Automatic laboratory-based strategy to improve the diagnosis of type 2 diabetes in primary care

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Abstract

Introduction: To study the pre-design and success of a strategy based on the addition of hemoglobin A1c (HbA1c) in the blood samples of certain primary care patients to detect new cases of type 2 diabetes.

Materials and methods: In a first step, we retrospectively calculated the number of HbA1c that would have been measured in one year if HbA1c would have been processed, according to the guidelines of the American Diabetes Association (ADA). Based on those results we decided to prospectively measure HbA1c in every primary care patient above 45 years, with no HbA1c in the previous 3 years, and glucose concentration between 5.6-6.9 mmol/L, during an 18 months period. We calculated the number of HbA1c that were automatically added by the LIS based on our strategy, we evaluated the medical record of such subjects to confirm whether type 2 diabetes was finally confirmed, and we calculated the cost of our intervention.

Results: In a first stage, according to the guidelines, Hb1Ac should have been added to the blood samples of 13,085 patients, resulting in a cost of 14,973€. In the prospective study, the laboratory added Hb1Ac to 2092 patients, leading to an expense of 2393€. 314 patients had an HbA1c value ≥ 6.5% (48 mmol/mol). 82 were finally diagnosed as type 2 diabetes; 28 thanks to our strategy, with an individual cost of 85.4€; and 54 due to the request of HbA1c by the general practitioners (GPs), with a cost of 47.5€.

Conclusion: The automatic laboratory-based strategy detected patients with type 2 diabetes in primary care, at a cost of 85.4€ per new case.

Key words: type 2 diabetes; HbA1c; diagnosis; preanalytical phase; test request appropriateness; costs; cost analysis

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Introduction

Hemoglobin A1c (HbA1c) has traditionally been used for the follow-up and management of patients with type 2 diabetes. It was not until 2010, when the American Diabetes Association (ADA) proposed its role as a tool to diagnose the disease (1). Indeed, the guidelines (2) recommend the test to screen asymptomatic adults of any age with overweight, obesity or any additional risk factor for type 2 diabetes. Additionally, in absence of these risks factors, HbA1c analysis should be performed in patients above 45 years old. If the initial HbA1c value is < 6.5% (48 mmol/mol), the test should be repeated at least every 3 years (2,3); if the first test is above that cut-off an additional test is needed to confirm the disease (2).

Given the relatively recent role of HbA1c as a diagnostic tool (2,4-6), and the existing high variability in the test requesting (7-10) it seems necessary to

establish algorithms to improve its use. Indeed, recent evidence indicates that HbA1c is significantly under-requested in Spain (11). Although there are additional tools for the diagnosis of the disease as oral glucose tolerance test and random plasma glucose measurement, a low HbA1c requesting could contribute to poor diagnosis and management of type 2 diabetes (11). In fact some studies to identify occult diabetes through community screening strategies reported in the literature, show a success in detection and a cost per new case of diabetes ranging from 94.6€ ($100) to 700.8€ ($741) (12-16).

The overall role, and specific potential benefits and drawbacks of HbA1c as a diagnostic parameter are largely unknown. We hypothesized that common availability of blood samples in the clinical laboratory presented an opportunity to identify subjects with type 2 diabetes. This appeared feasible since HbA1c is stable and can be measured in the same samples that are used for hematological testing. Furthermore, analysis of samples that are already available in the laboratory avoids the major costs of blood collection, transportation, and logging into an information system (17). We presumed that an algorithm to identify samples appropriate to be tested for HbA1c in primary care patients would detect new cases of type 2 diabetes.

The aim of the present research is first to present a completely automated strategy designed in the clinical laboratory in collaboration with general practitioners (GPs) based on the addition of HbA1c in the blood samples of certain primary care patients to detect new cases of type 2 diabetes; and second to study the success of such algorithm in terms of number of detected cases and economic cost *per* new case.

Materials and methods

Materials

The laboratory is located at the University Hospital of San Juan (Alicante, Spain), a 370-bed suburban community hospital belonging to the National Public Health System that serves a population of 234,551 inhabitants, including 9 different primary care centers (PCC). It receives samples from inpatients, outpatients and primary care patients.

Venous blood was collected by routine phlebotomy by expert phlebotomists, according to the recommendations of the Clinical Laboratory Standard Institute (CLSI) (18) in the morning between 8.00-9.30 AM in every PCC.

The blood samples were collected into a BD Vacutainer tubes (Becton Dickinson, NJ, USA). After labeling, tubes are stored in a cold lock box awaiting the refrigerated commercial transport at 10 AM, by couriers and delivered to the hospital laboratory sample reception desk, where the specimens are analyzed and the fasting glucose results are available before 12.30 PM. Sample transport was monitored by means of our monthly indicators (19). Laboratory requests are made electronically from the electronic health record system by the GPs and the reports are sent out automatically from the laboratory information system (LIS) to the patient's electronic medical record.

Methods

We developed an automatic, computer-aided algorithm to identify the samples appropriate to be tested for type 2 diabetes and designed a study in which HbA1c was measured in such blood samples from our laboratory. In a first stage, a meeting was held between the laboratory professionals and the GP coordinator representing the nine PCCs to discuss the new indications of HbA1c to study a potential methodology and the choice of predefined criteria for the design and establishment of a strategy founded in additional HbA1c measurement and based in current guidelines (3). In a further encounter, the same group conducted a retrospective search in the LIS to study how many HbA1c would have been added in a one year period based on the current guidelines (in absence of risks factors, HbA1c analysis should be performed in patients above 45 years old), to acknowledge the potential strategy cost and the existing degree of inappropriate request of HbA1c as a tool to diagnose type 2 diabetes. In view of the

significant number of HbA1c that would have been needed to comply with the guidelines, and hence the high cost of this potential strategy, the team decided not to add the test to every primary care patient older than 45, but to perform the following strategy: every time a GP requests a cell blood count (CBC) (sample availability to measure HbA1c) and a fasting glucose to a patient older than 45 without a prior HbA1c request in the past 3 years, the LIS automatically adds such test if glucose values in the current request are between 5.6 and 6.9 mmol/L. Additionally, when HbA1c value is ≥ 6.5% (48 mmol/mol), the LIS recommends a second HbA1c request, through a comment in the laboratory report.

Thereafter, a report was sent to the GPs coordinators of the different PCCs informing about the proposed strategy, and a two months reflection period was established to communicate the strategy to every GP in the 9 different PCCs. In a last meeting, this strategy was approved. The study was also approved by the Hospital Research Committee.

We retrospectively calculated the number of additional HbA1c that would have been measured during the year 2012 if the test would have been processed in every primary care patient older than 45 years with a CBC request and no HbA1c request in the current blood sample and in the prior three years.

From March 2013 to August 2014, same type of patients, that additionally presented fasting glucose values between 5.6 and 6.9 mmol/L were prospectively identified and were established as the predefined criteria for additional HbA1c measurement. We calculated the number of HbA1c test that were indeed automatically added by the LIS based on our established strategy, as detailed above, and also when was requested by GP (in certain patients who accomplished all the prior criteria it was the GP that initially had ordered the HbA1c). We also counted the number of patients detected who fell into the category of 'increased risk for diabetes' as per ADA HbA1c criteria (HbA1c results between 5.7% and 6.4% (39-47 mmol/mol)).

The electronic medical record of every subject with an HbA1c result ≥ 6.5% (48 mmol/mol) was evaluated by the attending GP and/or a pathologist to investigate whether the HbA1c values could have been potentially explained due to medication, and whether type 2 diabetes was finally confirmed or discarded, or if the patient was still waiting to confirm/discard type 2 diabetes. The final diagnosis of type 2 diabetes was based on an additional HbA1c ≥ 6.5% (48 mmol/mol), fasting glucose ≥ 7.0 mmol/L, or 2 hour glucose after a 75 g oral glucose tolerance test ≥ 11.1 mmol/L (3).

Finally, we calculated the total economic cost *per* patient diagnosed as diabetic, in both groups when HbA1c was requested by GP or by means of our strategy, taking into account the total number of additional HbA1c tests and the cost of reagent (1.15€ *per* HbA1c test; number of performed tests x 1.15 euros).

Bio-Rad Variant II (www.biorad.com) ion-exchange HPLC instrument (NGSP-certified and anchored to the Diabetes Control and Complication Trial (DCCT) reference study and to the IFCC Reference Method), was used to measure HbA1c in whole blood. Glucose concentration was measured using hexokinase method in a Cobas 8000® Chemistry System (Roche Diagnostics, Basel, Switzerland).

Results

Retrospective analysis

During 2012, the laboratory received requests for 91,219 primary care patients. 61,955 (67.9%) subjects were older than 45 years. 25,242 (40.7%) patients did not have an HbA1c requested the previous 3 years. Among those, the GPs did not order simultaneously HbA1c for 17,348 patients (68.8%). 13,085 (75.4%) had a CBC requested and hence sample availability. Figure 1 summarizes the patient selection.

The economic cost if in each of those samples HbA1c would have been measured was 15,048€.

Prospective study

In the prospective study, the laboratory received requests for 133,399 primary care patients. Figure 2 summarizes the patient selection. 4342 (3.6%) of

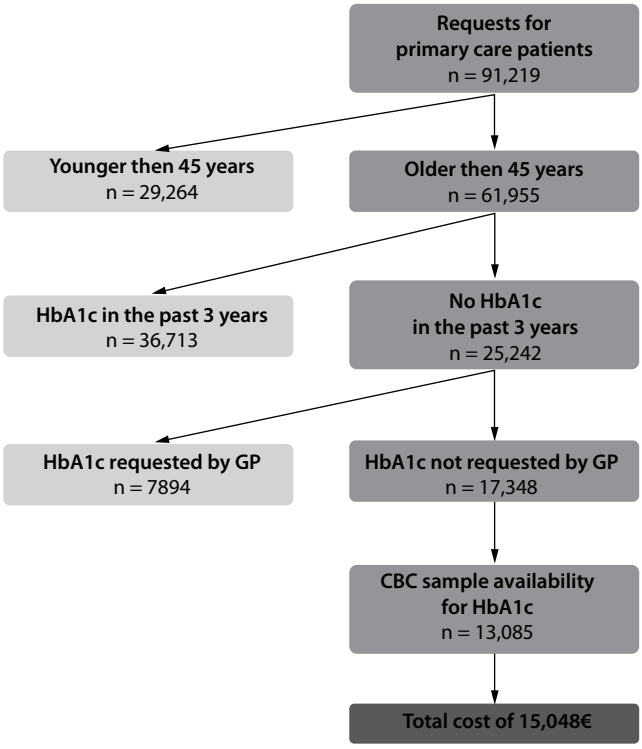

Figure 1. Flow diagram of patient selection for the pre-intervention retrospective analysis.
During the year 2012, the laboratory received 91,219 primary care requests. 13,085 patients were > 45, did not have an HbA1c measured in the past three years or requested in the considered blood sample, and had blood sample for us to measure HbA1c. The hypothetical total economic cost of adding Hb1Ac to those patients would have been 15,048€.

these primary care patients were older than 45 years without a prior HbA1c requested in the past three years and a glucose result between 5.6 and 6.9 mmol/L. In 2250 (51.8%) cases HbA1c was requested by the GPs and 2092 (48.2%) HbA1c were added due to our strategy. The total cost of the tests added by our algorithm was 2393€.

The results of the HbA1c showed that, 3614 patients that did not have an HbA1c requested the previous 3 years fell into the category of 'increased risk for diabetes' as *per* ADA HbA1c criteria (Figure 2). In 2674, HbA1c was requested by the GPs and in 940 (26.0%) HbA1c was added due to our strategy.

314 (7.2%) subjects who were older than 45 years without a prior HbA1c requested in the past three years and a glucose result between 5.6 and 6.9 mmol/L had HbA1c values ≥ 6.5% (48 mmol/mol). After reviewing the medical records, 141 (44.9%) were excluded from the analysis: 117 patients were already known diabetic (In 109 patients, HbA1c was requested by the GPs; in 8 it was added through our strategy), 7 were on high dose corticosteroids, 6 died before we were able to check their medical records, and 11 were residents from other health care areas whose medical records were not available for review. Of the 173 (55.1%) remaining patients, 82 (47.3%) were diagnosed as type 2 diabetes, and 24 (13.8%) are still waiting to confirm/discard type 2 diabetes, despite our written recommendation. Considering those 82 patients, the first HbA1c was requested by the GPs in 54 (65.8%) patients, and automatically added by the LIS based on our strategy for 28 (34.2%) subjects. This data is illustrated in Figure 3.

Each case of type 2 diabetes diagnosed represented a cost of 47.5€ when HbA1c was requested by GPs and 85.4€ when registered by means of our strategy.

Discussion

Our strategy regarding the automatic addition of HbA1c to primary care patients detected new cases of type 2 diabetes that would have had otherwise remained occult. The cost *per* new identified case was significantly lower than the referred in previous studies (12-16). When HbA1c was initially requested by the GPs according to the current guidelines, the success rate to diagnose of type 2 diabetes was higher and the cost *per* new case was lower; However, due to the low cost *per* case, cheaper than in other studies, our strategy appears still payable in spite of almost two times more expensive (12-16). Interestingly enough, 37% of the abnormal HbA1c values corresponded to already known diabetic patients; the fact that the test was not requested in the previous 3 years, indicates a poor management of the disease.

The high number of patients detected labeled as 'increased risk for diabetes' as *per* ADA HbA1c criteria, is of most importance as it enables the GP to target strategies to minimize risk of progression to type 2 diabetes.

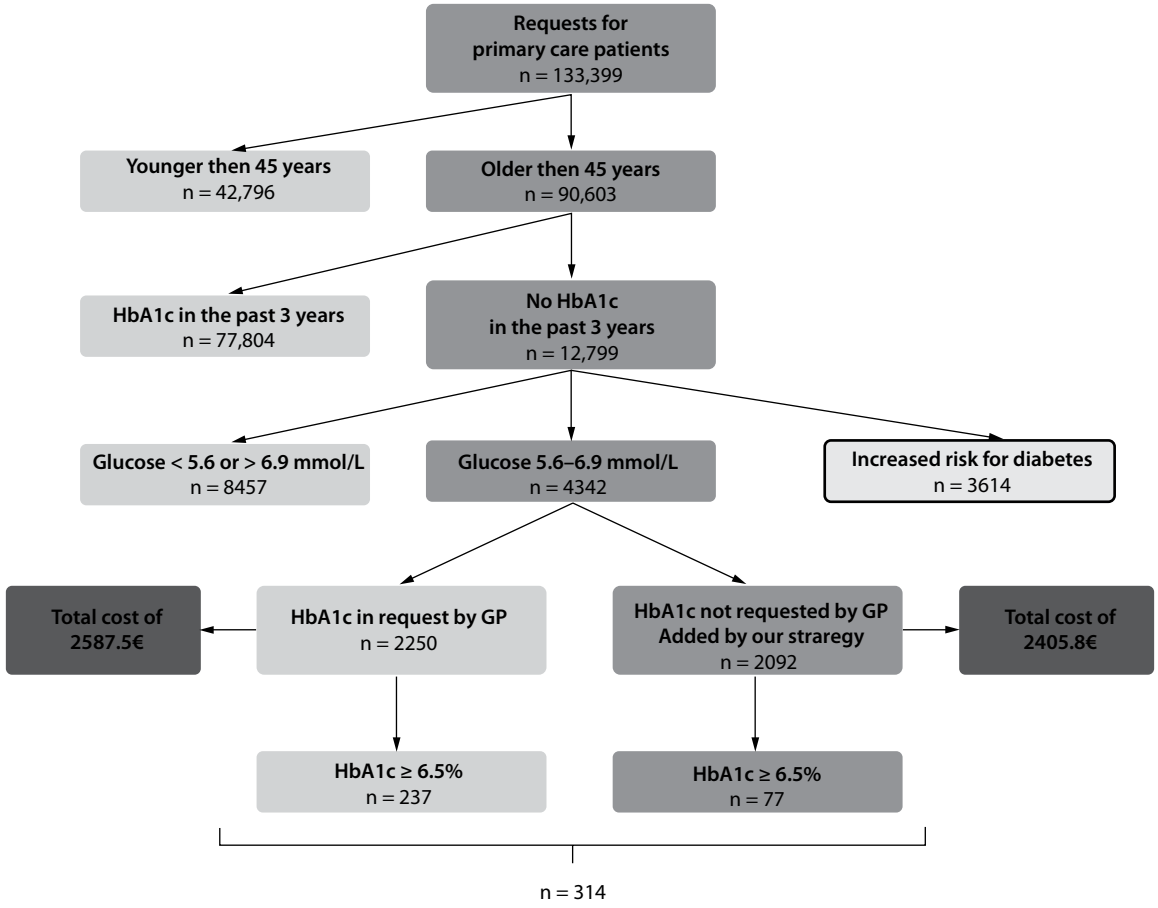

Figure 2. Flow diagram of patient selection for the post-intervention prospective analysis.
During the 18 months period, the laboratory received CBC requests for 133,399 patients. 12,799 were > 45 and did not have an HbA1c measured in the past three years. 4342 had glucose between 5.6-6.9 mmol/L. The GPs had already requested HbA1c in 2250 of those subjects; 2092 were added by the LIS according to our strategy. The total economic cost of adding Hb1Ac to those 2092 patients was 2393€.

Previous evidence regarding blood spot-based measures of glucose homeostasis and type 2 diabetes prevalence show that incorporating HbA1c and glucose values to blood samples in a nationally representative population of young US adults, increased prevalence of type 2 diabetes from 2.9% to 6.8% (20).

The initial retrospective LIS database search served to collect information regarding the potential inappropriate request of HbA1c to diagnose type 2 diabetes. Based on this data, and considering the high cost, we decided not to systematically register HbA1c in all primary care patients above 45 with no HbA1c the prior three years. In contrast, we decided to proceed with the strategy we propose in this manuscript. At present, we do not know how many type 2 diabetes cases would have been detected if we had added HbA1c to every patient older than 45 years without an HbA1c requested in the previous three years, regardless of their level of glucose. What we know, is that this alternative strategy would have been much more expensive. However, each institution may make its own decision based on its economic constraints. Once test inappropriateness is detected and confirmed, there are numerous strategies to achieve a proper requesting. Automatic strategies through the LIS are very easy to do establish and follow

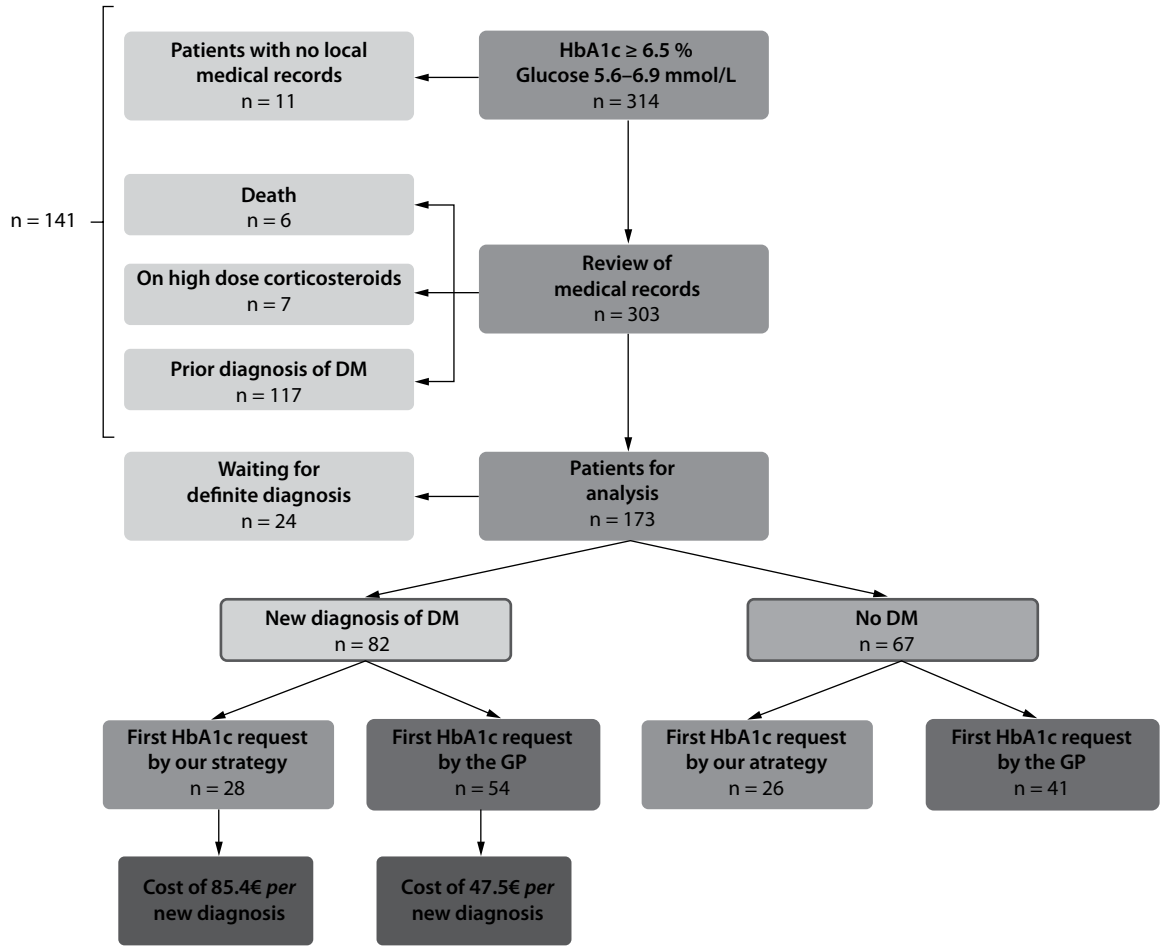

Figure 3. Flow diagram of patient selection for the 314 patients with an HbA1c above 6.4% (47 mmol/mol) in the post-intervention period.
141 patients were excluded. 173 patients were included in the analysis. 82 were diagnosed as type 2 diabetes (DM). Out of those 82 patients, the first HbA1c was requested by the GPs in 54 patients, and added by our strategy for 28 subjects. Each case of DM diagnosed represented a cost of 47.5€ when HbA1c was requested by GPs and 85.4€ when registered by means of our strategy.

once they are designed (21). Unlike educational or administrative strategies (20), the former are automatic and can easily be maintained over time without the need of additional resources.

By applying our strategy a new type 2 diabetes case is detected *per* 75 HbA1c measured, at a cost that appears affordable and reasonable, taking into account the potential reduction in type 2 diabetes complications that may result from an early diagnosis and disease management. Previous studies highlight the large economic burden of type 2 diabetes and its complications on the individual and health care system (22). Early detection of the disease is vital since it brings the opportunity for prompt interventions aimed at preventing or delaying the progression of the disease and its known severe associated complications (23). In fact, the largest components of medical expenditures of diagnosed type 2 diabetes for 2012 in the United States were hospital inpatient care and prescription medications to treat the complications (22). Our intervention would adapt to every setting and population; it is self-regulating and thus easy to export. The number of "extra" HbA1c would depend on the prior test request. The proposed strategy would not produce any additional

expense if the test was requested to detect type 2 diabetes according to our intervention design.

When the GPs requested HbA1c to detect type 2 diabetes, the success in detecting new cases was higher. The GPs initially request HbA1c on primary care patients, as advised by the guidelines. Additionally, some other risk factors beyond the guidelines may also prompt them to request the test. That first step should identify most patients with type 2 diabetes. The laboratory, on the other hand, dealt with a subgroup of patients; since a significant proportion of subjects should have been already identified by the primary care physicians in the prior first round. Hence, the chance of identifying a new case is lower, and therefore the cost *per* patient is higher.

The study has two additional and collateral findings. The fact that some diabetic patients did not have HbA1c measured over a period of three years suggests that HbA1c was under-requested to follow-up type 2 diabetes, and certain patients were not correctly managed. Furthermore, the fact that 14% of patients with a first HbA1c value ≥ 6.5% (48 mmol/mol)– a result with meaningful clinical value – were ignored in spite of the comment in the laboratory report agrees with previous studies on ignored laboratory results (24,25), indicating that more actions are needed to unmask tests results with high clinical value (26).

Our study had certain limitations. First, the strategy was limited to primary care patients with a request for a CBC. There were patients that did not have the chance to participate in this computer-aided algorithm since they did not had a CBC request and hence sample availability to measure HbA1c. Second, the strategy was too simplified and could lead to fact that large proportion of patients below 45 years old, with risk factors cannot be screened with this intervention. Another handicap is that the economic costs of our strategy may not apply to other countries, since our laboratory belongs to the Public Health Network, where reagent prices are very low. However, the main limitation of our study is that we currently do not know how many of the 24 patients that are currently waiting for type 2 diabetes confirmation, will be diagnosed. Nevertheless, we considered it was necessary to communicate the results as soon as possible due to their relevance in the detection of new cases of type 2 diabetes.

A simple and automated strategy designed in the clinical laboratory, in consensus with the requesting clinicians, based on the LIS and the American Diabetes Association guidelines, detected new cases of type 2 diabetes in primary care at a cost of 85.4€.

Potential conflict of interest

None declared.

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