Incidental Findings of Sickle Cell Trait From an Everyday Diabetes Test: Should General Health Care Providers and Testing Centers Report, Retest, or Refer?

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The hemoglobin A_{1c} (A1C) test is increasingly used as a diagnostic and screening test for type 2 diabetes. With an estimated 8.8% of adults globally having diabetes, effective screening, diagnosis, and monitoring is of major global importance (1). The biomarker of A1C refers to glycated hemoglobin A molecules and has gained prominence in the diagnosis of type 2 diabetes because it offers certain advantages over plasma glucose testing regimens (2). It is well established that some of the hundreds of hemoglobin (Hb) variants, including the clinically relevant HbS, HbE, HbC, and HbD (3,4), may interfere with the validity of A1C results. Thus, testing strategies and tools employing A1C should ideally identify variants when they are present.

Incidental findings of Hb variants present several ethical challenges for laboratories, health care providers, patients, and their families. These challenges have, to date, received little attention. This article reviews some of the advantages of detecting sickle cell trait, identified by the routine A1C test, but also several related ethical dilemmas. We explore issues such as whether informed consent is necessary, how the results should be communicated, how patients may be affected by knowing their carrier status, the timing of communications, complications caused by partial results, and the circumstance of being a "healthy carrier" while potentially experiencing symptoms.

A multidisciplinary team and a patient diagnosed as a sickle cell carrier through the A1C test worked together to explore these ethical challenges to produce this article. We hope it will instigate discussion around the issues presented and ultimately lead to the development of appropriate international guidelines.

What Does the Sickle Cell Allele Have to Do With the A1C Test for Type 2 Diabetes?

Sickle Hb (HbS) is one of the most common Hb variants. Worldwide, an estimated 300 million people have sickle cell trait (SCT) and ~4.4 million people have sickle cell disease (SCD), the overall name for a group of disorders (5,6). The phenotype for SCT is HbAS, and for SCD, it is HbSS, HbSC, and some other variants. SCD can be life-threatening or can increase risks of complications such as stroke, organ failure, and acute chest syndrome (7). Although SCT is usually clinically silent, there are rare sequelae (e.g., hematuria and splenic infarction [8,9]) and a higher risk of type 2 diabetes–related complications such as retinopathy, nephropathy, and hypertension (10). The sickle cell allele is present worldwide, and although 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 (6).

Whereas there are few methodological variations in the glucose assays used to diagnose diabetes, the different methods and systems available for A1C testing, by comparison, is a challenge in terms of understanding when Hb variants might interfere with the system in use. According to the National Glycohemoglobin Standardization Program (NGSP) in the United States, there are five methods available for measuring A1C: immunoassay, enzymatic assays, ion-exchange high-performance liquid chromatography (HPLC), capillary electrophoresis, and boronate affinity HPLC. More than 200 analytical systems developed by ~70 companies are in use, and more than

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TABLE 1 Methods and Systems for A1C Testing and Their Susceptibility to Interference From Hb Variants (17,18)

Number of methods available for A1C tests	5
Number of A1C testing system manufacturers	~70
Number of systems developed to measure A1C (including multiple versions of the same system)	~239
Number of systems available in the United States (including multiple versions of the same system)	~156
Number of systems evaluated and reported by NGSP as using robust methods	37 (~16% of all systems)
Number of these robust studies in which there was interference of results by Hb variants (C, S, E, D, elevated F, and carbamylated Hb)	21 (57% of robustly evaluated systems)
Number of these robust studies reporting interference by HbS	19 (51% of systems evaluated using robust methods)

150 of them are available in the United States. The various testing methods also have a range of susceptibility to interference by, and ability to recognize, Hb variants (11–14). Some of these systems are in laboratories, whereas some are used at the point of care (15). Table 1 summarizes the NGSP's data on A1C testing systems.

Although the number of systems with a reported interference by HbS is relatively low, these could be in the more commonly used systems, and the figures demonstrate that there is relatively little research to determine whether there is HbS interference for the majority of them. According to the NGSP, only 16% of all systems have been evaluated using robust methods, 57% of these showed an interference with at least one Hb type, 51% for HbS. Interference was found with more than one method type, but within each method type, interference was shown with some systems but not with others (16). Furthermore, these systems may also require expert interpretation of results. For example, the electrophoretic principle is based on the separation of constituent particles in a mobile/liquid phase, interaction, and subsequent retention in a solid phase, according to physicochemical properties. Elution from the solid phase, and subsequent detection, results in a chromatogram in which the area of the peak corresponds to the concentration of the compounds detected. Electrophoresis is essentially separating hemoglobins with different properties, such as glycated Hb or its variants, which results in different peaks in a chromatogram. Expertise is required to adequately interpret chromatographs, as some variants may be "hidden" in the HbA peak, potentially changing its height, width, or shape. Therefore, it is important for the physician to know if a variant that interferes with the validity of the A1C test is present so an alternative method or analytical technique may be used.

Example of an Incidental Finding of Sickle Cell Trait From an A1C 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 SCT? The patient involved in the case described here queried the result of "hemoglobin variant detected" with his family physician, who said he was probably a carrier for SCD; only on request of the patient was he referred for a sickle cell test to confirm this. On confirmation of SCT status, no genetic counseling was offered.

Figure 1 shows the chromatogram held in the laboratory files for this patient, showing an HbS variant detected using the Tosoh (HPLC) system for the A1C test requested by his primary care provider. Figure 2 shows how the result was first communicated to the referring provider and ultimately to the patient, who had requested a printout from a series of blood tests.

The information provided in Figure 2 about the hemoglobin variant is fairly limited in its usefulness because it does not provide information on what the variant might be or whether there are combinations of different variants. The information in Figure 1 may be more useful in this respect, but this is not generally released in laboratory reports because of the expert interpretation often required. Therefore, what primary care providers may infer from this information may be highly variable, particularly because the result was classified as "normal." Providers may choose to discuss further tests to establish which Hb variant a patient has, or patients may come to their own conclusions with or without the aid of an online search revealing research, policies, and SCT-linked death prevention campaigns (17,18).

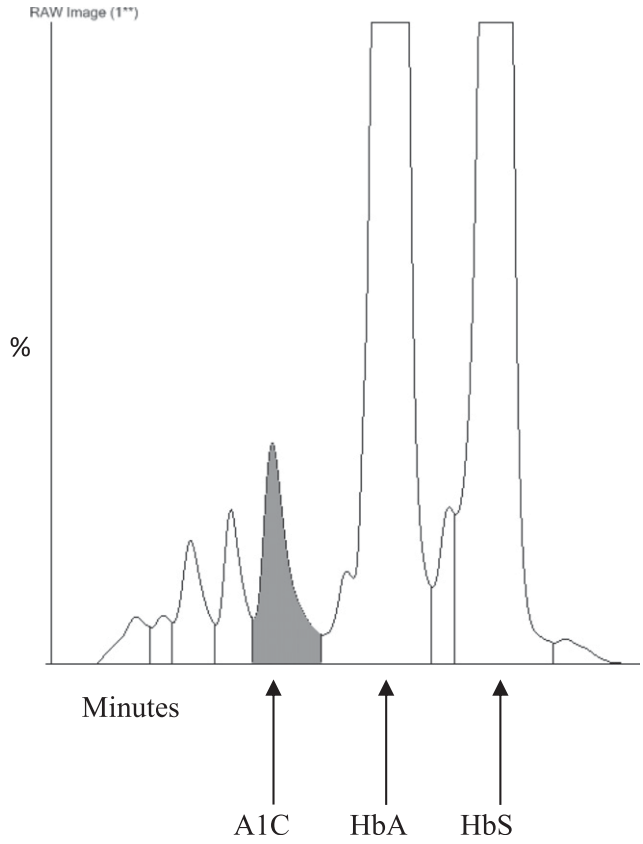

FIGURE 1 Chromatogram (raw image) for a patient with HbAS detected through an A1C test, from the laboratory file.

There are no international guidelines for reporting incidental findings of possible Hb variants through A1C tests. Although the World Health Organization guidelines on the use of the A1C test refer to interference from hemoglobin variants, they do not advise on whether, when, or how to inform primary care providers or patients when a variant is detected (19).

Almost a year after the test described above was produced, the laboratory involved refined its reporting to care providers with the note shown in Figure 3 when there are heterozygous variants only (e.g., SCT). It is highly unlikely that reporting is uniform across hospital laboratories in the United Kingdom or globally even when they use the same testing systems.

Advantages of Detecting SCT Through A1C Testing

There could be some advantages for detecting hemoglobin variants through type 2 diabetes screening. The first is that it is important to note for such patients that a diagnosis of type 2 diabetes must not be made on the basis of A1C testing from a system affected by variants. This point is important for affected individuals but also at a population level in regions such as sub-Saharan Africa, where 10–40% of people have SCT (20) but many may not know their status because screening programs are rare. The A1C test may still have some use for monitoring patients who are already diagnosed with type 2 diabetes because the comparisons are then between patients' own results over time rather than between different patients.

The A1C test generally is not suitable in any clinical condition that affects the life span (~120 days) of erythrocytes (e.g., in the presence of some Hb variants, intravascular hemolysis, liver disease, or in cases involving a rapid onset of diabetes such as gestational diabetes or type 1 diabetes). Cases involving HbAS such as the one presented here are not even as simple as expecting the Hb to be neatly divided into 50% HbA and 50% HbS because people with HbAS almost always have more HbA than HbS. With SCT, HbS levels may vary between 20 and 45%, so there is considerable variation even within those with SCT. Interpreting these results requires someone with expertise in hemoglobinopathies (21). Additionally, most people have a small percentage of fetal hemoglobin (HbF), so a standardized value for A1C in SCT would probably not be possible. Additionally, some point-of-care A1C testing systems, often those used in pharmacies and family medicine practices in the United Kingdom, have no capacity to detect variants, so the absence of variant detection should not be assumed to be completely reliable.

HbA1c levl – IFCC standardized – (KST47) – 34 mmol/mol 20.00-41.00mmol/mol
01 Normal
See comment below
Haemoglobin variant detected. HbA1c may be useful for monitoring diabetic control provided there is no reduction in red cell life. Diabetes is defined by an HbA1c > 47 mmol/mol and optimum glucose control at HbA1c < 59 mmol/mol.
More info go to www.pathology.[TRUSTNAME].nhs.uk and search for HbA1C

FIGURE 2 Extract of a laboratory report showing the exact wording of the A1C result in Figure 1 that was sent to the primary care provider and then passed on to the patient.

Haemoglobin variant detected. Variants have an unpredictable effect on red cell survival, and therefore HbA1c cannot be used for diagnosis of diabetes (suggest fasting glucose). However, HbA1c may still be useful for monitoring glycaemic control.

FIGURE 3 Updated wording on A1C results sent to health care providers, adopted 1 year after the results shown in Figures 1 and 2.

The second advantage is that further testing can be performed to confirm a carrier status such as SCT. Knowing the carrier status gives affected individuals the opportunity to make informed reproductive choices and to 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 the countries where SCT is most common (22). Even where newborn screening is offered, parents may not have been informed of, understood, or remembered the result (23). In one report, an estimated 40% of people in the United States with SCT did not know their status (24). Therefore, detecting SCT through a relatively common test such as A1C could increase diagnoses and knowledge of carrier status. Such detection could also alert family members to the possibility of a child being born with SCD, especially when newborn screening is absent or sporadic. In sub-Saharan Africa, resources for treatments are limited, and an estimated 50–80% of infants born with SCD in Africa die before the age of 5 years (25). In 2009, the United Nations General Assembly declared SCD to be a major public health concern (26), with 1 in 30 deaths of children <5 years of age worldwide linked to hemoglobin disorders and most of these being SCD (27).

Ethical Challenges Presented by Incidental Findings of SCT Through A1C Testing

There may be more challenges than advantages presented by incidental findings of Hb variants, some of which are discussed here.

The first ethical challenge is that any test in which Hb variants are incidentally revealed could be considered a genetic test, or a partial one. Some health care providers may not have anticipated this result, gained consent for this kind of genetic screening, or judged consent to be necessary. In the absence of guidelines for how and when to communicate incidental findings of SCT found through A1C, this lack of obtained consent may put them in a difficult position because not obtaining consent goes against many general guidelines for genetic screening (28–31). Patients are likely to have no idea that agreeing to get a test for diabetes may result in an unexpected indication that they are a carrier of the sickle cell gene. Therefore, patients and providers would have to be fully informed of the consequences of agreeing to such a test.

While we note that the trait is largely silent, it does have some rare clinical consequences, which creates the further dilemma for laboratories and health care providers of having information that might have clinical significance, but not passing that information on. Additionally, there is a risk of under-diagnosis of type 2 diabetes through A1C testing (32). Thus, the second ethical challenge is that communicating results is not always straightforward. Even within a formalized program such as the United Kingdom's newborn screening program, there are concerns about communicating SCT status (33). These concerns include inconsistencies in who should give the information and how, how much detail should be provided, health care provider competence when divulging complex genetic information to nonspecialist health professionals (34), and whether health records of who has SCT are sufficiently robust (35). Although identifying which professional or organization is best placed to inform patients of their newly discovered status is important, it is also possible that appropriate access to services such as genetic counseling may not be available.

A third ethical challenge is that neither patients nor their care providers may be able to predict the full social impact of knowing their status as a sickle cell carrier. Patients may wish to avoid any subsequent racism and stigma they may experience in revealing their SCT status (36). Although the different clinical impacts of SCT are disputed, there is a clear potential for societal discrimination with regard to known carrier status in several areas such as employment (37), insurance (38), sports (39), the criminal justice system (40), and marriageable status in some communities (41).

A fourth ethical challenge is that patients need to have control over their test results and the timing of the release of those results to other family members. The results could create an unexpected moral dilemma for patients regarding whether to disclose to a wider group of relatives. For example, the patient in the case described above was a minor, and one parent requested a printout of a general blood screening when "hemoglobin variant detected" was included in a "normal" A1C result report. A quick online check indicated that SCT would be the most likely explanation for this notation. Imagine a scenario, then, in which the father of a child he thought was biologically his received this result and already knew that neither he nor his partner had SCT. This circumstance potentially could have 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 even more devastating for children to suddenly learn that they are not biologically related to their parents. This is one of the many reasons why patients and their families need some degree of control over the revealing of carrier status, as well as confirmation of the

results on a separate sample, since mislabeled samples are common.

Yet another ethical challenge is presented if patients are not directly told they have an Hb variant but are told for whatever reason that they should not be screened for type 2 diabetes using an A1C test. With partial information such as this, patients may seek online information and guess that they have SCT and be anxious that the trait can cause sudden death as reported in some online sources. They may even confuse SCT with SCD and erroneously conclude that they have a serious long-term condition. This challenge encompasses questions such as: Is partial information worse than no information? Can the information be withheld? Should family members be informed?

A final ethical challenge could be in the everyday understanding of how SCT affects or does not affect the body. It is confusing for patients when they are told it is both a "diagnosis" and that it is either mostly benign 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 recognized by their physicians. This scenario may leave anyone with SCT worried and unresolved in how they interpret their symptoms and how they interact with family members and their wider community (42). A call for health care providers to stop ignoring reports of SCT-related 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 health care" (43).

Ways Forward for Testing Centers, Health Care Providers, Policymakers, and Patients

Despite there being some potential advantages for detecting hemoglobin variants through A1C testing, there are several ethical and practical dilemmas to be navigated. There are questions regarding what the different A1C testing systems have to offer in terms of diagnosis, whether and when patients should be told about detected variants, and what sorts of counseling and support patients should be offered. As awareness and reporting of the various limitations of A1C tests increases, health care services need to plan for the future to provide patients and health care providers resources and support. Guidelines for screening and reporting of Hb variants detected in the process of assessing diabetes status are urgently needed and should be developed with the involvement of affected communities to resolve these problems.

This is not an isolated issue; other tests can also potentially reveal incidental findings of SCT (e.g., when sickled red blood cells are identified in urine and subsequent testing reveals SCT) (44). This article has not covered thalassemias, but there is synergy with the situation described here where a full blood count may be considered an indirect genetic test because 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 (45), this kind of predicament involving incidental results will only present more ethical, legal, and psychosocial problems and would benefit from the investment of time and energy now to develop guidance and identify solutions.

Should family health care providers or the laboratories they work with report Hb variant results? Should they offer a further test to confirm which variant a patient may have? Should they refer such patients for genetic counseling?

There appear to be three main choices available with regard to A1C testing and SCT. First would be to dispute the notion of "incidental" genetic findings and assert that any test that (even indirectly) produces genetic findings must be declared to clients beforehand as an indirect genetic test, with appropriate permission obtained and counseling provided. The second option would be to accept the concept of "incidental" genetic findings, and when SCT confounds a diabetes test, ask the client for permission to investigate further with a confirmatory test for SCT and explain the implications of this course of action. The final option would be to again accept the concept of "incidental" genetic findings and focus only on the reliability of the information for assessing diabetes, effectively ignoring the SCT information except for its role as a confounder of the diabetes-relevant information. The first option is ethically the purest but is potentially expensive, whereas the third option seems unethical, especially when the information could be of potential benefit to patients and their families. The second choice at least has the possible ethical benefits of affording clients the opportunity to decide whether to know about their SCT status. Further research is needed to explore these issues for testing centers, practitioners, patients, and their family members in more detail to form a basis for international guidelines. Efforts to identify the best way forward, therefore, would benefit from a dialogue involving all parties involved in managing aspects of this test and its results, including laboratories, test system manufacturers, health care providers, and most importantly people with SCT and their families and communities.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

A.C.d.C. initiated the idea, interacted with the patient mentioned for permissions and feedback, wrote and revised the manuscript, and handled the submission process. K.M.A., F.B., M.J.B., S.M.D., A.M., and D.C.W. contributed equally to the knowledge required to build the technical information and arguments in the manuscript, including reviewing and revising the manuscript. A.C.d.C. is the guarantor of this work and, as such, had full access to all the patient and laboratory information used in the article and takes responsibility for the integrity of this information.

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