in the age effect for the three patient groups, were examined, but neither were found to be supported by the data. The analysis was conducted in the R statistical software<sup>19</sup>.

### RESULTS

A total of 22,396 samples suitable for HbA1c analysis were received in the study time interval. After excluding samples for the reasons listed above, HbA1c was measured in 1142 CB, 1113 ED and 2250 IP samples (Figure 1). A total of 4505 HbA1c tests were performed, of which 327 (7.3%) had test readings of  $\geq$ 6.5% ( $\geq$ 48 mmol/mol) consistent with the diagnosis of diabetes. After examination of the hospital record and/or contacting the family practitioner, we had 120 cases (2.7% of total tested) of previously unsuspected diabetes. Of the 120 new cases of diabetes, 11 (1.0%) were community-based participants, 21 (1.9%) were from the Emergency Department group and 88 (3.9%) were hospital inpatients (Figure 1).

Analysis of the tested cohort (known diabetes subjects removed) showed that mean HbA1c levels were  $5.4 \pm 0.4\%$  ( $36 \pm 5 \text{ mmol/mol}$ ) for CB,  $5.5 \pm 0.5\%$  ( $37 \pm 0.5\%$  ( $37 \pm 5 \text{ mmol/mol}$ ) for ED and  $5.6 \pm 0.5\%$  ( $38 \pm 6 \text{ mmol/mol}$ ) for IP participants (Table 1). The CB and ED subjects were, respectively, an average of 7.4 and 9.7 years younger than the IP subjects (Table 1). Considering that HbA1c increased linearly with age (0.5% from age 20 to 90; p<0.001), the HbA1c results were adjusted for age difference between the groups. IP age-adjusted HbA1c was still found to be greater than CB HbA1c (p<0.001). Age-adjusted HbA1c results for ED patients were not different from the other groups. Besides age, patient gender was also an important consideration, with females having HbA1c results 0.13\% less than males (p<0.05). Also, the age-related increase in HbA1c is more pronounced for men than for women (p<0.05). Of note, age, gender and group only explained 12% of the variability in HbA1c results.

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Subjects with a new diagnosis of diabetes were significantly older than the non-diabetic subjects in each of the tested groups and were more likely to be from the ED and IP groups (Table 1 and 2). The prevalence of previously undiagnosed diabetes was lowest at 0% in the CB group less than 40 years of age and greatest at 5.8% in the IP group over the age of 54 (Table 2).

The American Diabetes Association has classified subjects with HbA1c levels in the range of 5.7-6.4% (39-47 mmol/mol) as having pre-diabetes<sup>15</sup>. Of the subjects in our study, 24.8%, 28.7% and 39.5% of CB, ED and IP subjects, respectively, had HbA1c levels in this range (Table 2).

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Diabetes mellitus is an ideal condition to screen for, as it fulfils all of the principles of screening that need to be met according to the World Health Organisation<sup>20</sup>. The challenge is to perform regular screening of the population in a time- and cost-effective manner. Population-based surveys, including the AUSDIAB study in Australia, indicate that about 50% of subjects with diabetes have not been diagnosed<sup>3</sup>. In this study, we investigated whether opportunistic diabetes screening through measuring HbA1c in blood samples ordered for other reasons could assist to uncover some of these cases of undiagnosed diabetes.

HbA1c levels were measured in samples from three separate populations: communitybased, the participants being more likely to be relatively well and under continuing general practitioner care (CB); participants who had attended only the Emergency Department in the last 12 months (as far as our records showed) (ED); and hospitalised participants reflecting a group of sicker individuals (IP). Efforts were made to eliminate testing samples in participants who were likely to have already been diagnosed with diabetes or who were likely to have been screened for diabetes within the previous 12 months. It was anticipated that objective evidence of undiagnosed diabetes mellitus might be quite different between these 3 groups.

In the subjects eventually tested, the rates of previously undiagnosed diabetes were 1.0%, 1.9% and 3.9% in the CB, ED and IP groups, respectively. Despite efforts to exclude testing samples from subjects already with a diagnosis of diabetes, 1.4%, 4.7% and 6.2% of the subjects in the three respective groups did have a previous diagnosis. Age was a major

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factor in determining risk. Subjects <40 years of age had rates of previously unknown diabetes of 0.0%, 0.5%, and 1.3% in the CB, ED and IP groups, respectively, compared to 1.5%, 4.0%, and 5.8% in subjects >54 years of age.

Previous studies have also investigated the prevalence of undiagnosed diabetes in a hospital setting. Wexler et al from the USA found a comparable 5% of unsuspected diabetes in hospitalised patients using the cut off >6.5% (>48 mmol/mol)<sup>6</sup>. An Australian study from Adelaide by Valentine et al found 11.1% of unsuspected diabetes, which is much higher than our results<sup>17</sup>. However, their methodology only tested HbA1c on those with bloods taken at admission with a random plasma glucose >5.5 mmol/L, so it is not truly representative of hospital inpatients, rather those most likely to have diabetes. This study also was reliant on correct coding for diabetes on discharge in order to exclude previously known diabetes. For the current study, efforts to exclude previous diabetes were much more rigorous with careful review of the hospital record if available and phone calls to the subjects' family doctors.

The current study also differed from the previous studies, in that community-based (CB) and emergency department patients not admitted to the hospital (ED) were included. The rate of unknown diabetes in the CB group was quite low at 1.0%. This is much lower than the rate of undiagnosed diabetes in the community-based AUSDIAB cohort, but a proportion of the AUSDIAB cohort would not have been engaged in regular medical care<sup>3</sup>. General practitioners predominantly care for the CB subjects of the current study, such that the low level of unsuspected diabetes in these subjects may be indicative of a high level of awareness of diabetes and screening by them within the ACT region. For this

reason, opportunistic pathology-based diabetes screening in this group and in this locale may not be as rewarding as the other groups.

The ED group had twice the rate of unknown diabetes compared to the CB group at 1.9%. An opportunistic approach to diabetes screening may be much more relevant to the ED group, as a higher proportion are likely not to be engaged with routine care with a family doctor. This group is likely to also include frequent attendees to hospital with chronic illness, although many of these subjects would have been excluded because of record of other pathology testing in the preceding 12 months. As expected, the IP group had the highest rate of unknown diabetes at 3.9%.

An important contributor to any screening program cost is sample collection and data entry. The procedure we describe removes these costs. In an opportunistic screening, costs could also be reduced by enhanced computer systems to identify samples to be tested and inclusion of the result in the routine pathology reporting to the subjects' treating doctors. It has recently been noted that screening for diabetes in the UK did not reduce mortality at 10 years<sup>21,22</sup>. However, intensive treatment following diagnosis reduces complications, and over a longer period mortality is also reduced<sup>10</sup>.

In conclusion, within this Australian setting, opportunistic diabetes screening using HbA1c on FBC samples collected for other purposes is possible and cost effective. Patients presenting to the Emergency Department or admitted to hospital and being older than 54 years of age are most likely to have previously unknown diabetes.

### ACKNOWLEDGEMENTS

We thank Dr Brent Henderson of CSIRO Maths and Information Sciences for his statistical advice and Prof Jim Butler of Australian National University for his advice relating to health economics.

### CONTRIBUTORS

AJS and RK collected and tabulated the data; JLK collected and tabulated data and contributed to the writing of the paper; EKS helped plan and implement the study; CJN helped plan the study, reviewed the data and helped write the paper, JDW and JMP helped plan the study and reviewed the data; and PEH helped plan the study, reviewed the data and helped write the paper. He is the guarantor of the study. All the authors reviewed the final version of the manuscript.

### FUNDING

This project was supported by a grant from the Canberra Hospital Private Practice Trust Fund.

### DATA SHARING STATEMENT

There is no additional data available.

### **COMPETING INTERESTS**

All authors have completed the Unified Competing Interest form at wwww.icmje.org/coi\_disclosure.pdf (available on request from the corresponding author) and declare: no financial relationships with any organizations that might have an interest in

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the submitted work in the past 3 years, and no other relationships or activities that could

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**Table 1.** Subject age and HbA1c characteristics within tested community-based, EmergencyDepartment and inpatient participant groups\*

	Community-based	Emergency	Inpatient
	(n=1126)	(n=1061)	(n=2114)
Age (years)			
Mean (± SD)	51.8 (± 17.1)	49.5 (± 20.5)	59.2 (± 19.1)
Median	52	47	61
Range	18-92	18-98	18-97
HbA1c (%) <sup>#</sup>			
Mean (± SD)	5.4 (± 0.4)	5.5 (± 0.5)	5.6 (± 0.5)†
Median	5.4	5.5	5.6
Range	3.7-8.9	4.0-10.3	3.2-12.2
HbA1c (mmol/mol) <sup>#</sup>			
Mean (± SD)	36 (± 5)	37 (± 5)	38 (± 6) †
Median	36	37	38
Range	17-71	20-89	11-110
Mean (± SD) of age (y	ears) of subjects with H	lbA1c % (mmol/mol):	
<5.7 (<39)	48.5 (± 16.8)	44.2 (± 18.8)	54.7 (± 19.8)
5.7-5.9 (39-41)	60.7 (± 13.6)	59.9 (± 18.9)	63.4 (± 17.8)
6.0-6.4 (42-47)	63.1 (± 15.3)	64.1 (± 19.5)	66.7 (± 14.5)
≥6.5 (≥48)	59.5 (± 10.2)	65.0 (± 18.1)	67.7 (± 15.6)

\* Tested subjects subsequently found to have previously known diabetes were excluded from this analysis. <sup>#</sup> Data are dually reported in the traditional NGSP % haemoglobin and the new recommended IFCC mmol/mol format. <sup>†</sup> IP HbA1c results were found to be significantly greater than CB across the age range (P<0.001).

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**Table 2.** Subjects within HbA1c categories according to age within tested community-based, Emergency Department and inpatient groups\*

	Community-based	Emergency	Inpatient	
Number [%] subjects with HbA1c % (mmol/mol) <sup>#</sup> :				
Age <40 years				
<5.7 (<39)	276 [92.9]	333 [88.1]	305 [80.5]	
5.7-5.9 (39-41)	15 [5.1]	31 [8.2]	53 [14.0]	
6.0-6.4 (42-47)	6 [2.0]	12 [3.2]	16 [4.2]	
≥6.5 (≥48)	0 [0.0]	2 [0.5]	5 [1.3]	
Total	297 [100]	378 [100]	379 [100]	
Age ≥40 to <55 years	6			
<5.7 (<39)	245 [79.0]	203 [72.2]	290 [63.5]	
5.7-5.9 (39-41)	39 [12.6]	54 [19.2]	101 [22.1]	
6.0-6.4 (42-47)	23 [7.4]	21 [7.5]	57 [12.5]	
≥6.5 (≥48)	3 [1.0]	3 [1.1]	9 [2.0]	
Total	310 [100]	281 [100]	457 [100]	
Age 55 and above				
<5.7 (<39)	317 [61.1]	200 [49.8]	595 [46.6]	
5.7-5.9 (39-41)	135 [26.0]	111 [27.6]	345 [27.0]	
6.0-6.4 (42-47)	59 [11.4]	75 [18.7]	264 [20.7]	
≥6.5 (≥48)	8 [1.5]	16 [4.0]	74 [5.8]	
Total	519 [100]	402 [100]	1278 [100]	
All subjects				
<5.7 (<39)	838 [74.4]	736 [69.3]	1190 [56.3]	
5.7-5.9 (39-41)	189 [16.5]	196 [18.5]	499 [23.6]	
6.0-6.4 (42-47)	88 [7.8]	108 [10.2]	337 [15.9]	
≥6.5 (≥48)	11 [1.0]	21 [2.0]	88 [4.2]	
Total	1126 [100]	1061 [10]	2114 [100]	

 Tested subjects subsequently found to have previously known diabetes were excluded from this analysis. <sup>#</sup> Data are dually reported in the traditional NGSP % haemoglobin and the new recommended IFCC mmol/mol format.

### **FIGURE LEGEND**

Figure 1: Flow diagram showing the process involved in selecting full blood count (FBC) samples for opportunistic HbA1c testing and the overall testing results.

Subjects were divided into community-based (CB), emergency department (ED) and inpatient (IP) groups based on origin of sample collection. Samples were excluded from testing according to reasons indicated (upper three grey boxes). Of the subjects tested, those found to have elevated HbA1c  $\geq$  6.5% ( $\geq$  48 mmol/mol), and to have previously known diabetes, were excluded (lower grey box). The number of subjects found to have previously undiagnosed diabetes is shown in the lower white boxes. LIS-laboratory inquiry system; GP-general practitioner; 12/12-12 months. 

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Figure 1 254x366mm (72 x 72 DPI)



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Journal:	BMJ Open
Manuscript ID:	bmjopen-2013-003411.R1
Article Type:	Research
Date Submitted by the Author:	10-Aug-2013
Complete List of Authors:	Simpson, Aaron; The Canberra Hospital, Chemical Pathology Krowka, Renata; The Canberra Hospital, Chemical Pathology Kerrigan, Jennifer; The Canberra Hospital, Chemical Pathology Southcott, Emma; The Canberra Hospital, Chemical Pathology Wilson, J; The Canberra Hospital, Endocrinology; Australian National University, Medical School Potter, Julia; The Canberra Hospital, Chemical Pathology; Australian National University, Medical School Nolan, Christopher; Australian National University, Medical School; The Canberra Hospital, Endocrinology Hickman, Peter; The Canberra Hospital, Chemical Pathology; Australian National University, Medical School
<b>Primary Subject Heading</b> :	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Pathology
Keywords:	Diabetes and Endocrinology, Diabetes screening, Chemical pathology < PATHOLOGY, HbA1c

SCHOLARONE<sup>™</sup> Manuscripts

## **Opportunistic pathology-based screening for diabetes**

Aaron J Simpson, Registrar<sup>1,2</sup> Renata Krowka, Registrar<sup>1</sup> Jennifer L Kerrigan, Research Assistant<sup>1</sup> Emma K Southcott, Research Assistant<sup>1,3</sup>, J Dennis Wilson, Director<sup>2,3</sup> Julia M Potter, Professor<sup>1,3</sup> Christopher J Nolan, Professor<sup>2,3</sup>, Peter E Hickman, Director<sup>1,3</sup>.

Departments of <sup>1</sup>Chemical Pathology and <sup>2</sup>Endocrinology, The Canberra Hospital, Canberra, ACT, 2605, Australia; <sup>3</sup>Australian National University Medical School, Canberra, ACT, 0200, Australia.

Corresponding author:

Prof Christopher J Nolan

Department of Endocrinology

The Canberra Hospital

Woden, ACT 2606, Australia

Tel +61 2 6244 2228

Email: christopher.nolan@anu.edu.au

### ABSTRACT

**OBJECTIVE:** To determine the potential of opportunistic glycated haemoglobin (HbA1c) testing of pathology samples to detect previously unknown diabetes.

**DESIGN:** Pathology samples from participants collected for other reasons and suitable for HbA1c testing were utilised for opportunistic diabetes screening. HbA1c was measured with a Biorad Variant II turbo analyser and HbA1c levels of ≥6.5% (48 mmol//mol) was considered diagnostic for diabetes. Confirmation of previously unknown diabetes status was obtained by review of hospital medical records and phone calls to general practititioners.

SETTING: Hospital pathology laboratory receiving samples from hospital and communitybased settings.

PARTICIPANTS: Participants were identified based on blood sample collection location into community-based (CB), emergency department (ED) and inpatient (IP) groups. Exclusions pre-testing were made based on electronic patient history of; age <18 years, previous diabetes diagnosis, query for diabetes status in the past 12 months, evidence of pregnancy, and sample collected post surgery or transfusion. Only one sample per individual participant was tested.

**RESULTS:** Of 22,396 blood samples collected, 4,505 (1,142 CB, 1,113 ED, 2,250 IP) were tested of which 327 (7.3%) had HbA1c levels ≥6.5% (48 mmol//mol). Of these 120 (2.7%)

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were determined to have previously unknown diabetes (11 [1.0%] CB, 21 [1.9%] ED, 88 [3.9%] IP). The prevalence of previously unknown diabetes was substantially higher (5.4%) in hospital-based (ED and IP) participants aged over 54 years.

**CONCLUSIONS:** Opportunistic testing of referred pathology samples can be an effective method of screening for diabetes especially in hospital-based and older persons.

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### **ARTICLE SUMMARY**

### **Article focus**

- Diabetes is a common condition with a high rate of undiagnosed persons.
- Opportunistic screening for diabetes using HbA1c in blood samples taken for other reasons could uncover undiagnosed persons.
- Blood samples from community-based, emergency department and inpatient patient groups were opportunistically tested for HbA1c  $\geq$ 6.5%.

### Key messages

- Opportunistic diabetes screening using HbA1c showed previously unknown diabetes in 1.0%, 1.9% and 3.9% of community-based, emergency department, and inpatient persons, respectively.
- The prevalence of unknown diabetes was substantially higher in hospital-based persons older than 54 years.
- Opportunistic testing of referred pathology samples can be an effective method of screening for diabetes.

### INTRODUCTION

Diabetes is an important and common disease with significant morbidity and mortality<sup>1</sup>. Its worldwide prevalence in 2010 was estimated to be 285 million with this expected to increase to 439 million in  $2030^2$ . More than 90% of those affected have type 2 diabetes<sup>1</sup>. In 2000 in Australia, the prevalence of diabetes in persons  $\geq$  25 year olds was 7.5%, and importantly, half of those with diabetes had not been diagnosed prior to the survey<sup>3</sup>.

The high prevalence of undiagnosed type 2 diabetes is due to the insidious nature of its onset. The delay in clinical diagnosis of type 2 diabetes has been estimated to be at least 5-7 years<sup>4</sup>. This is of clinical relevance as both micro- and macro-vascular complications are often already present at the time of diagnosis<sup>4,5,6</sup>. As the association between hyperglycaemia and the development of retinopathy is very strong, the presence of this complication at the time of diabetes diagnosis is very likely a consequence of the prior undiagnosed diabetes<sup>7</sup>. Even though hyperglycaemia is associated with a greater risk of macrovascular disease events, the causative role of hyperglycaemia in these complications is less clear<sup>8,9</sup>. Nevertheless, the UK Prospective Diabetes Study showed that better glycaemic control in type 2 diabetes patients over 10 years reduced microvascular complication rates and, with longer term follow-up, macrovascular events and death from any cause<sup>10,11</sup>. Thus, early detection and treatment of type 2 diabetes has the potential to significantly reduce the morbidity and mortality associated with this disease. However there has been recent debate relating to the cost-benefit analysis of diabetes screening versus population-based health promotion approaches to reduce risk<sup>12,13</sup>.

Recently, the World Health Organisation (WHO), the American Diabetes Association (ADA) and the National Health Scheme (NHS) in the UK endorsed the use of glycated haemoglobin (HbA1c) for the diagnosis of diabetes<sup>14,15,16</sup>, and more recently an Australasian working party has similarly recommended use of HbA1c for diagnostic purposes<sup>17</sup>. The recommendation is that diabetes is diagnosed by a HbA1c level of  $\geq$ 6.5% (48 mmol/mol). The ADA also endorsed the use of HbA1c in the range of  $\geq$ 5.7% and <6.5% ( $\geq$ 39 and <48 mmol/mol)) for the diagnosis of pre-diabetes<sup>15</sup>. This allows for the development of new approaches to the screening for diabetes. A USA based study showed that HbA1c could be used to detect undiagnosed diabetes in hospitalised patients<sup>6</sup>. In a recent Australian study of hospitalised patients, using a diagnostic HbA1c cut off of  $\geq$ 6.5%, undiagnosed diabetes was found in 11%<sup>18</sup>.

A major contributor to cost in screening programs is the organisation and collection of blood samples. In this study, we used blood samples already available to ACT Pathology (Canberra, ACT, Australia) from referral for unrelated tests to assess prevalence of undiagnosed diabetes using HbA1c. Three separate groups were assessed: community patients referred for pathology testing by family physicians, patients attending only the Emergency Department, and hospitalised inpatients.

### METHODS

### **Ethical considerations**

This study was approved by the ACT Health Human Research Ethics Committee. Approval without obtaining participant consent was based on the recommendations of Section 2.3.6 of the National Statement on Ethical Conduct in Human Research (2007), particularly part b *"the benefits of the research justify any risk or harm associated with not seeking consent"*, part c *"it is impracticable to obtain consent"* and part g *"in case the results have significance for participants" welfare there is, where practicable, a plan for making information arising from the research available to them"*<sup>19</sup>.

### Participants

ACT Pathology is a certified laboratory with the National Glycohemoglobin Standardisation Program (NGSP) and provides pathology testing services to both acute hospital patients (inpatient and emergency) and community patients. HbA1c measurement requires a sample collected into an EDTA tube and this is the same sample required for a full blood count (FBC). We used samples referred to the laboratory for a FBC for our screening study. The ACT Pathology laboratory Information System (LIS) was used to search for consecutive FBC samples from April 2010 - January 2011. There were some breaks in collection due to research assistant unavailability. A total of 22,396 FBC requests were identified and the pathology electronic history for the respective participants was exported into LabWizard (Pacific Knowledge Systems, Surry Hills, NSW, Australia). The participants were separated into three groups: community-based persons (CB), persons attending the emergency department without admission to hospital (ED), and hospital inpatients (IP). (Figure 1).

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Samples were excluded if they were duplicate samples from the same participant, if the participant was <18 years of age, if the participant was pregnant, or if the participant was post-surgery or had had a transfusion. Other exclusion criteria were any requests for HbA1c testing in the previous 12 months, evidence of diabetes screening by a glucose tolerance test or a glucose load test in the previous 12 months, and a previous diagnosis of diabetes identified from within the laboratory information system (LIS) from clinical notes, results indicative of diabetes, or requests for investigating diabetes. Samples from participants presenting to the Emergency Department who had a record of any pathology testing in the previous 12 months were also excluded (Figure 1).

### Sample collection and HbA1c assay

Samples were collected after completion of the FBC analysis and stored at -80°C prior to HbA1c testing. Samples that were not located, had insufficient volume or were visibly degraded were removed from the testing cohort (Figure 1). HbA1c was measured in 4505 samples using a Biorad Variant II Turbo Analyser (Bio-Rad Laboratories Pty., Ltd., Hercules, CA, USA). The interassay CV based on the NGSP HbA1c % values was 2.3% at a HbA1c of 5.15% and 1.7% at a HbA1c of 9.77%. Samples were not stored for a period longer than 6 months prior to being tested.

### Diagnosis of unknown diabetes

From the tested samples a diagnosis of diabetes was made if the HbA1c was ≥6.5% (48 mmol/mol). To determine if this diagnosis was previously known or unknown for the

respective individual, the hospital record (if available) was searched and the family practitioner was contacted (by phone) to determine prior history.

### **Statistical analysis**

HbA1c data are dually reported in the traditional NGSP HbA1c % format and the SI unit mmol/mol as endorsed by the International Federation of Clinical Chemistry. Descriptive statistics used include means ± SD, median, maximal and minimal as indicated.

An analysis of variance was conducted to investigate age and gender determinants of the measured HbA1c in the three patient groups. Age in years was included as a linear effect, rather than as specific age categories, because HbA1c was found to change in a smooth linear fashion with age. This linear effect was allowed to vary between males and females in the final model. More flexible non-linear age effects, and formulations that allowed differences in the age effect for the three patient groups, were examined, but neither were found to be supported by the data. The analysis was conducted in the R statistical software<sup>20</sup>.

### RESULTS

A total of 22,396 samples suitable for HbA1c analysis were received in the study time interval. After excluding samples for the reasons listed above, HbA1c was measured in 1142 CB, 1113 ED and 2250 IP samples (Figure 1). A total of 4505 HbA1c tests were performed, of which 327 (7.3%) had test readings of  $\geq$ 6.5% ( $\geq$ 48 mmol/mol) consistent with the diagnosis of diabetes. After examination of the hospital record and/or contacting the family practitioner, we had 120 cases (2.7% of total tested) of previously unsuspected diabetes. Of the 120 new cases of diabetes, 11 (1.0%) were community-based participants, 21 (1.9%) were from the Emergency Department group and 88 (3.9%) were hospital inpatients (Figure 1).

Analysis of the tested cohort (known diabetes subjects removed) showed that mean HbA1c levels were  $5.4 \pm 0.4\%$  ( $36 \pm 5$  mmol/mol) for CB,  $5.5 \pm 0.5\%$  ( $37 \pm 5$  mmol/mol) for ED and  $5.6 \pm 0.5\%$  ( $38 \pm 6$  mmol/mol) for IP participants (Table 1). The CB and ED subjects were, respectively, an average of 7.4 and 9.7 years younger than the IP subjects (Table 1). Considering that HbA1c increased linearly with age (0.5% from age 20 to 90; p<0.001), the HbA1c results were adjusted for age difference between the groups. IP age-adjusted HbA1c was still found to be greater than CB HbA1c (p<0.001). Age-adjusted HbA1c results for ED patients were not different from the other groups. Besides age, patient gender was also an important consideration, with females having HbA1c results 0.13% less than males (p<0.05). Also, the age-related increase in HbA1c is more pronounced for men than for women (p<0.05). Of note, age, gender and group only explained 12% of the variability in HbA1c results.

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Subjects with a new diagnosis of diabetes were significantly older than the non-diabetic subjects in each of the tested groups and were more likely to be from the ED and IP groups (Table 1 and 2). In fact, previously undiagnosed diabetes was not detected at all in the CB group less than 40 years of age compared to a rate of 5.8% detection in the IP group over the age of 54 (Table 2).

The American Diabetes Association has classified subjects with HbA1c levels in the range of 5.7-6.4% (39-47 mmol/mol) as having pre-diabetes<sup>15</sup>. Of the subjects in our study, 24.8%, 28.7% and 39.5% of CB, ED and IP subjects, respectively, had HbA1c levels in this range (Table 2).

### DISCUSSION

Diabetes mellitus is an ideal condition to screen for, as it fulfils all of the principles of screening that need to be met according to the World Health Organisation<sup>21</sup>. The challenge is to perform regular screening of the population in a time- and cost-effective manner. Population-based surveys, including the AUSDIAB study in Australia, indicate that about 50% of subjects with diabetes have not been diagnosed<sup>3</sup>. In this study, we investigated whether opportunistic diabetes screening through measuring HbA1c in blood samples ordered for other reasons could assist to uncover some of these cases of undiagnosed diabetes.

HbA1c levels were measured in samples from three separate populations: communitybased, the participants being more likely to be relatively well and under continuing general practitioner care (CB); participants who had attended only the Emergency Department in the last 12 months (as far as our records showed) (ED); and hospitalised participants reflecting a group of sicker individuals (IP). Efforts were made to eliminate testing samples in participants who were likely to have already been diagnosed with diabetes or who were likely to have been screened for diabetes within the previous 12 months. It was anticipated that objective evidence of undiagnosed diabetes mellitus might be quite different between these 3 groups.

In the subjects eventually tested, the rates of previously undiagnosed diabetes were 1.0%, 1.9% and 3.9% in the CB, ED and IP groups, respectively. Despite efforts to exclude testing samples from subjects already with a diagnosis of diabetes, 1.4%, 4.7% and 6.2% of the

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subjects in the three respective groups did have a previous diagnosis. Age was a major factor in determining risk. Subjects <40 years of age had rates of previously unknown diabetes of 0.0%, 0.5%, and 1.3% in the CB, ED and IP groups, respectively, compared to 1.5%, 4.0%, and 5.8% in subjects >54 years of age.

The family doctors of all the subjects newly diagnosed with diabetes in this study were notified such that confirmation of the diagnosis could occur and appropriate care could be initiated. The action taken by the family doctors, however, was not within the scope of this study. Considering that WHO and ADA state that a single HbA1c  $\geq$ 6.5% (48 mmol/mol) is diagnostic of diabetes, false positive diagnoses should occur rarely. Therefore, this method of screening should have a high positive predictive value.

Previous studies have also investigated the prevalence of undiagnosed diabetes in a hospital setting. Wexler et al from the USA found a comparable 5% of unsuspected diabetes in hospitalised patients using the cut off >6.5% (>48 mmol/mol)<sup>6</sup>. An Australian study from Adelaide by Valentine et al found 11.1% of unsuspected diabetes, which is much higher than our results<sup>17</sup>. However, their methodology only tested HbA1c on those with bloods taken at admission with a random plasma glucose >5.5 mmol/L, so it is not truly representative of hospital inpatients, rather representative of a group with an expected higher positive rate of diabetes. This study also was reliant on correct coding for diabetes on discharge in order to exclude previously known diabetes. For the current study, efforts to exclude previous diabetes were much more rigorous with careful review of the hospital record if available and phone calls to the subjects' family doctors.

The current study also differed from the previous studies, in that community-based (CB) and emergency department patients not admitted to the hospital (ED) were included. The

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 rate of unknown diabetes in the CB group was quite low at 1.0%. This is much lower than the rate of undiagnosed diabetes in the community-based AUSDIAB cohort, but a proportion of the AUSDIAB cohort would not have been engaged in regular medical care<sup>3</sup>. General practitioners predominantly care for the CB subjects of the current study, such that the low level of unsuspected diabetes in these subjects may be indicative of a high level of awareness of diabetes and screening by them within the ACT region. For this reason, opportunistic pathology-based diabetes screening in this group and in this locale may not be as rewarding as the other groups.

The ED group had twice the rate of unknown diabetes compared to the CB group at 1.9%. An opportunistic approach to diabetes screening may be much more relevant to the ED group, as a higher proportion are likely not to be engaged with routine care with a family doctor. This group is likely to also include frequent attendees to hospital with chronic illness, although many of these subjects would have been excluded because of record of other pathology testing in the preceding 12 months. As expected, the IP group had the highest rate of unknown diabetes at 3.9%.

An important contributor to any screening program cost is sample collection and data entry. The procedure we describe removes these costs. In an opportunistic screening, costs could also be reduced by enhanced computer systems to identify samples to be tested and inclusion of the result in the routine pathology reporting to the subjects' treating doctors. It has recently been noted that screening for diabetes in the UK did not reduce mortality at 10 years<sup>22,23</sup>. However, intensive treatment following diagnosis reduces complications, and over a longer period mortality is also reduced<sup>10</sup>.

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In conclusion, within this Australian setting, opportunistic diabetes screening using HbA1c on FBC samples collected for other purposes is possible and cost effective. Patients presenting to the Emergency Department or admitted to hospital and being older than 54 years of age are most likely to have previously unknown diabetes. This method of diabetes screening warrants further consideration.

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### ACKNOWLEDGEMENTS

We thank Dr Brent Henderson of CSIRO Computational Informatics for his statistical advice and Prof Jim Butler of Australian National University for his advice relating to health economics.

### CONTRIBUTORS

AJS and RK collected and tabulated the data; JLK collected and tabulated data and contributed to the writing of the paper; EKS helped plan and implement the study; CJN helped plan the study, reviewed the data and helped write the paper, JDW and JMP helped plan the study and reviewed the data; and PEH helped plan the study, reviewed the data and helped write the paper. He is the guarantor of the study. All the authors reviewed the final version of the manuscript.

### FUNDING

This project was supported by a grant from the Canberra Hospital Private Practice Trust Fund.

### DATA SHARING STATEMENT

There is no additional data available.

### **COMPETING INTERESTS**

All authors have completed the Unified Competing Interest form at www.icmje.org/coi\_disclosure.pdf (available on request from the corresponding author)

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and declare: no financial relationships with any organizations that might have an interest in

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Department and inpatient participant groups*			
	Community-based	Emergency	Inpatient
	(n=1126)	(n=1061)	(n=2114)
Age (years)			
Mean (± SD)	51.8 (± 17.1)	49.5 (± 20.5)	59.2 (± 19.1)
Median	52	47	61
Range	18-92	18-98	18-97
HbA1c (%) <sup>#</sup>	•		
Mean (± SD)	5.4 (± 0.4)	5.5 (± 0.5)	5.6 (± 0.5)†
Median	5.4	5.5	5.6
Range	3.7-8.9	4.0-10.3	3.2-12.2
HbA1c (mmol/mol) <sup>#</sup>			
Mean (± SD)	36 (± 5)	37 (± 5)	38 (± 6) †
Median	36	37	38
Range	17-71	20-89	11-110

**Table 1.** Subject age and HbA1c characteristics within tested community-based, EmergencyDepartment and inpatient participant groups\*

Mean (± SD) of age (years) of subjects with HbA1c % (mmol/mol): <5.7 (<39) 48.5 (± 16.8) 44.2 (± 18.8) 54.7 (± 19.8) 5.7-5.9 (39-41) 59.9 (± 18.9) 60.7 (± 13.6) 63.4 (±17.8) 6.0-6.4 (42-47) 64.1 (± 19.5) 63.1 (± 15.3) 66.7 (± 14.5) ≥6.5 (≥48) 59.5 (± 10.2) 65.0 (± 18.1) 67.7 (± 15.6)

\* Tested subjects subsequently found to have previously known diabetes were excluded from this analysis. <sup>#</sup> Data are dually reported in the traditional NGSP % haemoglobin and the new recommended IFCC mmol/mol format. <sup>†</sup> IP HbA1c results were found to be significantly greater than CB across the age range (P<0.001).

Table 2. Subjects within HbA1c categories according to age within tested community-

based, Emergency Department and inpatient groups*			
	Community-based	Emergency	Inpatient
Number [%] subjects v	with HbA1c % (mmol/m	ol) <sup>#</sup> :	
Age <40 years			
<5.7 (<39)	276 [92.9]	333 [88.1]	305 [80.5]
5.7-5.9 (39-41)	15 [5.1]	31 [8.2]	53 [14.0]
6.0-6.4 (42-47)	6 [2.0]	12 [3.2]	16 [4.2]
≥6.5 (≥48)	0 [0.0]	2 [0.5]	5 [1.3]
Total	297 [100]	378 [100]	379 [100]
Age ≥40 to <55 years			
<5.7 (<39)	245 [79.0]	203 [72.2]	290 [63.5]
5.7-5.9 (39-41)	39 [12.6]	54 [19.2]	101 [22.1]
6.0-6.4 (42-47)	23 [7.4]	21 [7.5]	57 [12.5]
≥6.5 (≥48)	3 [1.0]	3 [1.1]	9 [2.0]
Total	310 [100]	281 [100]	457 [100]
Age 55 and above			
<5.7 (<39)	317 [61.1]	200 [49.8]	595 [46.6]
5.7-5.9 (39-41)	135 [26.0]	111 [27.6]	345 [27.0]
6.0-6.4 (42-47)	59 [11.4]	75 [18.7]	264 [20.7]
≥6.5 (≥48)	8 [1.5]	16 [4.0]	74 [5.8]
Total	519 [100]	402 [100]	1278 [100]
All subjects			
<5.7 (<39)	838 [74.4]	736 [69.3]	1190 [56.3]
5.7-5.9 (39-41)	189 [16.5]	196 [18.5]	499 [23.6]
6.0-6.4 (42-47)	88 [7.8]	108 [10.2]	337 [15.9]
≥6.5 (≥48)	11 [1.0]	21 [2.0]	88 [4.2]
Total	1126 [100]	1061 [10]	2114 [100]

 Tested subjects subsequently found to have previously known diabetes were excluded from this analysis. <sup>#</sup> Data are dually reported in the traditional NGSP % haemoglobin and the new recommended IFCC mmol/mol format.

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### **FIGURE LEGEND**

Flow diagram showing the process involved in selecting full blood count Figure 1: (FBC) samples for opportunistic HbA1c testing and the overall testing results.

Subjects were divided into community-based (CB), emergency department (ED) and inpatient (IP) groups based on origin of sample collection. Samples were excluded from testing according to reasons indicated (upper three grey boxes). Of the subjects tested, those found to have elevated HbA1c  $\geq$  6.5% ( $\geq$  48 mmol/mol) and to have previously known diabetes were excluded (lower grey box). The number of subjects found to have previously undiagnosed diabetes is shown in the lower white boxes. LIS-laboratory inquiry system; GP-general practitioner.

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Figure 1 254x366mm (300 x 300 DPI) BMJ Open

### **Opportunistic pathology-based screening for diabetes**

Aaron J Simpson, Registrar<sup>1,2</sup> Renata Krowka, Registrar<sup>1</sup> Jennifer L Kerrigan, Research Assistant<sup>1</sup> Emma K Southcott, Research Assistant<sup>1,3</sup>, J Dennis Wilson, Director<sup>2,3</sup> Julia M Potter, Professor<sup>1,3</sup>, Christopher J Nolan, Professor<sup>2,3</sup>, Peter E Hickman, Director<sup>1,3</sup>.

Departments of <sup>1</sup>Chemical Pathology and <sup>2</sup>Endocrinology, The Canberra Hospital, Canberra, ACT, 2605, Australia; <sup>3</sup>Australian National University Medical School, Canberra, ACT, 0200, Australia.

Corresponding author:

Prof Christopher J Nolan

Department of Endocrinology

The Canberra Hospital

Woden, ACT 2606, Australia

Tel +61 2 6244 2228

Email: christopher.nolan@anu.edu.au

### ABSTRACT

**OBJECTIVE:** To determine the potential of opportunistic glycated haemoglobin (HbA1c) testing of pathology samples to detect previously unknown diabetes.

**DESIGN:** Pathology samples from participants collected for other reasons and suitable for HbA1c testing were utilised for opportunistic diabetes screening. HbA1c was measured with a Biorad Variant II turbo analyser and HbA1c levels of  $\geq$ 6.5% (48 mmol//mol) was considered diagnostic for diabetes. Confirmation of previously unknown diabetes status was obtained by review of hospital medical records and phone calls to general practititioners.

**SETTING:** Hospital pathology laboratory receiving samples from hospital and community-based settings.

**PARTICIPANTS**: Participants were identified based on blood sample collection location into community-based (CB), emergency department (ED) and inpatient (IP) groups. Exclusions pre-testing were made based on electronic patient history of; age <18 years, previous diabetes diagnosis, query for diabetes status in the past 12 months, evidence of pregnancy, and sample collected post surgery or transfusion. Only one sample per individual participant was tested.

**RESULTS:** Of 22,396 blood samples collected, 4,505 (1,142 CB, 1,113 ED, 2,250 IP) were tested of which 327 (7.3%) had HbA1c levels ≥6.5% (48 mmol//mol). Of these 120 (2.7%)

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were determined to have previously unknown diabetes (11 [1.0%] CB, 21 [1.9%] ED, 88 [3.9%] IP). The prevalence of previously unknown diabetes was substantially higher (5.4%) in hospital-based (ED and IP) participants aged over 54 years.

**CONCLUSIONS:** Opportunistic testing of referred pathology samples can be an effective method of screening for diabetes especially in hospital-based and older persons.

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### ARTICLE SUMMARY

### Article focus

- Diabetes is a common condition with a high rate of undiagnosed persons.
- Opportunistic screening for diabetes using HbA1c in blood samples taken for other reasons could uncover undiagnosed persons.
- Blood samples from community-based, emergency department and inpatient patient groups were opportunistically tested for HbA1c ≥6.5%.

### Key messages

- Opportunistic diabetes screening using HbA1c showed previously unknown diabetes in 1.0%, 1.9% and 3.9% of community-based, emergency department, and inpatient persons, respectively.
- The prevalence of unknown diabetes was substantially higher in hospital-based persons older than 54 years.
- Opportunistic testing of referred pathology samples can be an effective method of screening for diabetes.

### INTRODUCTION

Diabetes is an important and common disease with significant morbidity and mortality<sup>1</sup>. Its worldwide prevalence in 2010 was estimated to be 285 million with this expected to increase to 439 million in  $2030^2$ . More than 90% of those affected have type 2 diabetes<sup>1</sup>. In 2000 in Australia, the prevalence of diabetes in persons  $\geq$  25 year olds was 7.5%, and importantly, half of those with diabetes had not been diagnosed prior to the survey<sup>3</sup>.

The high prevalence of undiagnosed type 2 diabetes is due to the insidious nature of its onset. The delay in clinical diagnosis of type 2 diabetes has been estimated to be at least 5-7 years<sup>4</sup>. This is of clinical relevance as both micro- and macro-vascular complications are often already present at the time of diagnosis<sup>4,5,6</sup>. As the association between hyperglycaemia and the development of retinopathy is very strong, the presence of this complication at the time of diabetes diagnosis is very likely a consequence of the prior undiagnosed diabetes<sup>7</sup>. Even though hyperglycaemia is associated with a greater risk of macrovascular disease events, the causative role of hyperglycaemia in these complications is less clear<sup>8,9</sup>. Nevertheless, the UK Prospective Diabetes Study showed that better glycaemic control in type 2 diabetes patients over 10 years reduced microvascular complication rates and, with longer term follow-up, macrovascular events and death from any cause<sup>10,11</sup>. Thus, early detection and treatment of type 2 diabetes has the potential to significantly reduce the morbidity and mortality associated with this disease. However there has been recent debate relating to the cost-benefit analysis of diabetes screening versus population-based health promotion approaches to reduce risk<sup>12,13</sup>.

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Recently, the World Health Organisation (WHO)<sub>2</sub> and the American Diabetes Association (ADA) and the National Health Scheme (NHS) in the UK –endorsed the use of glycated haemoglobin (HbA1c) for the diagnosis of diabetes<sup>14,15,16</sup>, and more recently an Australasian working party has similarly recommended use of HbA1c for diagnostic purposes<sup>46</sup> purposes<sup>17</sup>. The recommendation is that diabetes is diagnosed by a HbA1c level of  $\geq 6.5\%$  (48 mmol/mol). The ADA also endorsed the use of HbA1c in the range of  $\geq 5.7\%$  and <6.5% ( $\geq$ 39 and <48 mmol/mol)) for the diagnosis of pre-diabetes<sup>15</sup>. This allows for the development of new approaches to the screening for diabetes. A USA based study showed that HbA1c could be used to detect undiagnosed diabetes in hospitalised patients<sup>6</sup>. In a recent Australian study of hospitalised patients, using a diagnostic HbA1c cut off of  $\geq 6.5\%$ , undiagnosed diabetes was found in 11%<sup>4718</sup>.

A major contributor to cost in screening programs is the organisation and collection of blood samples. In this study, we used blood samples already available to ACT Pathology (Canberra, ACT, Australia) from referral for unrelated tests to assess prevalence of undiagnosed diabetes using HbA1c. Three separate groups were assessed: community patients referred for pathology testing by family physicians, patients attending only the Emergency Department, and hospitalised inpatients.

### **METHODS**

### **Ethical considerations**

This study was approved by the ACT Health Human Research Ethics Committee. Approval without obtaining participant consent was based on the recommendations of Section 2.3.6 of the National Statement on Ethical Conduct in Human Research (2007), particularly part b *"the benefits of the research justify any risk or harm associated with not seeking consent"*, part c *"it is impracticable to obtain consent"* and part g *"in case the results have significance for participants' welfare there is, where practicable, a plan for making information arising from the research available to them"*<sup>1819</sup>.

### **Participants**

ACT Pathology (Canberra, ACT, Australia) is a certified laboratory with the National Glycohemoglobin Standardisation Program (NGSP) and provides pathology testing services to both acute hospital patients (inpatient and emergency) and community patients. HbA1c measurement requires a sample collected into an EDTA tube and this is the same sample required for a full blood count (FBC). We used samples referred to the laboratory for a FBC for our screening study. The ACT Pathology laboratory information Information system System (LIS) was used to search for consecutive FBC samples from April 2010 - January 2011. There were some breaks in collection due to research assistant unavailability. A total of 22,396 FBC requests were identified and the pathology electronic history for the respective participants was exported into LabWizard (Pacific Knowledge Systems, Surry Hills, NSW, Australia). The participants were separated into three groups: community-based persons (CB), persons attending the emergency department without admission to hospital (ED), and hospital inpatients (IP). (Figure 1).

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Samples were excluded if they were duplicate samples from the same participant, if the participant was <18 years of age, if the participant was pregnant, or if the participant was post-surgery or had had a transfusion. Other exclusion criteria were any requests for HbA1c testing in the previous 12 months, evidence of diabetes screening by a glucose tolerance test or a glucose load test in the previous 12 months, and a previous diagnosis of diabetes identified from within the laboratory information system (LIS) from clinical notes, results indicative of diabetes, or requests for investigating diabetes. Samples from participants presenting to the Emergency Department who had a record of any pathology testing in the previous 12 months were also excluded (Figure 1).

### Sample collection and HbA1c assay

Samples were collected after completion of the FBC analysis and stored at -80°C prior to HbA1c testing. Samples that were not located, had insufficient volume or were visibly degraded were removed from the testing cohort (Figure 1). HbA1c was measured in 4505 <u>samples</u> using a Biorad Variant II Turbo Analyser (Bio-Rad Laboratories Pty., Ltd., <u>GladesvilleHercules</u>, <u>NSWCA</u>, <u>AustraliaUSA</u>). The interassay CV <u>based on the NGSP HbA1c %</u> <u>values</u> was 2.3% at an HbA1c of 5.15% and 1.7% at an HbA1c of 9.77%. <u>Samples were not</u> <u>stored for a period longer than 6 months prior to being tested</u>.

### Diagnosis of unknown diabetes

From the tested samples a diagnosis of diabetes was made if the HbA1c was ≥6.5% (48 mmol/mol). To determine if this diagnosis was previously known or unknown for the

respective individual, the hospital record (if available) was searched and the family practitioner was contacted (by phone) to determine prior history.

### **Statistical analysis**

HbA1c data are dually reported in the traditional NGSP HbA1c % format and the <u>SI unit</u> <u>mmol/mol as endorsed bynew recommended the</u> International Federation of Clinical Chemistry <u>HbA1c mmol/mol format</u>. Descriptive statistics used include means ± SD, median, maximal and minimal as indicated.

An analysis of variance was conducted to investigate <u>age and gender</u> the variability <u>determinants of</u> the measured <u>HbA1CHbA1c</u> in the three patient groups, with variation considered across the age in years, sex and the three patient groups. Age in years was included as a linear effect, rather than as specific age categories, because <u>HbA1C-HbA1c</u> was found to change in a smooth linear fashion with age. This linear effect was allowed to vary between males and females in the final model. More flexible non-linear age effects, and formulations that allowed differences in the age effect for the three patient groups, were examined, but neither were found to be supported by the data. The analysis was conducted in the R statistical <u>software<sup>19</sup>software<sup>20</sup></u>.

### RESULTS

A total of 22,396 samples suitable for HbA1c analysis were received in the study time interval. After excluding samples for the reasons listed above, HbA1c was measured in 1142 CB, 1113 ED and 2250 IP samples (Figure 1). A total of 4505 HbA1c tests were performed, of which 327 (7.3%) had test readings of  $\geq$ 6.5% ( $\geq$ 48 mmol/mol) consistent with the diagnosis of diabetes. After examination of the hospital record and/or contacting the family practitioner, we had 120 cases (2.7% of total tested) of previously unsuspected diabetes. Of the 120 new cases of diabetes, 11 (1.0%) were community-based participants, 21 (1.9%) were from the Emergency Department group and 88 (3.9%) were hospital inpatients (Figure 1).

Analysis of the tested cohort (known diabetes subjects removed) showed that mean HbA1c levels were  $5.4 \pm 0.4\%$  ( $36 \pm 5$  mmol/mol) for CB,  $5.5 \pm 0.5\%$  ( $37 \pm 0.5\%$ -( $37 \pm 5$  mmol/mol) for ED and  $5.6 \pm 0.5\%$  ( $38 \pm 6$  mmol/mol) for IP participants (Table 1). The CB and ED subjects were, respectively, an average of 7.4 and 9.7 years younger than the IP subjects (Table 1). Considering that HbA1c increased linearly with age (0.5% from age 20 to 90; p<0.001), the HbA1c results were adjusted for age difference between the groups. IP age-adjusted HbA1c was still found to be greater than CB HbA1c (p<0.001). Age-adjusted HbA1c results for ED patients were not different from the other groups. Besides age, patient gender was also an important consideration, with females having HbA1c results 0.13\% less than males (p<0.05). Also, the age-related increase in HbA1c is more pronounced for men than for women (p<0.05). Of note, age, gender and group only explained 12% of the variability in HbA1c results.

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Subjects with a new diagnosis of diabetes were significantly older than the non-diabetic subjects in each of the tested groups and were more likely to be from the ED and IP groups (Table 1 and 2). In fact, The prevalence of previously upreviously undiagnosed diabetes was not detected at all in the lowest at 0% in the CB group less than 40 years of age compared to a rate and greatest at of 5.8% detection in the IP group over the age of 54 (Table 2).

The American Diabetes Association has classified subjects with HbA1c levels in the range of 5.7-6.4% (39-47 mmol/mol) as having pre-diabetes<sup>15</sup>. Of the subjects in our study, 24.8%, 28.7% and 39.5% of CB, ED and IP subjects, respectively, had HbA1c levels in this range (Table 2).



 

### DISCUSSION

Diabetes mellitus is an ideal condition to screen for, as it fulfils all of the principles of screening that need to be met according to the World Health Organisation<sup>20</sup>Organisation<sup>21</sup>. The challenge is to perform regular screening of the population in a time- and cost-effective manner. Population-based surveys, including the AUSDIAB study in Australia, indicate that about 50% of subjects with diabetes have not been diagnosed<sup>3</sup>. In this study, we investigated whether opportunistic diabetes screening through measuring HbA1c in blood samples ordered for other reasons could assist to uncover some of these cases of undiagnosed diabetes.

HbA1c levels were measured in samples from three separate populations: communitybased, the participants being more likely to be relatively well and under continuing general practitioner care (CB); participants who had attended only the Emergency Department in the last 12 months (as far as our records showed) (ED); and hospitalised participants reflecting a group of sicker individuals (IP). Efforts were made to eliminate testing samples in participants who were likely to have already been diagnosed with diabetes or who were likely to have been screened for diabetes within the previous 12 months. It was anticipated that objective evidence of undiagnosed diabetes mellitus might be quite different between these 3 groups.

In the subjects eventually tested, the rates of previously undiagnosed diabetes were 1.0%, 1.9% and 3.9% in the CB, ED and IP groups, respectively. Despite efforts to exclude testing samples from subjects already with a diagnosis of diabetes, 1.4%, 4.7% and 6.2% of the subjects in the three respective groups did have a previous diagnosis. Age was a major

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factor in determining risk. Subjects <40 years of age had rates of previously unknown diabetes of 0.0%, 0.5%, and 1.3% in the CB, ED and IP groups, respectively, compared to 1.5%, 4.0%, and 5.8% in subjects >54 years of age.

The family doctors of all the subjects newly diagnosed with diabetes in this study were notified such that confirmation of the diagnosis could occur and appropriate care could be initiated. The action taken by the family doctors, however, was not within the scope of this study. Considering that WHO and ADA state that a single HbA1c  $\geq$ 6.5% (48 mmol/mol) is diagnostic of diabetes, false positive diagnoses should occur rarely. Therefore, this method of screening should have a high positive predictive value.

Previous studies have also investigated the prevalence of undiagnosed diabetes in a hospital setting. Wexler et al from the USA found a comparable 5% of unsuspected diabetes in hospitalised patients using the cut off >6.5% (>48 mmol/mol)<sup>6</sup>. An Australian study from Adelaide by Valentine et al found 11.1% of unsuspected diabetes, which is much higher than our results<sup>17</sup>. However, their methodology only tested HbA1c on those with bloods taken at admission with a random plasma glucose >5.5 mmol/L, so it is not truly representative of hospital inpatients, rather <u>representative of a group those most likelywith an expected higher positive rate of to have</u> diabetes. This study also was reliant on correct coding for diabetes on discharge in order to exclude previously known diabetes. For the current study, efforts to exclude previous diabetes were much more rigorous with careful review of the hospital record if available and phone calls to the subjects' family doctors.

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The current study also differed from the previous studies, in that community-based (CB) and emergency department patients not admitted to the hospital (ED) were included. The rate of unknown diabetes in the CB group was quite low at 1.0%. This is much lower than the rate of undiagnosed diabetes in the community-based AUSDIAB cohort, but a proportion of the AUSDIAB cohort would not have been engaged in regular medical care<sup>3</sup>. General practitioners predominantly care for the CB subjects of the current study, such that the low level of unsuspected diabetes in these subjects may be indicative of a high level of awareness of diabetes and screening by them within the ACT region. For this reason, opportunistic pathology-based diabetes screening in this group and in this locale may not be as rewarding as the other groups.

The ED group had twice the rate of unknown diabetes compared to the CB group at 1.9%. An opportunistic approach to diabetes screening may be much more relevant to the ED group, as a higher proportion are likely not to be engaged with routine care with a family doctor. This group is likely to also include frequent attendees to hospital with chronic illness, although many of these subjects would have been excluded because of record of other pathology testing in the preceding 12 months. As expected, the IP group had the highest rate of unknown diabetes at 3.9%.

An important contributor to any screening program cost is sample collection and data entry. The procedure we describe removes these costs. In an opportunistic screening, costs could also be reduced by enhanced computer systems to identify samples to be tested and inclusion of the result in the routine pathology reporting to the subjects' treating doctors. It has recently been noted that screening for diabetes in the UK did not reduce mortality at

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10 years<sup>21</sup>years<sup>22</sup>,<sup>2223</sup>. However, intensive treatment following diagnosis reduces complications, and over a longer period mortality is also reduced<sup>10</sup>.

In conclusion, within this Australian setting, opportunistic diabetes screening using HbA1c on FBC samples collected for other purposes is possible and cost effective. Patients presenting to the Emergency Department or admitted to hospital and being older than 54 years of age are most likely to have previously unknown diabetes. This method of diabetes ther consider. screening warrants further consideration.

### ACKNOWLEDGEMENTS

We thank Dr Brent Henderson of CSIRO Maths and Information SciencesComputational Informatics for his statistical advice and Prof Jim Butler of Australian National University for his advice relating to health economics.

### CONTRIBUTORS

AJS and RK collected and tabulated the data; JLK collected and tabulated data and contributed to the writing of the paper; EKS helped plan and implement the study; CJN helped plan the study, reviewed the data and helped write the paper, JDW and JMP helped plan the study and reviewed the data; and PEH helped plan the study, reviewed the data and helped write the paper. He is the guarantor of the study. All the authors reviewed the final version of the manuscript.

### FUNDING

This project was supported by a grant from the Canberra Hospital Private Practice Trust Fund.

### DATA SHARING STATEMENT

There is no additional data available.

### **COMPETING INTERESTS**

All authors have completed the Unified Competing Interest form at wwww.icmje.org/coi\_disclosure.pdf (available on request from the corresponding author) and declare: no financial relationships with any organizations that might have an interest in

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the submitted work in the past 3 years, and no other relationships or activities that could

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**Table 1.** Subject age and HbA1c characteristics within tested community-based, EmergencyDepartment and inpatient participant groups\*

	Community-based	Emergency	Inpatient
	(n=1126)	(n=1061)	(n=2114)
Age (years)			
Mean (± SD)	51.8 (± 17.1)	49.5 (± 20.5)	59.2 (± 19.1)
Median	52	47	61
Range	18-92	18-98	18-97
HbA1c (%) <sup>#</sup>			
Mean (± SD)	5.4 (± 0.4)	5.5 (± 0.5)	5.6 (± 0.5)†
Median	5.4	5.5	5.6
Range	3.7-8.9	4.0-10.3	3.2-12.2
HbA1c (mmol/mol) <sup>#</sup>			
Mean (± SD)	36 (± 5)	37 (± 5)	38 (± 6) †
Median	36	37	38
Range	17-71	20-89	11-110
Mean (± SD) of age (y	ears) of subjects with H	HbA1c % (mmol/mol):	
<5.7 (<39)	48.5 (± 16.8)	44.2 (± 18.8)	54.7 (± 19.8)
5.7-5.9 (39-41)	60.7 (± 13.6)	59.9 (± 18.9)	63.4 (± 17.8)
6.0-6.4 (42-47)	63.1 (± 15.3)	64.1 (± 19.5)	66.7 (± 14.5)
≥6.5 (≥48)	59.5 (± 10.2)	65.0 (± 18.1)	67.7 (± 15.6)

\* Tested subjects subsequently found to have previously known diabetes were excluded from this analysis. <sup>#</sup> Data are dually reported in the traditional NGSP % haemoglobin and the new recommended IFCC mmol/mol format. <sup>†</sup> IP HbA1c results were found to be significantly greater than CB across the age range (P<0.001).

**Table 2.** Subjects within HbA1c categories according to age within tested community-based, Emergency Department and inpatient groups\*

	Community-based	Emergency	Inpatient	
Number [%] subjects with HbA1c % (mmol/mol) <sup>#</sup> :				
Age <40 years				
<5.7 (<39)	276 [92.9]	333 [88.1]	305 [80.5]	
5.7-5.9 (39-41)	15 [5.1]	31 [8.2]	53 [14.0]	
6.0-6.4 (42-47)	6 [2.0]	12 [3.2]	16 [4.2]	
≥6.5 (≥48)	0 [0.0]	2 [0.5]	5 [1.3]	
Total	297 [100]	378 [100]	379 [100]	
Age ≥40 to <55 years	6			
<5.7 (<39)	245 [79.0]	203 [72.2]	290 [63.5]	
5.7-5.9 (39-41)	39 [12.6]	54 [19.2]	101 [22.1]	
6.0-6.4 (42-47)	23 [7.4]	21 [7.5]	57 [12.5]	
≥6.5 (≥48)	3 [1.0]	3 [1.1]	9 [2.0]	
Total	310 [100]	281 [100]	457 [100]	
Age 55 and above				
<5.7 (<39)	317 [61.1]	200 [49.8]	595 [46.6]	
5.7-5.9 (39-41)	135 [26.0]	111 [27.6]	345 [27.0]	
6.0-6.4 (42-47)	59 [11.4]	75 [18.7]	264 [20.7]	
≥6.5 (≥48)	8 [1.5]	16 [4.0]	74 [5.8]	
Total	519 [100]	402 [100]	1278 [100]	
All subjects				
<5.7 (<39)	838 [74.4]	736 [69.3]	1190 [56.3]	
5.7-5.9 (39-41)	189 [16.5]	196 [18.5]	499 [23.6]	
6.0-6.4 (42-47)	88 [7.8]	108 [10.2]	337 [15.9]	
≥6.5 (≥48)	11 [1.0]	21 [2.0]	88 [4.2]	
Total	1126 [100]	1061 [10]	2114 [100]	

 Tested subjects subsequently found to have previously known diabetes were excluded from this analysis. <sup>#</sup> Data are dually reported in the traditional NGSP % haemoglobin and the new recommended IFCC mmol/mol format.

### **FIGURE LEGEND**

Figure 1: Flow diagram showing the process involved in selecting full blood count (FBC) samples for opportunistic HbA1c testing and the overall testing results.

Subjects were divided into community-based (CB), emergency department (ED) and inpatient (IP) groups based on origin of sample collection. Samples were excluded from testing according to reasons indicated (upper three grey boxes). Of the subjects tested, those found to have elevated HbA1c  $\geq$  6.5% ( $\geq$  48 mmol/mol)<sub>7</sub> and to have previously known diabetes<sub>7</sub> were excluded (lower grey box). The number of subjects found to have previously undiagnosed diabetes is shown in the lower white boxes. LIS-laboratory inquiry system; GP-general practitioner; 12/12-12 months.