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Newborn screening for tyrosinaemia type 1 using tandem mass spectrometry[1]

Extract

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The responsibility for the contents of the report lies solely with IQWiG.

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Key statement

Research question

The goal of this investigation was the benefit assessment of newborn screening for tyrosinaemia type 1 using tandem mass spectrometry in comparison with no screening regarding patient-relevant outcomes.

Conclusions

Since no comparative cohort studies were available that compared screening versus no screening, the diagnostic accuracy of the screening test and the benefit of earlier treatment were examined. The results of only one diagnostic accuracy study and 3 retrospective comparative cohort studies contained results relevant for this report. The study results show no dramatic effect, which would be necessary to demonstrate the benefit due to the low certainty of results.

The benefit or harm of newborn screening for tyrosinaemia type 1 using tandem mass spectrometry are unclear due to the limited informative value of the available evidence.

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Abbreviation	Meaning
FAA	fumarylacetoacetase
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MS/MS	tandem mass spectrometry
NTBC	nitisonone
PPV	positive predictive value
SA	succinylacetone

1 Background

This assessment focuses on newborn screening for tyrosinaemia type 1. Worldwide, 0.9 of 100 000 children are born with this rare inherited metabolic disorder [1]. In Germany, 25 cases with the disorder (ICD-10 E70.2[3]) were treated on an inpatient basis in 2013 [2]. The disorder manifests in early infancy or childhood, particularly in the form of severe liver and kidney damage. It is distinguished from other, even rarer types of tyrosinaemia (types 2 and 3) [1].

In tyrosinaemia type 1, a gene mutation causes problems in tyrosine breakdown and leads to the formation of harmful metabolic products: There are at least 40 autosomal recessive mutations that can lead to a deficiency of the enzyme fumarylacetoacetase (FAA) [3,4]. FAA is necessary for the last step in the degradation pathway of the amino acid tyrosine. In the absence of this enzyme, the toxic substances succinylacetone (SA), succinylacetate and maleylacetoacetate are formed. They can cause various acute, subacute and chronic manifestations by severely damaging the liver, kidney, brain and/or nervous system [4-8].

Various laboratory chemical methods are available for diagnosing tyrosinaemia type 1 on the basis of blood or urine samples. In some countries, tyrosine levels are currently or were in the past measured in the first few days of life in the context of regular screening. However, tyrosine levels are not necessarily elevated (yet) at this early stage [4,6,8]. Therefore, false negative results were common [5,9,10], and another approach was developed [11,12]. This screening test is based on measuring the SA levels in (dried) blood samples. Since SA is only formed in case of insufficient levels of the enzyme FAA, elevated SA levels are considered pathognomonic for tyrosinaemia [3,9,13,14]. In Germany, if tyrosinaemia is suspected, the diagnosis is therefore currently established by the detection of SA in (dried) blood and/or urine [4]. The initial diagnosis can also be established by detecting gene mutations, but this is not widely done in practice [3,4]. Positive findings are confirmed by gene analysis [6].

Tyrosinaemia type 1 may be acute (neonatal), subacute or chronic (infantile). In the acute and subacute types, vomiting, bleeding, sepsis, hypoglycaemia, renal tubulopathy and acute liver failure may arise in the first few months of life. Chronic tyrosinaemia type 1 may also clinically manifest later, in the course of the first few years of life, in the form of hepatomegaly, hepatic cirrhosis, growth disorders, rickets, haematoma, tubulopathy and neuropathy as well as neurologic crises. The risk of hepatocellular carcinoma (HCC) increases as well [6]. In untreated children who develop symptoms before the 2nd month of life, a 2-year survival rate of 29% was observed [15]. Generally, survival rates are thought to be lower the earlier symptoms arise [7,15].

[3] 10th revision of the International Statistical Classification of Diseases and Related Health Problems, disorders of tyrosine metabolism.

In addition to a low-protein diet, treatment can include the administration of nitisonone (NTBC). Since this drug has become available, liver and kidney transplantation have played a lesser role, but some patients may still require them [6,7].

In Germany, expanded newborn screening is performed according to the Paediatric Directive ("Kinder-Richtlinie"). This screening allows the early diagnosis of diseases that "significantly threaten the physical and mental development of children" (Appendix 2, §1 [16]). The Paediatric Directive [16] defines the target diseases of the screening as well as the tests to be used for each disease. According to the Directive, the blood of the newborn is placed on filter paper and allowed to dry. The analysis is performed using conventional laboratory techniques as well as tandem mass spectrometry (MS/MS). Currently, the Directive does not specify tyrosinaemia type 1 as a target disease. With MS/MS, however, the concentration of biochemical markers for tyrosinaemia type 1 could be determined.

Newborn screening is intended to allow the immediate treatment start in affected children (Appendix 2, §1 [16]). Early diagnosis and the immediate start of treatment can particularly prevent liver and kidney damage in patients with tyrosinaemia type 1, thereby reducing the risk of organ failure and transplantation as well as the risk of death.

2 Research question

The goal of this investigation was the benefit assessment of newborn screening for tyrosinaemia type 1 using tandem mass spectrometry in comparison with no screening regarding patient-relevant outcomes.

3 Methods

The benefit of newborn screening for tyrosinaemia type 1 could be demonstrated in 2 ways: First, it could be assessed on the basis of comparative intervention studies of the entire screening chain, taking into account patient-relevant outcomes. Second, the individual components of the screening chain could be assessed, which was done in this benefit assessment. Comparative studies on treatment start and studies on diagnostic accuracy were used for this purpose.

The target population of studies on treatment start were patients with tyrosinaemia type 1. The test intervention was an earlier treatment start. The comparator intervention was a later treatment start. The diagnosis for patients with earlier treatment start had to be transferable to the screening situation. This means that patients had to have been identified by the newborn screening and/or treatment had to have started in the first month of life. The employed interventions had to conform to the current treatment standard in terms of their type (NTBC) and time of start (no more than 2 months after diagnosis).

The following patient-relevant outcomes were considered in the investigation:

- mortality (overall survival, disease-specific survival)
- morbidity (e.g., liver failure, liver transplantation, hepatocellular carcinoma, neurologic crises)
- hospitalizations
- developmental disorders (e.g., disorders of cognitive, psychosocial, emotional, gross motor and fine motor development)
- adverse events
- health-related quality of life of the child (measured by proxy ratings, for instance)

Comparative cohort studies (including retrospective studies or those with historical comparison) comparing earlier with later treatment start were included in the benefit assessment. There were no limitations regarding the study duration.

In studies on diagnostic accuracy, newborns were the target population. The index test was the determination of the SA concentration of blood samples on filter paper by means of MS/MS. The reference tests were gene analysis and/or follow-up in case of normal findings. Outcomes included patient-specific data for calculating diagnostic accuracy. Diagnostic cohort and case-control studies were included.

A systematic literature search for primary literature was performed in the databases MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In parallel, relevant systematic reviews were searched in the databases MEDLINE, Embase, the Cochrane

Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database.

Furthermore, systematic reviews and publicly accessible trial registries were searched, and documents sent by the Federal Joint Committee (G-BA) and documents provided in the hearing procedure for the preliminary report plan were screened. In addition, the authors of relevant study publications were contacted in order to clarify important questions.

The selection of relevant studies was performed by 2 reviewers independently of each other. Data extraction was conducted in standardized tables. To evaluate the qualitative certainty of results, the risk of bias at the study and outcome levels was assessed and rated as low or high. The results of the individual studies were described, organized by outcomes.

No additional statistical analysis was performed.

For each outcome, a conclusion was drawn on the probability of benefit and harm by grading into 4 categories based on the certainty of conclusions: The evidence is considered either “proof” (highest certainty level), an “indication” (moderate certainty), a “hint” (lowest certainty) or none of these 3. The latter is the case if no data are available or if conclusions 1 to 3 cannot be drawn on the basis of the available data. In that case, the conclusion “there is no hint of a benefit or harm” is drawn.

4 Results

4.1 Results of the information retrieval

The systematic literature search in the bibliographical databases resulted in 7 publications on 6 studies that met the inclusion criteria defined for this report. The last search was performed on 14 June 2016.

No additional relevant documents or studies were identified by the search in further sources.

One study on the treatment of tyrosinaemia was identified whose relevance could not be conclusively determined. No ongoing studies were identified.

No comparative intervention study was available on the screening chain. In total, 5 studies (5 documents) on the treatment start and one study on diagnostic accuracy (2 documents) were therefore identified as relevant for the research question of this benefit assessment.

4.2 Characteristics of the studies included in the assessment

The studies comparing earlier versus later treatment start and the study on diagnostic accuracy are briefly outlined below. In all included studies on treatment start, patients were treated with NTBC.

Bartlett 2014 retrospectively analysed all 38 patients who were treated at a Birmingham hospital between 1989 and 2009. Earlier and later treatment start were compared, but the publication included inconsistent information on age at treatment start and at diagnosis (treatment allegedly started before diagnosis in 4 patients). This inconsistency could not be clarified by an enquiry to the author. Therefore, the results were not used in the benefit assessment.

Larochelle 2012 described 78 patients with tyrosinaemia type 1 who were diagnosed by newborn screening in Canada. Patients were classified into groups according to the start of NTBC treatment. Treatment started by the 30th day of life in 24 patients and later in 26 patients. Twenty-eight patients were not treated with NTBC and were irrelevant for the benefit assessment. The groups were compared with one another, and individual patient data were provided as well. Patients were followed until liver transplantation or for 5 years up to database closure (1 August 2009). Among the patients who started NTBC treatment after the 30th day of life, 22 of 26 received dietary treatment before NTBC treatment for about 2 to 85 months, while 4 patients were not treated despite diagnosis. It is possible that NTBC was not yet available at that time. In only 3 of the 26 patients who started treatment after the 30th day of life, the diagnosis and start of NTBC treatment were separated by a maximum period of 2 months. The relevant comparator group therefore included 3 patients. The relevant intervention group included 24 patients. Relevant results were those on mortality, liver transplantation, neurologic crises, kidney failure, hospitalization due to tyrosinaemia and

adverse events in the form of photophobia. HCC and liver failure were only presented for patients receiving a liver transplantation.

Masurel-Paulet 2008 retrospectively described all 46 accessible tyrosinaemia patients who were treated in France. While they compared earlier versus later treatment start, earlier treatment could start as late as in the 6th month after birth in this publication. This did not correspond to the test intervention defined for the benefit assessment. However, patient-specific information was provided as well. On its basis, patients could be grouped as needed for the benefit assessment: In 3 patients, NTBC treatment was started in the first month after birth, while it was started later in 39 patients. The mean treatment duration was 4.9 years. HCC, liver transplantation and adverse events were reported. Mortality could be derived.

In **Mayorandan 2014**, questionnaires were sent to 22 metabolism centres in Europe, Turkey and Israel; 21 of these centres also provided individual data for 168 patients. These data were used to group patients by age at the start of treatment, among other things, and compare them. Information was missing on the follow-up period per group and completeness of the cohort. Therefore, the data could not be used.

In **McKiernan 2015**, 12 patients diagnosed by screening and treated with NTBC were compared with 5 siblings who suffered from the disease. In the case of one of the siblings, NTBC was not yet available; this sibling was therefore not included in the benefit assessment. Among the patients diagnosed by screening, 2 of 12 were treated with NTBC after the first month of life and were therefore also assigned to the patient group with later treatment start (comparator group). For the benefit assessment, it included 6 patients, while the intervention group included 10. The patients were followed for at least 4.5 years, and liver transplantation, liver failure and deaths were reported. The completeness of the cohort and its composition could not be estimated.

The diagnostic cohort study **La Marca 2011** reported on results from a newborn screening programme in Tuscany, Italy. From 2007 onward, the SA content of blood samples on filter paper was determined for 136 075 newborns. Positive test results (total of n=2) were verified by gene analysis. For negative results, no systematic follow-up and no reference test were described, with the consequence that the data only permit calculating the positive predictive value (PPV).

4.3 Overview of the available assessment-relevant outcomes

Data on patient-relevant outcomes could be extracted from 3 of 5 **studies comparing earlier versus later treatment start**. Table 1 shows an overview of the available data on patient-relevant outcomes from the included studies. Data on the outcomes of developmental disorders and health-related quality of life could not be used from any study.

Relevant data on mortality and liver transplantation could be extracted from the 3 publications. **Masurel-Paulet 2008** also contained usable data on HCC. Adverse events were

only described across all patients and could therefore not be used. Liver failure data were extracted from **McKiernan 2015**. **Larochelle 2012** also provided usable data on neurologic crises, kidney failure, hospitalizations and adverse events.

Table 1: Matrix of existing and applicable outcomes of the studies on treatment start

Study	Outcomes										
	Morbidity										
	Mortality	Liver failure	Liver transplantation	HCC	Neurologic crises	Epilepsy	Kidney failure	Hospitalizations	Developmental disorders	Adverse events	Health-related quality of life as well as psychosocial aspects
Bartlett 2014											
Larochelle 2012	●		●		●		●	●		●	
Masurel-Paulet 2008	●		●	●							
Mayorandan 2014											
McKiernan 2015	●	●	●								
HCC: hepatocellular carcinoma											

Since in the **La Marca 2011 study on diagnostic accuracy**, only positive test results were verified, only the PPV could be calculated as a measure of diagnostic accuracy.

4.4 Assessment of the risk of bias at study level and outcome level

The studies comparing earlier versus later treatment start that were relevant for the benefit assessment were assessed to have a high risk of bias since they were non-randomized, among other things.

The La Marca study on diagnostic accuracy was assessed to have a high risk of bias. This was due to missing data on patient selection and on the index test as well as an insufficient description of the patient flow and chronological sequence.

4.5 Results on patient-relevant outcomes

The results on patient-relevant outcomes from the studies on treatment start are described below.

4.5.1 Results on mortality

Data were available from 3 studies. None of the 24, 3 and 10 patients who started treatment early (intervention group) died. Among the patients with later treatment start (comparator group), 0 of 3 patients, 1 of 39 patients and 1 of 6 patients (0%, 3% and 17%) died. This clearly does not represent a dramatic effect. No effect measures were calculated.

4.5.2 Results on liver failure

Data were available from one study. None of the patients in the intervention group (0 of 10) were reported to have had liver failure. In the comparator group, 3 of 6 patients (50%) had liver failure. Clearly, this does not represent a dramatic effect, particularly in consideration of the low number of patients. No effect measures were calculated.

4.5.3 Results on liver transplantation

Data were available from 3 studies. Liver transplantation was necessary in 0 of 3 patients, 2 of 39 patients and 1 of 6 patients (0%, 5% and 17%) in the comparator groups. No liver transplantation was reported in the intervention groups (0 of 24 patients, 0 of 3 patients and 0 of 10 patients). This clearly does not represent a dramatic effect. No effect measures were calculated.

4.5.4 Results on HCC

Data were available from one study. HCC was diagnosed in none of the patients of the intervention group (0 of 3 patients) and in 1 of 39 patients (3%) of the comparator group. This clearly does not represent a dramatic effect. No effect measures were calculated.

4.5.5 Results on neurologic crises

Data were available from one study. Neurologic crises were reported in none of the patients of the intervention group (0 of 24 patients; 0%) and in none of the patients of the comparator group (0 of 3 patients; 0%). This clearly does not represent a dramatic effect. No effect measures were calculated.

4.5.6 Results on kidney failure

Data were available from one study. Kidney failure was reported in none of the patients of the intervention group (0 of 24 patients; 0%) and in none of the patients of the comparator group (0 of 3 patients; 0%). This clearly does not represent a dramatic effect. No effect measures were calculated.

4.5.7 Results on hospitalizations

Data were available from one study. Hospitalization due to tyrosinaemia type 1 was necessary in none of the patients of the intervention group (0 of 24 patients; 0%) and in none of the patients of the comparator group (0 of 3 patients; 0%). This clearly does not represent a dramatic effect. No effect measures were calculated.

4.5.8 Results on adverse events

Data were available from one study. Adverse events in the form of photophobia were reported in none of the patients in the intervention group (0 of 24 patients; 0%) and in none of the patients in the comparator group (0 of 3 patients; 0%). This clearly does not represent a dramatic effect. No effect measures were calculated.

4.5.9 Results on diagnostic accuracy

On the basis of **La Marca 2011**, a PPV of 100% was calculated for the index test (95% confidence interval: [15.8%; 100%], with 2 positive test results). Sensitivity and specificity could not be calculated because necessary information was missing. Neither sensitivity nor subgroup analysis were performed.

4.6 Studies of unclear relevance

For one entry in the trial registry search, relevance could not be definitively clarified. The entry relates to a study that could have been relevant for comparing earlier versus later treatment start. The study entry does not indicate whether the study population also includes patients who would be relevant for the benefit assessment. The study was completed in 2006, and results had not been published by the time the preliminary report was completed. No inquiries were made to the author.

Evidence map

The available data are insufficient for the balancing of benefit and harm of earlier versus later treatment start and for assessing diagnostic accuracy. No evidence map is presented.

5 Classification of the assessment result

Tyrosinaemia type 1 is a very rare disease; therefore, the assessment method was modified accordingly. Nevertheless, only one study on diagnostic accuracy and 3 relevant retrospective cohort studies on treatment start were available for assessing the individual components of the screening chain. Studies that generally compared treatment versus no treatment were not relevant.

For the benefit assessment, no data were available on the damage to health caused by the screening. Positive screening results can be verified by gene analysis. Hence, relevant health consequences of positive screening results are probably limited to negative psychological consequences and stress for parents during the time period between the positive screening results and the receipt of the negative results of the confirmatory diagnostics.

6 Conclusions

Since no comparative cohort studies were available that compared screening versus no screening, the diagnostic accuracy of the screening test and the benefit of earlier treatment were examined. The results of only one diagnostic accuracy study and 3 retrospective comparative cohort studies contained results relevant for this report. The study results show no dramatic effect, which would be necessary to demonstrate the benefit due to the low certainty of results.

The benefit or harm of newborn screening for tyrosinaemia type 1 using tandem mass spectrometry are unclear due to the limited informative value of the available evidence.

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Please see full report for full reference list.

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The full report (German version) is published under

https://www.iqwig.de/en/projects-results/projects/non-drug-interventions/s15-01-newborn-screening-for-tyrosinaemia-type-1-using-tandem-mass-spectrometry.6807.html