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Public Health
England

NHS Sickle Cell and Thalassaemia Screening Programme

Handbook for newborn laboratories



January 2017

Public Health England leads the NHS Screening Programmes

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Introduction

This is the fourth edition of the Laboratory Handbook which updates that published in October 2012. This handbook is for staff working in screening laboratories. It describes the policies and guidance that set out the requirements for laboratories involved in newborn screening. Information for laboratories is regularly updated in the laboratory section of the GOV.UK screening site^[1] and laboratories must check this section frequently. **The policies described relate to a screening programme and not a diagnostic service.**

The workload of the newborn screening laboratory should exceed 20,000 specimens per year (ideally 50,000). This ensures appropriate economies of scale and confidence in the interpretation of abnormal results. Providers must comply with the national guidance for the management of safety concerns and incidents in screening programmes and NHS England guidance for the management of serious incidents^[2].

The British Committee for Standards in Haematology (BCSH) has published guidance about screening^[4].

We would like to thank all those who have contributed to the handbook, which has been produced in accordance with the PHE style guide.

If you wish to reference or acknowledge this document, please use the following format: NHS Sickle Cell and Thalassaemia Screening Programme, Handbook for Laboratories, 4th edition; January 2017.

At the time of going to print, all information and contact details were correct. Please note this handbook is available on GOV.UK^[3].

Haemoglobinopathies

The haemoglobinopathies are a heterogeneous group of more than 1,000 mutations, which are categorised into two main groups: the haemoglobin variants and the thalassaemias. The haemoglobin variants (also called the abnormal haemoglobins) arise from an alteration in the globin protein structure, whereas the thalassaemias arise from inadequate production of structurally normal globin protein. There are also thalassaemic haemoglobinopathies that are produced when a structurally abnormal haemoglobin is synthesised at a reduced rate, for example HbE. Some of the abnormalities are easily detected by simple biochemical procedures, whereas others are biochemically silent.

The frequency of different haemoglobinopathies varies in different ethnic groups and certain haemoglobinopathies are often associated with a family history. However, it is important to remember that no haemoglobinopathy is exclusive to any single ethnic group; thus all persons are theoretically at risk of carrying an abnormal gene. It is not unusual for people to inherit more than one haemoglobin abnormality and many populations are at risk of a range of affected genes. Many haemoglobin mutations have no associated clinical significance, whereas others are associated with severe morbidity and mortality, most notably sickle cell disease and beta (β) thalassaemia major. Carriers are usually asymptomatic.

Sickle cell disease

Sickle haemoglobin (HbS) is a haemoglobin variant in which valine replaces glutamic acid, which is the sixth amino acid in the β globin chain. Other much rarer haemoglobins have been reported that have this same glutamic acid to valine substitution, but also an additional substitution elsewhere in the β chain. All of these variants will cause sickle cell disease in the situations described below for HbS.

Sickle cell disease results from the inheritance of certain genotypes, including:

- homozygosity for HbS (sickle cell anaemia)
- compound heterozygosity for HbS and an interacting gene, such as HbC (Hb SC disease)
- β thalassaemia (Hb S/ β thalassaemia)

A more comprehensive list can be found in Box 1.

The sickling disorders are associated with severe life-threatening vaso-occlusive crises, overwhelming sepsis, splenic sequestration, aplastic crises, stroke, priapism, pulmonary hypertension, proliferative retinopathy and chronic organ damage, such as avascular necrosis of the hips and shoulders. There is substantial evidence that early administration of prophylactic penicillin markedly reduces the incidence of pneumococcal sepsis. There is also evidence that pneumococcal vaccines can increase immunity to pneumococcal infections in children with sickle cell disease. Clinical monitoring to detect acute splenic sequestration reduces morbidity and mortality from homozygous sickle cell anaemia (Hb SS) in infancy and early childhood. Studies have demonstrated the benefits of: early diagnosis by newborn screening programmes, parental education, and comprehensive care for patients with sickle cell disease and β thalassaemia major.

Screening helpline

Laboratories may have questions about screening policy or interpretation of results that cannot be answered easily by reference to this handbook or textbooks. Oxford University Hospitals NHS Trust provides, on behalf of the screening programme, a support service for screening laboratories via designated telephone helplines and secure email.

Telephone: 01865 572 767

Email: lab.support@nhs.net

FAX: 01865 572 775

Newborn screening

The objective of the newborn screening programme is to detect infants with sickle cell disease during the neonatal period. This allows early diagnosis and helps to improve outcomes through early treatment and care. It is essential that infants with these conditions are diagnosed reliably and that they are clearly reported as having a sickle cell disease (Box 1) and that the necessary clinical follow up is arranged. The analytical methods used detect most cases of β thalassaemia major and related conditions. Alpha and β thalassaemia carriers are not identified.

Newborn sickle cell screening is offered to all babies born in England and the other UK countries. The screening is offered at 5 to 8 days of age as part of the NHS Newborn Blood Spot (NBS) screening programme. Additionally, babies up to 12 months of age who become the responsibility of the provider organisation must be offered screening if there is no documented evidence of a conclusive result for the conditions currently recommended by the UK National Screening Committee (UK NSC).

The NBS screening programme has published generic standards^[5] for newborn screening, against which the screening services will be assessed.

Informed consent

The NBS screening programme has developed guidance on informed consent^[6].

Clinically significant haemoglobinopathies that must be detected

Current screening methods detect many haemoglobin variants. Those for which there is evidence that early intervention is likely to be beneficial, and which are therefore specified as part of the national screening programme, are shown in Box 1.

Box 1: Sickle cell disease.

Sickle cell anaemia (Hb SS)

Hb SC disease

Hb S/ β thalassaemia^a

Hb S/D^{Punjab}

Hb S/E

Hb S/O^{Arab}

Hb S/V^b

Hb S/HPFH^c

Notes

^aThis is inclusive of Hb S/ β^+ , Hb S/ β^0 , Hb S/ $\delta\beta$, Hb S/ $\gamma\delta\beta$, Hb S/ $\epsilon\gamma\delta\beta$ and Hb S/Lepore.

^bThe use of FSV, “V” as denoted in this publication has been in use since the first edition (2005) as a technical term to designate variants which are not S, C, D^{Punjab}, E, and O^{Arab}, as there are more than 1,000 it is not practical to list them. This term is only used in the analytical/technical descriptions and has never been intended nor recommended for use in reports. The clinical advisor to the NHS Sickle Cell and Thalassaemia (SCT) screening programme has recommended that infants with the FSV pattern are reported as “condition suspected” (status code 08). These variants do not require full identification by the newborn first or second line laboratories but must be referred for clinical assessment and passed into the diagnostic pathway where applicable. This also acts as a failsafe for screening laboratories where a baby with sickle cell disease has a coexisting alpha chain variant that may result in diagnostic confusion.

^cIn general HbS with hereditary persistence of fetal haemoglobin (Hb S/HPFH) is regarded as a milder condition than the other sickling conditions. It is the policy of the screening programme that follow up is offered to distinguish it from other more significant abnormalities. It is not possible at birth to differentiate those conditions which produce only HbF and HbS on analysis; Hb SS, Hb S/ β thalassaemia syndromes and Hb S/HPFH. For the purpose of this programme it is essential to detect and report all such cases as ‘results consistent with sickle cell disease’ without further detail to enable follow up and diagnostic testing.

Since there are many Hb ‘D’ variants with the same analytical characteristics (unless using more specific techniques such as tandem mass spectrometry (MSMS)) and characterisation of the variant may take time, it is recommended that all ‘D’ haemoglobins with the same analytical characteristics of D^{Punjab} (also called D^{Los Angeles}) are provisionally identified as this haemoglobin, the only clinically significant haemoglobin D variant. DNA analysis or mass spectrometry can then be used to elucidate the diagnosis.

Beta thalassaemia syndromes

Beta thalassaemia syndromes are another group of conditions that are likely to be detected by the screening programme and in which the patient can benefit from follow up. The UK NSC has agreed that, in line with other national screening programmes, clinically significant findings of conditions which are not part of the screening programme, but are detected by current screening methods, must always be reported to the relevant clinician to enable management of the consequences of such findings.

Little or no haemoglobin A (HbA) on newborn screening is clinically significant since it may indicate little or no β -chain synthesis. The policy of the screening programme is that in all cases where the apparent HbA concentration is 1.5% or less of the total haemoglobin the result must be reported as F only (or FE only if E is present) and followed up clinically. A review of the efficacy of this approach has been published^[7] and further evidence is currently being collated to formally validate this action value.

The newborn screening programme will not detect all cases that subsequently manifest as β thalassaemia major since some of these babies have an HbA value greater than 1.5% at birth. Newborn screening laboratories must report possible Hb E/ β thalassaemia. This is because many of these children will become transfusion dependent or have thalassaemia intermedia. Note that homozygous HbE and Hb E/ β^0 thalassaemia will look identical on the initial screening test and will need to be differentiated in the diagnostic pathway.

Other carriers and 'clinically benign' haemoglobinopathies likely to be detected by screening

While the purpose of this programme is to detect infants with sickle cell disease, most of the analytical procedures currently in use also detect homozygotes and compound heterozygotes, and carriers of the other common haemoglobin variants (C, D^{Punjab}, E and O^{Arab}). Results of infants who are found to be homozygotes or compound heterozygotes for a common haemoglobin variant must be reported by the laboratory and follow-up counselling should be offered. These are shown in Box 2.

Box 2: Conditions that are usually clinically benign.

Hb CC and C/ β thalassaemia
Hb DD and D/ β thalassaemia
Hb CD
Hb CE
Hb DE
Hb EE

For MSMS, samples with results outside the designated action values must be sent for second-line testing (for action values^[8])

When using high performance liquid chromatography (HPLC), capillary electrophoresis (CE) or isoelectric focusing (IEF) a small number of other variants may be detected. These may not be immediately identifiable and most will be benign. The number of neonates with one of these other variants is likely to be small. It is national policy that laboratories must not report variants other than S, C, D^{Punjab}, E and O^{Arab} (this includes Hb Bart's). However, laboratories must send certain specimens for second-line testing. They are:

- samples with 1.5% HbA or less
- samples with variants (peaks) more positively charged than HbA (eluting after HbA by HPLC and located to the right of HbA on CE)

This policy is designed to ensure that:

- samples with little or no normal adult haemoglobin (HbA) have the result confirmed before reporting
- HbS (or one of the designated haemoglobins) is not missed even if it falls outside the predefined analytical windows

HbO^{Arab}, which has no defined analytical window, will still be detected. Using HPLC or CE and IEF there is a risk that newborn HbO^{Arab} carriers may not be positively identified. This is due to the difficulty in obtaining appropriate quality control material. Hb S/O^{Arab} compound heterozygotes will be detected and followed up clinically as per the recommendations for all cases with HbS and no HbA.

The '[Reporting results](#)' section of this publication provides the recommended wording for reporting the results for these mainly clinically benign variants, either homozygous, compound heterozygous or carriers and uses the newborn status code 04 'Condition not suspected'^[9].

For any other report, the recommended wording must state that 'haemoglobins S, C, D^{Punjab}, E and O^{Arab} have not been detected. Note that carriers of β thalassaemia and Hb Lepore are not detected by the techniques used for newborn screening'.

Sample requirements

Four good quality spots are necessary to complete the proper processing of the specimen. The demographics must be completed so the sample can be processed and to assist patient follow up. The document titled 'Guidelines for newborn blood spot sampling' publishes the full sample requirements^[10].

Due to the nature of dried blood spots, there is deterioration of the blood sample from the time it is taken, as oxidation of the haemoglobin results in methaemoglobin formation. This degradation is likely to be greater at higher temperatures, but in normal circumstances it should not prevent analysis using the techniques described below. In occasional cases where there has been a delay in the card being sent to the laboratory, or if it has been kept in unsuitable conditions, excessive oxidation may occur rendering the sample unsatisfactory for analysis.

Pregnancies at a 1 in 4 risk of a clinically significant haemoglobinopathy

Couples known to be at high risk (1 in 4) of having a baby with sickle cell disease or β thalassaemia major might wish to know the result for their child before the normal time for reporting the result from the blood spot. To be a known '1 in 4' high-risk pregnancy, the haemoglobin results must be known for both parents. Local policies should be in place to have a newborn blood spot for sickle testing taken earlier at the parents' request. Alternatively, a liquid capillary blood specimen (not cord blood) can be taken for analysis soon after birth. This is not part of the screening pathway and must be considered as an aspect of parental choice.

This blood specimen must be analysed in a specialist laboratory, which has expertise in haemoglobinopathy analysis in the newborn period. It is the responsibility of the laboratory undertaking such an analysis to inform the newborn laboratory of the result.

The fact that such a specimen has been taken should be noted by the midwife on the newborn screening blood spot card. The screening laboratory will undertake the routine screen as usual and this test will act as a 'failsafe' and quality check. It is imperative that the test result is given to the parents as soon as possible to decrease their natural anxiety about the status of their child. Testing of the liquid specimen must be seen as a parallel test to the screening specimen and not a substitute.

Risks of transfusions containing red cells on screening results

The presence of transfused red cells in the neonate will interfere with the interpretation of the results from the haemoglobin analysis of the blood spot. This could possibly invalidate the results. A small number of babies are transfused *in utero* but for babies transfused postdelivery it must be policy in all neonatal units to take a blood spot specimen for sickle cell screening before giving a transfusion^[10].

DNA extracted from the white cells in the blood spot is analysed, thus overcoming the complications caused by the presence of transfused red cells on the blood spot card. At present Kings College Hospital and Sheffield Children's Hospital provide this service. **However, this service does not eliminate the need to take a pretransfusion specimen.**

The DNA test will detect the presence of the sickle globin gene. This test is able to differentiate between babies with:

- only the sickle gene present
- those with the sickle gene and another globin gene (either a normal beta gene or a beta gene with another variant)
- no sickle gene present

If the sickle gene is detected the baby must be referred for clinical follow up. This test does not confirm the identity of the nonsickle haemoglobin. Parents may wish for further standard haematology tests on their baby if they are known to be at risk of another haemoglobinopathy. This is not considered part of the newborn screening programme and should be initiated in a clinical setting. However, testing using techniques other than DNA should not normally be undertaken until at least 4 months after the last transfusion.

Percentages of HbA in untransfused babies at different gestational ages

Figures 1 and 2 are derived from data provided by the newborn screening laboratory of Birmingham Children's Hospital, who used a BioRad VNBS analyser with valley-to-valley integration. The figures provide guidance about the expected levels of adult haemoglobin (HbA) in newborn babies and babies up to one year of age. The data on newborn babies is derived from 30,000 measurements and is presented as a percentile chart. The data on older babies from one month to one year is derived from 89 measurements and is therefore less statistically valid.

The purpose of the graphs is to provide guidance about the expected percentage of HbA that is seen in babies born from 23 weeks gestation up to one year of age. Increased percentages of HbA can be found following transfusion. The graphs may help to determine if the amount of HbA is appropriate for the age of the baby.

The primary way in which the transfused baby should be identified is the information provided by the healthcare professional who completes the blood spot card. However, this data field on the card is not always completed.

Figure 1. Percentage of HbA in routine specimens taken from untransfused babies with gestations from 23 to 42 weeks.

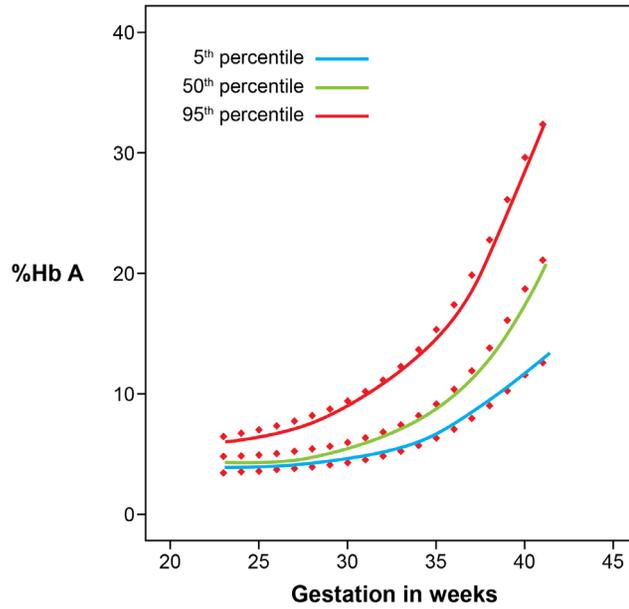
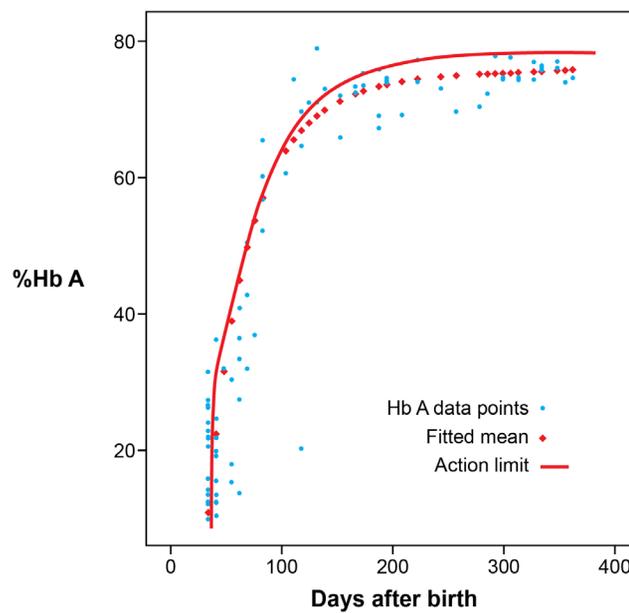


Figure 2. Percentage of HbA in untransfused babies one month to one year old.



The newborn screening laboratories can use the information provided in these graphs to reduce unnecessary referrals for DNA testing, especially in older babies. This is important as the failsafe screening test for sickle haemoglobin on transfused babies using DNA methods must only be used when a baby has received a transfusion and no pretransfusion sample has been taken.

Sample analysis

Newborn screening for sickle cell disease using haemoglobin eluted from dried blood spots can be reliably undertaken using a primary screen to detect the different haemoglobin fractions present. In the case of suspected abnormality, a second-line test on the same specimen using a different scientific principle must be carried out to validate the initial findings.

It is important to note that unequivocal identification of haemoglobin variants can only be achieved by either protein sequence analysis, by mass spectrometry or analysis of DNA. Occasionally the presumptive identification of a haemoglobin variant using screening methods is incorrect due to comigration of variants. Screening is not a diagnostic service and no screening programme has a sensitivity and specificity of 100%, however, haemoglobins S, C, D^{Punjab}, E and O^{Arab} should be detected reliably.

Acceptable analytical protocols

The analytical procedures employed must be capable of detecting haemoglobins S, C, D^{Punjab}, E, and O^{Arab}, in addition to HbF and HbA. Newborn samples are typically composed of HbF (75%) with approximately 25% HbA and small quantities of acetylated HbF. The procedures used must therefore be sensitive, reliable and reproducible in terms of detecting small quantities of HbA and the abnormal haemoglobin fractions listed, in the presence of large amounts of HbF.

The methods used must be validated for newborn specimens and the use of procedures or instruments designed for adult specimens is not recommended.

Four types of analysis are in use for newborn screening for sickle cell disease using dried blood spot samples: (1) HPLC; (2) CE; (3) MSMS; and (4) IEF. These methods are suitable for first-line screening. An alternative procedure using a different principle must be used for second-line testing to validate the result. Minimum requirements for quality control material for these techniques can be found at^[1]. When using HPLC or CE the haemoglobin separations (traces) must be checked due to the possibility of misclassification of fractions. All results must be read and then checked by different suitably qualified individuals, one of which must be a registered scientist.

High performance liquid chromatography

HPLC uses an ion exchange resin, held in a column cartridge, in conjunction with a buffer gradient. As the ionic strength and/or pH of the buffer changes certain haemoglobins are eluted from the column and the presence of haemoglobin is detected using a spectrophotometric technique. The time from injection to the point at which the haemoglobin fraction elutes is known as the retention time of the haemoglobin and is a reproducible measurement for a particular column, buffer, exchange resin and temperature.

However, it is quite common for different haemoglobins to elute at the same retention time. Thus the retention time is not a unique identifier. HbF is eluted separately from HbA. Haemoglobins S, C, D, E and O^{Arab} also have separate retention times and characteristic chromatographic profiles. In addition, the relative proportions of the different haemoglobins are recorded. It is therefore possible to detect the difference between carriers and affected infants and also to differentiate some types of compound heterozygosity of HbS with β^+ thalassaemia.

Capillary electrophoresis

CE uses a combination of ion migration and electro-osmotic flow to separate protein molecules. When a voltage is applied across the capillary tube filled with an electrolyte solution, the solution begins to move towards one of the electrodes due to electro-osmotic flow. This drives the bulk flow of materials past the detector in the same way that a pump pushes the liquid in HPLC. The haemoglobin molecules move towards the detector at different speeds depending on their ionic charge and electrophoretic mobility. Both electro-osmotic flow and electrophoretic mobility are occurring at the same time, working in opposite directions to provide greater resolution.

This method of separation should not be confused with simple electrophoretic mobility as seen in cellulose acetate electrophoresis. Combining electro-osmotic flow and electrophoretic mobility is a separate phenomenon and is exploited in CE for maximum separation power. Even so, it is quite common for different haemoglobins to migrate at the same rate and appear at the same position. Thus position is not a unique identifier.

HbF is separated from HbA. Haemoglobins S, C, D, E and O^{Arab} also have different mobility rates and characteristic profiles. In addition, the relative proportions of the different haemoglobins are recorded. It is therefore possible to detect the difference between carriers and affected infants and also to differentiate some types of compound heterozygosity of HbS with β^+ thalassaemia.

Tandem mass spectrometry

Mass spectrometry generates charged molecules or molecular fragments and measures their mass-to-charge ratio (m/z). Differences in m/z can be used to separate molecules or atoms and to determine chemical and structural information of molecules, such as peptides. There are 3 main components to the procedure:

1. Ionisation of the analytical material.
2. Determination of the m/z based on the movement of the ions through electrical and/or magnetic fields.
3. The detection of the ions.

Electrospray ionisation employs a high voltage applied to a liquid to create an aerosol to produce ions for analysis. It has the advantage of producing multiply-charged intact ions from relatively large parent species.

MSMS employs 3 coupled quadrupole analysers in a linear arrangement. The first and third quadrupoles (Q1 and Q3) are mass analysers, with the second (Q2), operating with a fixed radio frequency voltage and used as a collision cell with ion focusing properties.

At this time the only CE-marked commercial reagent set available is produced by SpotOn Clinical Diagnostics. Methodological information relates to the use of these reagents. Any MSMS instrument used for this work must perform as well as, or better than, the instruments deemed acceptable in the NHS SCT Programme pilot^[1], as assessed by the action value limits and the false positive rate.

Unlike HPLC, CE and IEF, the analysis is not performed on intact haemoglobins but on fragmented globin chains (peptide fragments). The method incorporates a series of experiments performed simultaneously to detect: HbS, HbC, HbD^{Punjab}, HbE and HbO^{Arab}. The method is mutation-specific therefore all cases containing the mutation under investigation will be detected and misclassification of coeluting variants should not occur. The signal for the wild-type beta and gamma globin is also assessed, acting as a surrogate for HbA and HbF. The gamma/beta wild type ratio represents the relative proportion of HbF to HbA. Therefore a high ratio suggests low HbA and prematurity or β thalassaemia and a low ratio indicates a low HbF which may be due to age, transfusion or gamma thalassaemia.

An internal standard is also included to act as a methodological control. The material is a synthetic, stable isotope-labelled, sickle sequence peptide with an extension peptide, which requires tryptic activity to generate the stable isotope-labelled peptide to be detected in the analysis. Low values are indicative of incomplete digestion but may also be seen if the sensitivity/performance of the instrument has deteriorated.

High values indicate reduced ion suppression, which may be found in samples with low haemoglobin content or where the digestion process has not accessed all of the sample. Accidental addition of multiple shots of reagent will also result in high values. Laboratories must monitor the internal standard values for drift/trends as an indication of the MSMS performance within and between runs.

Results are expressed as a ratio of variant haemoglobin divided by corresponding wild-type signal. To determine which samples are potentially screen positive and therefore require second-line testing, common action values have been derived from the numeric ratio of the variant and wild type signal in each acquisition^[1].

Isoelectric focusing

IEF gives good separation of HbF from HbA and variant haemoglobins S, C, D^{Punjab}, E and O^{Arab}. The separation of different haemoglobins is accomplished through application of a haemoglobin sample onto a precast agarose gel containing ampholytes at pH 6 to 8. Ampholytes are low molecular weight amphoteric molecules with varying isoelectric points (pIs). When an electric current is applied, these molecules migrate through the gel to their pIs forming a stable pH gradient. The haemoglobin variants also migrate through the gel until they reach the point at which their pI equals the corresponding pH of the gel. At this point, the net charges on the variants are zero and migration ceases. The electric field counteracts diffusion and the haemoglobin variants form discrete thin bands. IEF can be semiautomated, rendering the technique suitable for screening large numbers of samples.

General analytical considerations

Users must be aware that the laboratory handbook highlights common analytical and diagnostic issues, but every laboratory must follow the principles of good laboratory practice including satisfying themselves that they understand the capabilities and limitations of their chosen technique. The equipment and protocol chosen must fulfil the requirements of the screening programme and UKAS/ISO 15189 and demonstrate suitable performance on external quality assurance (EQA).

The use of rules to screen samples for further action/reporting or the use of postanalytical data analysis algorithms must have software quality control procedures, including regular process audit, to ensure that quality is not compromised. It is essential that the process is risk assessed and that there are failsafe mechanisms in place. Raw data, such as HPLC chromatograms and CE plots must always be reviewed and any postanalytical procedures including algorithms must be fully documented and traceable to ensure consistency of quality.

The application of HPLC and IEF for newborn screening has a disadvantage in that the process also separates the normally occurring adducted fractions, that is acetylated HbF (HbF₁) and degraded haemoglobin fractions which can make interpretation difficult. The retention times and migration patterns of different haemoglobin variants are not unique and thus the results obtained can only be regarded as provisionally identifying the variant(s) concerned.

If HPLC is used as the screening technique it is essential to check and maintain the positions of the windows which are used as the first stage identification of any variants found. This is usually achieved by the use of retention time markers.

If CE is used, appropriate control material must be used to ensure optimal analytical performance. Optical density (OD) levels greater than 0.07 and the presence of sufficient HbF are required to determine the migration position and thus permit 'zoning' and a provisional identification of haemoglobins present in the sample. If failure to zone is due to low OD, this is usually related to the amount of haemoglobin in the sample. This should be corrected by increasing the spot to diluent ratio and allowing a longer elution time. Extreme care is needed if extraneous haemoglobin is added to a clinical sample to allow zoning.

The addition of haemoglobins that were not present in the initial sample will make the electropherogram more difficult to interpret and may lead to the misinterpretation of the results. Such modified samples must be analysed with a unique identifier distinguishable from both the original specimen and from any other clinical sample. Experiments have shown that denatured HbF (acetylated F) which increases with age of the sample, appears in zone N9 but can appear on the borders of zone N10. When only a small amount of HbA is present the two may overlap, falsely increasing the measured level of HbA. Caution is needed in interpreting such results.

If MSMS is used, the instrument must be optimised using the synthetic peptide standards with documented traceability and quality must be used to ensure optimum detection of required haemoglobins. Failure to optimise target masses can result in misidentification. MSMS cleaning protocols must always be followed. Appropriate controls must be run with each plate of samples. The internal standard results must be monitored and within the limits established for the instrument/laboratory. A high internal standard result is usually indicative of low haemoglobin concentration in the blood spot. During reagent addition care must be taken to avoid splashing between wells as this may result in false positives. If using an instrument/software which can produce a value of zero for the denominator the resulting ratio will also be zero regardless of the value of the numerator and a positive result can be missed.

If IEF is used, then control haemoglobins must be run with each plate. Care must be taken to ensure that there is clear delineation between the bands for adjacent specimens. This can be achieved by firmly blotting the gel and blotting again after the template has been added before the addition of the sample.

When using the percentages of the haemoglobin fractions to interpret the results, the possibility of the presence of transfused blood must be considered (Figures 1 and 2).

Interpretation of results

Results of sickle cell screening are interpreted according to the different haemoglobin fractions present, which in unaffected infants are HbF (as the major fraction) and HbA. If the results of the first-line screen show the presence of any abnormal fraction, second-line testing must be considered according to the guidelines on page 14. For MSMS any ratio falling outside of the action value limits must have second-line testing. Extreme care must be taken if discrepancies are found when interpreting second-line testing following MSMS analysis. For example, cases with F, S and an unknown variant (FSV) will almost invariably give a ratio indicative of a sickle carrier whereas second-line testing should reveal the variant. These individuals need to be referred into clinical follow up.

Also, variants with a double substitution one of which is the haemoglobin under investigation will give a positive ratio. These variants may not be detected by second-line testing as they may not separate from HbA, thus it is essential that clear positive first-line MSMS results for HbS are not discounted without careful review. If the concentration of HbA on the blood spot is abnormally high or comprises all of the haemoglobin present, then the possibility of a transfusion before the blood being taken must be considered. Using MSMS such a sample would show a low gamma/beta ratio. This presentation may also be observed when there is contamination of the blood spot with adult blood as a result of poor practice and in cases of gamma thalassaemia. It is important to exclude both transfusion and contamination by adult blood.

Status code 04

Results usually show the presence of HbF and HbA. It is usual in a term infant for the percentage of HbA to be between 5 and 30%. This figure varies according to gestation and the laboratory must consider gestational age when requesting repeat sampling (Figures 1 and 2). Additionally, a small number of other variants may be detected when using HPLC, CE or IEF. These may not be immediately identifiable and most will be benign. The number of neonates with one of these other variants is likely to be small. It is national policy that variants other than S, C, D^{Punjab}, E and O^{Arab} must not be reported. For MSMS all ratios would be within action value limits.

The following guidelines require both first- and second-line results to be taken into consideration.

Sickle cell disease

Results from infants with sickle cell disease show the presence of HbF and HbS in the absence of HbA (that is FS); or HbF and HbS with another haemoglobin variant (for example, FSC); or HbF, HbS and HbA where the quantity of HbS is greater than HbA (Hb S/ β^+ thalassaemia). In cases of sickle cell disease (F+S only) the quantity of HbS found is usually between 4 and 10% for a full-term baby and less in a premature baby. With some HPLC systems a very small peak elutes in the HbA0 window and so a baby with Hb SS may appear to have Hb S/ β^+ thalassaemia, but with experienced personnel checking the chromatograms, this is not usually a problem. Expected results from infants with sickle cell disease are shown in Table 1.

| Newborn screening results | Disease |
|---------------------------|----------------------------------|
| FS | Hb SS |
| FS | Hb S/ β^0 thalassaemia |
| FS | Hb S/ $\delta\beta$ thalassaemia |
| FS | Hb S/Lepore |
| FS | Hb S/HPFH |
| FSA or FS | Hb S/ β^+ thalassaemia |
| FSC | Hb SC |
| FSD | Hb S/D ^{Punjab} |
| FSE | Hb S/E |
| FSO ^{Arab} | Hb S/O ^{Arab} |

Hb S/ β thalassaemia

Caution must be exercised in the interpretation of results where the amount of HbS is greater than HbA, as the cause may be Hb S/ β^+ thalassaemia. If HbS is greater than HbA, check the parents' results if these are available. If the parents' results are not available, the HbS would normally be expected to be greater than 120% of the HbA result for a diagnosis of Hb S/ β thalassaemia to be made. Again, the actual quantities of HbA and HbS found will vary according to gestational age.

Sickle cell carrier

Results from infants who are sickle cell carriers will show the presence of HbF, HbA and HbS. The quantity of HbA should exceed the quantity of HbS, but in some cases the amounts of HbS and HbA are almost equal.

Heterozygotes for other haemoglobin variants

Results from infants who are carriers for other haemoglobin variants will show the presence of HbF and HbA and the haemoglobin variant. Again, the quantity of the variant is usually less than the quantity of the HbA and the exact quantities will vary with gestational age.

Homozygotes or compound heterozygotes for nonsickling conditions

Results from infants who are homozygous or compound heterozygotes for conditions other than sickle cell disease, will show the presence of HbF and the haemoglobin variant(s) only. No HbA will be detected. Results from some automated analysers may be misleading in that an apparent small HbA0 peak may be present, but this should not be a problem with experienced personnel checking the chromatograms.

β thalassaemia major

Results from a child with severe β thalassaemia will usually have only HbF present and no HbA. The policy of the screening programme is that in all cases where the apparent HbA concentration is 1.5% or less of the total haemoglobin, the result must be reported as F only, and followed up. In a small survey of newborn babies with confirmed β thalassaemia major, 81% had apparent HbA present in the screening specimen. Therefore caution must be exercised in cases where there appears to be a small amount of HbA. Additionally, many different mutations give rise to severe β thalassaemia and some of these may result in the presence of very small amounts of HbA. For MSMS a unique pattern is usually present, a high gamma/beta ratio along with results above the action values for some of the other haemoglobins under investigation, this is due to the low beta wild-type expression.

It is important to emphasise that not all thalassaemias will be detected by the newborn screening programme. The majority of babies with β thalassaemia major will be detected by a very low HbA¹ at birth, but for the other thalassaemias there are no reliable indicators that will be detected using currently available screening methods.

DNA analysis is required to elucidate the diagnosis.

¹Assessed as 1.5% or less by HPLC/CE and/or values above designated gamma/beta action values for MSMS.

Risk assessment

This is a screening programme rather than a diagnostic service so it will not detect:

- β thalassaemia major or intermedia with an HbA or gamma/beta ratio value outside designated action limits
- any target haemoglobin whose result falls outside designated action limits
- β , $\delta\beta$ and $\gamma\delta\beta$ thalassaemia carriers
- Hb H disease and α thalassaemia carriers
- Hb S/ β thalassaemia with a high expression of HbA
- rare clinically significant haemoglobins (for example, high affinity haemoglobins, unstable haemoglobins and methaemoglobin forming variants)
- some rare haemoglobin variants that are clinically significant in the presence of HbS
- undeclared transfused babies whose HbA level is below the action values shown in Figures 1 and 2
- any significant variant which is misinterpreted as a result of an undeclared blood transfusion, in particular the risk that an Hb FS may be reported as Hb FAS

Reporting results

The following guidelines, on reporting analytical data and the genetic implications (conclusions) of that data plus table 2, should provide sufficient information to allow all unaffected and over 95% of abnormal cases to be reported in a standardised manner.

All reports must include the sample date. The haemoglobins present must be reported in the order of the greatest to the least percentage/proportion and analytical fact must be separated from interpretative opinion. The factual results must be given and then a clear conclusion, which may include recommendations. The conclusion must always be given in full text, for example, 'Results consistent with sickle cell carrier' is the conclusion for Hb FAS or 'Results consistent with sickle cell disease' for an analytical result of Hb FS. Reports and templates used must be clearly presented and laid out so that misinterpretation is avoided.

Detail on the status codes required for use when reporting newborn screening results to child health systems and for administrative use can be found at^[9]. These codes are used to support the transfer of information between the respective computer systems and they are not intended to be used for clinical purposes. The codes are designed to be generic for all of the conditions that are screened for in the NBS screening programme. Table 2 provides examples of the main status code for the different types of results, more details can be found in the document.

| Table 2: Reporting newborn sickle cell screening results. [Note: 'Thalassaemia' = $\beta 0$, $\beta +$, $\delta\beta$, $\gamma\delta\beta$ and Hb Lepore as appropriate] | | | |
|---|---|--|--|
| Analytical results (Hb written in order of %) | Diagnostic possibilities | Report format | Status code for Child Health reporting |
| Sickle cell disease | | | |
| FS (Fetal and sickle haemoglobin) | Sickle cell anaemia (81%) Sickle cell - β thalassaemia (17%) Sickle cell - HPFH (2%) The figures for the birth prevalence of the sickle cell disease were obtained from 146 children identified by newborn screening in London and confirmed by parental result. | Results consistent with sickle cell disease Clinical referral required Actual genotype will require further investigation | 08 |
| FSA (Fetal haemoglobin, sickle haemoglobin and a small amount of haemoglobin A) | Sickle cell - β thalassaemia Transfusion Sickle cell carrier | Results consistent with sickle cell disease Result valid only if not transfused Clinical referral required Actual genotype will require further investigation | 08 |
| FSC (Fetal haemoglobin, sickle haemoglobin and haemoglobin C) | Haemoglobin SC disease | Results consistent with Hb SC disease Clinical referral required | 08 |

| Table 2: Reporting newborn sickle cell screening results. [Note: ‘Thalassaemia’ = $\beta 0$, $\beta +$, $\delta\beta$, $\gamma\delta\beta$ and Hb Lepore as appropriate] | | | |
|---|---|--|--|
| Analytical results (Hb written in order of %) | Diagnostic possibilities | Report format | Status code for Child Health reporting |
| FSD (with the characteristics of D ^{Punjab}) Fetal haemoglobin, sickle haemoglobin and haemoglobin D | Haemoglobin SD disease | Results consistent with Hb SD disease Clinical referral required | 08 |
| FSE (Fetal haemoglobin, sickle haemoglobin and haemoglobin E) | Haemoglobin SE disease | Results consistent with Hb SE disease Clinical referral required | 08 |
| FSO ^{Arab} (Fetal haemoglobin, sickle haemoglobin and haemoglobin O ^{Arab}) | Haemoglobin SO ^{Arab} disease | Results consistent with Hb SO ^{Arab} disease Clinical referral required | 08 |
| FSV (Fetal haemoglobin, sickle haemoglobin and unidentified haemoglobin variant) | Usually clinically benign but requires referral for clinical assessment | Possible Sickle Cell Disease Referral required for clinical assessment to confirm diagnosis | 08 |

| Table 2: Reporting newborn sickle cell screening results. | | | |
|---|---|---|--|
| [Note: 'Thalassaemia' = β^0, β^+, $\delta\beta$, $\gamma\delta\beta$ and Hb Lepore as appropriate] | | | |
| Analytical results (Hb written in order of %) | Diagnostic possibilities | Report format | Status code for Child Health reporting |
| Other potentially clinically significant conditions | | | |
| F only (Fetal haemoglobin [or with haemoglobin A outside designated action values]) | Possible β thalassaemia major Prematurity Homozygous HPFH HPFH with β thalassaemia | Only fetal haemoglobin detected Clinical referral required | 07 |
| FE (Fetal haemoglobin and haemoglobin E [with haemoglobin A outside designated action values]) | Haemoglobin E/ β thalassaemia; a form of haemolytic anaemia which may cause transfusion dependence Haemoglobin E disease; a mild form of haemolytic anaemia Haemoglobin E with HPFH | Possible homozygous HbE or Hb E/ β thalassaemia Clinical referral required | 07 |
| FEA (Fetal haemoglobin, haemoglobin E and haemoglobin A) | Compound heterozygote for HbE and β^+ thalassaemia; which may cause transfusion dependence | Possible compound heterozygous HbE and β^+ thalassaemia. Clinical referral required Valid if not transfused | 07 |

| Table 2: Reporting newborn sickle cell screening results. | | | |
|---|---|---|--|
| [Note: 'Thalassaemia' = β^0, β^+, $\delta\beta$, $\gamma\delta\beta$ and Hb Lepore as appropriate] | | | |
| Analytical results (Hb written in order of %) | Diagnostic possibilities | Report format | Status code for Child Health reporting |
| Benign conditions and carriers | | | |
| FC or FD or FO ^{Arab} (Fetal haemoglobin and haemoglobin C or haemoglobin D or haemoglobin O ^{Arab}) | Homozygous HbC or D or O ^{Arab} Compound heterozygote for HbC or D or O ^{Arab} and β thalassaemia or HPFH | Possible homozygous HbC or D or O ^{Arab} Possible compound heterozygous HbC or D or O ^{Arab} and β thalassaemia or HPFH | 07 |
| FCA or FDA or FO ^{Arab} A (Fetal haemoglobin and haemoglobin C or D or O ^{Arab} and haemoglobin A) | Compound heterozygote for HbC or D or O ^{Arab} and β^+ thalassaemia | Possible compound heterozygous HbC or D or O ^{Arab} and β^+ thalassaemia Valid if not transfused | 07 |
| FAS (Fetal haemoglobin, haemoglobin A and haemoglobin S) | Sickle cell carrier; usually clinically benign but genetically significant | Results consistent with sickle cell carrier Valid if not transfused | 05 |
| FAC or FAD or FAE or FAO ^{Arab} (Fetal haemoglobin, haemoglobin A and haemoglobin C or D or E or O ^{Arab}) | HbC carrier or HbD carrier or HbE carrier or HbO ^{Arab} carrier; clinically benign but genetically significant | Results consistent with HbC carrier or HbD carrier or HbE carrier or HbO ^{Arab} carrier Valid if not transfused | 0601 FAC 0602 FAD 0603 FAE 0604 FAO ^{Arab} |

| Table 2: Reporting newborn sickle cell screening results. [Note: ‘Thalassaemia’ = $\beta 0$, $\beta +$, $\delta\beta$, $\gamma\delta\beta$ and Hb Lepore as appropriate] | | | |
|---|---|--|--|
| Analytical results (Hb written in order of %) | Diagnostic possibilities | Report format | Status code for Child Health reporting |
| FV, FVA and FAV (Fetal haemoglobin, with or without haemoglobin A and a haemoglobin variant [not S, C, D, E or O ^{Arab}]) | Most likely clinically insignificant haemoglobin but may be genetically significant | Hbs S, C, D, E and O ^{Arab} not detected. Note – Carriers of beta thalassaemia and Hb Lepore cannot be excluded at this age. Valid if not transfused | 04 |
| FA (Fetal and adult haemoglobin) | No haemoglobin variant detected | Hbs S, C, D, E and O ^{Arab} not detected. Note – Carriers of beta thalassaemia and Hb Lepore cannot be excluded at this age. Valid if not transfused | 04 |

If the newborn baby has had a blood transfusion and any of the transfused red cells are still present, misleading data and conclusions may result. This includes in utero transfusions a fetus may have received. It is therefore essential that clinicians realise this fact and consideration must be given to having a footnote on all haemoglobinopathy results, such as ‘Results valid only if not transfused’, or something similar.

Issuing laboratory reports

The parents and general practitioner (GP) must be informed of all the outcomes of screening. The approach adopted must follow general guidance from the NHS NBS screening programme.

Laboratories are responsible for sending all screening results to child health departments, or their equivalent^[9].

This information will be used to assess coverage of the screening programme and to provide a mechanism for reporting ‘normal’ results to parents and other healthcare professionals. Presumptive positive results must be reported without delay by the laboratory to the designated healthcare professional.

Action required for particular categories of results

Infants with status code 08 – sickle cell disease suspected

Screen positive results must be reported as per local pathways, for example, to the clinician and/or designated sickle cell and thalassaemia centre and confirmation of receipt documented. The designated sickle cell and thalassaemia centres ensure that affected babies enter the care pathway and return the confirmatory diagnostic results back to the newborn screening laboratories to confirm enrolment into care and for validation of the screening result.

Local protocols must be in place to ensure that all screen positive results are given to parents by a trained healthcare professional face-to-face by 28 days of age. The baby must also enter the care of a specialist haemoglobinopathy centre by 90 days of age^[11].

Infants found to have a condition other than sickle cell disease which requires follow up

These results must be reported as per local pathways, for example, to the designated sickle cell and thalassaemia centre and confirmation of receipt documented. Parents should be informed by personal contact. Copies of all reports must be sent to the GP and health visitor. These babies must also be referred to the

appropriate specialist network lead. The confirmatory diagnostic results must be returned to the newborn screening laboratories to confirm enrolment into care and for validation of the screening result.

Infants homozygous or compound heterozygous for non sickling haemoglobins which do not require follow up

These results must be reported as per local pathways for example to the designated sickle cell and thalassaemia centre and confirmation of receipt documented. Parents and GPs must also be informed by a locally agreed mechanism.

Infants heterozygous for haemoglobins S, C, D, E or O^{Arab}

These results must be reported as per local pathways for example to the designated sickle cell and thalassaemia centre and confirmation of receipt documented. Parents and GPs must also be informed by a locally agreed mechanism.

Infants with no abnormality detected or haemoglobin variants other than S, C, D, E or O^{Arab}

The child health department or equivalent must provide the results in written form to the child's parents and GP. The wording for reporting the results for these infants with no abnormality detected or haemoglobin variants other than S, C, D, E or O^{Arab} uses the newborn status code 04 'Condition not suspected'. The wording must state that 'haemoglobins S, C, D^{Punjab}, E and O^{Arab} have not been detected. Note that carriers of β thalassaemia and Hb Lepore are not detected by the techniques used for newborn screening'.

Premature infants

HbA is normally detectable by 30 weeks gestation and is sometimes detected by 24 weeks. Results from premature infants must be interpreted with caution. Premature infants who show a HbA or gamma/beta ratio value outside designated action limits must have repeat testing with an appropriate technique to check for the presence of sickle cell disease or β thalassaemia major.

Annual data returns

Newborn screening laboratories must provide an annual data return, using the template developed in conjunction with the NHS NBS programme centre^[12].

Newborn screening laboratories must also collate and submit the data required for the relevant key performance indicators for the newborn screening programme.

Quality assurance and accreditation

All commissioners and service providers must refer to the public health functions agreement (Section 7A) service specification (No 18), and supporting standards and handbook to ensure a service is set up correctly and is meeting the standards set by the national screening programme.

Laboratories offering screening for the Sickle Cell and Thalassaemia Screening Programme must:

- be accredited by the UK Accreditation Service (UKAS) to ISO. 'Medical laboratories – Requirements for quality and competence (ISO 15189) or be CPA accredited and actively transitioning towards ISO 15189
- participate in EQA schemes accredited to ISO. 'Conformity assessment. General requirements for proficiency testing schemes (ISO 17043)'
- meet the screening programme quality assurance requirements mapped to ISO 15189
- and use ISO 15189 accredited reference laboratories

The UK Accreditation Service (UKAS) will assess both the ISO and the screening requirements on behalf of PHE Screening Quality Assurance Services and the Sickle Cell and Thalassaemia Screening Programme.

Lines of responsibility

Lines of responsibility can be found in the 'Health Professional Handbook'^[6].

Clinical network arrangements

See NHS standard contract for specialised services for haemoglobinopathy care^[11].

Failsafe arrangements

The NBS failsafe solution helps to ensure that all babies born in England are offered screening. It identifies babies who have not been screened or who require a repeat sample to be taken early in the postnatal period so that screening can be offered.

Laboratories involved in newborn screening

See 'UK Newborn Screening Laboratories Network'^[13] for the laboratory directory.

Useful organisations and websites

The Oxford Laboratory provides, on behalf of the screening programme, a dedicated sickle cell and thalassaemia laboratory support service for antenatal and newborn laboratories and other healthcare professionals involved in the screening programme.

Telephone: 01865 572 767

Email: lab.support@nhs.net

FAX: 01865 572775

NHS Sickle Cell and Thalassaemia Screening Programme enquiries:

Telephone: 020 3682 0890

Email: Phe.screeninghelpdesk@nhs.net

Website: gov.uk/phe/screening

[British Committee for Standards in Haematology](#)

[SCT screening e-learning for health care professionals](#)

[NHS Choices: screening for sickle cell and thalassaemia](#)

[National Sickle Cell/Thalassaemia Centres](#)

[Royal College of Paediatrics and Child Health](#)

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10. NHS Newborn Blood Spot Screening Programme, '[Guidelines for Newborn Blood Spot Sampling](#)', March 2016 (viewed on 9 December 2016)
11. NHS England, '[2013/14 NHS Standard contract for specialised services for haemoglobinopathy care \(all ages\)](#)', 2013 (viewed on 9 December 2016)
12. GOV.UK [Internet]. Newborn blood spot screening programme: standards and data [cited 2016 Dec 9]. Available from: www.gov.uk/government/collections/newborn-blood-spot-screening-programme-standards-and-data
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About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. PHE is an operationally autonomous executive agency of the Department of Health.

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About PHE Screening

Screening identifies apparently healthy people who may be at increased risk of a disease or condition, enabling earlier treatment or better informed decisions. National population screening programmes are implemented in the NHS on the advice of the UK National Screening Committee (UK NSC), which makes independent, evidence-based recommendations to ministers in the four UK countries. The Screening Quality Assurance Service ensures programmes are safe and effective by checking that national standards are met. PHE leads the NHS Screening Programmes and hosts the UK NSC secretariat.

PHE Screening, Floor 2, Zone B, Skipton House, 80 London Road, London SE1 6LH

www.gov.uk/topic/population-screening-programmes

Twitter: [@PHE_Screening](https://twitter.com/PHE_Screening) Blog: phescreening.blog.gov.uk

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