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Newborn screening for sickle cell disease (SCD)[1]

Extract

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Key statement

Research question

The objective of this study is to assess the benefit of newborn screening for sickle cell disease (SCD). Newborn screening for SCD in combination with a shortened timeline until diagnosis and treatment was assessed in comparison with no screening with regard to patient-relevant outcomes.

Conclusion

In terms of the prevention of deaths of affected children, there is a hint of benefit in favour of newborn screening for SCD, if followed by further interventions such as education of family members and infection prevention, in comparison with no screening. This hint of benefit is based on 1 retrospective, historical-comparative screening study showing a dramatically high effect of the intervention, despite being associated with a high risk of bias regarding the results. No ongoing studies on the screening chain were found.

To answer the question of which diagnostic test methods are suitable for SCD screening in Germany, studies on diagnostic quality were examined as supplementary information. The evidence from these studies was insufficient for calculating sensitivity and specificity. The positive predictive values of some studies show, however, that there are suitable test methods for identifying newborns with SCD (all babies identified by means of tandem mass spectrometry and high-performance liquid chromatography really had SCD).

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List of abbreviations

Abbreviation	Meaning
ELISA	Enyzme-linked immunosorbent assay
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GPOH	Gesellschaft für Pädiatrische Onkologie und Hämatologie (Society for Paediatric Oncology and Haematology)
Hb	Haemoglobin
HbA	Haemoglobin A
HbC	Haemoglobin C
HbF	Haemoglobin F (foetal haemoglobin)
HbS	Haemoglobin S (sickle cell haemoglobin)
HPLC	High-performance liquid chromatography
IEF	Isoelectric focusing
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MS/MS	Tandem mass spectrometry
PCR	Polymerase chain reaction
PPV	Positive predictive value
RCT	Randomized controlled trial
SCD	Sickle cell disease
SCD-S/S	Homozygous sickle cell disease (genotype 2 HbS mutations)
VOPT	Verification of only positive testers

1 Background

Sickle cell disease (SCD) is an autosomal recessive disorder based on a genetic abnormality of haemoglobin (a haemoglobin S mutation [HbS mutation]). Both homozygous sickle cell disease (SCD-S/S) and compound heterozygosity lead to the clinical picture of SCD. The disease is frequently found in combination with β-thalassaemia (SCD-S/β-thalassaemia) or a mutation leading to the haemoglobin variant HbC (SCD-S/C). Other, rare combinations have also been reported [1].

No reliable information is available on the prevalence and number of children born with SCD in Germany, but an estimated 3000 people currently live with the disease in Germany [2, 3]. According to a survey based on data from the AOK, a German statutory health insurance fund, on the 2009 and 2010 birth cohorts, the prevalence among those insured by AOK is 0.196 per 1000 newborns [4]. The estimated global prevalence of SCD is 2.28 per 1000 [5]. Prevalence varies widely by region and correlates with the spread of malaria. SCD is particularly common in sub-Saharan Africa, parts of the eastern Mediterranean, the Middle East, and India and has spread globally through migration [1, 6]. Accordingly, the estimated prevalence is 10.68 per 1000 in Africa and 0.07 per 1000 in Europe [5]. Broken down to annual births, an estimated 230 000 children (0.74% of births) are born with SCD in sub-Saharan Africa, compared to only 1300 children in all of Europe [1]; extrapolated to Germany, this would correspond to about 200 children per year. In Germany, SCD can be assumed to occur only among descendants from the aforementioned regions (Sub-Saharan Africa, Eastern Mediterranean, Middle East, and India).

Haemoglobin molecules in erythrocytes are responsible for transporting oxygen in the blood. Each haemoglobin molecule consists of 4 amino acid chains (globins). Haemoglobin A (HbA), the most common physiological haemoglobin in healthy adults, consists of 2 α-globin and 2 β-globin subunits. In SCD, a point mutation in the gene encoding β-globin (HbS mutation) results in an amino acid substitution in the β-globin: glutamic acid is replaced by valine. The resulting sickle cell haemoglobin (HbS) differs from HbA in its structural characteristics.

Sickle cell haemoglobins aggregate into fibres when the haemoglobin molecules have released oxygen. These HbS fibres damage erythrocytes and cause them to take on a sickle shape [1, 7]. Compared to healthy, round erythrocytes, these pathological erythrocytes have a shorter lifespan and break down more quickly (called haemolysis). This typically leads to chronic haemolytic anaemia [7]. In addition, sickle cells are less flexible, which increases the viscosity of blood and results in recurrent and often painful vascular occlusion.

The severity of SCD and the onset of symptoms and complications vary [1, 6, 8, 9]. Most of the haemoglobin formed in a foetus is foetal haemoglobin F (HbF), which does not consist of 2 α-globins and 2 β-globins like HbA, but of 2 α-globins and 2 γ-globins; therefore, due to a mutation in the gene for β-globin, SCD manifests only after birth, when the prenatally dominant

HbF is increasingly replaced by HbS [10]. From about the 3rd month of life, the concentration of HbS is high enough to potentially cause symptoms.

Haemolytic anaemia, high blood viscosity, and vaso-occlusion result in reduced oxygen supply to the tissues. Chronic damage to almost all organs may result [1, 6, 11]. Acute organ complications include cerebral infarction, acute chest syndrome, kidney failure, splenic infarction, splenic sequestration, sepsis, and aplastic anaemia. Dehydration, hypoxia, fever, and infections can trigger symptoms and complications [6, 9].

Treatment approaches aim to prevent vaso-occlusive crises and eliminate the factors which trigger symptoms and complications [12–16]. The German guideline from the Consortium of the German Society for Paediatric Oncology and Haematology (GPOH) recommends not only preventive behavioural measures for SCD treatment [9], such as providing education on the signs of acute complications and instructions on how to behave (also see [12]), infection prevention including vaccinations (also see [13–16]), but also lifelong, structured long-term monitoring and treatment of people with SCD [9]. The administration of hydroxycarbamide [17, 18], preoperative transfusions before major surgeries, if necessary [19], transfusions to prevent or treat complications [20, 21], and as a curative approach, stem cell transplantation, are recommended.

SCD can be diagnosed with a blood sample. Biochemical methods (such as isoelectric focusing [IEF], capillary electrophoresis [CE], and high-performance liquid chromatography [HPLC]) are used to analyse haemoglobin molecules following biochemical lysis. Newer procedures include mass spectroscopy and molecular genetic analysis of the gene encoding β-globin [1, 22]. Dried blood spots on filter paper can be used for SCD diagnostics. In the German expanded newborn screening programme performed in accordance with the G-BA's paediatric guideline [23], in the 36th to 72nd hour of life, a blood sample is taken of the newborn from a vein or the heel, dripped onto filter paper cards and examined for various diseases. SCD is not among the diseases tested in the expanded newborn screening. According to a survey using routine data of children from the 2009 and 2010 birth cohorts insured by the AOK, only 15.4% were diagnosed early, i.e. in the 1st or 2nd quarter year of life. The median age at diagnosis is currently the 7th quarter year of life [4].

The objective of newborn screening for SCD is to identify and treat children earlier. Newborn screening for SCD has been established in the USA [24], England [25], France [26], Spain [27], the Netherlands [28], and Belgium [29].

2 Research question

The objective of this study is to assess the benefit of newborn screening for SCD. Newborn screening for SCD in combination with a shortened timeline until diagnosis and treatment was assessed in comparison with no screening with regard to patient-relevant outcomes.

3 Methods

Comparative studies of the screening chain were included in the benefit assessment. If such studies were not available or were of insufficient quantity or quality, comparative intervention studies at the start of therapy as well as studies on diagnostic quality were to be assessed as the individual components of the screening chain (linked evidence).

Comparative intervention studies of the screening chain

Newborns were the target population of the benefit assessment. The experimental intervention was newborn screening for SCD in combination with moving up the diagnosis and treatment. The comparator intervention was either the absence of a screening strategy or the issuance of a diagnosis without further interventions and treatment.

The study examined the following patient-relevant outcomes:

- mortality (overall survival, disease-specific survival)
- morbidity (e.g. pain, organ damage, developmental disorders and growth retardation, infections, hospital stays, impaired performance due to anaemia, breathing difficulty, and fatigue)
- adverse events
- health-related quality of life of the child

Randomized controlled trials (RCTs) were to be included in the benefit assessment. If RCT-based evidence was insufficient for the benefit assessment, non-randomized comparative intervention studies and comparative cohort studies (including retrospective studies or studies with historic control) were included. There were no restrictions regarding the study duration.

Studies on the start of treatment

Studies in patients with SCD were to be included in the assessment. Diagnoses issued for patients with an earlier start of treatment had to be transferable to the newborn screening situation. An earlier start of treatment was the intervention to be examined. A later start of treatment was the comparator intervention. The above-mentioned patient-relevant outcomes were to be examined. RCTs were to be included in the assessment. If the RCT-based evidence was insufficient for the assessment, non-randomized comparative intervention studies and comparative cohort studies (including retrospective studies or studies with historic control) were to be included. There were no restrictions regarding the study duration.

Studies on diagnostic quality

For the assessment of diagnostic quality, studies in newborns were additionally included. The index test was SCD screening using filter paper cards. The reference standard was genetic analyses as well as follow-up in case of negative findings. Diagnostic cross-sectional, cohort,

and case control studies from which it was possible to derive data for calculating diagnostic quality for SCD detection were included.

Information retrieval

A systematic search for primary literature was conducted in the databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews, and HTA Database.

The following sources of information and search techniques were additionally used: trial registries, documents sent by the G-BA, reviews of reference lists, and documents made available from hearing procedures.

Relevant studies on the screening chain were selected by 3 persons independently from one another. The results of the selection were summarized after the full text assessment. Relevant studies on diagnostic quality were selected by 2 reviewers independently from one another. Any discrepancies were resolved by discussion between the two reviewers.

Data were extracted into standardized tables. To assess the qualitative certainty of conclusions, the risk of bias at study and outcome levels was assessed and rated as high or low. The results of the individual studies were organized according to outcomes and described.

To the extent that the studies were comparable in terms of their research questions and relevant characteristics and no meaningful heterogeneity was observed, the results from individual studies were to be quantitatively combined in metaanalyses.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of these 3 scenarios. The latter was the case if no data were available or the available data did not permit classification into one of the 3 other categories. In that case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was to be drawn.

4 Results

4.1 Results of the comprehensive information retrieval

The information retrieval found 1 study (1 document) on the screening chain to be relevant for the research question of this benefit assessment (see Table 1).

No ongoing studies were identified. The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 24 April 2019.

Table 1: Study pool of the benefit assessment (comparative intervention studies of the screening chain)

Study	Available documents	
	Full publication (in professional journals)	Results report from the study registries
King 2007	Yes [30]	No

For the separate assessment of suitable diagnostic testing procedures, the information retrieval identified 8 studies (9 documents) as relevant (see Table 2). No ongoing studies were identified.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search for studies on diagnostic quality took place on 24 April 2019.

Table 2: Study pool on diagnostic quality (assessment of suitable testing procedures)

Study	Available documents	
	Full publication (in professional journals)	Results report from the study registries
Boemer 2006	Yes [31]	No
Boemer 2011	Yes [32]	No
Colombatti 2019	Yes [33]	No
Grosse 2016	Yes [34]	No
Kunz 2016	Yes [35]	No
Lin 2004	Yes [36]	No
Lobitz 2014	Yes [37, 38]	No
Lobitz 2018	Yes [39]	No

4.2 Comparative intervention studies of the screening chain

4.2.1 Characteristics of the studies included in the evaluation

As a comparative study of the screening chain, King 2007 [30] was found. The study describes an intervention programme for newborn screening for SCD in Jamaica and compares its results with those of a historic cohort reported in an observational study in the same geographic region, the Jamaican Sickle Cell Cohort Study [40, 41].

Three hospitals participated in the newborn screening for SCD intervention programme; between November 1995 and July 2006, they screened a total of 150 803 newborns for SCD and provided treatment to those with SCD-S/S diagnosis. Victoria Jubilee Hospital Kingston, the largest maternity hospital in Jamaica, screened newborns for SCD over the entire period, while 2 other hospitals in the Kingston region started screening in October 1997 and April 1998, respectively.

For the screening, umbilical cord blood was spotted onto a filter paper card at birth and transported to a central laboratory, the laboratory of the Kingston Sickle Cell Unit (SCU). Samples were first tested using haemoglobin electrophoresis on cellulose acetate. Suspicious samples were then analysed using agarose gel electrophoresis (King 2007 [30] with reference to Serjeant 1974 [42]). Whenever haemoglobinopathy was detected or samples were unsuitable or results unclear, parents were invited for definitive diagnostics. If the parents did not follow the invitation, a nurse visited the families and encouraged them to present the child to the SCU for definitive diagnostics.

According to the screening programme, differential and confirmatory diagnostic tests were to be performed in the 4th to 6th week of life. For children with a confirmed diagnosis of SCD-S/S, the intervention goal was enrolment in the further measures of the programme before the 4th month of life. This meant that parents were to present their children to an initial consultation at one of the participating hospitals before the 4th month of life. During the initial consultation, parents were educated about sickle cell disease and taught to palpate their child's spleen. From the 4th month of life, children were to receive penicillin prophylaxis and be examined on a routine basis every 3 months until the 5th year of life (every 6 months after the 5th year of life).

The parents of 40 out of the 435 newborns who had positive SCD-S/S screening results, had the disease confirmed in differential diagnostics, and were enrolled in the further intervention program failed to come in for initial consultation. For the purpose of evaluating the screening programme, the results of the remaining 395 newborns with SCD-S/S were analysed.

King 2007 compared the probability of survival of this SCD-S/S birth cohort enrolled in an intervention programme (intervention cohort) with the results of the first subpopulation of the Jamaican Sickle Cell Cohort Study (Serjeant 1993 [40], Lee 1995 [41]), which were reported in earlier publications.

The Jamaican Sickle Cell Cohort Study is an observational study, which was initiated to generate information on the clinical course of SCD. Between June 1973 and December 1981, the Victoria Jubilee Hospital Kingston examined 100 000 newborns for SCD. At birth, umbilical cord blood was collected and analysed by means of haemoglobin electrophoresis on cellulose acetate, with subsequent agarose gel electrophoresis of positive samples [42]. Over the entire period, 315 children were diagnosed with SCD-S/S; their results were presented in 3 subpopulations and analysed [30, 41].

At the start of the Jamaican Sickle Cell Cohort Study, little was known about factors potentially influencing the course of disease. Therefore, scientists compared 125 children with diagnosed SCD-S/S to a group without SCD. They analysed both groups in terms of mortality and morbidity [40], and this interim analysis revealed correlations between infections and severe complications of SCD. As a result, they developed interventions and tested them in the further course of the observational study. King 2007 reports that the introduction of parental education in 1979 was associated with a considerable reduction in lethality of acute splenic sequestration. Initial studies on infection prevention started in children aged 6 months and older in May 1978 [15]. The Jamaican Sickle Cell Cohort Study, which started as an observational study, incrementally developed into an interventional study. One hundred and five children with SCD-S/S from the 1st subpopulation, who were born and diagnosed between July 1973 and December 1975, remained untreated in their first few years of life and represent the comparator group for this benefit assessment.

4.2.2 Overview of assessment-relevant outcomes

Data on patient-relevant outcomes were extracted from King 2007. Table 3 presents an overview of the available data on patient-relevant outcomes from the included studies. Data were reported on the outcome of morbidity (hospital stays, "severe diseases", invasive pneumococcal diseases), but given their operationalization, they were not usable for the benefit assessment. No data were reported for the outcome of quality of life.

Table 3: Matrix of patient-relevant outcomes

Study	Outcomes		
	Mortality	**Morbidity**	**Health-related quality of life**
King 2007	●	○	-
● data on probability of survival reported and usable ○ data reported, but not usable for the benefit assessment - outcome not surveyed			

4.2.3 Assessment of the risk of bias at study and outcome levels

The comparative study of the screening chain (King 2007) was assessed as being associated with a high risk of bias. This was due to the historic control group and the lack of confounder control. Data were collected retrospectively from clinical practice; therefore, lack of blinding must be assumed. Furthermore, no information was available on baseline data, but they can be assumed to be comparable since the newborns were from the same region.

Since a high risk of bias at study level directly affects the risk of bias of all surveyed outcomes, the risk of bias at outcome level for mortality was also rated as high in King 2007.

4.2.4 Results on patient-relevant outcomes

For newborns with homozygous sickle cell disease (SCD-S/S), the results on mortality from the comparative study of the screening chain (King 2007) show a dramatic effect in favour of newborn screening for SCD in combination with earlier diagnosis and further interventions (intervention group) in comparison with no screening strategy or diagnosis without subsequent interventions (comparator group).

King 2007 reported the probability of survival up to the 1st, 2nd, 3rd, 5th, and 10th year of life. Before their 1st birthdays, 0.01% of newborns with SCD-S/S died in the intervention group versus 0.10% in the comparator group. A considerable group difference and dramatic effect were revealed with an odds ratio of 0.09 (95% CI [0.03; 0.30]) and a p-value of < 0.001. This results in a hint of benefit of newborn screening for SCD in combination with earlier diagnosis and further interventions in comparison with no screening.

Consistent effects were found for the analyses up to the 5th year of life. For the 2nd and 3rd year of life, the mortality rate was 0.01% in the intervention group versus a rise to 0.14% (2nd year of life) and 0.17% (3rd year of life) in the comparator group. The corresponding odds ratios for group difference were 0.06 (95% CI [0.02; 0.20]) up to the 2nd year of life and 0.04 (95% CI [0.02; 0.15]) up to the 3rd year of life, each with p-values < 0.001. The results up to the 5th year of life reveal a dramatic effect as well. The mortality rate was 0.02% in the intervention group and 0.19% in the comparator group. The odds ratio for group difference was 0.09 (95% CI [0.04; 0.22]) with a p-value < 0.001. The results on mortality rate up to the 10th year of life are not statistically significant. In the intervention group, 0.09% of newborns died, compared to 0.23% in the comparator group. The group difference has an odds ratio of 0.33 (95% CI [0.07; 1.64]) with a p-value of 0.176.

4.3 Studies on diagnostic quality

On the basis of the screening chain study included in the benefit assessment, it is not possible to draw a conclusion as to which diagnostic test methods are suitable for identifying newborns with SCD in the context of newborn screening performed in Germany. To assess suitable diagnostic test methods, studies on diagnostic quality were therefore additionally examined.

4.3.1 Characteristics of the studies included in the evaluation

Eight studies on diagnostic quality were included. All studies are cohort studies using a verification-of-only-positive testers (VOPT) design.

Boemer 2006 [31] describes the results of a newborn screening programme in Belgium from June 2003 through February 2005. Samples were taken 5 days after birth in the form of blood spots on filter paper. The authors analysed the data of 27 010 newborns tested for HbS and HbC by means of ELISA (enzyme-linked immunosorbent assay).

Boemer 2011 [32] is a 3-year experience report of the screening program in Belgium and reports the results of 43 736 newborns. Samples were taken in the form of blood spots on filter paper cards between the 3rd and 5th day of life, and the analyses for HbS, HbC, and β-thalassaemia were conducted using tandem mass spectrometry (MS/MS).

Colombatti 2019 [33] reported the results of 5439 newborns participating in newborn screening in 2 Italian regions between May 2016 and November 2017. Samples were taken in the form of blood spots on filter paper cards during or immediately after metabolic newborn screening. The authors analysed the samples by means of HPLC.

Grosse 2016 [34] described the results of newborn screening in Germany from January to July 2013 and November 2013 to May 2014. Sampling for HbS, HbC, and β-thalassaemia screening was performed in the first 36 to 72 hours after birth. The authors used HPLC for the analysis of blood spots on filter paper cards from 16 697 newborns.

Kunz 2016 [35] reported the results from 37 838 newborns who participated in newborn screening in Germany from October 2012 through February 2013. Sampling for HbS and β-thalassaemia screening was performed between the 36th and 72nd hour of life, with the analysis being performed with allele-specific polymerase chain reaction (PCR).

Lin 2004 [36] described the results of a US newborn screening programme with 1861 samples tested for HbS and HbC by means of IEF. No information was provided on the study period or the timing of the sampling.

Lobitz 2014 [37, 38] reported the results from 34 084 newborns who participated in newborn screening in Germany from September 2011 through November 2012. Samples were taken between the 36th and 72nd hour after birth in the form of blood spots on filter paper cards. The authors analysed the data by means of HPLC and capillary electrophoresis (CE) to screen for HbS, HbC and β-thalassaemia.

Lobitz 2018 [39] described the screening results of 29 079 newborns who were examined between November 2015 and September 2016 in Germany. The samples for HbS, HbC, and β-thalassaemia screening were taken between the 36th and 72nd hour after birth in the form of blood spots on filter paper cards and analysed by means of MS/MS and CE.

4.3.2 Available assessment-relevant outcomes

For the assessment of suitable diagnostic test methods, 8 studies on diagnostic quality [31–37, 39] were examined. Due to the consistent use of the VOPT design, only the positive predictive value (PPV) was available as a measure of diagnostic quality.

4.3.3 Assessment of the risk of bias and transferability

With respect to diagnostic quality, 7 out of 8 studies whose results were usable to assess suitable diagnostic test methods were rated as having a low risk of bias at study level. Lin 2004 [36] had

a high risk of bias at study level since there were uncertainties regarding patient selection as well as the index test. In 6 out of 8 studies, concerns regarding transferability were rated as low. In Boemer 2006 [31], concerns were rated as high since it is unclear whether the ELISA method it used is suitable for newborn screening for SCD; these doubts were raised because the employed antibodies do not differentiate between carrier status and disease, which other methods do. The index test used in Kunz 2016 [35] did not differentiate between carrier status and disease either.

4.3.4 Results on outcomes

The evidence from the 8 included studies was insufficient for calculating sensitivity and specificity. The PPVs of individual studies show that suitable test methods are available for identifying children with SCD.

In 2 studies [32, 39], the MS/MS procedure was used to analyse the blood spots on filter cards. There were no false positive results (PPV 100; 95% CI: [78.5 and 64.6, respectively; 100]). Three further studies [33, 34, 37] using HPLC analysis reported no false positive results either (PPV 100; 95% CI: [51.0, 64.6, and 78.5, respectively; 100]). In Lin 2004 [36], the IEF method did not generate any false positive results (PPV 100; 95% CI: [20.7; 100] with one positively tested newborn). The ELISA technique [31] (PPV 2.4; 95% CI: [0.8; 6.8]) and PCR analysis [35] (PPV 3.2; 95% CI: [1.1; 9.0]) revealed false positive newborns in the 2 included studies; this is particularly due to the fact that these test methods show positive results not only in case of disease, but also for carriers.

Given the small number of examined newborns in each study, PPV is of very little informative value, however. Due to the different index tests, it is not possible to calculate a pooled effect.

4.4 Evidence map

In light of the limited amount of evidence, no evidence map was created.

The results on the outcome of mortality show a hint of benefit of newborn screening for SCD in combination with earlier diagnosis and treatment in comparison with no SCD screening.

The results of the studies on diagnostic quality [32–34, 36, 37, 39] used for supplementary information show that the MS/MS method and HPLC are suitable for identifying newborns with SCD. Data on the number of false negative results are not available.

5 Classification of the assessment result

The results of this benefit assessment are based on 1 retrospective screening study with historical control; however, this single study reveals a dramatically high effect of the intervention. The study (King 2007) evaluated an SCD screening programme in Jamaica. The Jamaican screening program includes measures for infection prevention and parental education. These measures are also recommended as essential components of the early treatment of newborns with SCD in established guidelines of Western industrial nations [9, 43–45]. Furthermore, the basic medical care for acute complications – today and at the time the study was conducted – includes immediate antibiotic treatment in the presence of fever and a blood transfusion in case of enlarged spleen or low haemoglobin values. Therefore, the observations can be assumed to be transferable from Jamaica to Germany.

Since the test method used in King 2007 no longer meets current laboratory standards, transferability to the German healthcare system was put into question. Therefore, the diagnostic quality of the most common test procedures was also examined as supplementary information.

Established diagnostic tests for SCD exist and are suitable for being integrated into the German newborn screening programme. Newborns with positive screening results, for instance from MS/MS or HPLC, did in fact have SCD since these studies did not report any false positive results. Since test accuracy can be influenced by a variety of factors, laboratory staff training, laboratory standards, and defined minimum quantities of sample material for analysis are essential aspects in the nationwide application of such screening.

All examined tests also identified heterozygous carriers. Carriers do not manifest SCD. Collecting information on carrier status as part of a health screening is problematic in terms of §16 of the German Genetic Diagnostics Act since, according to the justification of the law, screening for carriers of recessive disorders is purportedly unlawful [46].

According to a written opinion provided as part of the introduction of SCD screening, it is important to ensure appropriate qualification and sensitization of healthcare providers as well as appropriately designed tutorials for family members. In April 2017, a consensus meeting of European experts (EuroBloodNet) already took place, which, among other things, discussed the organization and methods of SCD screening and specified recommendations [47]. In late 2016, a patient registry was initiated by the GPOH consortium for sickle cell disease in an effort to provide better care to affected patients in the long term [48]. At the paediatric after-care clinic *Kindernachsorgeklinik Berlin-Brandenburg gGmbH*, a model project for family-oriented rehabilitation for children and adolescents with SCD and their family members has been ongoing since 2016 [49].

There is no sign of publication bias in the available data.

6 Conclusion

In terms of the prevention of deaths of affected children, there is a hint of benefit in favour of newborn screening for SCD, if followed by further interventions such as education of family members and infection prevention, in comparison with no screening. This hint of benefit is based on 1 retrospective, historical-comparative screening study showing a dramatically high effect of the intervention, despite being associated with a high risk of bias regarding the results. No ongoing studies on the screening chain were found.

To answer the question of which diagnostic test methods are suitable for SCD screening in Germany, studies on diagnostic quality were examined as supplementary information. The evidence from these studies was insufficient for calculating sensitivity and specificity. The PPVs of some studies show, however, that there are suitable test methods for identifying newborns with SCD (all babies identified by means of tandem mass spectrometry and HPLC really had SCD).

7 References for English extract

Please see full final report for full reference list.

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The full report (German version) is published under
https://www.iqwig.de/de/projekte-ergebnisse/projekte/nichtmedikamentoese-verfahren/s-projekte/s18-01-screening-auf-sichelzellkrankheit-bei-neugeborenen.9543.html

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

A.1.1 Comparative intervention studies of the screening chain

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to April Week 2 2019
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to April 22
- Ovid MEDLINE(R) Daily Update April 22, 2019
- Ovid MEDLINE(R) Epub Ahead of Print April 22, 2019

#	**Searches**
1	exp Anemia, Sickle Cell/
2	Hemoglobinopathies/
3	(sickle cell* adj3 (disease* or anemia* or anaemia*)).ti,ab.
4	(hemoglobinopath* or haemoglobinopath*).ti,ab.
5	((hemoglobin* or haemoglobin*) adj1 SC*).ti,ab.
6	or/1-5
7	exp Infant/
8	(newborn* or neonat* or pediatric* or infant*).ti,ab.
9	or/7-8
10	Neonatal Screening/
11	and/6,10
12	*Mass Screening/
13	screen*.ti,ab.
14	or/12-13
15	and/6,9,14
16	or/11,15
17	16 not (comment or editorial).pt.
18	17 not (exp animals/ not humans.sh.)

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process

- PubMed – pubmednotmedline

Search	Query
#1	Search (sickle cell* [TIAB] AND (disease* [TIAB] OR anemia* [TIAB] OR anaemia* [TIAB]))
#2	Search (hemoglobinopath* [TIAB] OR haemoglobinopath* [TIAB])
#3	Search ((hemoglobin* [TIAB] OR haemoglobin* [TIAB]) AND SC*[TIAB])
#4	Search (#1 OR #2 OR #3)
#5	Search (newborn* [TIAB] OR neonat* [TIAB] OR pediatric* [TIAB] OR infant* [TIAB])
#6	Search screen*[TIAB]
#7	Search (#4 AND #5 AND #6)
#8	Search (#7 NOT medline[SB])

3. Embase

Search interface: Ovid

- Embase 1974 to 2019 April 22

#	Searches
1	(sickle cell* adj3 (disease* or anemia* or anaemia*)).ti,ab.
2	(hemoglobinopath* or haemoglobinopath*).ti,ab.
3	((hemoglobin* or haemoglobin*) adj1 SC*).ti,ab.
4	or/1-3
5	exp infant/
6	(newborn* or neonat* or pediatric* or infant*).ti,ab.
7	or/5-6
8	newborn screening/
9	and/4,8
10	screen*.ti,ab.
11	and/4,7,10
12	or/9,11
13	12 not medline.cr.
14	13 not (exp animal/ not exp humans/)
15	14 not (Conference Abstract or Conference Review or Editorial).pt.

4. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 4 of 12, April 2019
- Cochrane Central Register of Controlled Trials: Issue 4 of 12, April 2019

ID	Search
#1	[mh "Anemia, Sickle Cell"]
#2	[mh ^Hemoglobinopathies]
#3	(sickle cell* near/3 (disease* or anemia* or aenemia*)):ti,ab
#4	(hemoglobinopath* or haemoglobinopath*):ti,ab
#5	((hemoglobin* or haemoglobin*) near/1 SC*):ti,ab
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	[mh Infant]
#8	(newborn* or neonat* or pediatric* or infant*):ti,ab
#9	#7 OR #8
#10	[mh ^"Neonatal Screening"]
#11	#6 AND #10
#12	[mh ^"Mass Screening" [mj]]
#13	screen*:ti,ab
#14	#12 OR #13
#15	#6 AND #9 AND #14
#16	#11 OR #15 in Cochrane Reviews, Cochrane Protocols, Trials

5. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	(MeSH DESCRIPTOR Anemia, Sickle Cell EXPLODE ALL TREES)
2	(MeSH DESCRIPTOR Hemoglobinopathies)
3	(sickle cell* AND (disease* or anemia* or anaemia*))
4	(hemoglobinopath* OR haemoglobinopath*)
5	((hemoglobin* OR haemoglobin*) AND SC*)
6	(#1 OR #2 OR #3 OR #4 OR #5)
7	(MeSH DESCRIPTOR infant EXPLODE ALL TREES)
8	(newborn* or neonat* or pediatric* or infant*)
9	(#7 OR #8)
10	(MeSH DESCRIPTOR neonatal screening)

Line	Search
11	(#6 AND #10)
12	(MeSH DESCRIPTOR Mass Screening)
13	(screen*)
14	#12 OR #13
15	#6 AND #9 AND #14
16	#11 OR #15
17	(#16) IN HTA

A.1.2 Studies on diagnostic accuracy

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to April Week 2 2019
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to April 22, 2019
- Ovid MEDLINE(R) Daily Update April 22, 2019
- Ovid MEDLINE(R) Epub Ahead of Print April 22, 2019

The following filters were adopted:

- Systematic Review: Wong [50] – High specificity strategy
- Corrao [51] – Optimized search strategy for detecting scientifically strong studies on treatment through PubMed

#	Searches
1	exp Anemia, Sickle Cell/
2	Hemoglobinopathies/
3	(sickle cell* adj3 (disease* or anemia* or anaemia*)).ti,ab.
4	(hemoglobinopath* or haemoglobinopath*).ti,ab.
5	((hemoglobin* or haemoglobin*) adj1 SC*).ti,ab.
6	or/1-5
7	exp Infant/
8	(newborn* or neonat* or pediatric* or infant*).ti,ab.
9	or/7-8
10	Chromatography, High Pressure Liquid/
11	(high* adj2 liquid chromatograph*).ti,ab.
12	hplc*.ti,ab.

#	Searches
13	exp Electrophoresis/
14	electrophoresis*.ti,ab.
15	isoelectric focusing*.ti,ab.
16	exp Mass Spectrometry/
17	mass spectrometr*.ti,ab.
18	or/10-17
19	and/6,9,18
20	19 not review.pt.
21	cochrane database of systematic reviews.jn.
22	(search or MEDLINE or systematic review).tw.
23	meta analysis.pt.
24	or/21-23
25	and/19,24
26	or/20,25
27	26 not (comment or editorial).pt.
28	27 not (exp animals/ not humans.sh.)

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search (sickle cell* [TIAB] AND (disease* [TIAB] OR anemia* [TIAB] OR anaemia* [TIAB]))
#2	Search (hemoglobinopath* [TIAB] OR haemoglobinopath* [TIAB])
#3	Search ((hemoglobin* [TIAB] OR haemoglobin* [TIAB]) AND SC*[TIAB])
#4	Search (#1 OR #2 OR #3)
#5	Search (newborn* [TIAB] OR neonat* [TIAB] OR pediatric* [TIAB] OR infant* [TIAB])
#6	Search (high* [TIAB] AND liquid chromatograph* [TIAB])
#7	Search hplc*[TIAB]
#8	Search electrophoresis*[TIAB]
#9	Search isoelectric focusing*[TIAB]

Search	Query
#10	Search mass spectrometr*[TIAB]
#11	Search (#6 OR #7 OR #8 OR #9 OR #10)
#12	Search (#4 AND #5 AND #11)
#13	Search (#12 NOT medline[SB])

3. Embase

Search interface: Ovid

- Embase 1974 to 2019 April 22

#	Searches
1	sickle cell anemia/
2	hemoglobinopathy/
3	(sickle cell* adj3 (disease* or anemia* or anaemia*)).ti,ab.
4	(hemoglobinopath* or haemoglobinopath*).ti,ab.
5	((hemoglobin* or haemoglobin*) adj1 SC*).ti,ab.
6	or/1-5
7	exp infant/
8	(newborn* or neonat* or pediatric* or infant*).ti,ab.
9	or/7-8
10	high performance liquid chromatography/
11	(high* adj2 liquid chromatograph*).ti,ab.
12	HPLC*.ti,ab.
13	exp electrophoresis/
14	electrophoresis*.ti,ab.
15	isoelectric focusing*.ti,ab.
16	exp mass spectrometry/
17	mass spectrometr*.ti,ab.
18	or/10-17
19	and/6,9,18
20	19 not medline.cr.
21	20 not (exp animal/ not exp humans/)
22	21 not (Conference Abstract or Conference Review or Editorial).pt.

4. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 4 of 12, April 2019
- Cochrane Central Register of Controlled Trials: Issue 4 of 12, April 2019

ID	Search
#1	[mh "Anemia, Sickle Cell"]
#2	[mh ^Hemoglobinopathies]
#3	(sickle cell* near/3 (disease* or anemia* or aenemia*)):ti,ab
#4	(hemoglobinopath* or haemoglobinopath*):ti,ab
#5	((hemoglobin* or haemoglobin*) near/1 SC*):ti,ab
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	[mh Infant]
#8	(newborn* or neonat* or pediatric* or infant*):ti,ab
#9	#7 OR #8
#10	[mh ^"Chromatography, High Pressure Liquid"]
#11	(high near/2 liquid chromatograph*):ti,ab
#12	hplc*:ti,ab
#13	[mh Electrophoresis]
#14	electrophoresis*:ti,ab
#15	isoelectric focusing*:ti,ab
#16	[mh "Mass Spectrometry"]
#17	mass spectrometr*:ti,ab
#18	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	#6 AND #9 AND #18 in Cochrane Reviews, Cochrane Protocols, Trials

5. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	(MeSH DESCRIPTOR Anemia, Sickle Cell EXPLODE ALL TREES)
2	(MeSH DESCRIPTOR Hemoglobinopathies)
3	(sickle cell* AND (disease* or anemia* or anaemia*))
4	(hemoglobinopath* OR haemoglobinopath*)
5	((hemoglobin* OR haemoglobin*) AND SC*)
6	(#1 OR #2 OR #3 OR #4 OR #5)
7	(MeSH DESCRIPTOR infant EXPLODE ALL TREES)

Line	Search
8	(newborn* or neonat* or pediatric* or infant*)
9	(#7 OR #8)
10	(MeSH DESCRIPTOR Chromatography, High Pressure Liquid)
11	(high AND liquid chromatograph*)
12	(hplc*)
13	(MeSH DESCRIPTOR electrophoresis EXPLODE ALL TREES)
14	(electrophoresis*)
15	(isoelectric focusing*)
16	(MeSH DESCRIPTOR Mass Spectrometry EXPLODE ALL TREES)
17	(mass spectrometr*)
18	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19	(#6 AND #9 AND #18) IN HTA

A.2 – Searches in study registries

A.2.1 Comparative intervention studies of the screening chain

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
(sickle cell OR hemoglobinopathy OR hemoglobin sc disease) AND (screening OR chromatography OR hplc OR electrophoresis OR isoelectric focusing OR mass spectrometry)

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
("sickle cell" OR hemoglobinopath* OR haemoglobinopath* OR "hemoglobin sc" OR "haemoglobin sc") AND (screening OR chromatography OR hplc OR electrophoresis OR "isoelectric focusing" OR "mass spectrometry")

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategies
sickle cell AND screening OR sickle cell AND chromatography OR sickle cell AND hplc OR sickle cell AND electrophoresis OR sickle cell AND isoelectric focusing OR sickle cell AND mass spectrometry
hemoglobin* AND screening OR hemoglobin* AND chromatography OR hemoglobin* AND hplc OR hemoglobin* AND electrophoresis OR hemoglobin* AND isoelectric focusing OR hemoglobin* AND mass spectrometry
haemoglobin* AND screening OR haemoglobin* AND chromatography OR haemoglobin* AND hplc OR haemoglobin* AND electrophoresis OR haemoglobin* AND isoelectric focusing OR haemoglobin* AND mass spectrometry

A.2.2 Studies on diagnostic accuracy

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
(sickle cell OR hemoglobinopathy OR hemoglobin sc disease) AND (screening OR chromatography OR hplc OR electrophoresis OR isoelectric focusing OR mass spectrometry)

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
("sickle cell" OR hemoglobinopath* OR haemoglobinopath* OR "hemoglobin sc" OR "haemoglobin sc") AND (screening OR chromatography OR hplc OR electrophoresis OR "isoelectric focusing" OR "mass spectrometry")

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategies
sickle cell AND screening OR sickle cell AND chromatography OR sickle cell AND hplc OR sickle cell AND electrophoresis OR sickle cell AND isoelectric focusing OR sickle cell AND mass spectrometry
hemoglobin* AND screening OR hemoglobin* AND chromatography OR hemoglobin* AND hplc OR hemoglobin* AND electrophoresis OR hemoglobin* AND isoelectric focusing OR hemoglobin* AND mass spectrometry
haemoglobin* AND screening OR haemoglobin* AND chromatography OR haemoglobin* AND hplc OR haemoglobin* AND electrophoresis OR haemoglobin* AND isoelectric focusing OR haemoglobin* AND mass spectrometry