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**Incidental finding of sickle cell trait from an everyday diabetes test – should the family physician report? retest? refer?**

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Complete List of Authors:	Cronin de Chavez, Anna; University of Leeds, School of Healthcare, Faculty of Medicine Dyson , Simon; De Montfort University, School of Allied Health Sciences Babbington, Fiona ; Leeds Teaching Hospitals NHS Trust, Blood Sciences Berghs , Maria ; De Montfort University, School of Allied Health Sciences Atkin, Karl; University of York, Health Sciences Whitelaw, Donald; Bradford Teaching Hospitals NHS Foundation Trust, Diabetes and endocrinology Miller , Adrian; Leeds Teaching Hospitals NHS Trust, Blood Sciences

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## Incidental finding of sickle cell trait from an everyday diabetes test – should the family practitioner report? retest? refer?

### In Brief

The HbA<sub>1c</sub> test is increasingly widely used as a diagnostic and screening test for diabetes mellitus type 2 (T2DM) but the presence of haemoglobin variants, such as sickle haemoglobin, can ~~cause some~~ interfere with results in some analytical systems. These interferences are ~~sometimes reported~~ ~~on~~occasionally reported by ~~laboratory results~~, leading unprepared patients to suspect they ~~are~~ may be sickle cell carriers and seek confirmation through a sickle cell test.

Incidental findings of Hb variants, and the reporting thereof, present multiple ethical challenges to laboratories, medical practitioners, patients and their family members, ~~but and~~ there appears to be no international or national guidelines on how to deal with the reporting of these findings.

This paper explores issues such as whether informed consent is ~~or isn't~~ necessary,; how the results should be communicated,; how the patient may be affected by knowing their carrier status,; the timing of communications,; complications caused by partial results, and being a 'healthy carrier' at the same time as potentially experiencing symptoms.

### Introduction

~~The~~ HbA<sub>1c</sub> ~~test~~ is increasingly widely used as a diagnostic and screening test for T2DM ~~diabetes mellitus type 2~~. With an estimated 8.8% of adults globally having diabetes mellitus, effective screening, diagnosis and monitoring is of major global importance<sup>1</sup>. The biomarker of HbA<sub>1c</sub> refers to glycated haemoglobin A (A<sub>1c</sub>) molecules and has gained prominence in the diagnosis of T2DM due to certain advantages over plasma glucose testing regimens ~~some advantages over plasma glucose tests~~<sup>2</sup>.

It is well established that that some haemoglobin (Hb) variants, of which there are hundreds, including the clinically relevant HbS, HbE, HbC, and HbD<sup>3, 4</sup> may interfere with the validity of the HbA<sub>1c</sub>

results, meaning these ~~testing strategies and tools~~ should ideally identify variants where ~~they are present~~ necessary.

Incidental findings of Hb variants present several ethical challenges for laboratories, medical practitioners, patients and their families ~~members~~. These challenges have, to date, received little attention. This paper discusses some of the advantages of detecting sickle cell trait, ~~identified by the routine triggered through the everyday~~ HbA<sub>1c</sub> test, but also several ethical dilemmas.

A multidisciplinary team and a patient ~~that was~~ diagnosed as a sickle cell carrier through the HbA<sub>1c</sub> test worked together to explore these ethical challenges to produce this paper. ~~It and we~~ it is hoped this ~~paper~~ will ~~initiate instigate discussion discourse~~ around the issues presented and ultimately ~~lead~~ to the development of appropriate international guidelines ~~for practice~~.

## What does the sickle cell allele have to do with the HbA<sub>1c</sub> test for type 2 diabetes ~~type 2~~?

Sickle haemoglobin (HbS) is one of the most common haemoglobin variants. Worldwide an estimated 300 million people have sickle cell trait (SCT) and ~4.4 million people have sickle cell disease (SCD), SCD being the overall name for a group of disorders<sup>5,6</sup>. Sickle cell disease can be life threatening, or increase risk of complications such as stroke, organ failure and acute chest syndrome<sup>7</sup>. Although SCT is usually clinically silent, there are rare ~~complications sequelae e.g. such as~~ haematuria and splenic infarction<sup>8,9</sup> and ~~potentially~~ a higher risk of ~~T2DM diabetes type 2~~ related complications such as retinopathy, nephropathy, and hypertension<sup>10</sup>. The sickle cell allele is present worldwide ~~and w-~~ Whilst there is perhaps more awareness and research of SCT in African American populations, a higher incidence of SCT is also found in Middle Eastern, Mediterranean, Indian and Latin American populations<sup>6,11</sup>.

Whereas there ~~is a handful of~~ are few methodological variations ~~in~~ of the glucose ~~tolerance test assays~~ used to diagnose diabetes mellitus, the different methods and systems available ~~and vast number of systems used available~~ for the HbA<sub>1c</sub> test, in comparison, is a challenge in terms of understanding when Hbhaemoglobin variants might ~~interfere~~ with the system in use. According to the National Glycohaemoglobin Standardisation Programme (NGSP) in the U.S.A. there are ~~6~~ six method types available for measuring HbA<sub>1c</sub>: ~~which are~~ immunoassay, borate affinity, enzymatic, ion-exchange high performance liquid chromatography (HPLC) and capillary electrophoresis ~~and or~~ borate affinity; HPLC. Currently, there are ~~>~~ There are over 200 analytical systems developed by approximately 70 companies, and ~~>~~ 150+ of ~~them~~ se systems ~~are~~ available in the USA. There is also a range of susceptibility to interference by, and ability to recognise, Hb variants<sup>11,12,13,14,15</sup>. Some of these systems are in laboratories, ~~while and~~ some are used as ~~in~~ point of care situations ~~facilities~~<sup>156</sup>. Table 1 below summarises the NGSP's data on HbA<sub>1c</sub> testing systems:

*Table 1. Numbers of methods, systems for HbA<sub>1c</sub> tests and their interference with variants*

Whilst the number of systems with a reported interference by HbS is relatively low, these could be in the more widely commonly used systems, and the figures demonstrate there is relatively little research to confirm whether or not there is interference of HbS with the majority of ~~them~~ se systems. According to NGSP, only 16% of all systems have been evaluated using robust methods, 57% of these showed an interference with at least one Hbhaemoglobin type and 19% with HbS. Interference was found with more than one method type but the same method came out with no interference with other systems<sup>167</sup>. Furthermore, ~~these systems~~ may also require expert interpretation of results. For example, the electrophoretic principle is based on the separation of constituent particles ~~e.g. haemoglobin~~ in a mobile/liquid phase, ~~and~~ interaction and subsequent retention ~~by on~~ a solid phase according to ~~in the system, according to their~~ physicochemical properties. Elution from the solid phase, and subsequent detection, results in a chromatogram where the area of the peak corresponds with concentration of the analytes ~~compounds~~ detected. ~~The~~ electrophoresis is essentially separating haemoglobins with different properties, such as glycosylated Hb or variants, which result in different peaks in a

chromatogram. ~~An expert eye~~ Expertise is required to ~~properly adequately~~ interpret chromatographs, as some variants may be “hidden” in the HbA peak, ~~potentially sometimes~~ changing its height, width and/or shape. Therefore it is important for the physician to know if a variant that interferes with the validity of the HbA<sub>1c</sub> test is present, so that an alternative method or analytical technique may be used.

~~to use an alternative method if screening for diabetes type 2 where there is no variant interference because the results may not be comparable with internationally established reference values based on HbAA studies.~~

## Example of an incidental finding of sickle cell trait from a HbA<sub>1c</sub> test

Against this background of a huge diversity of methods and systems, what might the patient experience be of the result of this test for someone who had **no** prior knowledge of having sickle cell trait (HbAS)? The patient involved in the case described here queried the result of ‘haemoglobin variant detected’ with their family physician, who said they were probably a carrier for sickle cell disease and only on the request of the patient, referred him for a sickle cell test to confirm this. ~~on request of the patient.~~ On confirmation of SCT status, no support of genetic counselling was offered to the patient.

Below is an example of a chromatogram held in the laboratory files for the above patient, showing a HbS variant detected using the Tosoh (HPLC) system when a HbA<sub>1c</sub> test was requested by a the primary care practitioner:

*Fig 1 Example of chromatogram for a patient with HbAS detected through a HbA<sub>1c</sub> test, in laboratory files only:-*

Fig 2 below shows how the above result was first communicated to the referring practitioner and ultimately the patient who had requested a printout from a series of blood tests.

*Fig 2 Extract of lab report showing wording of the HbA<sub>1c</sub> result sent to the practitioner and then passed onto the patient*

The information provided in Fig. 2 on the haemoglobin variant is fairly limited in its usefulness because it does not provide information on what the variant might be, whether there is one copy of the variant allele (heterozygous; e.g. HbAS) or two (homozygous; e.g. HbSS) or a combination of different haemoglobin variants. The information in [Figure 1](#) may be more useful in this respect, but this is not generally released in [laboratory](#) reports due to the expert interpretation often required. Therefore, what primary care practitioners may infer from this may be highly variable, ~~or nothing at all~~, particularly as the result has been classified as 'Normal'. They may choose to ~~or not to~~, discuss further tests to establish which Hb variant the patient has, or the patient may come to their own conclusions with or without the aid of an online search [revealing research, policies and SCT linked death prevention campaigns<sup>17,18</sup>](#).

There are currently no international guidelines for the reporting of incidental finding of possible [Hbhaemoglobin](#) variants through HbA<sub>1c</sub> tests. Although the [World Health Organisation](#) [W.H.O.](#) guidelines on the use of the HbA<sub>1c</sub> test refer to interference from haemoglobin variants, they do not advise on if, when or how to inform a primary care practitioner or patient of a variant [that has been detected<sup>19,19</sup>](#).

Almost a year after the above test ~~was produced, the laboratory~~ ~~he trust~~ involved refined its reporting to practitioners with the following note, where there are heterozygous variants only [e.g.i.e.](#) HbAS. It is highly unlikely that reporting is uniform across hospital [laboratories](#) ~~trusts~~ in the UK even when using the same systems:

*Fig 3 Updated wording of the HbA<sub>1c</sub> result sent to the practitioners a year after the above result*

## **Advantages of detecting a sickle cell trait through the HbA<sub>1c</sub> test**

There could be some advantages for detecting haemoglobin variants through ~~diabetes type 2/T2DM~~ screening. The first ~~advantage~~ is that it is important to note for such a patient that a diagnosis of ~~T2DM type 2 diabetes mellitus~~ must not be made using a HbA<sub>1c</sub> testing system affected by variants. This is important for ~~affectedsueh~~ individuals but also at a population level in regions such as sub-Saharan Africa where between 10% and 40% of people have SCT<sup>2020</sup>, but many may not know their status as screening programmes are rare. The HbA<sub>1c</sub> test may still, however, have some use for monitoring a patient who has already been diagnosed with ~~diabetes-T2DM~~ because the comparison is then between the patient's own results over time rather than comparing with others.

The HbA<sub>1c</sub> test is generally not suitable ~~for rapid-onset~~ in any ~~clinical conditionsituation where there isn't enough HbA with a normal~~ that affects the lifespan (~120 days) of erythrocytes e.g. the presence of ~~sueh as for~~ some Hb variants, intravascular haemolysis, and in liver disease, or where there is a rapid onset of diabetes ~~but a normal HbA<sub>1c</sub>~~ such as gestational diabetes and type 1 diabetes (T1DM). The case of HbAS, like that presented here, isn't even as simple as expecting the Hb to be neatly divided into ~~half 50%~~ HbA and ~~50%half~~ HbS, as people with HbAS almost always have more HbA than HbS, and due to in a In a sickle cell genetic carrier HbS levels may vary between 20 and 45%, so there is considerable variation even within those who are HbAS. Interpreting these results requires someone with expertise in haemoglobinopathies<sup>21,24</sup>. Additionally, most people have a small percentage of foetal haemoglobin (HbF), so a standardised value for HbA<sub>1c</sub> in HbAS types would probably not be possible. Additionally some point of care HbA<sub>1c</sub> testing systems, often those used in pharmacies and GP-family physician practices in the UK have no capacity to detect variants, so the *absence* of variant detection should not be assumed to be completely reliable.

The second advantage is that further testing ~~;~~ can be done to confirm a carrier status such as SCT. Knowing their carrier status gives ~~them-affected individuals~~ the opportunity to make informed reproductive choices and inform family members so they can consider getting tested for SCT. A few countries worldwide have neonatal screening for sickle cell, but these are not always where SCT is most common<sup>2220</sup>. Even where newborn screening is offered parents may not have been informed of

the result, understood it or remembered it<sup>2223</sup>. In one report aAn estimated 40% of people in the USA with SCT did not know their status<sup>2423</sup>. Therefore, detecting SCT through a relatively common test such as HbA<sub>1c</sub> could increase the diagnosis and knowledge of carrier status. It could also alert family members of the possibility of a child being born with SCD, especially where newborn screening is absent or sporadic. In sub-Saharan Africa, treatments are limited and an estimated 50–80% of infants born with SCD in Africa die before the age of 5 years of age<sup>2524</sup>. In 2009 the UN General Assembly declared SCD to be a major public health concern<sup>2625</sup> with 1 in 30 deaths of children under-5 worldwide linked to haemoglobin disorders, most of these being SCD<sup>2726</sup>

## Ethical challenges presented by incidental findings of sickle cell trait through the HbA<sub>1c</sub> test

~~However~~ there may be more challenges than advantages presented by incidental findings of Hb variants, some of which are discussed belowhere.

The first ethical challenge is that any testing in which Hbhaemoglobin variants are incidentally revealed could be considered a genetic test, or a partial one. Some practitioners may not have anticipated this result, gained consent for this kind of genetic screening, or judged consent to be necessary. This may put them in a difficult position as not obtaining consent goes against many guidelines for ~~consent for~~ genetic screening<sup>2827,28, 29, 30,29,30,31, -</sup> whilst leaving the health practitioner unsupported in the absence of any guidelines of what to do when Hb variant ~~results appear~~ is present in their patient. This problem, if following such guidelines, ~~is~~ potentially an additional burden on health care professionals, especially where SCT is most common. Patients are likely to have no idea agreeing for a test for diabetes may throw up an unexpected indication they are a carrier of the sickle cell gene. Therefore patients, as well as practitioners, would have to be fully informed of the consequences of agreeing to such a test. While we note the trait is largely ‘silent’, it does have some

(rare) clinical consequences, which does create the further dilemma of having information which might have a clinical significance, but not passing that information on. Additionally there is a risk of under diagnosis of ~~diabetes type 2~~T2DM with the HbA<sub>1c</sub> test.<sup>3231</sup>

The second ethical challenge is that communicating results is not always straightforward. Even within a formalized programme such as the UK's newborn screening programme, concerns are raised about communicating SCT status<sup>3332</sup>. Concerns include inconsistencies: ~~variation~~ in who gives the information and how,<sup>33</sup> how much detail to provide,<sup>33</sup> practitioner competence when devolving complex genetic information to non-specialist health professionals<sup>3433</sup>, and whether health records of who has SCT are sufficiently robust<sup>3534</sup>. Although identifying which professional or organisation is best placed to inform the patient of the newly discovered status is important, it is possible that appropriate access to services, such as genetic counselling ~~appropriate for~~ may not actually be available.

A third ethical challenge is that neither the patient nor the practitioner might be able to predict the full social impact of knowing their status as a sickle cell carrier. Subsequent racism and stigma may also be experienced in revealing sickle trait status which the patient may want to avoid<sup>3635</sup>. Whilst the different clinical impacts of SCT are disputed, there is a clear potential for societal discrimination through carrier status being known in several areas such as employment<sup>3637</sup>, insurance<sup>3738</sup>, sports<sup>3938</sup>, the criminal justice system<sup>4039</sup> and marriageable status in some communities<sup>4140</sup>.

A fourth ethical challenge is that patients need to have control over the results and their timing of their release to other family members. The result may perhaps create an unexpected moral dilemma for an individual, about whether to disclose to wider family members or not. For example, the patient in this case was a minor where one parent had requested a printout of a general blood screening where the wording 'haemoglobin variant detected' was included in the 'normal' HbA<sub>1c</sub> result. A quick online check indicated sickle cell trait to be the most likely explanation for this. Imagine a scenario then where the father of a child he thought was biologically his, received this result and he already knew neither he nor his partner had SCT. This result could have potentially immediate disastrous

consequences for the couple's relationship and family dynamics, even without a second test to confirm the variant type. It could be equally, or perhaps more, devastating for a child to suddenly learn that they are not biologically related. ~~In addition, in the case of a minor both parents may have access to the results, leaving people potentially unprepared for situations such as unexpected paternity.~~ This is one of the reasons why patients and their families need some degree of control over the revealing of carrier status, as well as confirmation of the result on a separate sample (mislabelled samples are common).

A ~~fifth~~another ethical challenge is presented if a patient is not directly told they have a Hb variant, but are told they should not be screened for ~~diabetes type 2-T2DM~~ using the HbA<sub>1c</sub> test, for whatever reason. With partial information such as this the patient may seek online information and guess they have SCT and anxious that the trait can cause sudden death as reported with some online sources. They may even confuse SCT with SCD and erroneously conclude they have a serious long-term condition. Within this challenge are questions such as: is partial information worse than no information? Can the information be withheld? Should family members be informed?

A ~~sixth~~final ethical challenge could be in the everyday understanding of how SCT affects, or doesn't affect the body. It is confusing for patients when they are told it is both a "diagnosis" and is either mostly benign and/or is a "healthy carrier" state. In addition to numerous research articles available on the internet, of varying quality (based on evidence) and relevance, there are numerous online accounts of SCT patients reporting a range of symptoms they believe to be caused by SCT but not recognised by their physicians. This may leave anyone with SCT worried and unresolved in how they ~~think of~~interpret their ~~body~~ symptoms, and how they interact with family members and their wider community<sup>4241</sup>. A call for a resolution to recognition of symptoms was made at a recent symposium including people with the trait: *'You can't use this to discriminate against us, nor will you use it to deny us healthcare'*<sup>4342</sup>.

## Ways forward for testing centres, health care providers, policy makers and patients

In conclusion, despite some potential advantages for detecting haemoglobin variants through ~~the~~ HbA<sub>1c</sub> testing, there are several ethical and practical dilemmas to be navigated. There are questions around what the different HbA<sub>1c</sub> systems have to offer in terms of diagnosis, if patients should be told, and at what stage, and what counselling and support should they be offered? As awareness and reporting grows around the various limitations of the HbA<sub>1c</sub> tests, healthcare services need to plan for the future to ~~ensure-provide~~ patient and practitioner resources and support. Guidelines for screening and reporting of ~~Hbhaemoglobin~~ variants detected in the process of assessing diabetic status currently revealed incidentally in the process of some tests for diabetes type 2 in a more controlled manner urgently need ~~-development~~ drawing up, with the involvement of affected communities, to resolve these problems. This is not an isolated issue, there are other tests that can potentially throw up incidental findings of sickle cell trait, for example where sickled red blood cells were identified in urine and subsequent test revealed SCT<sup>4443</sup>. This article has not covered thalasseмии but there is synergy with the situation described here a parallel example in which where a full blood count may be considered an is indirectly ~~a~~ genetic test as it would reveal a patient's status as a thalassaemia carrier. On a much wider scale, with the rise of genomic testing and precision medicine<sup>4544</sup> this kind of predicament with incidental results will only present more ethical, legal and psychosocial problems and would benefit from time and energy being invested in guidance and solutions.

Should therefore the family physician, or the laboratories they work with report Hb variant results? Should they offer a further test to confirm which variant they have? Should they refer the patient for genetic counselling?

There appears to be three principle-main choices available in the scenario of the HbA<sub>1c</sub> test and sickle cell trait. Firstly, either : ~~Either: (1) D~~ dispute the very notion of “incidental” genetic findings and

assert that any test that (indirectly) produces genetic findings must be declared to the client as an ~~(indirect)~~ genetic test beforehand and appropriate permission (and counselling?) provided. Secondly, accept ~~Or (2): Accept~~ the concept of “incidental” genetic findings, but then when sickle cell trait confounds the diabetes test, ask the client for permission to investigate possible SCT further with a confirmatory test for ~~sickle cell trait~~ SCT (and discuss with the client the implications of this) ~~Or (3) Accept~~ Thirdly, accept the concept of “incidental” genetic findings and focus only on the reliability of the information for assessing diabetes, effectively ignoring the sickle cell trait information except for its role as a confounder of the diabetes-relevant information. Option 1 is ethically the purest but potentially expensive, whereas ~~Option 3 seems downright unethical especially where the information could be of potential benefit to the patient and their family,~~ but Option 2 does at least have the possible ethical benefits of affording to the client the decision about whether or not to know about a sickle cell trait status ~~(something that newborns aren't asked when sickle cell trait is an incidental diagnosis to universal newborn screening for sickle cell disease)~~. Finding ways forward, therefore, would benefit from a dialogue of all parties managing aspects of this test and its results; laboratories, manufacturers, physicians and most importantly people with sickle cell trait, their families and communities.

## Key messages

- ~~The~~ HbA<sub>1c</sub> ~~test~~ is increasingly used as a standard test for ~~diabetes type 2~~ T2DM screening and monitoring and is ~~done performed~~ by a variety of analytical ~~range of~~ methods. However, result validity, ~~its validity~~, in some cases, can be affected in the presence of some Hb-haemoglobin

variants ~~e.g. (such as)~~ sickle haemoglobin (HbS) ~~in some systems~~ and other ~~in~~ conditions where ~~red~~ cell lifespan may be ~~ables than~~ normal, e.g. liver disease.

- Some, but not all, HbA<sub>1c</sub> test systems detect Hb variants, and further testing may be required to confirm presence of and type of ~~Hbhaemoglobin~~ variants
- There are currently no international, ~~U.S., or U.K. or national level~~ guidelines on how and when incidental findings should be reported to the referring practitioner or patient
- Potential advantages of detecting HbS could be to avoid HbA<sub>1c</sub> tests in future for ~~diabetes type 2~~ ~~T2DM~~ screening ~~and diagnosis~~, but the test may still be useful for monitoring HbA<sub>1c</sub> changes over time ~~within individuals in patients where the diagnosis has already been made~~, and for the detection of SCT and SCD in ~~the wider family group~~ ~~other family members~~.
- Ethical challenges of detecting HbS include that consent is often not requested; appropriate communication of the result may be difficult and unsupported by services thereafter; unexpected paternity being revealed; accessing incorrect information about SCT symptoms may create anxiety and confusion; being told partial information may lead to incorrect inferences of more serious conditions and revealing sickle trait status may result in a discrimination and stigmatisation by a range of sources and mechanisms.
- ~~Further~~ research is needed to explore these issues for testing centres, practitioners, patients and their family members in more detail ~~and to form a basis for international guidelines~~.

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Author contributions:

A Cronin de Chavez initiated the idea, liaised with the patient mentioned for permissionspermissions and feedback, wrote muchalot of the paper, revisions and carried out the submission.

Atkin K, Babbington F, Berghs M, Dyson SM, Miller A, Whitelaw D all contributed equally to the knowledge required to build the technical information and arguments in this paper. This included working from a basic skeleton version of the problem in focus, and each commenting on and/or re-writing sections of multiple drafts that were prepared before submission. All are in agreement with the submitted version. All participated in answering the editor's and reviewers comments from the first version.

All authors have stated that there is no conflict of interest

Dr. Anna Cronin de Chavez is the guarantor of this work and, as such, had full access to all the patient and laboratory information used in this article and takes responsibility for the integrity of this information

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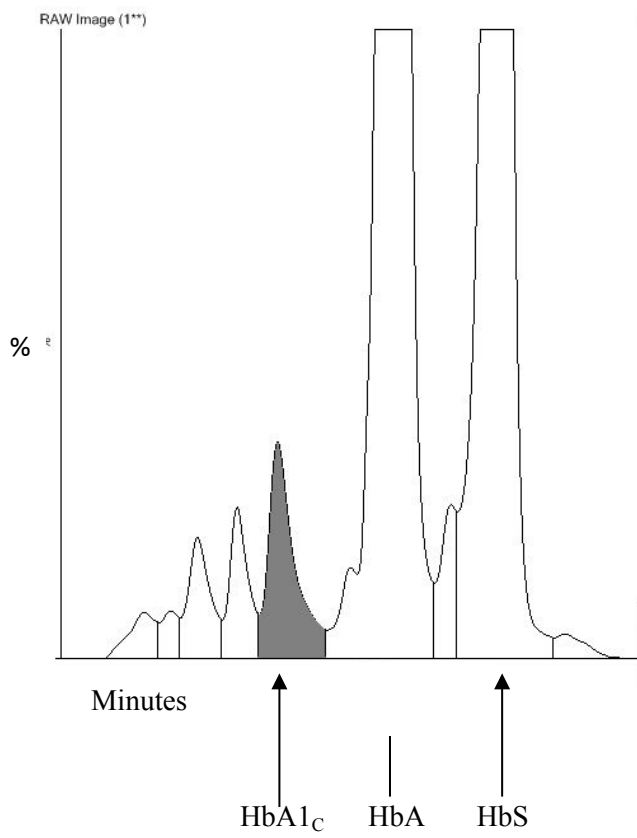
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**Fig 1** Example of chromatogram for a patient with HbAS detected through a HbA<sub>1c</sub> test, in laboratory files only



*Fig 2 Extract of lab report showing wording of the HbA<sub>1c</sub> result sent to the practitioner and then passed onto the patient*

HbA<sub>1c</sub> level – IFCC standardized – (KST47) – 34 mmol/mol 20.00-41.00mmol/mol  
01 Normal  
See comment below  
Haemoglobin variant detected. HbA<sub>1c</sub> may be useful for monitoring diabetic control provided there is no reduction in red cell life. Diabetes is defined by an HbA<sub>1c</sub> > 47 mmol/mol and optimum glucose control at HbA<sub>1c</sub> < 59 mmol/mol.  
More info go to [www.pathology.\[TRUSTNAME\].nhs.uk](http://www.pathology.[TRUSTNAME].nhs.uk) and search for HbA<sub>1c</sub>

***Fig 3 Updated wording of the HbA<sub>1c</sub> result sent to the practitioners a year after the above result***

Haemoglobin variant detected. Variants have an unpredictable effect on red cell survival and therefore HbA<sub>1c</sub> cannot be used for diagnosis of diabetes (suggest fasting glucose). However, HbA<sub>1c</sub> may still be useful for monitoring glycaemic control.

*Table 1. Numbers of methods, systems for HbA<sub>1c</sub> tests and their interference with variants*

Number of methods available for HbA <sub>1c</sub> tests	6 <sup>17</sup>
Number of A <sub>1c</sub> testing systems manufacturers	Approx. 70 <sup>17</sup>
Number of systems developed to measure A <sub>1c</sub> (including versions)	Approx. 239 <sup>17</sup>
Number of systems available in the USA (including versions)	Approx. 156 <sup>17</sup>
Number of systems evaluated as reported by NGSP as using 'robust' methods	37 (approx. 16% of all systems)
Number of 'robust' studies reported by NGSP where there is interference of results by Haemoglobin variants (C, S, E, D, elevated F and Carb)	21 <sup>18</sup> (57% of systems evaluated)
Number of the above 'robust' studies reported evaluating interference of HbS	19 <sup>18</sup> (19% of systems evaluated)