Annual Report 2022

Malformation Monitoring Centre Saxony-Anhalt

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG

SACHSEN-ANHALT
Ministerium für Arbeit, Soziales, Gesundheit und Gleichstellung

Annual Report 2022
of the Federal State of Saxony-Anhalt
about the frequency of cengenital malformations and anomalies as well as genetically cause diseases

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Gender note:

For reasons of better comprehensibility, the annual report of the Malformation Monitoring Centre Saxony-Anhalt uses the masculine form. All persons and designations refer equally to all genders.

Introduction

Dear reader,

It can be seen as a miracle and happiness in equal measure when new parents hold their newborn in their arms and when the life of mothers and fathers changes fundamentally. It is always good news that the majority of children who are born in Saxony-Anhalt are born healthy. In 2022, our Federal State counted 14,506 live births.

However, a look into the statistics also reveals that last year 582 pregnancies were affected by at least one major malformation. This corresponds to a share, similar to the previous years, of four percent. Every single case, whether diagnosed prenatally or postnatally, is tragic and affected infants and their families and relatives face very special challenges. It is then helpful to have professional support from experienced midwives, family midwives, nurses, doctors and early intervention specialists. I am proud of the fact that Saxony-Anhalt has many dedicated avalable specialists for these situations.

Why does a malformation registration makes sense? Saxony-Anhalt is the only Federal State with a comprehensive population-based malformation registration in Germany. The continuation of this epidemiological observation is documented for the 2022 birth cohort in this annual report. The main task is to analyze the frequency of relevant malformations in order to identify temporal and regional trends. With regard to the temporal trends, on the one hand a short-term accumulation of malformations is of interest, but on the other hand also the long-term trend with well-known statistical fluctuations over several years is observed. Together with regional trends, it may be possible to identify unexpected clusters. Another task is to develop preventive measures and to check their effectiveness, such as monitoring the effect of folic acid prophylaxis.

One focus of this year‘s report is the question regarding interactions caused by drugs in women during pregnancy and breastfeeding and how they can affect the growing organism. The aim of malformation registration is not at least to inform and educate the population as part of health reporting.

I would like to thank all those who dedicate their professional or private lives to support children and their families who are affected by malformations.

Your sincerely

Petra Grimm-Benne
Federal Minister of Labor, Social Affairs, Health and Integration of the State of Saxony-Anhalt

Table of Contents

Figures

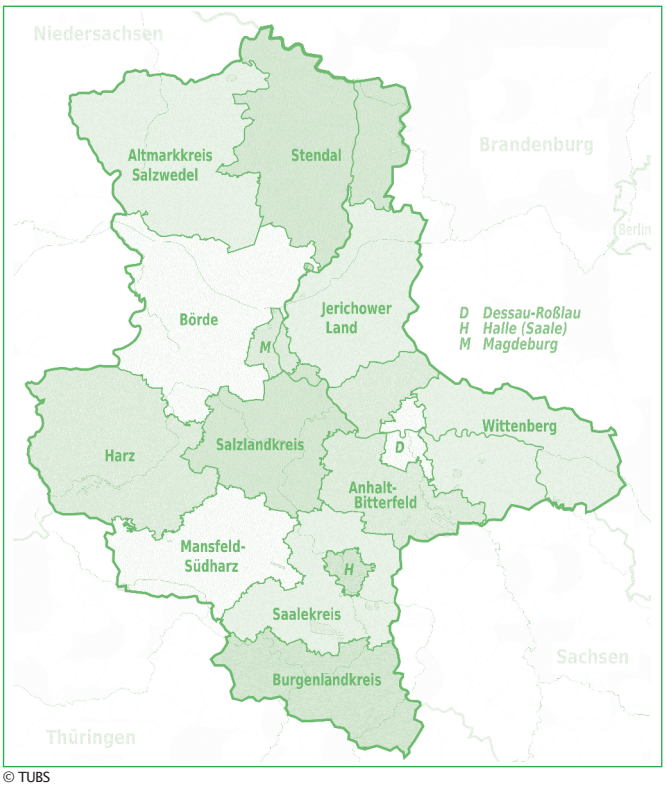
Abbreviations

AABR	automated auditory brainstem response
ASD	atrial septal defect
AVSD	Atrioventricular septal defect
ATC	Anatomical-Therapeutic-Chemical classification
AV-Block	atrioventricular block (= cardiac block)
bds.	bilateral
BMI	Body-Mass-Index
BP	basis prevalence
(c)CMV	(connatal) cytomegalovirus infection
CHD	Congenital Heart Defects
CI	confidence interval
CNS	central nervous system
dB	Decibel
DIV	Double Inlet Ventricle
DORV	Double Outlet Right Ventricle
DUP	dilated Uropathy
EUROCAT	European Surveillance of Congenital Anomalies
ENT	ears, nose, throat
FAS	fetal alcohol syndrome
FASD	fetal Alcohol Spectrum Disorder
G-BA	Federal Joint Committee
HLHS	hypoplastic left heart syndrome / left heart hypoplasia syndrome
IA	Induced abortion(s)
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICSI	intracytoplasmic sperm injection
IUGR	intrauterine growth restriction
LB	Live birth(s)
MCA	Multiple congenital anomalies
NHS	Newborn hearing screening
NIPT	non-invasive prenatal test (cell-free DNA-analysis)
NT	nuchal translucency
n. (o.) s.	not otherwise specified
OR	odds ratio
P	prevalence
PDA	persistent ductus arteriosus
PFO	persistent foramen ovale
SA	spontaneous abortion
SB	Stillbirth(s)
SD	Standard deviation
TEOAE	transistoric evoked otoacustisc emissions
TGV	transpositions of great vessels
TORCH	Acronym made up of the first letters of important prenatal infections: Toxoplasmosis, other (other, e.g. syphilis, listeriosis), rubella, cytomegalovirus (CMV) and herpes simplex
VSD	Ventricular septal defect
WOP	Week of pregnancy

1 Births and fetuses 2022 in the registration region

District/major cities	Live births*	Stillbirths*	Live births and stillbirths in total	*Spontaneous abortions (>16 WOG)#*	*Terminations of pregnany#*
Altmarkkreis Salzwedel	548	o. A.	550**	-	*4*
Anhalt-Bitterfeld	994	9	1,003	*2*	*2*
Börde	1,095	o. A.	1,097**	*2*	*9*
Burgenlandkreis	1,116	o. A.	1,118**	*2*	*2*
Dessau-Roßlau	488	4	492	-	*1*
Halle	1,882	9	1,891	*3*	*3*
Harz	1,272	7	1,279	*3*	*12*
Jerichower Land	556	4	560	*1*	*2*
Magdeburg	1,999	3	2,002	*5*	*6*
Mansfeld-Südharz	761	o. A.	763**	-	*2*
Saalekreis	1,214	9	1,223	*3*	*3*
Salzlandkreis	1,152	3	1,155	*2*	*3*
Stendal	680	7	687	*4*	*4*
Wittenberg	749	o. A.	750**	-	*2*
Country in Saxony-Anhalt n.d.	-	9	-	-	-
Saxony-Anhalt	**14,506**	**64**	**14,570**	**27**	**55**

* Source: © Statistical Office Saxony-Anhalt, Halle (Saale), 2023
** extrapolated figure
# Data Malformation Monitoring Centre Saxony-Anhalt



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https://de.wikipedia.org/wiki/Datei:Saxony-Anhalt,_administrative_divisions_-_de_-_colored.svg#filelinks

2 Participating institutions of the region 2022

2.1 Maternity units / paediatric units / paediatric surgery / paediatric cardiology (ordered by location)

- AMEOS Klinikum Aschersleben
- Helios Klinik Jerichower Land Burg
- Städtisches Klinikum Dessau
- Altmark-Klinikum Krankenhaus Gardelegen
- AMEOS Klinikum Halberstadt
- Krankenhaus St. Elisabeth und St. Barbara Halle (Saale)
- Universitätsklinikum Halle (Saale)
- Helios Klinik Köthen
- Herzzentrum Leipzig - Universitätsklinik für Kinderkardiologie *(outside of Saxony-Anhalt)*
- Klinikum Magdeburg
- Krankenhaus St. Marienstift Magdeburg
- Universitätsklinikum Magdeburg A.ö.R.
- Carl-von-Basedow-Klinikum Saalekreis Merseburg
- SRH Klinikum Naumburg
- Harzklinikum Dorothea Christiane Erxleben Klinikum Quedlinburg *(Maternity clinic until April 2022)*
- Altmark-Klinikum Krankenhaus Salzwedel
- Helios Klinik Sangerhausen
- Johanniter-Krankenhaus Stendal
- Harzklinikum Dorothea Christiane Erxleben Klinikum Wernigerode
- Evangelisches Krankenhaus Paul Gerhardt Stift Wittenberg
- SRH Klinikum Zeitz

2.2 Institutions of pre- and postnatal diagnostics (ordered by location)

- Dr. H. und C. Seidel, Fächarzte für Frauenheilkunde und Geburtshilfe, Dessau-Roßlau
- Dipl. Heilpädagogin Schlote, Glindenberg/Magdeburg
- Dr. Perlitz, Fachärztin für Frauenheilkunde und Geburtshilfe, Haldensleben
- Krankenhaus St. Elisabeth und St. Barbara Halle, Klinik für Geburtshilfe, Pränatale Ultraschalldiagnostik: CA Dr. Seeger, OÄ Dr. Radusch
- Universitätsklinikum Halle (Saale), Universitätsklinik und Poliklinik für Geburtshilfe und Pränatalmedizin, Pränatale Ultraschalldiagnostik: OA Dr. Riemer
- Zentrum für Pränatale Medizin Halle: S. Rißе, N. Manthey
- Dr. Ababei, Fachärztin für Humangenetik, Magdeburg
- Dr. Blaschke, Fachärztin für Kinder- und Jugendmedizin, Magdeburg
- Dr. Karstedt, Facharzt für Kinder- und Jugendmedizin, Kinderkardiologie, Magdeburg
- Dr. Karsten, Facharzt für Frauenheilkunde und Geburtshilfe, Magdeburg
- Klinikum Magdeburg, Klinik für Frauenheilkunde und Geburtshilfe, Pränatale Ultraschalldiagnostik: OÄ Dr. Schleef
- Dr. Lüss, Facharzt für Kinder- und Jugendmedizin, Magdeburg
- Universitätsklinkum Magdeburg A.ö.R., Institut für Humangenetik
- Universitätsklinkum Magdeburg A.ö.R., Universitätsfrauenklinik, Pränatale Ultraschalldiagnostik: OÄ Dr. Gerloff
- Universitätsklinkum Magdeburg A.ö.R., Institut für Klinische Chemie, Screeninglabor
- Trackingstelle Neugeborenen-Hörscreening Sachsen-Anhalt, Magdeburg
- Dr. Welger, Fachärztin für Frauenheilkunde und Geburtshilfe, Magdeburg
- Dipl.-Med. Fiedler und Giesecke, Fachärzte für Orthopädie, Merseburg
- Altmark-Klinikum Krankenhaus Salzwedel, Klinik für Frauenheilkunde und Geburtshilfe, Pränatale Ultraschalldiagnostik: CA Dr. Müller
- Dr. Achtzehn, Dr. Adams, Fachärzte für Kinder- und Jugendmedizin, Wanzleben
- Harzklinikum Dorothea Christiane Erxleben Klinikum Wernigerode, Klinik für Gynäkologie und Geburtshilfe, Pränatale Ultraschalldiagnostik: OÄ Dr. Schulze

2.3 Pathological-anatomical institutes (ordered by location)

- Institut für Pathologie Dr. Bilkenroth, Dr. Irmscher, Dr. Lupatsch, Eisleben
- Universitätsklinikum Halle (Saale), Institut für Pathologie
- Klinikum Magdeburg, Institut für Pathologie
- Universitätsklinikum Magdeburg A.ö.R., Institut für Pathologie
- Harzklinikum Dorothea Christiane Erxleben Klinikum Quedlinburg, Institut für Pathologie
- Praxis für Pathologie PD Dr. Schultz, Dr. Lüders, Dr. Hainz, Stendal

3 Malformation registration in Saxony-Anhalt 2022

3.1 General informations

There is no other way, our thanks for the continued interdisciplinary cooperation to you as sender should be placed again at the beginning of the current annual report (data evaluation birth cohort 2022).Without the cooperation and participation of numerous colleagues from all health professions in the project „Monitoring of Congenital Malformation Saxony-Anhalt“, the data basis creation for the present epidemiological analysis would not be possible.

According to the Statistical Office, an average of 40 children were born alive per day in Saxony-Anhalt in 2022. In total, 14,506 infants were born, which were 1,518 fewer than in 2021. In August, the highest number of births was registered with 1,345 infants.
The reason for taking medication during pregnancy is not only the increasing maternal age and the rising proportion of women with chronic illnesses. There are also acute illnesses during pregnancy, estimated at 1 to 2 % of all pregnant women, who have to undergo surgery, for which medication must be prescribed. So we focued this year on the topic „Drug safety during pregnancy and teratogenic effects as a cause of malformations“. You will find further data analyses regarding this topic in Chapter 14.1.

After the SARS-CoV-2 pandemic, we were still unable to find any further evidence of a teratogenic effect in the analysis of the 2022 birth cohort. Here, EUROCAT can refer to data from 36 active malformation registers from 18 European countries.
With 1.7 million births, the network of congenital malformation registers covers around 30% of the European birth population. The Monitoring of Congenital Malformation Saxony- Anhalt has been working in the EUROCAT network since 1992 (https://eu-rd-platform.jrc.ec.europa.eu/eurocat).
We have been cooperationg since 1993 also with the WHO-associated network organization, the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), an association of 42 birth defect registers from 38 countries around the world (www. icbdsr.org). In November 2023, PD Dr. med. A. Rißmann was nominated for a two-year term as Chair of the Executive Committee of the ICBDSR.

Saxony-Anhalt is the only Federal State with a comprehensive, population based malformation registration in Germany. This is only possible thanks to the continuous support of the Ministry of Labor, Social Affairs, Health and Integration of the Federal State of Saxony-Anhalt. Special thanks are extended to the head of department Mrs. K. Müller. We would like to thank for the continuous good cooperation with Department 23, in particular with Dr. med. Henze and Mr. M. Schiener.

We would also like to thank the Medical Faculty of Medicine at Otto von Guericke University Magdeburg, in particular Prof. Dr. med. H.-J. Heinze, as Medical Director and Mr. M. Bohn, as Commercial Director 2022 for the continued productive cooperation. We would also like to thank the Dean, Prof. Dr. rer. nat. D.C. Dietrich for her support as well.

3.2 Registration and analysis

Our present annual report contains data about children/fetuses with congenital malformations and chromosomal disorders of the Federal State of Saxony-Anhalt, whereby we refer to the place of residence of the mother during pregnancy respecively at the time of birth.

Basis of the annual prevalence calculations forms the total number of births, i.e. live and stillbirths, of Saxony-Anhalt. The prevalence of congenital malformations and anomalies as well as genetically caused diseases includes: live births, stillbirths, terminations of pregnancy (of all WOG) as well as spontaneous abortions from the 16th WOG.

The expected date of delivery is used as basis for analysing the termination of pregnancy, e.g. 2022 is considered the year of birth although some terminations of pregnancy after prenatal diagnostics took place at the end of 2021. This method is common on an international scale. In contrast, the time of delivery of spontaneous abortions is not corrected as the abortion is registered in the month when it actually took place. Data about live births and stillbirths is provided annually in mid-year by the Statistical Office Halle for the previous year. The shown percentages and prevalences are rounded values.

All data transmitted to the Monitoring of Congenital Malformations is medically controlled upon receipt and the diagnoses are encoded according to ICD-10 and according to a further extension (Adaptation of the Royal College of Paediatrics and Child Health). Details about intake of medication during pregnancy are registered by using the internationally recommended ATC codes.

The total number of infants with major malformations as well as the geographical distribution of appearance in the big cities and districts is outlined in chapter 6 and 7. Infants with only minor malformations or rather norm variations are not evaluated separately since this data is only collected incompletely in the end and not target of permanent observation.

Chapter 9 outlines the most frequent single diagnoses of major malformations registered from 2010 to 2022.

Similar to the previous years, we analysed the reported pathological prenatal screening results separately in Chapter 8.

Chapter 10 contains again the analysis of the so-called indicator birth defects. As we have presented data in this way for a number of years, it is possible to evaluate the current prevalences of 2022 in comparison to the last 12 years (2010-2021). Here, a total number of 205,254 births forms basis for the basis prevalence calculation 2010 to 2021.

The graphical presentation of the annual prevalences allows to identify frequent appearances and gives a good overview about rarely appearing indicator births defects. The exact calculation of confidence levels is based on the binominal distribution with a confidence probability of 95%. To discover a certain trend, the percentage change of an indicator malformation prevalence is presented as well for the whole publishing time of the Annual Report (Chapter 10.38).

Data regarding genetically caused diseases, chromosomal disorders, sequences, associations, complexes and embryopathies is outlined in chapter 11. Chapter 12 contains an analysis of malformation caused terminations of pregnancy.
As usual, the Newborn hearing screening forms part of the Report of the Monitoring of Congenital Malformations Saxony-Anhalt and is outlined in chapter 16.
Chapter 17 presents the Annual Report of the department of newborn screening in Saxony-Anhalt with data regarding congenital metabolic disorders and endocrinopathies.

3.3 Data quality and completeness / reporting procedure

The malformation monitoring receives information about newborns and fetuses from the maternity and pediatric clinics and from colleagues of pre and postnatal diagnostics (chapter 4.2). These are evaluated, coded and entered into the database of the malformation monitoring. Based on this data the annual report is compiled, scientific projects are processed and questions relating to malformations are resolved.

For the 2022 birth cohort, 1,600 new data records were added to the
malformation monitoring database. Similar to the number of births of Saxony-Anhalt
this figure is declining. For 2022, information is available about 10.9% of all children and foetuses who were registered in Saxony-Anhalt. Due to late registrations of children/foetuses since the last report was compiled, the number of data records for the 2021 cohort has increased from 1,733 to 1,777. For the birth year 2022, the Monitoring of Congenital Malformations received 1,900 reports, 371 of which came from outpatient facilities. For 14.7 % of the children/fetuses, we received reports from multiple senders. In order to validate a suspected malformation or to be able to record rare or complex malformations in a better qualitative way, this redundancy means a lot and is highly appreciated.

In terms of infants born in a clinic, most reports 2022 of children/fetuses came from the Helios Clinic Köthen. We are particularly grateful for this! The University Hospital Magdeburg and the St. Marienstift Magdeburg Hospital also submitted data about a large number of children/fetuses. Further hospitals in Aschersleben, Naumburg and Zeitz each reported exactly one child with a major malformation in 2022, although the total number of births at the three clinics together was over 1,000. One positive factor remains the tireless reporting work of the outpatient facilities, especially the Centre for Prenatal Medicine (Halle), Dr. Karstedt (specialist in paediatric and adolescent medicine, paediatric cardiologist) as well as Dr. Achtzehn and Dr. Adams (specialists in paediatric and adolescent medicine).

The informative value of statistics and the report is determined by the quality of the underlying data, i.e. the consistency of stored data, which in turn depends on the quality of the provided information. For this reason, complete and correct information on the registration sheet and the detailed description of the diagnoses are of great importance. For 2022, thanks to the excellent cooperation of all contributors, a very good quality of data has been achieved. Essential information is almost complete: Gender at 98.9 %, age of the mother at 99.3 % and the district at 99.9 % of the time. In 2022, the birth weight was missing 58 times, but only 9 times for live births. The head circumference, which is important for the assessment of microcephaly was missing in 23.3 % of the reports and in 20.3 % of the reported live births.

It is pleasing, that for the birth year 2022 we received only one fetal report of an indicator malformation which could not be assigned to a postnatal report. Since uncertain findings are not included into the prevalence calculations or some clinics do not remember to report every malformation, some malformations occur more frequently than shown in the report.

We receive two thirds of malformation registrations and indications of control cases by means of the „green documentation sheets“, which we provide free of charge to the reporting institutions. Documentation sheets may be ordered at any time by phone +49 391-6714174 or e-mail to monz@med.ovgu.de.
Additionally, it is also possible to report on so-called „white documentation sheets“. This form serves to register a basis data set. The indication of the above-mentioned information and possible risk factors like intake of medication or family histories and an exact description of the malformation and / or corresponding symptoms are important here.
Both documentation sheets are also available for download on our homepage www.angeborene-fehlbildungen.com. It is possible to complete the sheet manually or to enter the data directly into the PDF file, print it out and send it back to us. Mostly, we receive the reports by mail on our documentation form sheets. In many institutions fax reports have become the preferred method of transmission. Our fax number is: +49 391-6714176.
We will be at your disposal for answering any further questions about the reporting

5 Sex Ratio 2022

Sex ratio of all live births and stillbirths of Saxony-Anhalt according to the information of the Statistical Office, Saxony-Anhalt, Halle (Saale)

male	7,440 live births and stillbirths
female	7,130 live births and stillbirths
total	14,570 live births and stillbirths

Sex ratio m : f = 1.04

Sex ratio of all births with major malformations (including abortions)

male	316 births
female	258 births
unknown	8 births
total	582 births

Sex ratio m : f = 1.22

Sex ratio of all births with only minor malformations and anomalies

male	117 births
female	120 births
total	237 births

Sex ratio m : f = 0.98

Since 2016, the number of live births in Saxony-Anhalt is declining. In the year 2022, 14,506 live births were recorded. 64 children were stillborn in 2022. The ratio of live births and stillbirths of the current year is slightly smaller than in the entire reporting period (2022: 226.7:1 vs. 2010-2021: 237.9:1).

In 2022, there is, as usual in the reporting period, a slight androtropy in the sex ratio (2022: m : w = 1.04; 2010-2021: m : w = 1.05). For stillbirths, the sex ratio shows a figure of m : w = 1.19 (2010-2021). More girls than boys were stillborn in the last three years. In 2022, the sex ratio is strongly in favour of boys at m : w = 1.67.

In 2022, major malformations occurred in 582 live and stillborn children, medically induced abortions and spontaneous abortions from the 16th week of pregnancy, which are summarized under the term children/fetuses. The sex ratio of all children/fetuses with major malformations also indicates a boy‘s turn in 2022. In the reporting period, the ratio was between a minimum of m : w = 1.17 and a maximum of m : w = 1.47.

The gender distribution of the 237 children/fetuses reported in 2022 with only small malformations shows a gynaecotropy. In most of the previous years, a less pronounced androtropia can be seen. In the years 2010-2021, the sex ratio of children/fetuses with only

9 Organ system involvement and most frequent single diagnoses in infants and foetuses with major malformations

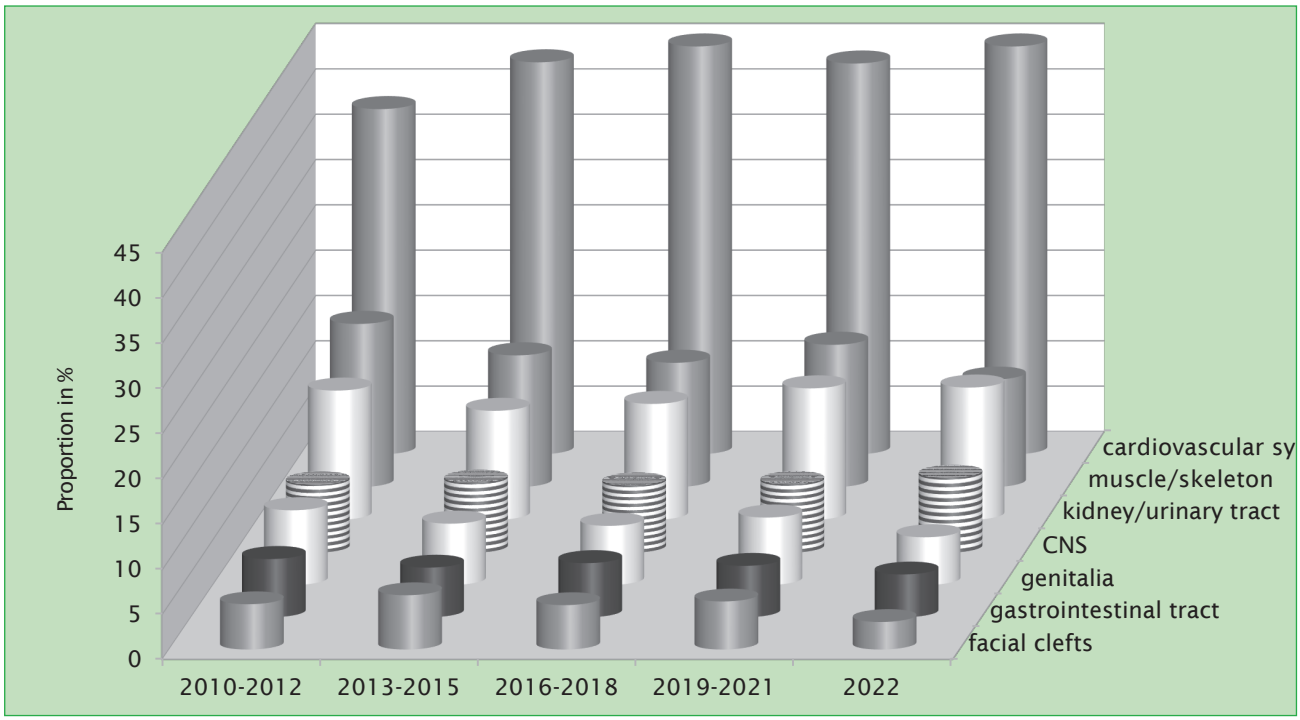


Fig. 5: Organ system involvement in major malformations (grouped)

The question which organ systems of children/fetuses are most affected by major malformations should be answered with the diagram shown above (Fig. 5). The proportion of children/fetuses that are affected by a malformation in these organ systems during the reporting period 2010-2022 in Saxony-Anhalt is shown for seven selected organ systems.

As of the year of birth 2022, 582 children/fetuses were diagnosed with major malformations in Saxony-Anhalt. These children are in 42.6 % of all cases (2022: 248) affected by multiple malformations. Infants with multiple malformations are listed several times in the diagram. The timeline is divided from 2010-2021 into four 3-year periods, and 2022 is shown separately.

The majority of malformations concern the cardiovascular system. In the reporting period (2010-2021) 43.0% of all children/fetuses with major malformations suffered from a cardiac malformation. In the current year (2022), the proportion (46.0%) is even higher, but does not reach the maximum value of 2017 (46.8 %).

During the reporting period of 2010-2021, 15.2% of children/fetuses with a major malformation showed a malformation of the musculoskeletal system. The musculoskeletal system is the second most affected organ system. After a maximum proportion in the previous year (2021: 20.6 %), there is currently a minimum proportion of children/fetuses with a malformation of the musculoskeletal system (2022: 11.9 %).

Almost as frequently as malformations of the musculoskeletal system, we regsitered malformations of the kidneys and urinary tract. On average, 13.0 % of children/fetuses with major malformations (2010-2021) of the kidneys and urinary tract were found. The proportion of children/fetuses varies between 9.4 % and 18.1 % and amounts to 14.6 % in 2022.

The current proportion of children/fetuses with malformations of the CNS system (2022: 8.2%) corresponds approximately to the average value of the previous years (2010-2021: 7.5%). Almost half of the CNS malformations are neural tube defects (2010-2021:8.3 per 10,000 children/fetuses) and hydrocephaly (2010-2021: 5.8 per 10,000 children/fetuses) (chapters 10.1 and 10.6).

In case of 5.3% of all children/fetuses with major malformations a severe diagnosis of the genital system was made in 2022. After a high proportion in the previous year (2021: 9.9%), the current value is significantly lower than the average of the years 2010-2021 (6.9% of all children/fetuses with major malformations).
The proportion of children/fetuses with malformations of the gastrointestinal tract is also significantly lower in 2022 (4.8%) than in 2010-2021 (5.9%).The lowest proportion in the reporting period was observed in 2015 (4.6%).

In 2022, only 3.1% of children/fetuses with major malformations had a facial cleft. This is the lowest proportion in the reporting period and it is significantly below the average value (2010-2021: 5,3 %). Approximately two thirds of facial clefts include cleft lip and cleft lip with cleft palate, which occured very raraly in 2022 with only 5.5 per 10,000 births (chapter 10.14).

Most frequent single diagnosis 2022 (only major malformations)

	ICD-10	Diagnosis	Children/Fetuses 2022*		Children/Fetuses 2010-2021**	
			Number	Prevalence /10.000	Prevalence /10.000	Confidence interval (CI 95%)
1.	Q21.1	Atrial septal defect (without PFO)	156	107.1	101.6	97.3 - 106.0
2.	Q21.0	Ventricular septal defect	73	50.1	47.4	44.4 - 50.4
3.	Q62.3	Dilated uropathy II.-IV. grade/ureterocele	38	26.1	25.0	22.9 - 27.3
4.	H90.	Hearing loss due to sound conduction or sound perception disorder	35	24.0	24.4	22.3 - 26.6
5.	Q90.	Down syndrome (trisomy 21)	29	19.9	21.0	19.1 - 23.1
6.	Q62.2	Megaureter	25	17.2	8.3	7.1 - 9.7
7.	Q66.0	Pes equinovarus congenitus (clubfoot)	18	12.4	13.9	12.3 - 15.6
8.	Q63.0	Accessory kidney/double system	17	11.7	8.1	6.9 - 9.4
9.	Q62.1	Atresia and stenosis of the ureter	15	10.3	9.4	8.1 - 10.8
10.	Q22.1	Pulmonary valve stenosis	13	8.9	6.7	5.6 - 7.9
11.	Q65.3-5	Subluxation of the hip joint (unilateral/bi-lateral/o. A. laterality)	12	8.2	8.1	6.9 - 9.5
	Q61.4	Renal dysplasia	12	8.2	6.2	5.2 - 7.4
12.	Q69.	Polydactyly (preaxial and postaxial)	11	7.5	12.3	10.8 - 13.9
13.	Q54.	Hypospadias	10	6.9	6.7	5.6 - 7.9
	Q25.1	Aortic coarctation	10	6.9	5.8	4.8 - 6.9
	Q35.	Cleft palate	10	6.9	4.2	3.4 - 5.2
	Q33.6	Hypoplasia/dysplasia of the lung	10	6.9	3.5	2.7 - 4.4
14.	Q60.0	unilateral renal agenesis	9	6.2	5.4	4.4 - 6.5
	Q03.	congenital hydrocephaly (without neural tube defect)	9	6.2	5.8	4.8 - 7.0
15.	Q21.2	Defects of the atrial and ventricular septum (AVSD/ASD I)	8	5.5	5.0	4.1 - 6.1
	Q05.	Spina bifida	8	5.5	4.8	3.9 - 5.8
16.	Q37.	Cleft lip and palate	7	4.8	10.3	8.9 - 11.8
	Q40.0	Hypoplasia/agenesis of the corpus callosum	7	4.8	4.8	3.9 - 5.9
	Q25.4	right aortic arch	7	4.8	3.6	2.8 - 4.5
	Q02.	Microcephaly	6	4.1	4.1	3.3 - 5.1
	Q25.6	Stenose der Arteria pulmonalis (periphere Pulmonalstenose)	6	4,1	3,1	2,4 - 4,0
	Q91.4-7	Patau-Syndrom (Trisomie 13)	6	4,1	1,6	1,1 - 2,2

* based on 14,570 births

** based on 205,254 births

The table above presents the most frequently observed major individual malformations in Saxony-Anhalt in 2022. It includes 27 major individual malformations, listed in descending order of prevalence.

In addition to the current prevalence, which is based on 14,570 births in 2022, the basis prevalence with reference to a population of 205,254 births (2010-2021) is also given.

Around every 100th child/fetus in Saxony-Anhalt is diagnosed with an atrial septal defect. This malformation is the most frequently registered single malformation (2022: 107.1; 2010-2021: 101.6 per 10,000 births). It was seen slightly more common than normal in 2022. About half as often as the atrial septal defect, we registered the ventricular septal defect. Within the ranking, it follows in second place with the usual number (2022: 50.1 per 10,000 births, 2010-2021: 47.4 per 10,000 births).

Places three to five are almost always occupied by the same three very different major malformations dilated uropathy II.-IV. degree/ureterocele (2022: 26.1 per 10,000 births), congenital hearing disorders (2022: 24.0 per 10,000 births) and Down`s syndrome (2022: 19.9 per 10,000 births). For all three malformations, the prevalence lies within the tolerance range in 2022.

Congenital megaureter occurred significantly more frequently in the current year with 17.2 per 10,000 births than in the whole reporting period (2010-2021: 8.3 per 10,000 births each).
It does normally not take the sixth place in the ranking and can be found normally around the eleventh place. Its prevalence rose to a maximum in 2022. Even the highest prevalence which was registered in 2016 since 2000 (11.0 per 10,000 births) was by far exceeded.

In 2022, clubfeet were diagnosed in Saxony-Anhalt with the usual frequency, with a prevalence just above the lower confidence limit (2022: 12.4 per 10,000 births, 2010-2021 births, 2010-2021: 13.9 per 10,000 births). The annual prevalence rates fluctuate between 6.5 (2013) and 17.9 (2019) per 10,000 births.

Duplex kidney follows significantly more frequent than usual (2022: 11.7 per 10,000 births;2010-2021: 8.1 per 10,000 births). The maximum value of the reporting period (2017: 12.3 per 10,000 births) was not reached, however.

At the usual ninth place and in the upper range of the basis prevalence in 2022, we registered the prevalence of atresia and stenosis of the ureter (10.3 per 10,000 births).

After an exceptionally low prevalence in the previous year, pulmonary valve stenosis (2021: 3.1; 2022: 8.9 per 10,000 births) occured in the current year with a prevalence well above the tolerance range of the basis prevalence of Saxony-Anhalt (2010-2021: 6.7 per 10,000 births).

A prevalence of 8.2 per 10,000 births and rank eleven was found for two malformations in 2022. While the prevalence of subluxation of the hip joint corresponds to the usual incidence, renal dysplasia was detected more frequently than expected (2010-2021: 6.2 per 10,000 births).

For polydactyly, the prevalence in 2022 is well below the normal level and the malformation is located therefore in an unusual twelfth place in the frequency list (2022: 7.5 per 10,000 births, 2010-2021: 12.3 per 10,000 births). Polydactyly is classified according to its localization as postaxial polydactyly (2022: 5.5 per 10,000 births; 2010-2021: 9.5 per 10,000 births) and the rarer indicator malformation preaxial polydactyly (2022: 2.1 per 10,000 births; Chapter 10.27). Both forms of polydactyly were diagnosed less frequently than usual in 2022.

With an annual prevalence (2022) of 6.9 per 10,000 births, four malformations are in 13th place. More frequently than expected we registered cleft palate (2010-2021: 4.2 per 10,000 births) and hypoplasia/dysplasia of the lung (2010-2021:3.5 per 10,000 births). For hypospadias and aortic isthmus stenosis, we calculated at the same annual prevalence, a value within the confidence interval of the basis prevalence in 2022.

The following two places are occupied this year by two malformations, which are inconspicuously within the confidence interval: unilateral renal agenesis and hydrocephaly (2022: 6.2 per 10,000 births). These are followed by defects of the atrial and ventricular septum and spina bifida (2022: 5.5 per 10,000 births).

In 2022, 21 major individual malformations occured more often than cleft lip with cleft upper jaw and palate (2022: 4.8 per 10,000 births; 2010-2021: 10.3 per 10,000 births), which is otherwise one of the ten most common malformations. In the previous year, cleft lip with cleft upper jaw and palate was observed very rarely. Since 2000, the current prevalence (2022) lies at a minimum value. As cleft lip with cleft palate forms thogether with cleft lip the indicator malformation cleft lip with cleft upper jaw and palate (chapter 10.14), the low prevalence also implies a low current annual prevalence of the indicator malformation cleft lip with cleft upper jaw and palate in Saxony-Anhalt.

For two other malformations, the same annual prevalence (2022: 4.8 per 10,000 births) applied, whereby at hypoplasia/agenesis of the corpus callosum the prevalence value is inconspicuously within the normal range and for the right aortic arch, which was seen more common than usual in 2022 (2010-2021: 3.6 per 10,000 births), the annual prevalence slightly lies above the upper limit of the confidence interval.

The annual prevalence of microcephaly was found to be 4.1 per 10,000 births in 2022, which corresponds to the basis prevalence. The same annual prevalence (2022) of 4.1 per 10,000 births was also found for two malformations that are not normally among the top places in the list of individual malformations, stenosis of the pulmonary artery (2010-2021: 3.1 per 10,000 births) and Patau syndrome (2010-2021: 1.6 per 10,000 births). By the birth year 2021, the indicator malformation Patau syndrome occured with a very unusually high prevalence (5.0 per 10,000 births), after a very mild increase in the previous years. This year‘s value is also significantly above the upper confidence limit (Chapter 10.34). The trend analysis showed a significant increase from 2009 to 2022 (Chapter 10.38).

10 Indicator Defects modified according to the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

10.0 Definitions

1. Neural tube defects:
common congenital malformations that occur when the neural tube fails to achieve proper closure during early embryogenesis, resulting in defective development of the associated vertebral arches. Synonyms: Spina bifida, anencephaly, NTD

2. Anencephaly:
a congenital malformation characterized by the total or partial absence of the cranial vault, the covering skin, and the brain missing or reduced to small mass. Inclusive craniorachischisis. Inclusive infants with iniencephaly and other neural tube defects as Encephalocele or open spina bifida, when associated with anencephaly. Exclusive acephaly, that is, absence of head observed in amorphous acardiac twins.

3. Spina bifida:
a family of congenital malformation defects in the closure of the spinal column characterized by herniation or exposure of the spinal cord and/or meninges through an incompletely closed spine. Inclusive meningocele, meningomyelocele, myelocele, myelomeningocele, rachischisis. Spina bifida is not counted when present with anencephaly. Exclusive spina bifida occulta, sacrococcygeal teratoma without dysraphism.

4. Encephalocele:
a congenital malformation characterized by herniation of the brain and/or meninges through a defect in the skull. Encephalocele is not counted when present with spina bifida.

5. Microcephaly:
is characterized by a too small occipito frontal skull circumference (two standard deviations below the norm, www.intergrowth21.ndog.ox.ac.uk according to Villar et al. Lancet 2014, chapter 10.5, https://www.sciencedirect.com/science/article/pii/S0140673614609326?via%3Dihub), relative to the gestational age- and sex-dependent normal distribution. Exclusive microcephaly associated with a neural tube defect.

6. Congenital hydrocephaly:
a congenital malformation characterized by dilatation of the cerebral ventricles, not associated with a primary brain atrophy, with or without enlargement of the head and diagnosed prenatally or at birth. Not counted when present with a neural tube defect. Exclusive macrocephaly without dilatation of ventricular system, skull of macerated fetus, hydranencephaly, and postnatally acquired hydrocephalus.

7. Arhinencephaly/holoprosencephaly:
a congenital malformation of the brain, characterized by various degrees of incomplete lobation of the brain hemispheres. Olfactory nerve tract may be absent. Holoprosencephaly includes cyclopia, ethmocephaly, cebocephaly, and premaxillary agenesis. Not counted when present with a neural tube defect.

8. Anophthalmos/microphthalmos:
apparently absent or small eyes. Some normal adnexal elements and eyelids are usually present. In microphthalmia, the corneal diameter is usually less than 10 mm and the antero posterior diameter of the globe is less than 20 mm.

9. Anotia/microtia:
a congenital malformation characterized by absent parts of the pinna (with or without atresia of the ear canal) commonly expressed in grades (I - IV) of which the extreme form (grade V) is anotia, absence of pinna. Exclusive small, normally shaped ears, imperforate auditory meatus with a normal pinna, dysplastic and low set ears.

10. Tetralogy of Fallot / Pentalogy:
a condition characterized by ventricular septal defect, overriding aorta, infundibular pulmonary stenosis, and often right ventricular hypertrophy. Included is Fallot pentalogy, which has an additional ASD.

11. Transposition of great vessels (TGV):
a cardiac defect where the aorta exits from the right ventricle and the pulmonary artery from the left ventricle, with or without other cardiac defects. Inclusive double outlet ventricle so called corrected transposition.

12. Hypoplastic left heart syndrome:
a complex cardiac defect with a hypoplastic left ventricle, associated with aortic and/or mitral valve atresia, with or without another cardiac defect.

13. Coarctation of the aorta:
an obstruction in the descending aorta, almost invariably at the insertion of the ductus arteriosus.

14. Cleft lip with or without cleft palate:
a congenital malformation characterized by partial or complete clefting of the upper lip, with or without clefting of the alveolar ridge or the hard palate. Exclusive midline cleft of upper or lower lip and oblique facial fissure (going towards the eye). In addition, cleft lip and cleft lip and palate are excluded in arhin- and holoprosencephaly, respectively.

15. Cleft palate without cleft lip:
a congenital malformation characterized by a closure defect of the hard and/or soft palate behind the foramen incisivum without cleft lip. Inclusive submucous cleft palate. Exclusive cleft palate with cleft lip, cleft uvula, functional short palate, and high narrow palate. In addition, left palate is excluded in arhin- or holoprosencephaly.

16. Choanal atresia, bilateral:
congenital obstruction (membraneous or osseous) of the posterior choana or choanae. Excludes choanal stenosis that does not require therapy.

17. Oesophageal atresia/stenosis:
a congenital malformation characterized by absence of continuity or narrowing of the esophagus, with or without tracheal fistula. Inclusive tracheoesophageal fistula with or without mention of atresia or stenosis of oesophagus.

18. Small intestine atresia/stenosis:
complete or partial occlusion of the lumen of a segment of the small intestine. It can involve a single area or multiples areas of the jejunum or ileum. Exclusive duodenal atresia. In cases with an omphalocele or gastroschisis, small intestine atresia/stenosis is excluded.

19. Anorectal atresia/stenosis:
a congenital malformation characterized by absence of continuity of the anorectal canal or of communication between rectum and anus, or narrowing of anal canal, with or without fistula to neighboring organs. Exclusive mild stenosis which does not need correction, and ectopic anus.

20. Hypospadias:
a congenital malformation characterized by the opening of the urethra on the ventral side of the penis, distally to the sulcus. Inclusive penile, scrotal, and perineal hypospadias. Exclusive ambiguous genitalia (intersex or pseudo hermaphroditism).

21. Epispadias:
a congenital malformation characterized by the opening of the urethra on the dorsal surface of the penis. Not counted when part of exstrophy of the bladder.

22. Indeterminate sex:
genital ambiguity at birth that does not readily allow for phenotypic sex determination. Inclusive male or female true or pseudohermaphroditism.

23. Potter sequence:
a congenital malformation characterized by complete absence of kidneys bilaterally or severely dysplastic kidneys.

24. Renal agenesis, unilateral:
a congenital malformation characterized by complete absence of one kidney unilaterally. Exclusive unilateral dysplastic kidney.

25. Cystic kidney:
a congenital malformation characterized by multiple cysts in the kidney. Inclusive infantile polycystic kidney, multicystic kidney, other forms of cystic kidney and unspecified cystic kidney. Exclusive single kidney cyst.

26. Bladder exstrophy:
complex malformation characterized by a defect in the closure of the lower abdominal wall and bladder. Bladder opens in the ventral wall of the abdomen between the umbilicus and the symphysis pubis. It is often associated with epispadias and structural anomalies of the pubic bones.

27. Polydactyly, preaxial:
extra digit(s) on the radial side of the upper limb or the tibial side of the lower limb. It can affect the hand, the foot, or both.

28. Limb reduction defects:
a congenital malformation characterized by total or partal absence or severe hypoplasia of skeletal structures of the limbs. Inclusive femoral hypoplasia and Roberts syndrome. Exclusive mild hypoplasia with normal shape of skeletal parts, brachydactyly, finger or toe reduction directly associated with syndactyly, general skeletal dysplasia and sirenomelia.

29. Diaphragmatic hernia:
a congenital malformation characterized by herniation into the thorax of abdominal contents through a defect of the diaphragm. Inclusive total absence of the diaphragm. Exclusive hiatus hernia, eventration and phrenic palsy.

30. Omphalocele:
acongenital malformation characterized by herniation of abdominal contents through the umbilical insertion and covered by a membrane which may or may not be intact. Exclusive gastroschisis (para umbilical hernia), a or hypoplasia of abdominal muscles, skin covere umbilical hernia

31. Gastroschisis:
a congenital malformation characterized by visceral herniation through a right side abdominal wall defect to an intact umbilical cord and not covered by a membrane. Excluded are aplasia or hypoplasia of the abdominal muscles, skin-enclosed umbilical hernia, and the omphalocele

32. Prune belly sequence:
a complex congenital malformation characterized by deficient abdominal muscle and urinary obstruction/distension. It can be caused by urethral obstruction secondary to posterior urethral valves or urethral atresia. In the affected fetus the deficiency of the abdominal muscle may not be evident. It can be associated with undescended testes, clubfoot, and limb deficiencies.

33. Down syndrome (Trisomy 21):
a congenital chromosomal malformation syndrome characterized by a well known pattern of minor and major anomalies and associated with excess chromosomal 21 material. Inclusive trisomy mosaicism and translocations of chromosome 21.

34. Patau syndrome (Trisomy 13):
a congenital chromosomal malformation syndrome associated with extra chromosome 13 materials. Inclusive translocation and mosaic trisomy 13.

35. Edwards syndrome (Trisomy 18):
a congenital chromosomal malformation syndrome associated with extra chromosome 18 material. Inclusive translocation and mosaic trisomy 18.

36. Turner syndrome:

Turner syndrome, also known as Ullrich-Turner syndrome or monosomy X, is caused by the partial or complete absence of one of the two X chromosomes in a girl (gonosomal monosomy). A mosaic or a gonosomal abnormality is possible.

37. Klinefelter syndrome/male gonosome abnormalities:

Klinefelter syndrome is caused by two or more X chromosomes in a male phenotype (Karoytype 47,XXY). Anomalies of the gonosomes in a male phenotype also include structural anomalies of the gonosomes or a gonosome mosaic.

Note:

The prevalences we calculated in the following chapters are population-based. The value indicates the number of births with malformations born in a certain population with reference to the total number of births in this population.
Since the birth cohort 2000, the coverage area of the malformation monitoring includes the entire Federal State of Saxony-Anhalt. The prevalence calculations starting with the birth cohort 2000 are based on live and stillbirths of mothers who have their place of residence in Saxony-Anhalt during pregnancy and at the time of birth. Between 1980 and 1993, the coverage area grew to include the former district of Magdeburg. After the district reform in 1993, it comprised 13 (1994/1995), 14 (1996/1997), 15 (1998) and 16 (1999) of 21 districts in Saxony-Anhalt. The calculation of the basic prevalences (2010 to 2021) is based on a total number of 205,254 births.

The analysis of indicator malformations is made in reference to the diagnosis. It is possible that one child has more than one indicator malformation. Therefore, the number of all indicator malformations might be higher than the total number of births with an indicator malformation.

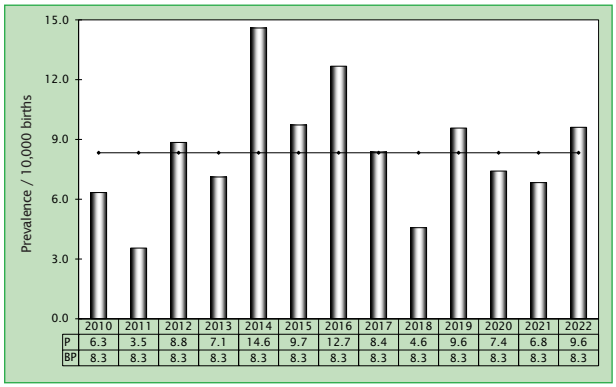
The in chapter 10 indicated comparison prevalences which correspond to the basis prevalences of Saxony-Anhalt are based on data of the years 2010-2021 of the 36 Full-Member-Register of European Surveillance of Congenital Anomalies (EUROCAT) from 18 different European countries. In order to comply with the provisions of the EU General Data Protection Regulation (GDPR) 2016/679 and to protect the privacy of people with congenital anomalies, from this report onwards the European comparative prevalences are rounded to 0.5 per 10,000. The assessment as it was carried out in the previous years of the current prevalences of Saxony-Anhalt in relation to these values is therefore only partially possible. The calculation of the EUROCAT prevalences is based on a total number of 8,520,000 to 8,540,000 births, which are indicated for the same reason with a range of 20,000 births. Source: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en).

10.1 Neural tube defects (Q00./Q01./Q05.)

	Year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	14	9.61	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	8.33	7.13 - 9.68	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	10.5	10.5 - 10.5	

For the 2022 birth cohort 14 neural tube defects were observed in Saxony-Anhalt. After the prevalence was very low at 6.8 per 10,000 births in 2021, the current annual prevalence for 2022 lies at 9.6 per 10,000 births within the confidence interval of the basis prevalence (2010-2021: 8.3 per 10,000 births). After a very high value in 2014 (14.6 per 10,000 births), the prevalences decreased again.

Neural tube defects include three types of neural occlusion defects: Anencephaly, spina bifida and encephalocele, which are considered separately in chapters 10.2 to 10.4. In most cases, the children/fetuses with a neural tube defect are affected by spina bifida (2010-2021: 57.3 % of neural tube defects). In 2022, four anencephalies, eight spina bifida and two encephaloceles were diagnosed in Saxony-Anhalt.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	6.3	3.5	8.8	7.1	14.6	9.7	12.7	8.4	4.6	9.6	7.4	6.8	9.6
BP	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3	8.3

Fig. 6: Development of prevalence/10,000 births with neural tube defects in Saxony-Anhalt since 2010.

NOTE

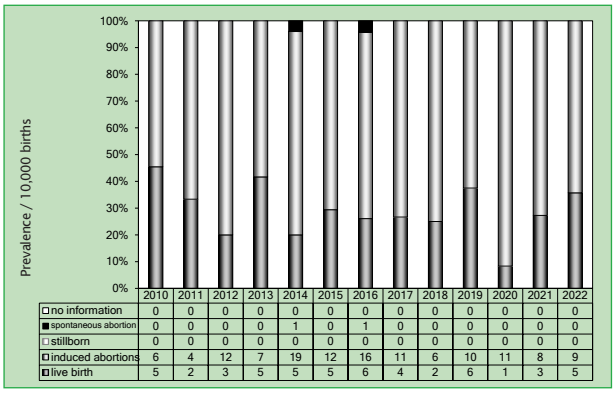
After a pregnancy affected by a neural tube defect, increased folic acid prophylaxis according to the recommendations of the medical societies (preparation available in Germany with 5 mg folic acid equivalent per day) should be explained to those who wish to have children. This higher dose is also recommended today for women with antiepileptic medication and chronic absorption disorders.

EUROCAT indicates a prevalence of neural tube defects in Europe (2010-2021) of 10.5 per 10,000 births. The confidence interval of the basis prevalence, as well as this year's prevalence value of Saxony-Anhalt, are below the confidence interval of the overall prevalence of the European registers.

additional information:

Pregnancy outcome	4 x Live birth 1 x Live birth deceased after 7 days of life 9 x induced abortion
Sex	3 x male 7 x female 4 x not specified
Number of isolated malformations/MCA	4 x MCA 10 x isolated

Five children with neural tube defects were live births in 2022, whereby one child with spina bifida and multiple malformations died in the 2nd month of life. Nine times the pregnancy was terminated (2022: 64.3%, 2010-2021: 71.3 % of children/fetuses with neural tube defects).



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
no information	0	0	0	0	0	0	0	0	0	0	0	0	0
spontaneous abortion	0	0	0	0	1	0	1	0	0	0	0	0	0
stillborn	0	0	0	0	0	0	0	0	0	0	0	0	0
induced abortions	6	4	12	7	19	12	16	11	6	10	11	8	9
live birth	5	2	3	5	5	5	6	4	2	6	1	3	5

Fig. 7: Pregnancy outcomes of neural tube defects in Saxony-Anhalt since 2010

In 2022, one neural tube defect per 1,041 births was registered in Saxony-Anhalt.

Neural tube defects are probably the most investigated congenital malformation within scientific studies. Already in 1995, several German specialist societies published their recommendation regarding primary prevention of folic acid sensitive neural tube defects. A periconceptional intake of 0.4 mg folic acid was recommended to women at child-bearing age. On the other hand, insufficient realisation of this recommendation is urged by recent studies as in case of unplanned pregnancy (first consultation of gynaecologist not before 5 to 7 WOGs) and by risk groups with low socio-economic status or migrants. An own sample confirmed this insufficient implementation*.

* *Literature
Wegner C, Kancherla V, Lux A, Köhn A, Bretschneider D, Freese K, Heiduk M, Redlich A, Schleef D, Jorch G, Rissmann A. Periconceptional folic acid supplement use among women of reproductive age and its determinants in central rural Germany:
Results from a cross sectional study. Birth defects research 2020; 112(14):

10.2 Anencephaly (Q00.)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	4	2.75	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.39	1.77 - 3.16	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.5	4.0 - 4.5	

Four births were affected by anencephaly in Saxony-Anhalt in 2022. Resulting from this, the current year's prevalence (2022: 2.7 per 10,000 births) corresponds to the basis prevalence (2010-2021: 2.4 per 10,000 births).

The trend analysis from 2009-2022 (Chapter 10.38) shows a significant upward trend with a percentage change of 14.61 % (CI 0.91 % to 32.72 %). It can be seen that since 2013 the annual prevalences are mostly within or significantly above the confidence interval of the basis prevalence, but in the early years of the reporting period (up to 2012) they were well below this.

The basis prevalence of anencephaly in Saxony-Anhalt is not as high as the Europe-wide by EUROCAT provided overall prevalence (2010-2021: 4.5 per 10,000 births). This means that the current prevalence value (2022) of Saxony-Anhalt can be rated as low compared to the European prevalence. Only in the years 2014, 2016 and 2021 the annual prevalences were close to the overall European prevalence.

additional information:

Pregnancy Outcome	4 x induced abortion
Sex	1 x male 3 x not specified
Number of isolated malformations/MCA	4 x isolated

In all three fetuses with anencephaly and one fetus with exencephaly, the malformation was detected by prenatal ultrasound between the 12th and 15th week of gestation and the pregnancies were terminated before the 18th week of gestation.

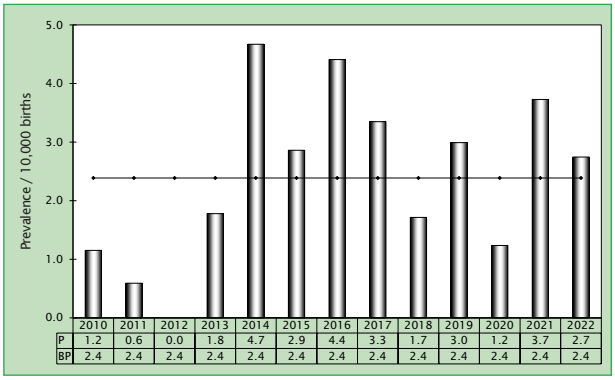


Fig. 8: Development of prevalence/10,000 births with anencephaly in Saxony-Anhalt since 2010

In 2022, one child/fetus with anencephaly was observed per 3,643 births in Saxony-Anhalt.

10.3 Spina bifida (Q05.)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	8	5.49	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.77	3.88 - 5.82	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.0	5.0 - 5.0	

IIn Saxony-Anhalt, eight children/fetuses were diagnosed with spina bifida (5.5 per 10,000 births) in 2022. This indicates that this year's prevalence can be found in the upper range of the basis prevalence (2010-2021: 4.8 per 10,000 births).

The confidence interval of the basis prevalence of Saxony-Anhalt spans a larger safety range in contrast to the interval of the average prevalence of the European registers (5.0 per 10,000 births) due to smaller numbers. The current prevalence value of Saxony-Anhalt, as well as the basis prevalence, match to the European prevalence.

additional information:

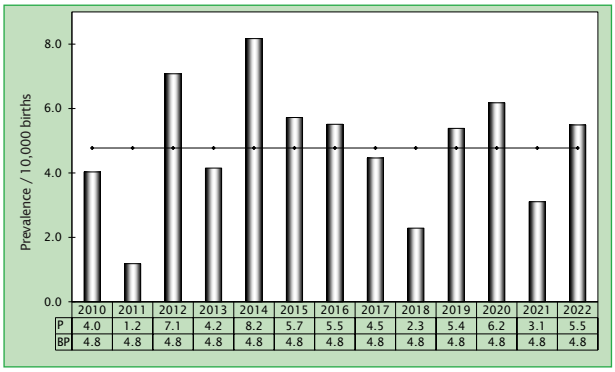
Pregnancy Outcome	4 x Live birth 1 x Live birth deceased after 7 days of life 3 x induced abortion
Sex	2 x male 6 x female
Number of isolated malformations/MCA	3 x MCA 5 x isolated

In case of all children/fetuses who were affected by spina bifida in 2022, this was already discovered prenatally. The pregnancies of two fetuses with sacral and one fetus with lumbar spina bifida and a hand malformation were terminated prematurely. In the course of the pregnancy, only in one case no hydrocephaly developed. One child had a thoracolumbar spina bifida and four children a lumbosacral spina bifida. One child with a meningomyelocele in addition to other severe malformations as a concomitant malformation of an Edwards syndrome died in the 2nd month of life.

Over the years of the reporting period (2010-2021), the proportion of live births fell slightly (Ø 39.6 %). In 2022, however, the share is significantly higher at 62.5 %. Stillbirths and spontaneous abortions were not recorded during the entire period (2010-2022). In the birth cohort 2022, only 37.5% of pregnancies of fetuses with spina bifida were terminated.

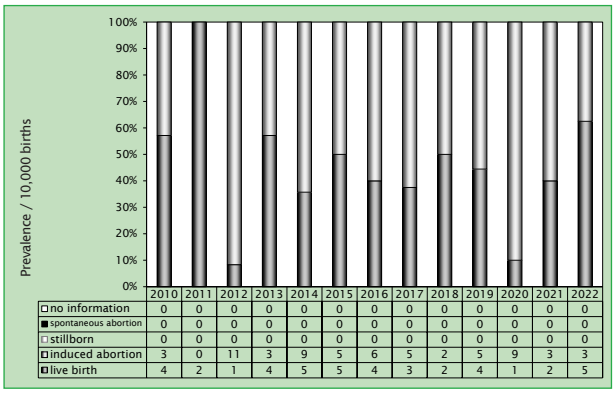
Malformation combinations (MCA) or superordinated syndromes detected:

- Edwards syndrome (mosaic) with: bilateral choanal atresia, VSD, ectopia ani, megacystis, epilepsy
- malformed hand
- bilateral sound perception disorder



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	4.0	1.2	7.1	4.2	8.2	5.7	5.5	4.5	2.3	5.4	6.2	3.1	5.5
BP	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8

Fig. 9: Development of prevalence/10,000 births with spina bifida in Saxony-Anhalt since 2010



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
no information	0	0	0	0	0	0	0	0	0	0	0	0	0
spontaneous abortion	0	0	0	0	0	0	0	0	0	0	0	0	0
stillborn	0	0	0	0	0	0	0	0	0	0	0	0	0
induced abortion	3	0	11	3	9	5	6	5	2	5	9	3	3
live birth	4	2	1	4	5	5	4	3	2	4	1	2	5

Fig. 10: Pregnancy outcomes of spina bifida in Saxony-Anhalt since 2010

In 2022, one child/fetus with spina bifida was observed per 1,821 births in Saxony-Anhalt.

10.4 Encephalocele (Q01.)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	2	1.37	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.17	0.75 - 1.74	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.0	1.0 - 1.5	

The indicator malformation encephalocele was detected during the years of the reporting
period only 24 times (prevalence 2022: 1.4 per 10,000 births). As in the two previous years (2020, 2021), the malformation does not occur every year in Saxony-Anhalt. After a high prevalence value (2016: 2.8 per 10,000 births), in the following five years there were 4 times values below the confidence interval of the basis prevalence. In 2022, two fetuses were diagnosed with encephalocele. This again results in a prevalence within the interval of the basis prevalence (2010-2021: 1.2 per 10,000 births).

The basis prevalence of Saxony-Anhalt corresponds to the EUROCAT prevalence for the years 2010-2021 (1.0 per 10,000 births), but due to the smaller population included, it has a significantly wider fluctuation range than the confidence interval of the European prevalence.

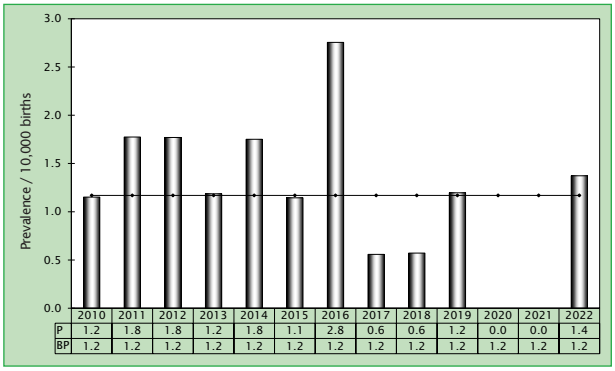
A meningoencephalocele was diagnosed in the 17th week of gestation and a frontal encephalocele in the 16th week of gestation during prenatal ultrasound screening. Both pregnancies were terminated.

additional information:

Pregnancy outcome	2 x induced abortion
Sex	1 x female 1 x not specified
Number of isolated malformations/MCA	1 x MCA 1 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- Rhombencephalosynapsis



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	1.2	1.8	1.8	1.2	1.8	1.1	2.8	0.6	0.6	1.2	0.0	0.0	1.4
BP	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2

Fig.11: Development of prevalence/10,000 births with encephalocele in Saxony-Anhalt since 2010

In 2022, one child/fetus with encephalocele was observed per 7,285 births in Saxony-Anhalt.

10.5 Microcephaly (Q02.)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	6	4.12	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.09	3.26 - 5.07	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.5	2.5 - 2.5	

In Saxony-Anhalt, six children/fetuses were diagnosed with microcephaly in 2022. This results in a prevalence of 4.1 per 10,000 births, which lies in the middle range of the confidence interval of the basis prevalence (2010-2021: 4.1 per 10,000 births). In case of three children and one fetus with arthrogryposis multiplex congenita, after taking into account the gestational age, gender and sex, the head circumferences deviated by more than -3 SD from normal. Two children showed at birth a deviation of more than -2 SD. To determine the diagnosis of microcephaly, the monitoring of congenital malformations uses the internationally valid percentile curves provided by the INTERGROWTH-21st project study. The diagnosis is often only made during the first year of life in the course of the non-development of the brain and skull.

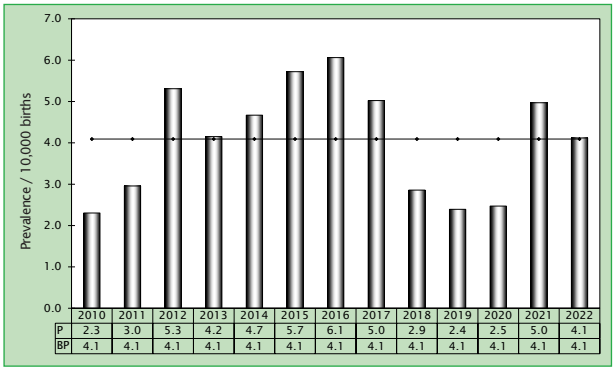
The confidence intervals of the overall prevalence of the European register (2.5 per 10,000 births) and the basis prevalence of Saxony-Anhalt do not overlap. The basis prevalence of Saxony-Anhalt is much higher. Compared to the overall European prevalence also the annual prevalence of Saxony-Anhalt for 2022 lies well above this.

additional information:

Pregnancy outcome	4 x Live birth 1 x Live birth deceased after 7 days of life 1 x induced abortion
Sex	2 x male 4 x female
Number of isolated malformations/MCA	5 x MCA 1 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- Patau syndrome with: bilateral six fingers and toes, clubfoot right, DUP II. degree, PFO and non hemodynamically effective PDA at full term infant, deep sacral dimple
- Arthrogryposis multiplex congenita with: bilateral cleft of the hard and soft palate, missing ovaries, club feet, low-set ears, hypertelorism, macroglossia, cleft tongue
- Wolf-Hirschhorn syndrome with: Sound conduction disorder with left ear canal atresia,
- preauricular appendage left, auricular appendage right, dysplastic ears, mandibular micrognathia, craniofacial dysmorphia
- ASD at full term infant, ventricular asymmetry (brain), umbilical hernia
- PFO at full term infant



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	2.3	3.0	5.3	4.2	4.7	5.7	6.1	5.0	2.9	2.4	2.5	5.0	4.1
BP	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1

Fig. 12: Development of prevalence/10,000 births with microcephaly in Saxony-Anhalt in 2010

In 2022, one child/fetus with microcephaly was observed per 2,428 births in Saxony-Anhalt.

10.6 Congenital Hydrocephaly (Q03.)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	9	6.18	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.85	4.85 - 6.99	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.0	5.0 - 5.5	

In the case of the indicator malformation hydrocephaly, only congenital hydrocephalies are considered, which have not developed as a result of neural tube defects, such as spina bifida (chapter 10.3). As in the previous year, nine children/fetuses in Saxony-Anhalt were born with congenital hydrocephaly in 2022. The annual prevalence calculated from this value (6.2 per 10,000 births) for the indicator malformation lies within the middle normal range of the prevalence of Saxony-Anhalt (2010-2021: 5.8 per 10,000 births).

EUROCAT shows an overall prevalence of congenital hydrocephaly of 5.0 per 10,000 births (2010-2021). The prevalence interval of the basis prevalence of Saxony-Anhalt is wider and spans that of the European malformation registers due to the smaller numbers, but the prevalence value lies at a similar level.

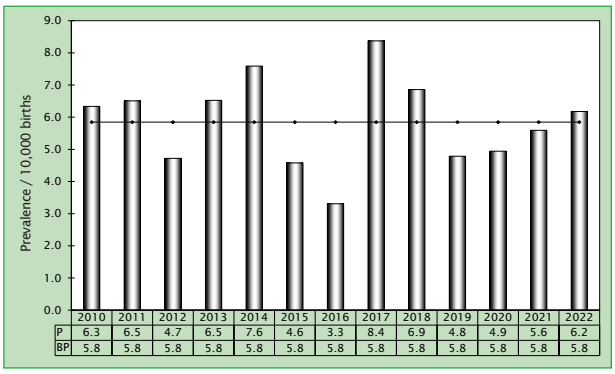
additional information:

Pregnancy Outcome	4 x Live birth 2 x Spontaneous abortion 3 x induced abortion
Sex	3 x male 6 x female
Number of isolated malformations/MCA	7 x MCA 2 x isolated

Congenital hydrocephaly developed twice at presence of a chromosomal disorder, one case resulted in a spontaneous abortion and once the pregnancy was terminated prematurely. In the three terminations of pregnancy hydrocephaly and other malformations and anomalies were detected between the 16th and 21st week of gestation during prenatal ultrasound. The four live births were delivered prematurely between the 30th and 36th week of gestation.

Malformation combinations (MCA) or superordinated syndromes detected:

- Patau syndrome with: median cleft of the hard and soft palate
- Triploidy with: Diaphragmatic hernia
- Left renal agenesis, DIV, VSD, pulmonary valve stenosis
- Exophthalmos with left orbital atoma
- Hypoplasia of cerebellum and corpus callosum
- Dolichocephaly
- Arachnoid cyst



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	6.3	6.5	4.7	6.5	7.6	4.6	3.3	8.4	6.9	4.8	4.9	5.6	6.2
BP	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8

Fig 13: Development of prevalence/10,000 births with congenital hydrocephalus in Saxony-Anhalt since 2010

In 2022, one child/fetus with congenital hydrocephaly per 1,619 births was observed in Saxony-Anhalt.

10.7 Arhinencephaly/Holoprosencephaly (Q04.1/Q04.2/Q87.3)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	1	0.69	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.80	1.27 - 2.48	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.5	1.5 - 1.5	

Die Indikatorfehlbildung Arhinencephalie/HoloprosenThe indicator malformation arhinencephaly/holoprosencephaly shows a basis prevalence of Saxony-Anhalt of 1.8 per 10,000 births (2010-2021) and is one of the rare malformations. On average, three cases per year can be expected in Saxony-Anhalt. After an unusually high prevalence last year (2021: 3.7 per 10,000 births), this year's prevalence with only one registered foetus with holoprosencephaly (2022: 0.7 per 10,000 births) lies significantly below the basis prevalence. However, this was also the case in seven other years of the reporting period. In 2014, no arhinencephaly/holoprosencephaly was observed in Saxony-Anhalt.

The confidence interval of the basis prevalence of Saxony-Anhalt covers with slightly wider limits the confidence interval of the by EUROCAT indicated European prevalence (2010-2021: 1.5 per 10,000 births). Both prevalences are similarly high over the reporting period. Accordingly, the current annual prevalence of Saxony-Anhalt, compared to that of EUROCAT, can also be considered to be low.

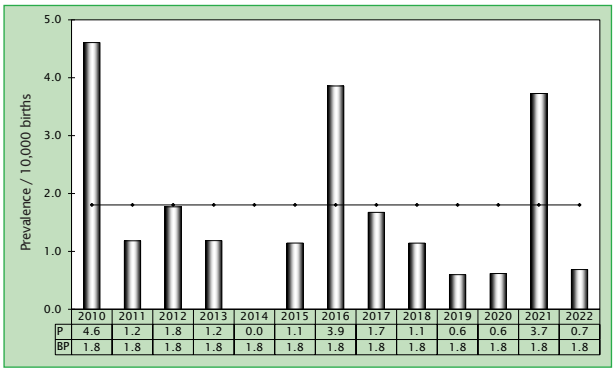
additional information:

Pregnancy outcome	1 x induced abortion
Sex	1 x male
Number of isolated malformations/MCA	1 x MCA

Arhincephaly occurred only once during the entire reporting period (2012), cyclopia only twice (2010, 2019).

Malformation combinations (MCA) or superordinated syndromes detected:

- Patau syndrome with: Cardiac malformation, medullary cystic kidneys, megacystis, craniofacial dysmorphia



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	4.6	1.2	1.8	1.2	0.0	1.1	3.9	1.7	1.1	0.6	0.6	3.7	0.7
BP	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8

Fig. 14: Development of prevalence/10,000 births with arhinencephaly/holoprosencephaly in Saxony-Anhalt since 2010

In 2022, one child/fetus with arhinencephaly/holoprosencephaly was observed per 14,570 births in Saxony-Anhalt.

10.8 Anophthalmos/Microphthalmos (Q11.0/Q11.1/Q11.2)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	3	2.06	↑
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.02	0.63 - 1.56	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.0	1.0 - 1.0	

With a basis prevalence of 1.0 per 10,000 births (2010-2021), the indicator malformation is one of the only rarely seen malformations. In the reporting period, no cases were observed in Saxony-Anhalt in two years and in four years only one case was observed. In 2022, there were three fetuses with anophthalmia/microphthalmia. The resulting annual prevalence (2.1 per 10,000 births) significantly exceeds that of the basis prevalence. However, the years 2010 and 2016 (2.3 and 2.2 per 10,000 births) showed even higher values.

The confidence limits of the basis prevalence of Saxony- Anhalt are wider than those of the confidence interval of the Europe-wide prevalence provided by EUROCAT (2010-2021: 1.0 per 10,000 births). While the prevalence of Saxony-Anhalt and the European prevalence are roughly at the same level, the annual prevalence of Saxony-Anhalt in 2022 lies significantly above the overall European prevalence.

additional information:

Pregnancy outcome	2 x Live birth 1 x Live birth deceased after 7 days of life
Sex	1 x male 2 x female
Number of isolated malformations/MCA	3 x MCA

Malformation combinations (MCA) or superordinated syndromes detected:

- Goldenhar syndrome with: bilateral combined sound conduction and perception disorder, anotia with atresia of the auditory canal and mandibular micrognathia left, microtia and preauricular appendage right
- Matthew Wood syndrome with: AVSD, truncus arteriosus communis, pulmonary valve malformation, coronary vascular malformation, mitral valve insufficiency, tricuspid insufficiency,
- pulmonary hypoplasia, duodenal atresia, pancreas anulare, hypoplastic kidneys and adrenal glands, persistent thymic hyperplasia, saddle nose
- VSD, combined sound conduction and perception disorder bilateral, pachygyria, corpus callosum agenesis, amblyopia ex ametropia, blepharophimosis, epilepsy, hemangioma (1.5 cm), right ovarian cyst

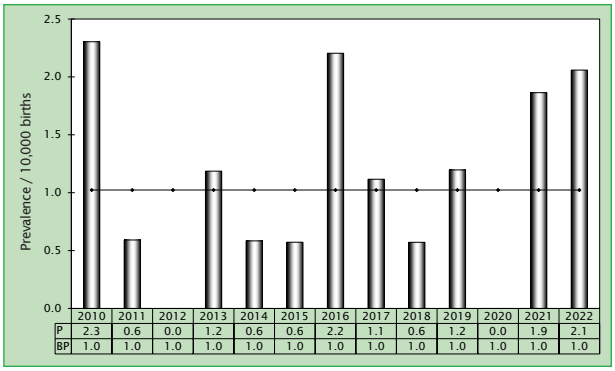


Fig. 15: Development of prevalence/10,000 births with anophthalmos/microphthalmos in Saxony-Anhalt since 2010

In 2022, one child/fetus with anophthalmia/microphthalmia was observed per 4,857 births in Saxony-Anhalt.

10.9 Microtia/Anotia (Q16.0/Q17.2)

Sachsen-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	3	2.06	↘
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.87	2.19 - 3.71	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	not specified	not specified	

With a prevalence of 2.1 per 10,000 births (three children), the indicator malformation microtia/anotia was in 2022, similar to the last two previous years, slightly below the basis prevalence of Saxony-Anhalt (2010-2021: 2.9 per 10,000 births).

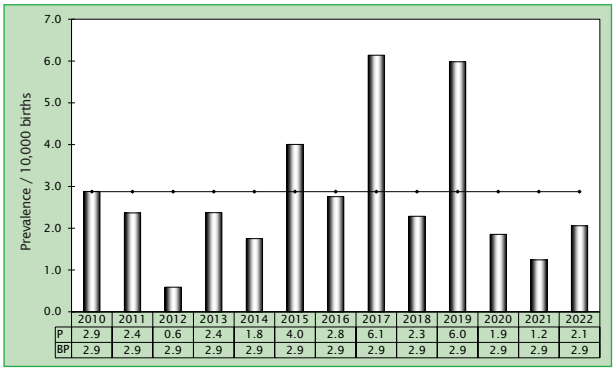
EUROCAT does not present a prevalence for the indicator malformation microtia/ anotia. For the grade IV auricular dysplasia (anotia) or atresia/ stricture of the bony auditory canal, EUROCAT gives a prevalene of 1.0 per 10,000 births (2010-2021). The basis prevalence of anotia determined for Saxony-Anhalt lies at 0.58 per 10,000 births (2010-2021;CI 0.30-0.89).

additional information:

Pregnancy outcome	2 x Live birth 1 x Live birth deceased after 7 days of life
Sex	2 x male 1 x female
Number of isolated malformations/MCA	3 x MCA

Detected malformation combinations (MCA) or superordinate syndromes:

- Goldenhar syndrome with: bilateral combined sound conduction and perception disorder with atresia of the auditory canal and mandibular micrognathia left, anophthalmia, preauricular appendage on the right
- Downs syndrome with: preductal aortic isthmus stenosis, AVSD, malposition of the heart, VSD, bilateral atresia of the auditory canal, dilated cerebral ventricles
- Sound conduction disorder left



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	2.9	2.4	0.6	2.4	1.8	4.0	2.8	6.1	2.3	6.0	1.9	1.2	2.1
BP	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9

Fig. 16: Development of prevalence/10,000 births with microtia/ anotia in Saxony-Anhalt since 2010

In 2022, one child/fetus with microtia/anaemia was observed per 4,857 births in Saxony-Anhalt.

10.10 Tetralogy of Fallot/Pentalogy (Q21.3/Q21.80)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	5	3.43	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.61	2.83 - 4.53	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.0	3.5 - 4.0	

The complex congenital cardiac malformation tetralogy of Fallot is a combination of pulmonary stenosis, VSD, riding aorta and right ventricular hypertrophy and is characterized by reduced pulmonary perfusion. Fallot pentalogy shows aditioanlly an ASD. The indicator malformation tetralogy of Fallot includes pentalogy. In the 2022 birth cohort in Saxony-Anhalt, tetralogy of Fallot occurred in five children/fetuses. This year's prevalence of 3.4 per 10,000 births (2022) is inconspicuous in the range of the basis prevalence of Saxony-Anhalt (2010-2021: 3.6 per 10,000 births).

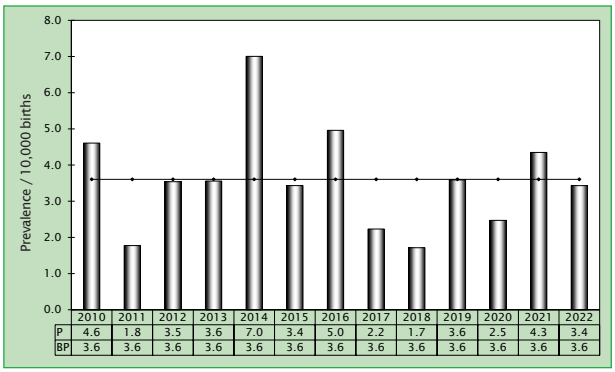
The confidence interval of the basis prevalence of Saxony-Anhalt corresponds approximately to the overall prevalence of the European register (2010-2021: 4.0 per 10,000 births). However, the confidence interval of Saxony-Anhalt has a wider range than that of the European overall prevalence.

additional information:

Pregnancy outcome	4 x Live birth 1 x Spontaneous abortion
Sex	4 x male 1 x female
Number of isolated malformations/MCA	5 x MCA

Malformation combinations (MCA) or superordinated syndromes detected:

- DORV
- ASD II, fused labia
- ASD at full term infant
- Corpus callosum agenesis
- Left inguinal hernia at full term infant



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	4.6	1.8	3.5	3.6	7.0	3.4	5.0	2.2	1.7	3.6	2.5	4.3	3.4
BP	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6

Fig.17: Development of prevalence/10,000 births with Tetralogy of Fallot (Q21.3) in Saxony-Anhalt since 2010

In 2022, one child/fetus with tetralogy of Fallot was observed per 2,914 births in Saxony-Anhalt.

10.11 Transposition of great vessels - TGV (Q20.1/Q20.3)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	6	4.12	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.87	3.96 - 5.93	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.0	5.0 - 5.5	

One of the most severe cyanotic congenital cardiac malformations, transposition of the great arteries (TGA), occurs when the aorta and the pulmonary artery are interchanged. Six children/fetuses with TGA were reported in 2022 to the Monitoring of Congenital Malformations. This results in an average annual prevalence of Saxony-Anhalt of 4.1 per 10,000 births. After a maximum value of the reporting period was registered in the previous year (2021: 8.1 per 10,000 births), the current annual prevalence in 2022 is in the lower normal range of the basis prrevalence of Saxony-Anhalt (2010-2021: 4.9 per 10,000 births).

When comparing the prevalences of Saxony-Anhalt with the by EUROCAT indicated European prevalence (2010-2021: 5,0 per 10,000 births), both confidence intervals of the prevalence of 2010- 2021 have approximately the same level. The confidence interval of the basis prevalence of Saxony-Anhalt however, spans a wider range due to the smaller numbers.

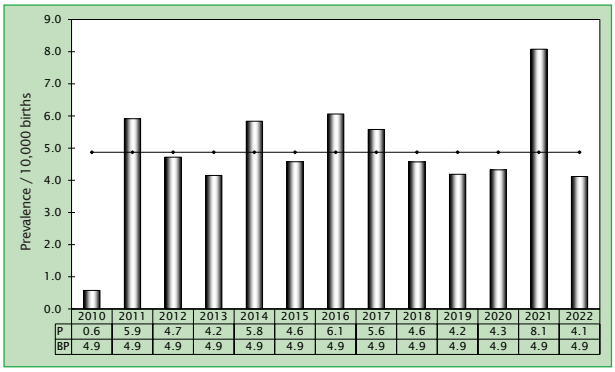
additional information:

Pregnancy outcome	5 x Live birth 1 x induced abortion
Sex	3 x male 3 x female
Number of isolated malformations/MCA	5 x MCA 1 x isolated

In one fetus, multiple severe malformations in several organ systems were seen in the 18th week of gestation and the pregnancy was terminated prematurely. Two live births were prenatally not suspicipous. In two cases the cardiac malformation was detected prenatally and the children were delivered in a specialized clinic.

Malformation combinations (MCA) or superordinated syndromes detected:

- Omphalocele, club hand with missing radius left, lobe transposition, VSD, ureteral agenesis left, horseshoe kidney on both sides, lung hypoplasia on both sides, malformation of the gallbladder, mandibular retrognathia, low-set ears, laterally ascending eyelid axes
- postductal aortic isthmus stenosis, aortic hypoplasia, common ventricle, coronary vascular malformation
- postductal aortic isthmus stenosis, aortic hypoplasia, bicuspid aortic valve, VSD
- tetralogy of Fallot
- VSD



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	0.6	5.9	4.7	4.2	5.8	4.6	6.1	5.6	4.6	4.2	4.3	8.1	4.1
BP	4.9	4.9	4.9	4.9	4.9	4.9	4.9	4.9	4.9	4.9	4.9	4.9	4.9

Fig. 18: Development of prevalence/10,000 births with transposition of great vessels in Saxony-Anhalt since 2010

In 2022, one child/fetus with transposition of the great vessels was observed per 2,428 births in Saxony-Anhalt.

10.12 Hypoplastic left heart syndrom (Q23.4)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	5	3.43	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.63	1.98 - 3.43	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.0	2.5 - 3.0	

The indicator malformation left ventricular hypoplasia is a very serious cardiac malformation complex. In 2022, five children/fetuses were affected in Saxony-Anhalt. The resulting annual prevalence (2022: 3.4 per 10,000 births) is within the confidence interval of the basis prevalence of Saxony-Anhalt (2010-2021: 2.6 per 10,000 births), and can be classified just below the upper limit.

The basis prevalence of Saxony-Anhalt for the years 2010-2021 and the European prevalence provided by EUROCAT (2010-2021: 3.0 per 10,000 births) are similarly high, although the confidence interval of Saxony-Anhalt has a much wider range.

additional information:

Pregnancy outcome	1 x Live birth 2 x Live birth deceased by the 7th day of life 1 x Spontaneous abortion 1 x induzierter Abort
Sex	3 x male 2 x female
Number of isolated malformations/MCA	3 x MCA 2 x isolated

Two children died within the first 24 hours, even before they could be operated on. In both cases no cardiac malformations were reported by prenatal ultrasound screening.

Malformation combinations (MCA) or superordinated syndromes detected:

- Down`s syndrome
- Aortic isthmus stenosis
- DIV

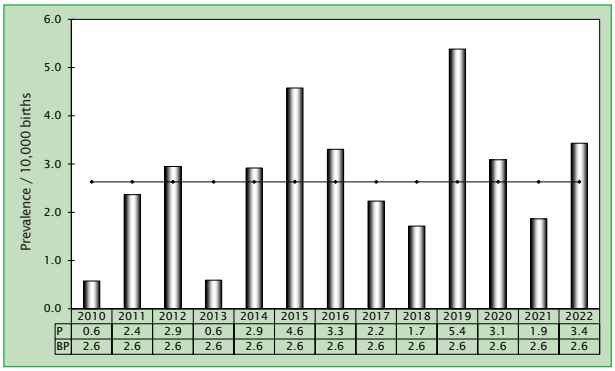


Fig. 19: Development of prevalence/10,000 births with hypoplastic left heart syndrome (Q23.4) in Saxony-Anhalt since 2010

In 2022, one child/fetus with left ventricular hypoplasia syndrome was observed per 2,914 births in Saxony-Anhalt.

10.13 Coarctation of aorta (Q25.1)

	year of 2022		
Saxony-Anhalt	Anzahl	prevalence/ 10,000 births	Comparison with baseline prevalence
	10	6.86	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.85	4.85 - 6.99	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.0	4.0 - 4.0	

In 2022, the indicator malformation coarctation of aorta occurred 10 times in Saxony-Anhalt. The resulting calculated prevalence of 6.9 per 10,000 births lies in the upper range of the confidence interval of the basis prevalence (2010-2021: 5.8 per 10,000 births). Over the reporting period, the prevalence of the indicator malformation coarctation of aorta varied between a minimum of 2.3 per 10,000 births (2013) and a maximum of 8.9 per 10,000 births (2017).

EUROCAT gives for the indicator malformation coarctation of aorta an overall prevalence of only 4.0 per 10,000 births (2010-2021). Similar to the fact, that the prevalence interval of the basis prevalence of Saxony-Anhalt exceeds the overall prevalence of the European malformation registers, this year's prevalence of Saxony-Anhalt can be found far above it.

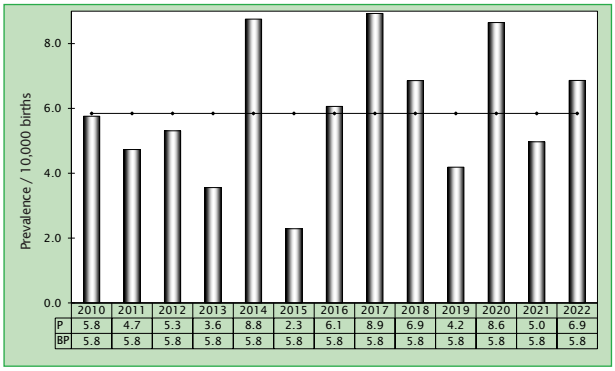
additional information:

Pregnancy outcome	7 x Live birth 1 x Live birth deceased by the 7th day of life 1 x Live birth deceased after 7 days of life 1 x induced abortion
Sex	5 x male 5 x female
Number of isolated malformations/MCA	9 x MCA 1 x isolated

A total of 6 serious cardiac malformations were detected prenatally, in three cases also a coarctation of aorta was described prenatally. One child with extensive cardiac malformations was operated on in a heart center, but died at the age of approximately six months. Seven children with coarctation of aorta were surgically corrected in a specialized heart center.

Malformation combinations (MCA) or superordinated syndromes detected:

- Downs syndrome with: AVSD, malposition of the heart,VSD, bilateral microtia and atresia of the auditory canal, dilated cerebral ventricles
- Turner syndrome
- Hypoplastic left heart syndrome
- DORV, aortic hypoplasia, common ventricle, coronary vascular malformation
- Dextro-transposition of the aorta, aortic hypoplasia, bicuspid aortic valve, VSD
- bilateral renal dysplasia and pulmonary hypoplasia
- Pulmonary valve insufficiency, PFO at full term infant
- bicuspid aortic valve, ASD at full term infant
- VSD, PFO at full term infant



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	5.8	4.7	5.3	3.6	8.8	2.3	6.1	8.9	6.9	4.2	8.6	5.0	6.9
BP	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8

Fig. 20: Development of prevalence/10,000 births with coarctation of aorta in Saxony-Anhalt since 2010

In 2022, one child/fetus with aortic isthmus stenosis was observed per 1,457 births in Saxony-Anhalt.

10.14 Cleft lip with or without cleft palate (Q36./Q37.)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	8	5.49	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	13.15	11.63 - 14.82	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	8.5	8.5 - 9.0	

The Monitoring of Congenital Malformations registered in 2022 only eight children/fetuses with the indicator malformation cleft lip and cleft lip with celft palate, i.e. with clefts of the upper lip with or without clefting of the alveolar ridge or the hard palate. A cleft lip with cleft palate was reported 7 times and once a cleft upper lip. A cleft lip and cleft jaw did not occur.

In the last 30 years, cleft lip and celft palate was not registered with such a low annual prevalence than in the current year (2022: 5.5 per 10,000 births). This minimum value is significantly below the normal range of the basis prevalence of Saxony-Anhalt (2010-2021: 13.2 per 10,000 births). At the beginning of the reporting period, the prevalence rose slightly until 2015 and since a maximum value was reached (2015:16.6 per 10,000 births), it has been falling again. The trend analysis (Chapter 10.38) therefore shows a significantly non-linear proportion and the development of the prevalence of the indicator malformation
(2009-2022) is classified as a non-linear change.

Compared to the prevalence of the EUROCAT registers (2010-2021: 8.5 per 10,000 births), the basis prevalence of Saxony-Anhalt for cleft lip and cleft lip with cleft palate is estimated to be considerably higher. However, the current annual prevalence (2022) of Saxony-Anhalt lies well below the European standard range.

additional information:

Pregnancy outcome	6 x Live birth 2 x induced abortion
Sex	7 x male 1 x female
Number of isolated malformations/MCA	3 x MCA 5 x isolated

A rare bilateral cleft lip and palate was reported twice, once in connection with bilateral conductive hearing loss. In the case of unilateral cleft lip with cleft palate, the left side is more frequently affected. This was also the case in 2022: of the four unilateral cleft lips with cleft jaw and palate, three were on the left and one on the right side and one cleft lip with cleft palate was on the right side. In case of one termination of pregnancy, there is no information about the side of appearence.

Malformation combinations (MCA) or superordinated syndromes detected:

- CATCH 22 (deletion 22q11.2)
- bilateral sound conduction disorder and delayed hip maturation, hypertrophied nails on the right
- facial cleft, midface hypoplasia, hypertelorism, maxillary micrognathia

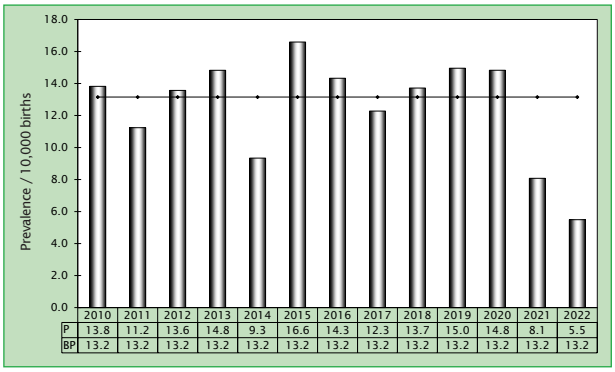


Fig. 21: Development of prevalence/10,000 births with cleft lip with or without cleft palate (Q36./Q37.) in Saxony-Anhalt since 2010

In 2022, one child/fetus with cleft lip and cleft lip and palate was observed per 1,821 births in Saxony-Anhalt.

10.15 Cleft palate (Q35.1/Q35.3/Q35.5/Q35.9)

	year of 2022		
Sachsen-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	10	6.86	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	7.06	5.96 - 8.31	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	6.0	5.5 - 6.0	

Cleft palates are clefts of the hard and soft palate in which there is no lip involvement. They occur in the 8th-10th week of gestation due to missing or insufficient fusion of the two paired palatal processes. As of birth year 2022, ten children/fetuses in Saxony-Anhalt were registed with cleft palates. The resulting prevalence of 6.9 per 10,000 births lies inconspicuously within the range of the basis prevalence (2010-2021: 7.1 per 10,000 births).

The confidence interval of the basis prevalence as well as the annual prevalence of Saxony-Anhalt are slightly above the interval of the average prevalence of the European registers (2010-2021: 6.0 per 10,000 births).

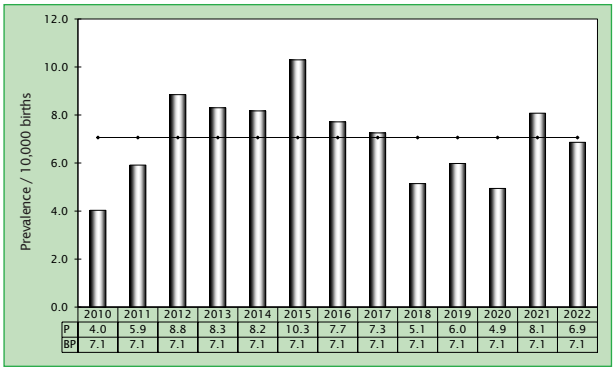
All cleft palates in 2022 were described as bilateral (7 x) or median (2 x), once no information is available.

additional information:

Pregnancy outcome	8 x Live birth 1 x Spontaneous abortion 1 x induced abortion
Sex	5 x male 5 x female
Number of isolated malformations/MCA	5 x MCA 5 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- Patau syndrome with: hydrocephaly
- severe microcephaly, bilaterl cleft of the hard and soft palate, missing ovaries, clubfeet, low-set ears, hypertelorism, macroglossia, cleft tongue
- Franceschetti syndrome with: bilateral sound conduction disorder
- and preauricular appendages, dysplastic ears, mandibular micrognathia, PFO at preterm infant
- ASD II, tricuspid regurgitation, non-haemodynamically effective PDA at full term infants, subluxation of the right hip joint on the right and delayed hip maturation on the left, DUP II. grade left, inguinal hernia, ankyloglosson
- arachnoid cyst, dilated cerebral ventricles, delayed right hip maturation



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	4.0	5.9	8.8	8.3	8.2	10.3	7.7	7.3	5.1	6.0	4.9	8.1	6.9
BP	7.1	7.1	7.1	7.1	7.1	7.1	7.1	7.1	7.1	7.1	7.1	7.1	7.1

Fig. 22: Development of prevalence/10,000 births with cleft palate in Saxony-Anhalt since 2010

In 2022, one child/fetus with cleft palate was observed per 1,457 births in Saxony-Anhalt.

10.16 Choanal atresia (Q30.0)

Sachsen-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	4	2.75	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.58	1.93 - 3.38	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.0	1.0 - 1.0	

The closure of the transition from the nasal cavity to the pharynx is referred to as choanal atresia. The indicator malformation choanal atresia only includes stenoses that require treatment, low-grade stenoses are excluded. After no child/fetus with choanal atresia was diagnosed in Saxony-Anhalt last year, four affected children were recorded in 2022. This results in a prevalence of 2.8 per 10,000 births. The annual prevalence rates fluctuate between very low values at the beginning of the reporting period and as well as in the years 2018 and 2021, each with a maximum of one child (0.6 per 10,000 births) and high values in the middle of the reporting period (2014, 2015, 2016) with at least eight children (maximum: 5.5 per 10,000 births). The trend analysis in Chapter 10.38 therefore shows a non-linear change over the years 2009-2022.

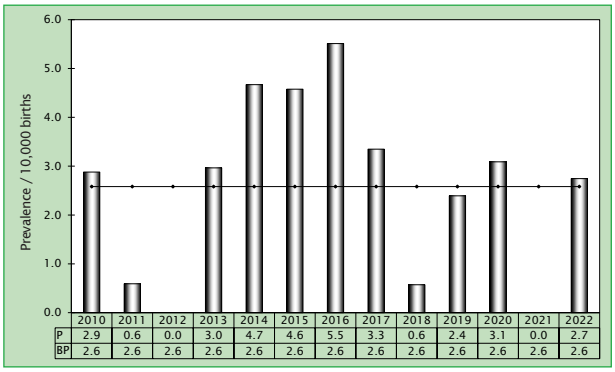
When comparing the prevalences of the indicator malformation choanal atresia of Saxony-Anhalt for the year 2022, as well as for the reporting period, with the prevalence provided by EUROCAT of the European registries for 2010-2021 (1.0 per 10,000 births), these are significantly above this.

additional information:

Pregnancy outcome	3 x Live birth 1 x Live birth deceased after 7 days of life
Sex	3 x male 1 x female
Number of isolated malformations/MCA	2 x MCA 2 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- Edwards syndrome (mosaic) with: bilateral lumbosacral spina bifida with hydrocephaly, VSD, ectopia ani, megacystis, epilepsy
- DUP IV. degree left and III degree right, megaureters, left ureteral stenosis, bladder neck obstruction, posterior urethral valves



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	2.9	0.6	0.0	3.0	4.7	4.6	5.5	3.3	0.6	2.4	3.1	0.0	2.7
BP	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6

Fig. 23: Development of prevalence/10,000 births with choanal atresia in Saxony-Anhalt since 2010

In 2022, one child/fetus with choanal atresia was observed per 3,643 births in Saxony-Anhalt.

10.17 Oesophageal atresia/-stenosis/-fistula (Q39.0-Q39.4)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	3	2.06	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.68	2.02 - 3.49	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.5	2.5 - 3.0	

Three children were born with esophageal atresia/stenosis/fistula in Saxony-Anhalt in 2022. This corresponds to an annual prevalence of 2.1 per 10,000 births. For the third year in succession, as in most years of the reporting period, the prevalence in 2022 was inconspicuously within the range of the basis prevalenve of Saxony-Anhalt (2010-2021: 2.7 per 10,000 births). A maximum of 4.7 per 10,000 births appeared in 2012, a minimum in 2014 (0.6 per 10,000 births).

The confidence interval of the basis prevalence of Saxony-Anhalt covers the interval limits of the overall prevalence of the European registers given by EUROCAT of the European registers (2010-2021: 2.5 per 10,000 births) as a result of the smaller numbers.

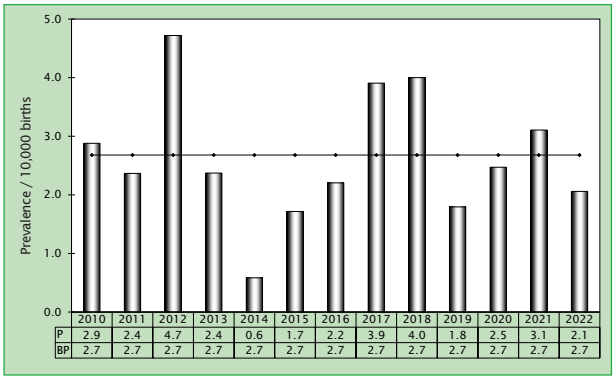
additional information:

Pregnancy outcome	3 x Live birth
Sex	2 x male 1 x female
Number of isolated malformations/MCA	2 x MCA 1 x isolated

In all three children with atresia of the esophagus, a fistula (type Vogt III b) was present between the trachea and the lower esophageal pocket. Once the malformation was discovered prenatally, twice a polyhydramnios was detected during the prenatal ultrasound screening.

Malformation combinations (MCA) or superordinated syndromes detected:

- Tracheomalacia, vascular ring through the anomalous right subclavian artery, PFO and stenosis of the pulmonary artery at full term infant, plexus cyst
- Duodenal atresia



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	2.9	2.4	4.7	2.4	0.6	1.7	2.2	3.9	4.0	1.8	2.5	3.1	2.1
BP	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7

Fig. 24: Development of prevalence/10,000 births with oesophageal atresia/stenosis/fistula in Saxony-Anhalt since 2010

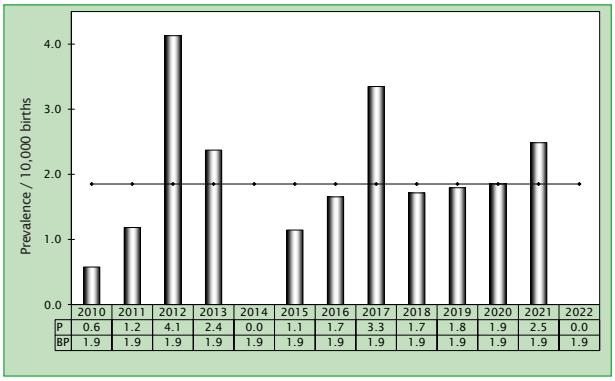
In 2022, one child/fetus with esophageal atresia/stenosis/fistula was observed per 4,857 births in Saxony-Anhalt.

10.18 Small intestinal atresia atresia/stenosis (Q41.1/Q41.2/Q41.8/Q41.9)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	0	0.0	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.85	1.31 - 2.54	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.0	1.0 - 1.0	

The indicator malformation small intestinal atresia/stenosis is with a basis prevalence of 1.9 per 10,000 births in Saxony-Anhalt (2010-2021) a not very frequently occurring malformation. The diagnosis of this malformation is usually only made postnatally. It occurs on average in Saxony-Anhalt three to four times per year. In the year 2022, congenital small intestinal atresia/stenosis did not occur at all, as in 2014. In the year 2012, a maximum value of 4.1 per 10,000 births was registered.

The basis prevalence of small intestinal atresia/stenosis of Saxony-Anhalt exceeds the prevalence value given by EUROCAT. The lower confidence limit of the basis prevalence of Saxony-Anhalt lies significantly above the European confidence interval.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	0.6	1.2	4.1	2.4	0.0	1.1	1.7	3.3	1.7	1.8	1.9	2.5	0.0
BP	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9	1.9

Fig. 25: Development of prevalence/10.000 births with small intestinal atresia/stenosis in Saxony-Anhalt since 2010

In 2022, no child/fetus with small bowel atresia/stenosis was observed in Saxony-Anhalt.

10.19 Anorectal atresia/stenosis (Q42.0-Q42.3)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	4	2.75	↘
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.61	2.83 - 4.53	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.5	3.5 - 3.5	

Four children (prevalence: 2.7 per 10,000 births) were registered in 2022 with the indicator malformation rectal and anal atresia/stenosis in Saxony-Anhalt. This means, that the current prevalence is slightly lower than expected and lies slightly below the tolerance range of the basis prevalence (2010-2021: 3.6 per 10,000 births).
A maximum value of the annual prevalence of the reporting period occurred in 2010 with 6.3 per 10,000 births. Since then, the figures have mainly been falling and the prevalences are in or below the normal range. Figure 31 (Chapter 10.38) shows that as in the last six annual reports, over the previous 14-year period, a significant downward trend for rectal and anal atresia/stenosis is recognizable. The percentage change for 2009-2022 lies at -15.07 % (CI -22.73 % to -4.25 %).

This year's prevalence of Saxony-Anhalt corresponds to the European average (2010-2021: 3.5 per 10,000 births). The confidence interval of the basis prevalence of Saxony-Anhalt coincides with that of the prevalence of the EUROCAT register. Due to the smaller numbers, it is wider than the interval of the overall European prevalence.

Rectal and anal atresia are often only recognized after birth. This was also the case in the current year. In case of one child, a rectal atresia with fistula occurred in 2022 as part of a hypospadias complex with complete penoscrotal clefting. Three other children were diagnosed with anal atresia, one with fistula, one without fistula and once there was no indication of presence of a fistula.

additional information:

Pregnancy outcome	4 x Live birth
Sex	3 x male 1 x female
Number of isolated malformations/MCA	2 x MCA 2 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- VSD, perineal hypospadias, scrotum bipartum
- perineal hypospadias, scrotum bipartum, hemangioma

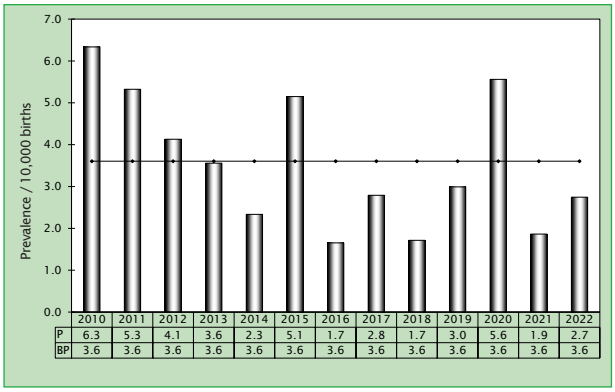


Fig. 26: Development of prevalence/10,000 births with anorectal atresia/-stenosis in Saxony-Anhalt since v2010

In 2022, one child/fetus with rectal and anal atresia/ stenosis was observed per 3,643 births in Saxony-Anhalt.

10.20 Hypospadias (Q54.0-Q54.3/Q54.8/Q54.9)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	27	18.53	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	23.48	21.43 - 25.68	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	18.5	18.5 - 19.0	

With a basis prevalence of 23.5 per 10,000 births for the period of 2010-2021, hypospadias is the second most common indicator malformation in the reporting period. In 2022, however, only 27 hypospadias were observed in Saxony-Anhalt. The resulting annual prevalence (2022: 18.5 per 10,000 births) is very low and lies significantly below the basis prevalence. Calculated on the basis of 7,440 live and stillborn boys the current prevalence (2022) lies at 36.3 per 10,000 boys, which also falls within the confidence interval of the basis prevalence (2010-2021: 45.80 per 10,000 boys; CI 41.81-50.08).
By far the highest rate of hypospadias was seen in the the first year of the reporting period, in 2010 (29.9 per 10,000 births), and the second highest rate in the following year (2011: 29.0 per 10,000 births). Since this peak, the prevalence values have been falling and are either within the confidence interval of the basis prevalence or below it, as in 2019, 2021 and 2022. This development is reflected in the trend calculation over the period from 2009-2022 (Chapter 10.38). It reflects a significant downward trend with a percentage change of -4.54 % (CI -8.44 % to -0.27 %).

In comparison to the by EUROCAT determined European prevalence (2010-2021: 18.5 per 10,000 births), Saxony-Anhalt's basis prevalence is to be rated as extraordinarily high. However, this year's annual prevalence is within the confidence interval of the overall European prevalence.

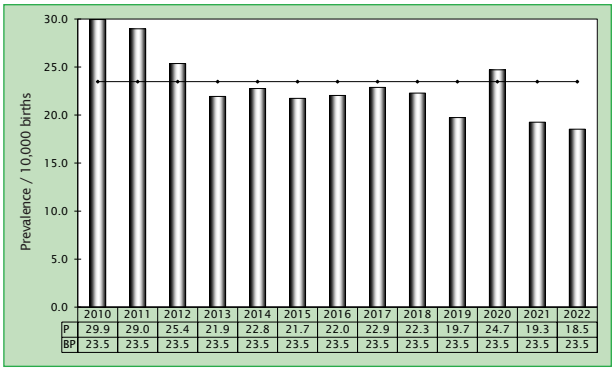
additional information:

Pregnancy outcome	26 x Live birth 1 x induced abortion
Sex	27 x male
Number of isolated malformations/MCA	6 x MCA 21 x isolated

17 boys had a mild form of hypospadias, a glandular hypospadias. Six of them had penile hypospadias, one penoscrotal and three perineal hypospadias.
The majority of the boys, who were affected by hypospadias were born alive in 2022, two thirds of them were born as full term infants.

Malformation combinations (MCA) or superordinated syndromes detected:

- Skraban-Deardorff syndrome with: craniofacial dysmorphia, hypoplastic nasal bone
- VSD, rectal atresia with fistula, scrotum bipartum
- Anal atresia without fistula, scrotum bipartum, hemangioma
- VSD, bilateral delayed hip maturation
- Megaureter, DUP I. degree left
- Palmure



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	29.9	29.0	25.4	21.9	22.8	21.7	22.0	22.9	22.3	19.7	24.7	19.3	18.5
BP	23.5	23.5	23.5	23.5	23.5	23.5	23.5	23.5	23.5	23.5	23.5	23.5	23.5

Fig. 27: Development of prevalence/10,000 births with hypospadias in Saxony-Anhalt since 2010

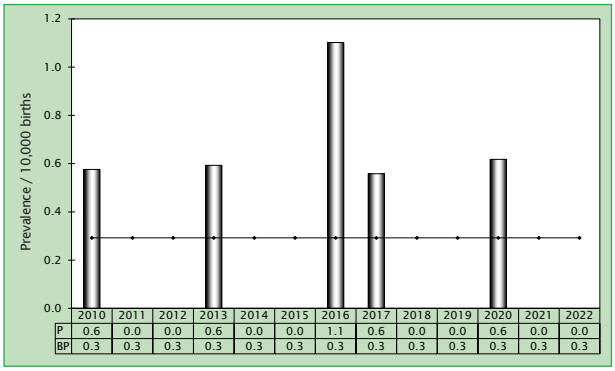
In 2022, one child/fetus with hypospadias was observed in Saxony-Anhalt for every 540 births (276 boys) was observed.

10.21 Epispadias (Q64.0)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	0	0.0	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births		Confidence interval (CI 95%)
	0.29		0.11 - 0.64
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births		Confidence interval (CI 95%)
	no information		no information

The indicator malformation epispadias is only observed very occasionally. Since 2010 only six children have been diagnosed with epispadias in Saxony-Anhalt. During the recent eight years of the reporting period, including the current year (2022), epispadias was not registered at all.

European-wide comparative values for the prevalence of epispadias are not available from EUROCAT.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	0.6	0.0	0.0	0.6	0.0	0.0	1.1	0.6	0.0	0.0	0.6	0.0	0.0
BP	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Fig. 28: Development of prevalence/10,000 births with epispadias in Saxony-Anhalt since 2010

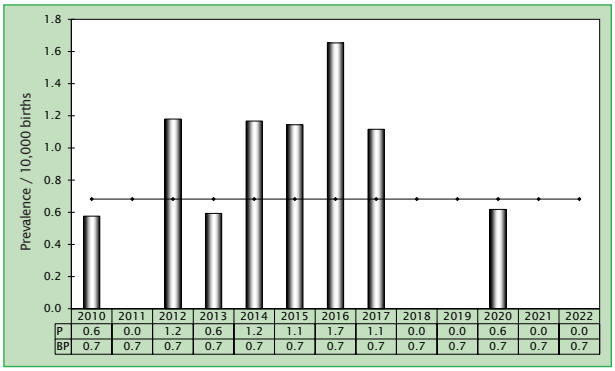
In 2022, no child/fetus with epispadias was observed in Saxony-Anhalt.

10.22 Indeterminate sex (Q56.)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	0	0.0	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.68	0.37 - 1.14	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.5	0.5 - 0.5	

Indifferent sex is a very rarely occurring malformation. Since 2018, only one child (2020) with the indicator malformation indifferent sex has been registered. Also in the current year (2022), this malformation was not detected in Saxony-Anhalt. The maximum prevalence of the reporting period was registered with three children in 2016 at 1.7 per 10,000 births.

EUROCAT indicates for the indifferent sex a prevalence of 0.5 per 10,000 births (2010-2021). The interval of the overall prevalence determined by EUROCAT of the European congenital malformation registers is due to the observed, much larger population smaller, than the prevalence interval of the basis prevalence of Saxony-Anhalt and is covered by the lower edge of the wider interval.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	0.6	0.0	1.2	0.6	1.2	1.1	1.7	1.1	0.0	0.0	0.6	0.0	0.0
BP	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7

Fig. 29: Development of prevalence/10,000 births with indeterminate sex in Saxony-Anhalt since 2010

In 2022, no child/fetus of indifferent sex was observed in Saxony-Anhalt.

10.23 Potter sequence (Q60.6)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	3	2.06	↘
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.78	2.10 - 3.60	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.5	1.0 - 1.5	

In case of a Potter sequence, both kidneys of a child/ fetus are either not present or not functional (polycystic or multicystic-dysplastic). An oligohydramnios develops, which is then the cause of further malformations such as club feet and lung hypoplasia. The subsequent malformations are not listed individually as malformations in the report. As in the previous year, this **year's prevalence** for the indicator malformation Potter Sequence **(2022: 2.1 per 10,000 births)** can be considered as rather low. Since the registration of a maximum value during the reporting period (2016: 5.0 per 10,000 births), prevalence rates have been falling. The current annual prevalence (2022) lies slightly below the basis prevalence (2010-2021: 2.8 per 10,000 births). Since 2017, the annual prevalence rates have always been within or below the confidence interval of the basis prevalence.

The confidence interval of the basis prevalence of Potter sequence in Saxony-Anhalt lies considerably below the average European prevalence provided by EUROCAT (2010-2021: 1.5 per 10,000 births). This year's prevalence value of Saxony-Anhalt is also well above the upper confidence limit of the prevalence given by EUROCAT.

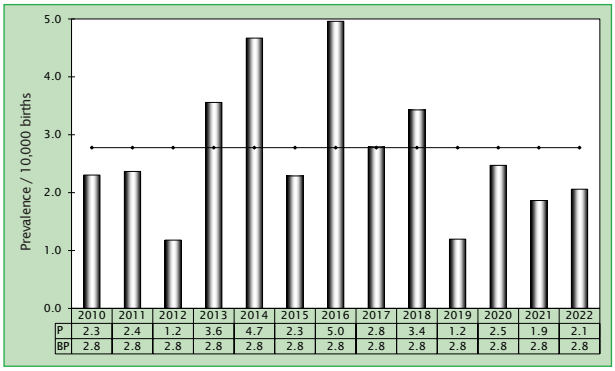
In 2022, both children and the fetus were affected by bilateral renal agenesis.

additional information:

Pregnancy outcome	1 x Live birth deceased by the 7th day of life 1 x Stillbirth 1 x induced abortion
Sex	3 x male
Number of isolated malformations/MCA	1 x MCA 2 x isoalted

Malformation combinations (MCA) or superordinated syndromes detected:

- VSD



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	2.3	2.4	1.2	3.6	4.7	2.3	5.0	2.8	3.4	1.2	2.5	1.9	2.1
BP	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8

Fig. 30: Development of prevalence/10,000 births with Potter sequence in Saxony-Anhalt since 2010

In 2022, one Potter sequence per 4.857 births was registered in Saxony-Anhalt.

NOTE

What are ACE inhibitors and what is Sartan fetopathie?

The group of pharmaceuticals „sartans" were developed from ACE inhibitors. Mainly used in the antihypertensive therapy, they have a teratogenic effect in case of maternal intake during second and third trimenon of pregnancy. The suspected pathomechanism of both substances results in a reduced perfusion of the foetal organs, in particular of the kidneys. That means both substances interrupt the renin-angiotensin system at different points. The result of such a fetal damage is an intrauterine oliguria. Since amniotic fluid production depends from the second trimenon on mainly from fetal urine production, an oligohydramnios can occur which might be diagnosed by prenatal ultrasound screening. This leads into occurrence of a potter sequence with lung and thorax hypoplasia, limbs deformity, characteristic face and further consequential problems. Affected infants often suffer postnatal from a renal failure which is in most cases not reversible. Additionally, a hypoplasia/dysplasia of the cranial bone can occur at insufficient cranial ossification (it is also possible that only gaping cranial sutures are present).

For further detailed information about this topic, please visit the website of the pharmacovigilance and advisory centre for embryonic toxicology (www.embyotox.de).

10.24 Renal agenesis, unilateral (Q60.0/Q60.2)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	9	6.18	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.41	4.45 - 6.51	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.0	4.0 - 4.0	

After two very low annual prevalence rates for the indicator malformation unilaterally missing kidney in the years 2020 and 2021, we registered nine affected children/foetuses in the current year, which is slightly more frequently again. For 2022, the **prevalence value** is calculated at **6.2 per10,000 births**, which is in the upper segment of the basis prevalence of Saxony-Anhalt for this malformation (2010-2021: 5.4 per 10,000 births).

The comparison with the prevalence provided by EUROCAT for 2010-2021 (4.0 per 10,000 births) suggests a prevalence rate for Saxony-Anhalt for both 2022 and the entire reporting period, far above the European average.

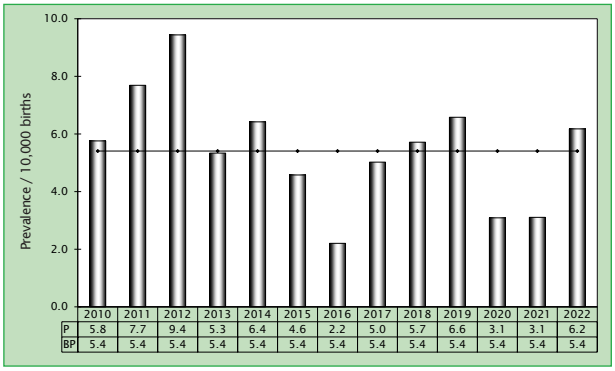
additional information:

Pregnancy outcome	7 x Live birth 2 x induced abortion
Sex	5 x male 4 x female
Number of isolated malformations/MCA	5 x MCA 4 x isolated

Agenesis of the kidney occurred 4 times on the left and five times on the right side. In two fetuses, unilateral renal agenesis occured among other severe malformations and the pregnancy was terminated prematurely.

Malformation combinations (MCA) or superordinated syndromes detected:

- Hydrocephaly, DIV, VSD, pulmonary valve stenosis
- VSD, non-haemodynamically effective PDA at full term infant
- VSD, hemangioma
- deformed skull (indentations), DUP III. degree right
- Clubfoot right



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	5.8	7.7	9.4	5.3	6.4	4.6	2.2	5.0	5.7	6.6	3.1	3.1	6.2
BP	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4

Fig. 31: Development of prevalence/10,000 births with unilateral renal agenesis in Saxony-Anhalt since 2010

In 2022, one child/fetus with unilateral renal agenesis was observed per 1,619 births in Saxony-Anhalt.

10.25 Cystic kidney (Q61.1-Q61.9)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	16	10.98	↑
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	7.16	6.05 - 8.42	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	no information	no information	

Polycystic kidneys are genetically caused. In this case numerous fluid-filled cysts are formed within the kidneys. With increasing kidney degeneration, kidneys lose their function due to the malformation, which eventually leads to kidney failure. With 16 children/fetuses with polycystic kidneys and the resulting second-highest annual **prevalence value** of the reporting period (**2022: 11.0 per 10,000 births**; maximum 2010: 11.5 per 10,000 births), the current annual prevalence exceeds the basis prevalence of Saxony-Anhalt (2010-2021: 7.2 per 10,000 births) significantly.

European comparative values for the prevalence of the indicator malformation polycystic kidneys are not available by EUROCAT.

additional information:

Pregnancy outcome	14 x Live birth 1 x Live birth deceased by the 7th day of life 1 x induced abortion
Sex	9 x male 7 x female
Number of isolated malformations/MCA	6 x MCA 10 x isolated

In case of one fetus with prenatally diagnosed Patau-syndrome, bilateral cystic kidneys were found in the 13th week of gestation among other serious malformations and the pregnancy was terminated prematurely. One child with aortic isthmus stenosis and bilateral multicystic renal dysplasia died on the second day of life.

Three further live births in 2022 had bilateral cystic kidney degeneration. In eleven children with unilateral cystic kidneys, the laterality of the malformation was balanced (5 x right, 5 x left, once no indication of the affected side).

Malformation combinations (MCA) or superordinated syndromes detected:

- Patau syndrome with: holoprosencephaly, cardiac malformation, megacystis, craniofacial dysmorphia
- preductal aortic isthmus stenosis, pulmonary hypoplasia
- DUP III. degree left, right renal hypoplasia and undescended testicles at full term infant
- left DUP II. degree and megaureter
- DUP II. degree right
- Hyperphenylalaninemia

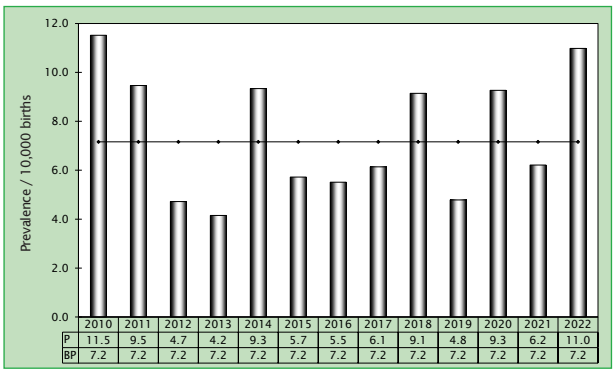


Fig. 32: Development of prevalence/10,000 births with cystic kidneys in Saxony-Anhalt since 2010

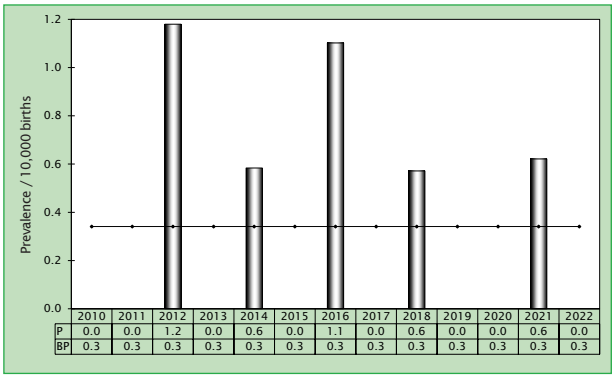
In 2022, one child with cystic kidney per 911 births was registered in Saxony-Anhalt.

10.26 Bladder Exstrophy (Q64.1)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	0	0.0	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.34	0.14 - 0.70	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	no information	no information	

Exstrophy of the urinary bladder is characterized by the lack of closure of the anterior abdominal wall. It is a malformation that is seen extremely rarely. If an epispadias is diagnosed at the same time, this is counted to the bladder exstrophy and is not evaluated individually.
The indicator malformation urinary bladder exstrophy was, as in the majority of the years of the reporting period (2010-2021), also in the current year (2022) not observed in Saxony-Anhalt.
Only in 2012 and 2016 two cases occurred as a maximum value, which means that in both years the upper confidence limit of the basis prevalence (2010-2021: 0.3 per 10,000 births) is already far exceeded. If there is exactly one case per year in Saxony-Anhalt, this corresponds to the normal range.

EUROCAT does not provide separate prevalence data for exstrophy of the bladder. For the urinary bladder exstrophy epispadias complex, a prevalence for 2010-2021 of the European registers is indicated with a value of 1.0 per 10,000 births (CI 1.0 - 1.5).



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	0.0	0.0	1.2	0.0	0.6	0.0	1.1	0.0	0.6	0.0	0.0	0.6	0.0
BP	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Fig. 33: Development of prevalence/10,000 births with bladder exstrophy in Saxony-Anhalt since 2010

In 2022, no bladder exstrophy was registered in Saxony-Anhalt.

10.27 Preaxial polydactyly (Q69.1/Q69.2)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	3	2.06	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.26	2.53 - 4.15	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	no information	no information	

In 2022, three children in Saxony-Anhalt were diagnosed with preaxial polydactyly. This means that after two years, with a prevalence in each case significantly above the basis prevalence (2020: 5.6 and 2021: 5.0 per 10,000 births), the **prevalence** of Saxony-Anhalt **(2022: 2.1 per 10,000 births)** lies again significantly below the basis prevalence (2010-2021: 3.3 per 10,000 births).
EUROCAT does not provide Europe-wide prevalence values for the indicator malformation preaxial polydactyly.

In only about one third of children/fetuses who have additionally fingers or toes, polydactyly affects the thumb or big toes. For polydactyly, preaxial and/or postaxial in total, the prevalence lies at 7.5 per 10,000 births in 2022. Even this prevalence does not reach the standard range of Saxony-Anhalt (2010-2021: 12.3 per 10,000 births) (chapter 9). For 2010-2021, EUROCAT calculates a Europe-wide prevalence for polydactylia of 10.5 per 10,000 births (CI 10.5-10.5).

additional information:

Pregnancy outcome	2 x Live birth 1 x Live birthv deceased by the 7th day of life
Sex	3 x female
Number of isolated malformations/MCA	1 x MCA 2 x isolated

Two children each had an additional right thumb. One child with thanatophoric dysplasia had, among other malformations, double thumbs on both sides. Preaxial polydactyly of the feet was not reported.

Malformation combinations (MCA) or superordinated syndromes detected:

- thanatophoric dysplasia type I with: bony thoracic malformation, pulmonary hypoplasia, left ventricular myocardial hypertrophy, prominent clitoris, low-set ears, bilateral brachydactyly and clinodactylyon of hands and feet

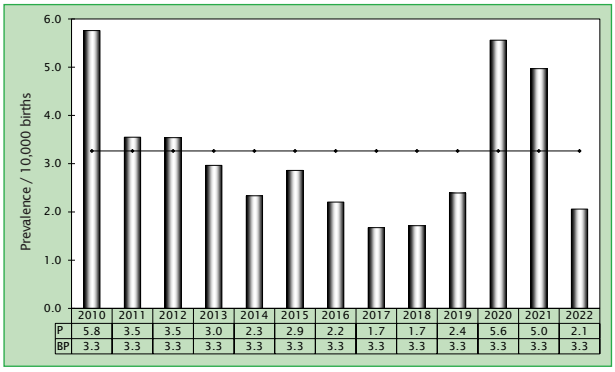


Fig. 34: Development of prevalence/10,000 births with preaxial polydactyly in Saxony-Anhalt since 2010

In 2022, one child/fetus with preaxial polydactyly was observed per 4,857 births in Saxony-Anhalt.

10.28 Limb reduction defects of both upper and lower limbs (Q71./Q72./Q73.)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	11	7.55	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	7.80	6.64 - 9.10	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.0	5.0 - 5.0	

ZAs of the year of birth 2022, eleven children/fetuses in Saxony-Anhalt were diagnosed with a reduction malformation of the extremities. This year's **prevalence (2022: 7.5per 10,000 births)** is similar to the basis prevalence of 7.8 per 10,000 births (2010-2021). Currently falling annual prevalence rates have been observed for the reduction malformations of the extremities since an increase was seen at the beginning of the reporting period up to a maximum value in 2012 (14.7 per 10,000 births). Over the period of the trend analysis (2009-2022) the change in prevalence is therefore classified as non-linear (Chapter 10.38).

Compared to the average prevalence of EUROCAT (2010-2021: 5.0 per 10,000 births), the basis prevalence of Saxony-Anhalt lies well above the normal range of the values of the European registers. The annual prevalence 2022 of Saxony-Anhalt also exceeds the European prevalence provided by EUROCAT.

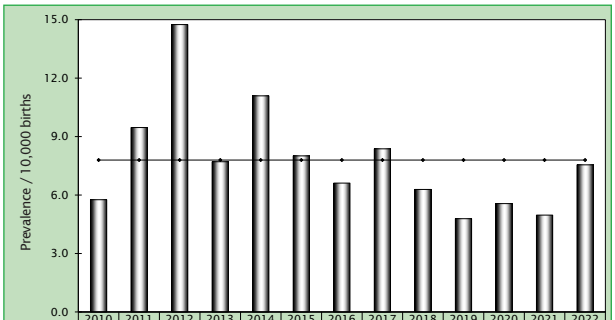
additional information:

Pregnancy outcome	4 x Live birth 1 x Live birth deceased by the 7th day of life 2 x Spontaneous abortion 4 x induced abortion
Sex	3 x male 7 x female 1 x no information
Number of isolated malformations/MCA	7 x MCA 4 x isolated

Only one fetus was affected by a bilateral reduction malformation of the extremities (club hands). There were two cases of right-sided reduction malformations and 6 times left-sided. Twice the laterality was not transmitted. Reduction malformations of the arms, hands and fingers were reported significantly more frequently (10x) than those of the lower extremities (1 x).

Malformation combinations (MCA) or superordinated syndromes detected:

- Edwards' syndrome with: Hypoplasia of the aorta, craniofacial dysmorphia
- omphalocele, DORV, lobe transposition, VSD, ureteral agenesis left, horseshoe kidney, bilateral lung hypoplasia, gallbladder malformation, mandibular retrognathia, low-set ears, laterally ascending eyelid axes
- Lumbar spina bifida with hydrocephaly
- Lung hypoplasia, malformation of the neck, sickle feet
- Amniotic cords on the left arm, low-set ears
- Left hand: syndactyly (digit II - V)
- Club feet



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	5.8	9.5	14.7	7.7	11.1	8.0	6.6	8.4	6.3	4.8	5.6	5.0	7.5
BP	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8

Fig. 35: Development of prevalence/10,000 births with limb reduction defects in Saxony-Anhalt since 2010

In 2022, one child/fetus with reduction malformations was observed per 1,325 births in Saxony-Anhalt.

10.29 Diaphragmatic hernia (Q79.0)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	5	3.43	↗
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.58	1.93 - 3.38	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.0	3.0 - 3.0	

With five affected children, the current **annual prevalence (2022: 3.4 per 10,000 births)** for the indicator malformation diaphragmatic hernia is slightly above the confidence interval of the basis prevalence of Saxony-Anhalt (2010-2021: 2.6 per 10,000 births). In the second half of the reporting period, three times (2018, 2020, 2021) an annual prevalence far above the upper confidence limit has been determined.

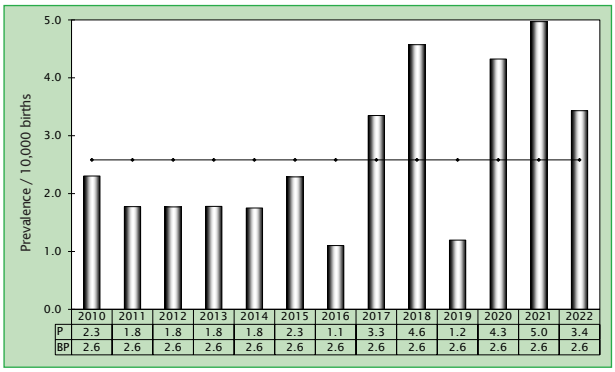
The confidence interval of the overall prevalence of the European malformation registers (2010-2021: 3.0 per 10,000 births) is at a slightly lower level than the basis prevalence of Saxony-Anhalt, but is completely covered by the wider confidence interval. The Saxony-Anhalt's annual prevalence for 2022 is therefore also above the European average prevalence.

additional information:

Pregnancy outcome	3 x Live birtht 1 x Live birth deceased by the 7th day of life 1 x induced abortion
Sex	3 x male 2 x female
Number of isolated malformations/MCA	1 x MCA 4 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- Triploidy with: hydrocephalus



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	2.3	1.8	1.8	1.8	1.8	2.3	1.1	3.3	4.6	1.2	4.3	5.0	3.4
BP	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6

Fig. 36: Development of prevalence/10,000 births with diaphragmatic hernia in Saxony-Anhalt since 2010

In 2022, one child/fetus with diaphragmatic hernia was observed per 2,914 births in Saxony-Anhalt.

10.30 Omphalocele (Q79.2)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	4	2.75	↘
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.61	2.83 - 4.53	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.0	4.0 - 4.0	

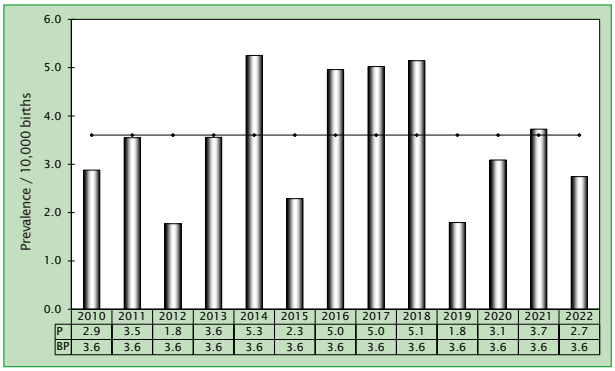
With four registered omphaloceles in 2022, the calculated annual **prevalence of 2.7 per 10,000 births**, which is close to the lower confidence limit, lies just outside the interval of the basis prevalence of Saxony-Anhalt (2010-2021: 3.6 per 10,000 births). The confidence interval of the basis prevalence of Saxony-Anhalt covers, due to the smaller population included, the narrower confidence interval of the European prevalence (2010-2021: 4.0 per 10,000 births). The prevalence of Saxony-Anhalt in 2022 is below the overall European prevalence.

additional information:

Pregnancy outcome	1 x Live birth 3 x induced abortion
Sex	2 x male 1 x female 1 x no information
Number of isolated malformations/MCA	4 x MCA

Malformation combinations (MCA) or superordinated syndromes detected:

- 2 x Edwards syndrome (1 x with hypoplastic nasal bone)
- DORV, lobe transposition, VSD, club hand with missing radius on the left, ureteral agenesis on the left, horseshoe kidney bilateral, bilateral lung hypoplasia, malformation of the gallbladder, mandibular retrognathia, low-set ears, lateral ascending eyelid axes
- VSD, pyloric hypertrophy, cholestasis



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	2.9	3.5	1.8	3.6	5.3	2.3	5.0	5.0	5.1	1.8	3.1	3.7	2.7
BP	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6

Fig. 37: Development of prevalence/10,000 births with omphalocele in Saxony-Anhalt since 2010

In 2022, one child/fetus with omphalocele per 3,643 births was observed in Saxony-Anhalt.

10.31 Gastroschisis (Q79.3)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	2	1.37	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.65	2.87 - 4.58	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.5	2.5 - 2.5	

As in the previous year, the indicator malformation gastrochisis occurred only twice in Saxony-Anhalt in 2022. The **current annual prevalence (2022: 1.4 per 10,000 births)** is significantly below the confidence interval of the basis prevalence (2010-2021: 3.7 per 10,000 births). In the second half of the reporting period, lower prevalence values were recorded on average than in the first half. However, a downward trend is not yet detectable. The confidence interval determined by EUROCAT across Europe of the prevalence for the years 2010-2021 (2.5 per 10,000 births) is far below the confidence interval of the basis prevalence of Saxony-Anhalt. This year's annual prevalence value of Saxony-Anhalt is still below the European comparative values.

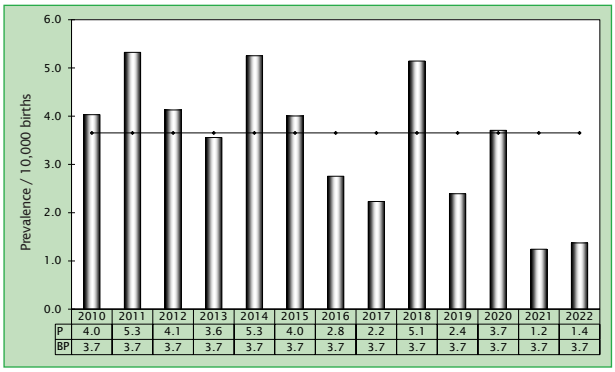
additional information:

Pregnancy outcome	2 x Live birth
Sex	2 x female
Number of isolated malformations/MCA	1 x MCA 1 x isolated

In both cases, the gastroschisis was noticed prenatally before the 20th week of gestation. They were delivered by primary caesarean section before the 35th week of pregnancy.

Malformation combinations (MCA) or superordinated syndromes detected:

- mitral valve insufficiency



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	4.0	5.3	4.1	3.6	5.3	4.0	2.8	2.2	5.1	2.4	3.7	1.2	1.4
BP	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7

Fig. 38: Development of prevalence/10,000 births with gastroschisis in Saxony-Anhalt since 2010

In 2022, one child/fetus with gastroschisis was observed per 7,285 births in Saxony-Anhalt.

10.32 Prune-Belly sequence (Q79.4)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	0	0.0	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.83	0.48 - 1.33	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.0	0.0 - 0.0	

In 2022, no child/fetus was registered in Saxony-Anhalt with a prune-belly sequence. The occurrence of this indicator malformation is rare. Between 2010 and 2021 there were only 17 affected infants in total. This results in a basis prevalence of the indicator malformation prune-belly sequence in Saxony-Anhalt of 0.8 per 10,000 births (2010-2021). The maximum prevalence (3.0 per 10,000 births) of the reporting period was reached in 2011.

Since two years, EUROCAT has been providing European prevalence figures for the prune-belly sequence. The comparison shows that the confidence interval of the Saxony-Anhalt basis prevalence of prune-belly sequence is considerably higher than the by EUROCAT indicated confidence interval of the overall prevalence (2010-2021: 0.0 per 10,000 births).

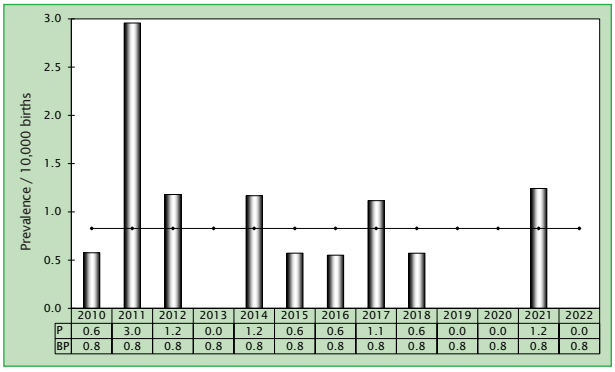


Fig. 39: Development of the prevalence/10,000 births with Prune belly syndrome in Saxony-Anhalt since 2010

In 2022, no child/fetus with prune-belly sequence was observed in Saxony-Anhalt.

10.33 Down´s syndrome - Trisomy 21 (Q90.)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	29	19.90	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	21.00	19.06 - 23.08	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	25.0	24.5 - 25.0	

In 2022, 29 children/fetuses in Saxony-Anhalt were diagnosed with Down syndrome. This results in an **annual prevalence (2022: 19.9 per 10,000 births)**, which can be located in the lower range of the confidence interval of the basis prevalence (2010-2021: 21.0 per 10,000 births). The European criterion of a rarely appearing disease of < 5.0 per 10,000 births does not apply to Down syndrome. For live births, the prevalence of Saxony-Anhalt (2010-2021) lies at 9.4 per 10,000 births. Down syndrome is one of the five most common major malformations (Chapter 9).

A comparison of the confidence interval of the basis prevalence of Saxony-Anhalt with that of the European registers (2010-2021: 25.0 per 10,000 births) shows, that the value of Saxony-Anhalt is far below this. The probability of developing trisomy 21 raises with higher maternal age. The reason for the higher Europe-wide prevalence level might be the fact that mothers in Saxony-Anhalt who give birth to their children are younger compared to the EU average (2013-2021: 29.5 years vs. 30.6 years*).

Over the period of the trend analysis (2009-2022) in Chapter 10.38 the non-linear change is significant due to the fluctuating numbers during the assessment of the trend.

additional information:

Pregnancy outcome	13 x Live birth 1 x Live birth deceased after 7 days of life 1 x Stillbirth 2 x Spontaneous abortion 12 x induced abortion
Sex	17 x male 11 x female 1 x no information
Number of isolated malformations/MCA	16 x MCA 13 x isolated

By the year of birth 2022, more than half of those infants affected by Down syndrome (51.7%) were live births. One child was stillborn. Twice the pregnancy ended spontaneously in the 17th and 18th week of gestation. Twelve pregnancies were terminated. They were terminated at Ø 21.2 weeks of gestation (median 21.0 weeks of gestation), after the first prenatal indication of Down syndrome was found at Ø 18.2 (median 18.0). The earliest abortion took place in the 16th week of gestation and the latest in the 31st week of pregnancy.

Malformation combinations (MCA) or superordinated syndromes detected:

- preductal aortic coarctation, AVSD, malposition of the heart, VSD, bilateral microtia at atresia of the auditory canal, dilated cerebral ventricles
- Hypoplastic left heart syndrome
- AVSD, ASD II, mitral valve insufficiency
- (AVSD), vascular ring through the anomalous right subclavian artery
- AVSD, narrowed left auditory canal
- 2 x AVSD
- Aortic valve insufficiency, PFO at full term infant
- 2 x VSD, ASD II
- VSD, pulmonary hypoplasia
- Duodenal atresia, VSD, vascular ring through the anomalous right subclavian artery
- Duodenal atresia, ASD II, syndactyly
- ASD II, PDA at full term infant
- bilateral combined conduction and perception disorder
- bilateral DUP III degree

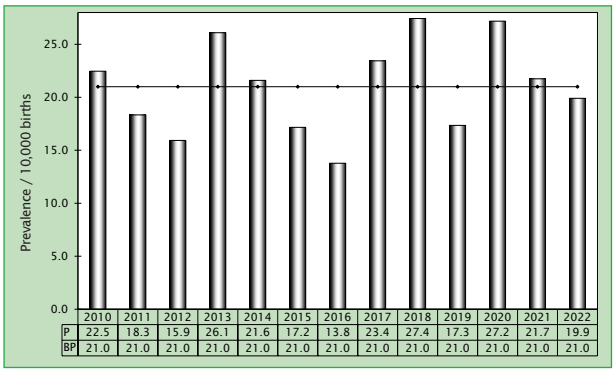


Fig. 40: Development of prevalence/10,000 births with Down`s syndrome in Saxony-Anhalt since 2010

In 2022, one Down`s syndrome per 502 births was registered in Saxony-Anhalt.

* Source: https://ec.europa.eu/eurostat/databrowser/view/DEMO_FORDAGEC__custom_8092017/default/table
eurostat-Titel: Live births by mother's age and birth order
last update: 09/25/2023

10.34 Patau syndrome - Trisomy 13 (Q91.4-Q91.7)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	6	4.12	↑
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.56	1.07 - 2.20	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.5	2.0 - 2.5	

As in the previous year, Patau syndrome has replaced Edwards' syndrome as the second most common trisomy. For the birth year 2022, with six children/fetuses and an **annual prevalence** of **4.1 per 10,000 births** the maximum of the reporting period (2021: 5.0 per 10,000 births) was not reached, but this year's prevalence is also considerably higher than the basis prevalence of Saxony-Anhalt (2010-2021: 1.6 per 10,000 births). Between 2010 and 2020 prevalence rates of less than 1.8 per 10,000 births were always were determined.

Over the years 2009-2022, the trend analysis (Chapter 10.38) shows a significant upward trend with a percentage change of 26.31 % (CI 9.85 % to 54.07 %). It can be seen that the annual prevalences between 2010 and 2014 were always below or within the lower range of the basis prevalence, between 2015 and 2020 in the medium tolerance range and since 2021 well above the upper limit of the confidence interval of the basis prevalence. The diagnosis of Patau syndrome has increasingly shifted to an earlier gestational age. It is probable that the earlier diagnosis increases the number of recognized Patau syndromes. The development remains in focus.

When comparing the by EUROCAT indicated average prevalence of the years 2010-2021 (2.5 per 10,000 births) with the basis prevalence of Saxony-Anhalt, the latter is higher. A statement whether both confidence intervals overlap is not possible due to the European values rounded to 0.5. The annual prevalence of Saxony-Anhalt in 2022 exceeds the overall European prevalence by far.

additional information:

Pregnancy outcome	1 x Live birth deceased after 7 days of life 1 x Spontaneous abortion 4 x induced abortion
Sex	3 x male 3 x female
Number of isolated malformations/MCA	3 x MCA 3 x isolated

Prenatal sonography was suspicious in five fetuses (12th to 14th weeks of gestation). These findings resp. an abnormal result of a NIPT (3 x) were the reason to carry out an invasive prenatal diagnostics (between the 13th and 18th week of gestation). In case of one live birth, no information of prenatal diagnosis is available. This infant died at the age of half a year.

Malformation combinations (MCA) or superordinated syndromes detected:

- Holoprosencephaly, cardiac malformation, medullary cystic kidneys, megacystis, craniofacial dysmorphia
- microcephaly, six fingers and toes on both sides, clubfoot right, DUP II. grade, PFO and non-hemodynamically effective PDA at full term infant, deep sacral dimple
- hydrocephaly, median cleft of the hard and soft palate

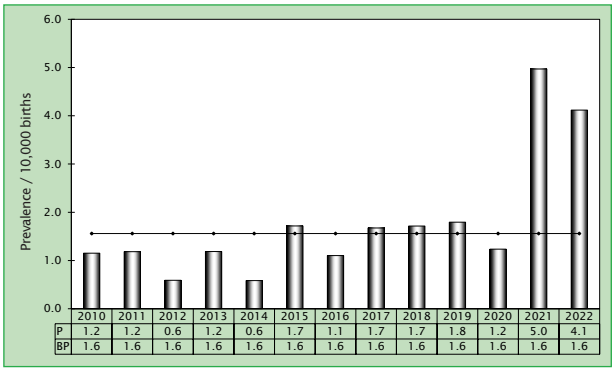


Fig. 41: Development of prevalence/10,000 births with a Patau syndrome in Saxony-Anhalt since 2010

In 2022, one child/fetus with Patau syndrome was observed per 2,428 births in Saxony-Anhalt.

10.35 Edwards syndrome - Trisomy 18 (Q91.0-Q91.3)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	5	3.43	↘
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.53	3.66 - 5.55	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	6.5	6.0 - 6.5	

Edwards' syndrome is the third most common trisomy in 2022 and was diagnosed in five children/fetuses. The therefore resulting **annual prevalence (2022: 3.4 per 10,000 births)** is slightly below the lower confidence limit of the basis prevalence of Saxony-Anhalt (2010-2021: 4.5 per 10,000 births). In 2018, the annual prevalence rose to a maximum value of 7.4 per 10,000 births and has been falling again since then.

The basis prevalence of Saxony-Anhalt is significantly lower than the overall European prevalence provided by EUROCAT (2010-2021: 6.5 per 10,000 births). As a result, the low annual prevalence of 2022 is also very low compared to the European prevalence. A higher age of the pregnant women favors the development of Edwards' syndrome. Presumably the higher maternal age compared to the average maternal age at birth in Saxony-Anhalt vs. European maternal age (2013-2021: 29.5 years vs. 30.6 years*) is probably reflected in the prevalence levels.

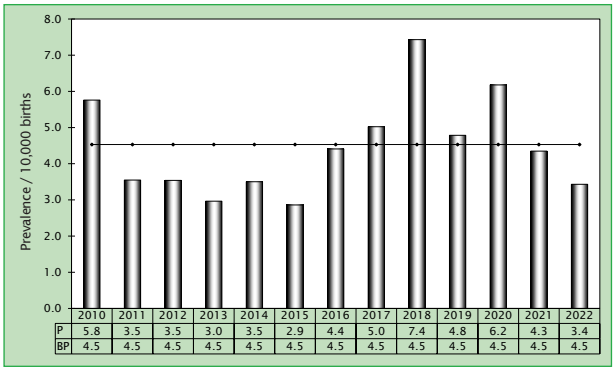
additional information:

Pregnancy outcome	1 x Live birth deceased by the 7th day of life 1 x Live birth deceased after 7 days of life 3 x induced abortion
Sex	4 x female 1 x no information
Number of isolated malformations/MCA	5 x MCA

One live birth was diagnosed prenatally with Edward's syndrome. It died shortly after birth. The pregnancy was terminated prematurely three times between the 15th and 18th week of gestation. The chromosomal findings were already confirmed prenatally with invasive chromosome analysis.

Malformation combinations (MCA) or superordinated syndromes detected:

- lumbosacral spina bifida with hydrocephaly, bilateral choanal atresia, VSD, ectopia ani, megacystis, epilepsy
- Club hand and shortening of the arm on the right, hypoplasia of the aorta
- Omphalocele, hypoplastic nasal bone
- Omphalocele
- Dislocated wrists, varus deformities of the feet



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	5.8	3.5	3.5	3.0	3.5	2.9	4.4	5.0	7.4	4.8	6.2	4.3	3.4
BP	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5

Fig. 42: Development of prevalence/10,000 births with Edwards syndrome in Saxony-Anhalt since 2010

In 2022, one Edwards syndrome per 2,914 births was registered in Saxony-Anhalt.

* Source: https://ec.europa.eu/eurostat/databrowser/view/DEMO_FORDAGEC__custom_8092017/default/table
eurostat-Titel: Live births by mother's age and birth order
last update: 09/25/2023

10.36 Turner syndrome (Q96.)

Saxony-Anhalt	year of 2022		
	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	4	2.75	↔
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.09	1.52 - 2.82	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.5	2.5 - 2.5	

The indicator malformation Turner syndrome, also known as monosomy X due to the unpaired sex chromosomes, was recorded in Saxony-Anhalt in 2022 4 times. For Turner syndrome, this results in the reporting period (2010-2021) of Saxony-Anhalt in a basis prevalence of 2.1 per 10,000 births. The **annual prevalence** reached a value of **2.7 per 10,000 births** in this year (2022), a value which lies close to the upper confidence limit, but still within the normal range of the basis prevalence.

The Europe-wide comparison shows that the following confidence interval specified by EUROCAT of the overall prevalence (2010-2021: 2.5per 10,000 births) is in the upper range of the confidence interval of the Saxony-Anhalt basis prevalence of the Turner syndrome. Due to the larger observed population, the European confidence interval is narrower and is covered by that of Saxony-Anhalt.

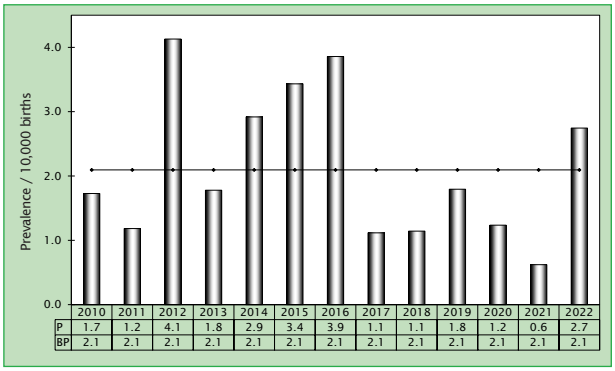
additional information:

Pregnancy outcome	1 x Live birth 1 x Stillbirth 2 x induced abortion
Sex	4 x female
Number of isolated malformations/MCA	3 x MCA 1 x isolated

One child in whom a mosaic monosomy X/triple X was detected during the 21st week of gestation died intrauterine. Two fetuses were found to have Turner syndrome after amniocentesis. Both of these pregnancies were terminated.

Malformation combinations (MCA) or superordinate syndromes:

- Triple X, sialidosis type 2, hydrothorax
- preductal aortic isthmus stenosis
- Streak gonads



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	1.7	1.2	4.1	1.8	2.9	3.4	3.9	1.1	1.1	1.8	1.2	0.6	2.7
BP	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1

Fig. 43: Development of prevalence/10,000 births with Turner syndrome in Saxony-Anhalt since 2010

In 2022, one Turner syndrome per 3,643 births was registered in Saxony-Anhalt.

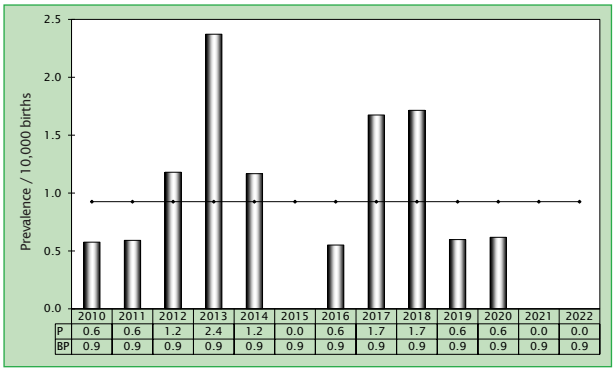
10.37 Klinefelter syndrome/male gonosome anomalies (Q98.)

	year of 2022		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison with baseline prevalence
	0	0.0	↓
	Reporting period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.93	0.56 - 1.45	
EUROCAT (Full members)	Period 2010-2021		
	Baseline prevalence/ 10,000 births	Confidence interval (CI 95%)	
	no information	no information	

No children/ fetuses with Klinefelter syndrome or a male gonosomal anomaly were affected in 2022, as in the previous year. Gonosomal anomalies with male phenotype are only registered very occasionally. In the entire reporting period (2010-2021), this indicator malformation occurred 19 times, which corresponds to a basis prevalence of 0.9 per 10,000 births (2010-2021) for the indicator malformation Klinefelter syndrome/ male gonosomal abnormalities in Saxony-Anhalt. With four registred cases, a maximum prevalence was reached in 2013 of 2.4 per 10,000 births.

Based on 105,229 live and stillborn boys (2010- 2021), this results in a basis prevalence of 1.81 per 10,000 boys (CI 1.09-2.82).

For the indicator malformation Klinefelter syndrome/ male gonosomal anomalies, EUROCAT does not provide any prevalence data.



	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
P	0.6	0.6	1.2	2.4	1.2	0.0	0.6	1.7	1.7	0.6	0.6	0.0	0.0
BP	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9

Fig. 44: Development of prevalence/10,000 births with Klinefelter syndrome/male gonosome anomalies in Saxony-Anhalt since 2010

In 2022, no child/fetus with Klinefelter syndrome/ male gonosomal abnormalities was observed in Saxony-Anhalt.

10.38 Trend analysis of indicator malformations

Chapters 10.1 to 10.37 of the annual report provide an overview about the frequency of indicator malformations, whose definitions (Chapter 10.0) are based on those of the ICBDSR (International Clearinghouse for Birth DefectsSurveillance and Research). The current prevalences of Saxony-Anhalt are compared to the prevalences of malformations in the reporting period and evaluated in a European context. The trend analysis in chapter 10.38 provides an evaluation of the development of the occurrence of indicator malformations over time in the years 2009 to 2022.

187 children/fetuses with an indicator malformation were regsitered in Saxony-Anhalt in 2022. 97 children/fetuses only had an isolated indicator malformation. 90 children/fetuses also had other malformations (MCA), of which 18 children/fetuses had two and five, three indicator malformations. Over the reporting period (2010-2021), 74.1% of those infants affected by an indicator malformation were live births. In the current year 2022, the figure was 71.7% (134 children). Of these, eleven died before their first birthday. Additionally, eleven fetuses died already intrauterine. The proportion of fetuses whose pregnancy was terminated prematurely was at 23.0 % (43 fetuses) and lies therefore slightly below the proportion in the reporting period (2010-2021: 23,5 %).

Only in case of 1.28% of all children/fetuses, we registered one of the 37 defined indicator malformations in Saxony-Anhalt in 2022. The calculated basis prevalence over the years 2010-2021 (1.43%, CI 1.38-1.48) is therefore significantly undercut.

The aim of the trend analysis presented in the following is to visualize long-term developments with regard to the occurrence of malformations. The strength and orientation of the changes in the indicator malformation prevalence is examined over the period from 2009-2022.

Trend estimation has been an integral part of the annual report for more than ten years. It is performed for indicator malformations that meet the basis requirement that, in the tested time period, the expected value for the malformation is at least five and the observed value is at least two. Indicator malformations belong, for the most part, to the rare diseases.
In order to fulfill the precondition for the test of change in case of small frequencies, two years are combined into one interval and the trend is analyzed. This procedure did not change during the last three years.

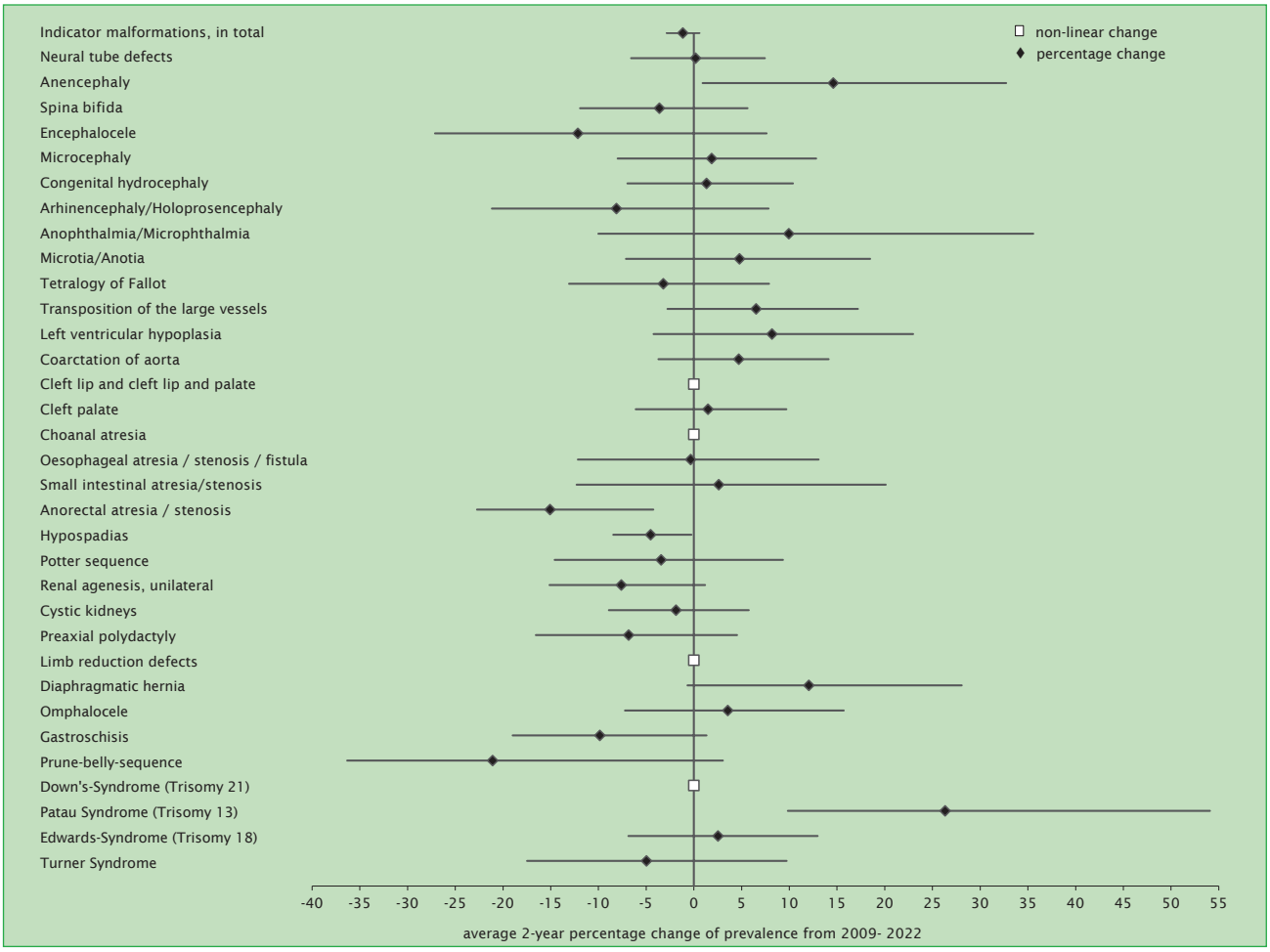


Fig. 45: Trend analysis 2009 to 2022 with average percentage change of two-year prevalence (95% CI)

Figure 45 on page 64 and the table on this page show the estimated average percentage changes in the two-year prevalence of the indicator malformations for which the above-mentioned initial conditions apply. The mathematical basis of the analysis is binary logistic regression based on the maximum likelihood method.

The measure of the strength and direction of the percentage annual change is the regression coefficient B. In the case of a significantly increasing trend characterised by a positive regression coefficient, this is entered into the diagram on the right side of the ordinate axis, including the CI of 95 %. In case of a decreasing trend, the regression coefficient can be found on the left side of the axis (in the negative range). The shown trend is significant if the confidence interval does not cover the zero value.

We tested the temporary change of the trend-coordinate and the non-linear coordinate for heterogeneity by use of the chi-squared test. We rate the trend as non-linear at a probability of $p > 0.05$ for the linear ratio and $p < 0.05$ for the non-linear ratio. In these cases, we identify a non-linear trend. This applies for cleft lip and cleft lip with cleft jaw and palate, choanal atresia, limb reduction malformations and Down's syndrome.

A probability value of $p < 0.05$ for the linear percentage and $p > 0.01$ for the **non-linear** percentage means that the linear percentage dominates, and the non-linear percentage can be neglected. The observed trend is significant, corresponding to the regression coefficient B. A **significant increasing trend** can be observed for anencephaly and Patau syndrome (trisomy 13) during the reporting period. A **significant decreasing trend**, according to a negative regression coefficient B and a non-effective non-linear component, is observed for rectal and anal atresia/stenosis and hypospadias.

All other below illustrated indicator malformations do not show a significant positive or negative trend: The chi-squared test gives for the linear and non-linear component a probability of $p > 0.05$. For this reason, no decision regarding a more frequently increase or decrease can be made, even though the non-linear percentage is not decisive for a trend evaluation.

	regression coefficient B in %	confidence interval (CI of 95 %)
indicator malformations, in total	-1.16	-2.84 to 0.58
Neural tube defects	0.18	-6.58 to 7.43
Anencephalie	14.61	0.91 to 32.72
Spina bifida	-3.61	-11.92 to 5.64
Encephalocele	-12.16	-27.13 to 7.61
Microcephaly	1.87	-7.99 to 12.82
Congenital Hydrocephaly	1.32	-6.97 to 10.38
Arhinencephaly/Holoprosencephaly	-8.13	-21.17 to 7.82
Anophthalmia/Microphthalmia	9.95	-10.00 to 35.56
Microtie/Anotie	4.78	-7.11 to 18.46
Tetralogy of Fallot	-3.21	-13.07 to 7.88
Transposition of the large vessels	6.52	-2.78 to 17.19
Left ventricular hypoplasia	8.18	-4.23 to 22.97
Aortic coarctation	4.71	-3.73 to 14.12
Cleft palate	1.48	-6.08 to 9.68
Oesophageal atresia/stenosis/fistula	-0.33	-12.15 to 13.07
Small intestinal atresia/stenosis	2.61	-12.28 to 20.11
Rectal and anal atresia/stenosis	-15.07	-22.73 to -4.25
Hypospadias	-4.54	-8.44 to -0.27
Potter sequence	-3.42	-14.59 to 9.33
Renal agenesis, unilateral	-7.61	-15.12 to 1.18
Cystic kidneys	-1.87	-8.92 to 5.76
Preaxial polydactyly	-6.84	-16.55 to 4.51
Diaphragmatic hernia	12.04	-0.66 to 28.07
Omphalocele	3.55	-7.23 to 15.71
Gastroschisis	-9.87	-18.98 to 1.32
Prune-belly sequence	-21.08	-36.33 to 3.03
Patau syndrome (Trisomy 13)	26.31	9.85 to 54.07
Edwards' syndrome (Trisomy 18)	2.54	-6.87 to 12.96
Turner syndrome	-4.98	-17.49 to 9.71

13 Summary

The annual report of the Federal State of Saxony-Anhalt about the frequency of congenital malformations and anomalies as well as genetically caused diseases is compiled every year from the data provided to the Monotoring of Congenital Malformations. In this current report the state-wide congenital malformation data of the time perriod 2010 to 2022 is evaluated population based, categorized and presented together with the official birth figures of the State Statistical Office of Saxony-Anhalt. The development of the calculated prevalences of the indicator malformations is discussed and the prevalences are compared with the European figures given by EUROCAT. In Germany, population-based malformation data has not been collected in any other Federal State for several years.

The evaluations of the annual report are based on a population of **14,570 births** in the year 2022 in Saxony-Anhalt (Chapter 1). In addition to the data of these children, data from **55 terminations of pregnancy and 27 spontaneous abortions from the 16th week of gestation** are included into the analyses.
With a numer of **14,506 live births** in 2022 in Saxony-Anhalt this value is as low as it was the last time in 1995 (14.568). In the reporting period (2010-2021) an average of 17,033 children were live births per year in Saxony-Anhalt. The birth rate has been falling since 2016.

According to the Federal Statistical Office (www.destatis.de), 738,819 children were live births in Germany in 2022, 7.1% fewer than in 2021 (795.492). The birth rate fell to 1.46 children per woman. Around 2.0 % of all newborns in Germany come from Saxony-Anhalt.

64 stillbirths, which are indicated by the State Statistical Office of Saxony-Anhalt for the year 2022 correspond to a ratio of one stillbirth to 227 live births. In the reporting period (2010-2021), the ratio is one stillbirth for every 238 live births.

In 2022, **582 children/fetuses** (3.99% of all births) are affected by **major malformations**. After a very low malformation rate last year (2021: 3.7 %), the prevalence of 2022 is significantly above the confidence interval of the basis prevalence (2010-2021: 3.84%, CI 3.76-3.93%; 205,254 children/fetuses). 514 of the children/fetuses with major malformations were live births. Of these, 17 children (3.3 %) died in the first year of life. With 8.8 % of all children/fetuses with malformations, terminations of pregnancy account for a lower proportion in 2022 than the average (2010-2021: 10.3 %) (Chapter 6).

As usual, the two cardiac malformations VSD and ASD are the **most common single diagnoses** (2010-2021: 1.0 %; 0.5 % of births) in 2022. Dilated uropathy II.-IV. degree/ureterocele, hearing loss and Down‘s syndrome, which are following in the frequency ranking, are within the expected range (Chapter 9).

By the year of birth 2022, 187 children/fetuses show one of the 37 clearly defined **indicator malformations** (chapter 10). A **higher annual prevalence** than the respective basis prevalence can be observed for anophthalmia/microphthalmia, cystic kidneys and Patau syndrome. **Lower prevalences** are seen for arhincephaly/holoprosencephaly, cleft lip and cleft lip with cleft jaw and palate, small intestinal atresia and stenosis, hypospadias, epispadias, indifferent sex, exstrophy of the urinary bladder, preaxial polydactyly, gastroschisis, prune-belly sequence and Klinefelter syndrome.

For the birth year 2022, the Monitoring of Congenital Malformations received 51 reports about **malformation caused termiantions of pregnancy**. Pregnancies of fetuses with multiple anomalies and other malformations (31.4%) were terminated the latest on average at 20.9 weeks of gestation. Fetuses with chromosomal aberrations (49.0 %) were aborted at an average of 20.4 weeks of gestations. And in case of CNS malformations (19.6 %), the termination took place at an average of 18.8 weeks of gestation (chapter 12).

Chapter 11 gives an overview about the occured syndromes, multiple and complex malformations. **Geneticlly caused diseases and microdeletions** are present in 42 children/fetuses in 2022. In nine children/fetuses a **sequence, association or a complex** was identified. Nine children suffered from fetopathy, five children/fetuses were affected by a **congenital infection**. Of the 5 children/fetuses with a **chromosomal aberration**, the majority has a Down`s syndrome (29 x) (chapter 11).

A special topic (chapter14.1) in this report is drug safety during pregnancy and teratogenic effects as a cause of malformations. About 4 to 6 % of congenital malformations are caused by exposure to teratogens. These include maternal diseases, infectious agents, physical agents, drugs and chemical substances. The effects are manifold: fetal growth restriction, congenital structural anomalies, impairment of functional performance or loss of the fetus and additionally depend on many factors, e.g. genotype of mother and fetus, route of exposure, dose, duration and time of exposure.

For the 2022 birth cohort, the monitoring of congenital malformations received **1,900 reports** about 1,600 children/fetuses (chapter 4). In 582 children/fetuses, at least one major malformation was described, a further 237 children/fetuses had minor malformations or anomalies. In addition to the data about children/fetuses with congenital malformations and anomalies as well as genetically caused diseases, data from children without malformations is important, as in scientifically based evaluations, risks can only be assessed by comparison (case-control study design).

With the help of many colleagues from different medical institutions who have been voluntarily and unselfishly reporting congenital malformations for many years, a solid database has been created, which also served as basis for the 2022 annual report. **We would therefore like to express our sincere thanks to all our „senders“, in the confidence that we will**

14. Focus theme

14.1 Drug safety during pregnancy and teratogenic effects as a cause of malformations

Introduction

A congenital malformation is a structural or functional anomaly that is present at birth,
regardless of when it is detected (prenatal, postnatal, in the course of life, post mortem) [1]. The group of functional anomalies also includes metabolic defects. Congenital malformations can be caused by various factors, such as genetially caused anomalies and/or environmental influences, whereby the underlying etiology often remains unknown [2].

The causes of congenital anomalies are both, genetic and non-genetic. The genetically caused anomalies include
- numerical or structural chromosomal disorders (e.g. Down's syndrome).
- single-gene disorders (monogenic disorders), e.g. autosomal recessive, autosomal dominant or X-chromosomal disorders

Non-genetic teratogenic etiologies include:
- maternal diseases, such as metabolic diseases (phenylketonuria (PKU), diabetes)
- alcohol, illegal drugs and chemical substances and medication
- infections during the prenatal period (cytomegalovirus (CMV), rubella, Zika virus)
- fetal malposition, e.g. due to multiple births, oligohydramnios

Today, in the majority of cases, so-called multifactorial disorders, which are caused by the interaction of several genes and environmental factors are held responsible for the development of malformations. Undesirable perinatal consequences due to the effect of a teratogen (external fertility-damaging factor) lead to diseases and malformations and are therefore an important public health problem. The special group of drug therapies during pregnancy and breastfeeding is a group of growing importance (increasing maternal age, increasing life expectancy at presence of chronic diseases, e.g. cystic fibrosis). The identification of adverse drug reactions
(ADR) during development is an important interdisciplinary scientific work [3]. Pregnant and and breastfeeding women are traditionally excluded from drug trials for safety reasons. This has the consequence that only 5% of drugs have adequate safety information about their use during pregnant or breastfeeding, which makes it very difficult for doctors and women to make informed decisions about their treatment. Nevertheless about 90% of women are confronted with a prescription medication at some point during their pregnancy [4].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Even pregnant women sometimes have to take medication. Often the reason for this has nothing to do with the pregnancy, e.g. headaches, allergies or chronic illnesses. Sometimes health problems begin or get worse when a woman is pregnant, examples are diabetes, morning sickness or high blood pressure. It is possible that women may take medication before they know that they are pregnant. Often there is not enough evidence to give women reliable information about how a particular medication could affect the fetus. Therefore, women as well as midwives, doctors and medical professionals should always record the use of medication during pregnancy. Their information can help women to make informed decisions about the benefits and risks of different treatments.

In Germany, the Pharmacovigilance and Counseling Center for Embryonal Toxicology of the Charité- University Hospital Berlin (better known as **Embryotox**) has the possibility to report that a women has taken a certain medication or to inquire how the individual risk can be assessed.

If you wish to report an exposure (without undesired events) you will find a list of the competent national authorities: https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human.
Your report will probably be entered into the EudraVigilance database, a collaboration between different actors in Europe. These include the European Medicines Agency, various national competent authorities (national regulatory authorities), the marketing authorization holders (companies that manufacture the medicinal products) and various sponsors of clinical trials (including physicians, academic centers, non-governmental organizations).

Analysis of the frequency of embryofetopathies

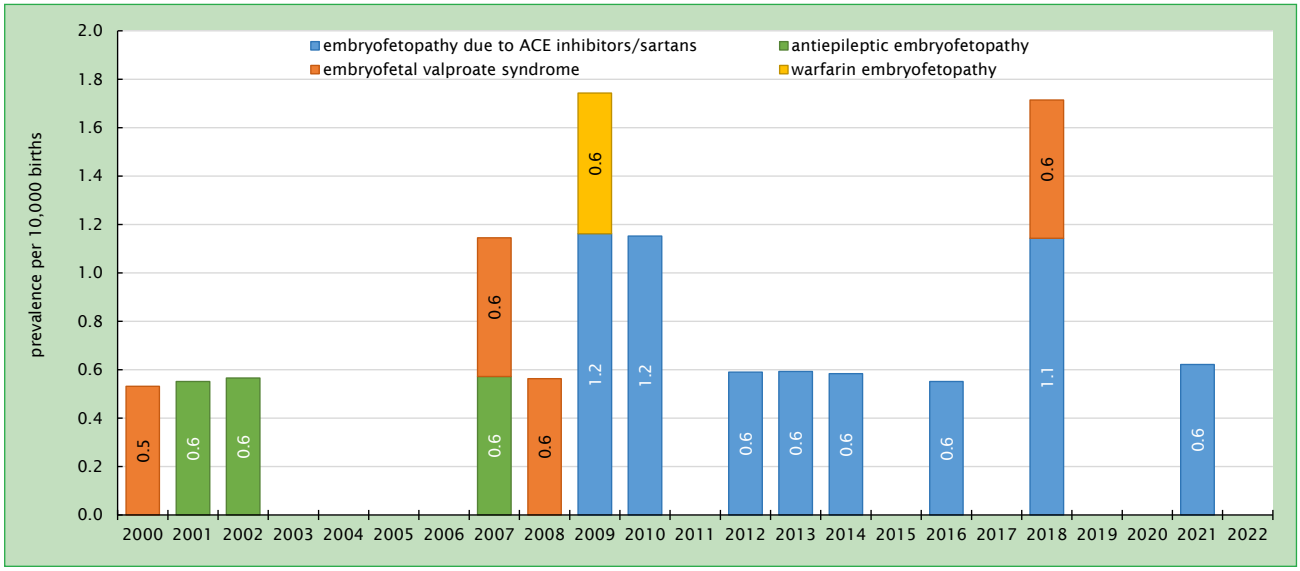

Fig. 49: Frequency distributions of known embryofetopathies (to sartans and ACE inhibitors; valproate; other antiepileptic drugs, warfarin) from the data analysis of reported cases of the Monitoring of Congenital Malformations Saxony-Anhalt from 2000 to 2022 with 395,511 births (live births and stillbirths)

Teratogenic mechanisms of action

A teratogen is an agent that can cause the listed abnormalities in a developing fetus.
It acts by inducing cell death, altering the normal growth of tissues or by interfering normal cell differentiation or other morphological processes. The consequences of these effects may include intrauterine fetal death, fetal growth restriction, a congenital structural abnormality (e.g. shortening of the limbs) or impairment of functional performance (e.g. altered neuronal connections in the central nervous system at presence of a fetal alcohol syndrome).
It is now assumed that around 4 to 6 % of congenital malformations are caused by exposure to teratogens of the environment [2]. These include maternal diseases (e.g. diabetes mellitus or phenylketonuria (PKU)), infectious agents (e.g. TORCH infections), physical influences (e.g. exposure to radiation or heat) and medication (e.g. thalidomide, anti-seizure medication) and chemical substances (e.g. mercury).

The reaction to the teratogenic active substance is very individual and is influenced by numerous factors. These include the genotype of the mother and the fetus (genetic susceptibility), the dose of the active substance, the route of exposure, the time of exposure and simultaneous exposure to other substances or diseases during pregnancy.

The „genetic constitution“ of both the fetus and the mother also determines the resistance or susceptibility to teratogenic effects. Thus, in fetuses with defects in folic acid metabolism (e.g. the pathogenic variants of the methylenetetrahydrofolate reductase gene (MTHFR)) are associated with an increased risk of structural malformations, such as neural tube defects [5], cleft lip with cleft jaw and palate and cardiac malformations [6]. The risk of these malformations can be reduced by maternal folic acid supplementation before conception and in early pregnancy [7]. The combination of different risk factors, the presence of a fetal MTHFR gene defect and insufficient maternal folate intake, can lead to a malformation (neural tube defect). The genetic predisposition of the mother and her state of health are also important for the mechanism of action of a teratogen. The development of a malformation depends on the ability of the pregnant woman to absorb and metabolize a teratogen. In addition, maternal diseases can act as teratogenic cofactors.

The route of exposure is also important for the potential teratogenic effects. For example, the absorption and effect of a drug is generally different if the exposure takes place via the skin than when administered systemically. Systemic administration can lead to abnormalities, whereas dermal administration does not. For example, fluconazole applied topically to the skin is considered safe, whereas systemically administered fluconazole is potentially teratogenic [8].

The dose and duration of exposure of the fetus to a teratogen are also important. Most drugs have threshold effects (i.e. there is a dose below which the occurrence of an adverse effect, such as malformations or functional impairments, is not higher than in exposed control subjects). Such threshold values are usually one to three orders of magnitude below the teratogenic dose of the drug [9]. A teratogen can be more harmful in a single large dose than in the same dose spread among several days, while another teratogen may be more harmful with prolonged exposure to a lower dose than when the same dose is administered all at once.

Interactions between medicines can also be of significance. Two drugs administered together can have synergistic effects. The drugs can act completely independently of each other or one medication can protect against the teratogenic effects of the other. For example the B vita-

min folate can protect against the risk of a neural tube defect if it is taken by women who are taking medication for epilepsy, such as carbamazepine [10].

The pattern and type of malformations depend partly on the time of exposure and/or the place of exposure. Significant exposure in the first 10 to 14 days after fertilization can lead to cell death. If a critical number of cells die, spontaneous abortion may occur. If only a few cells are damaged, their role can be compensated by other cells. This is known as the all-or-nothing theory. The embryo is most susceptible to teratogenic damage, as organogenesis takes place in the embryonic period. The embryonic period in humans can be defined as from fertilization until the end of the 10th week of gestation (8th week after conception) [11]. During the fetal period, teratogens can cause cell death, a delay in cell growth or inhibition of normal differentiation. This can lead to fetal growth restriction or to CNS disorders that may not yet be visible at birth. The eyes, the genitalia, the CNS and the hematopoietic system continue to develop during fetal period and remain susceptible to teratogenic disorders.

For example, it became apparent that risks exist in association with exposure to angiotensin-converting enzyme (ACE) inhibitors, a widely used drug to treat high blood pressure, during the second and third trimesters due to the blockade of the conversion of angiotensinogen I to angiotensin II in the developing fetal kidney. This exposure leads to hypotension, renal tubular dysplasia, anuria/oligohydramnios, growth restriction and bone defects of the skull [12, 13].

Misoprostol, a prostaglandin E1 analog, can cause severe vascular disorders in the first trimester (e.g. terminal limb defects, Moebius syndrome). It was also frequently used to induce terminations of pregnancy in the first and second trimester. However, this drug can be safely used during childbirth to initiate maturation of the cervix and to induce labor [14].

Some teratogens act within a narrow time window. For example, the teratogenic effect of thalidomide in the case of limb defects is limited to 21 to 36 days after conception, when the development of the limb buds begins. It is assumed that teratogenesis occurs after fertilization and occurs due to various mechanisms. Exposure prior to conception can theoretically cause genetic pathogenic variants, a process known as toxic mutagenesis. The timing of this process is different for men and women. In women, the replication of deoxyribonucleic acid (DNA) takes place during oogenesis, many years before ovulation. In contrast the ongoing process of spermatogenesis makes the man susceptible to pathogenic variants throughout his reproductive life. Examples of this are the possible effects of ionizing radiation to spermatogenesis and the possible effects of chemotherapeutic agents to the reproductive system [15].

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14.2 Performance of a chatbot with artificial intelligence as a source of patient information about taking of medication during pregnancy

Introduction

Not only Generation Z but also the people and institutions networked through it benefit from the Internet, which can answer almost any question within minutes. Especially in the field of medicine, people of all ages are increasingly turning to the Internet [1]. When searching for answers to medical questions, a person needs less than six minutes on average [2]. Internet searches are also often used to form an own opinion about what is said by doctors and to form their own picture for themselves. This means that a large amount of information from a wide variety of sources can be collected, but may also not be correctly classified by a layperson [3].
Well known and established among doctors, midwives and pregnant women alike, is the database and online search of the Pharmacovigilance and Center for Embryonal Toxicology of the Charité-Universitätsmedizin Berlin (Embryotox: https://www.embryotox.de, part of the European network Teratology Information Services: https://www.entis-org.eu).

But can the Internet and the ever-improving search engines be a realistic help for obtaining information on the desire to have children and pregnancy? Our focus is particularly on pregnant women or women who wish to have children, who are chronically ill and regularly take medication.

There are a number of special dietary and lifestyle features, which have an influence on the pregnant woman and the growing child. Especially if the pregnant woman is taking medication, possible effects of the medication on the child must be taken into account. It is therefore essential to have pharmacovigilance in mind (WHO: activities that deal with the detection, assessment, understanding and prevention of side effects or other drug-related problems [4]), in order to have the health of the pregnant woman and the development of the child at the highest possible level.

Informed patients through artificial intelligence?

For the quick and easy obtaining of information, especially in the pharmaceutical industry, chatbots with artificial intelligence, such as ChatGPT, could help. In order to find out how a chatbot system deals with specific inquiries, a systematic Internet research based on examples took place. By using ChatGPT, questions about taking medication during pregnancy were researched.

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A major advantage of ChatGPT is that it can be accessed at any time and does not involve any additional effort in terms of the way to the doctor, waiting times for an appointment or waiting times in the waiting room. This means that in case a question arises, it can be answered and any consequences can be implemented directly. For example, a pregnant woman with a headache can ask the chatbot directly which medication she can take at her current stage of pregnancy. Above all, ChatGPT is more helpful than normal Internet research, as it directly summarizes several sources and can therefore give a broader answer.

A major obstacle when visiting a doctor is that time with the doctor is always very short, as a doctor only has an average of eight minutes contact time with patients [5]. This makes good doctor-patient communication difficult, especially when the different types of patients have to be taken into account. Some patients want to know everything about their illness or the consequences of their illness and others do not want any information at all. Also problematic are patients who may not have the courage to ask more detailed questions if they have not understood something [6,7]. In addition, certain topics are associated with shame, which also stands in the way of open communication [7].

In contrast, there is no time limit with ChatGPT and you can ask as many questions as you want. Patients may also feel more confident to ask questions that might be considered problematic in society. Especially for pregnant women, there are many taboos that people do not want to aks openly. The ability to ask ChatGPT about the consequences of various medications or other substances, possibly also illegal substances, pregnant women or people who wish to have children to inform themselves about the consequences, without fearing possible condemnation from the doctor. This could lead to a better understanding people about their consumption behavior and the consequences for the unborn child.

It requires, however, especially in the case of pre-existing conditions with a lot of medication the consultation of a doctor, as it must always be decided individually whether a medication can be discontinued or whether the dose needs to be reduced.

ChatGPT could therefore be the first point of contact which facilitates the search for information in the Internet. In addition, ChatGPT always points out in the case of medical questions that a doctor should be consulted when it comes to medication.

Currently, only ChatGPT 3.5 is available free of charge and this version does not have access to real-time data, but only to data to which it has been trained. The current version has a state of knowledge until January 2022, but will continue to be trained and with each new version thereby improving the level of knowledge. In addition, the artificial intelligence (AI) is trained with the information provided by users. Documents can also be integrated into the chat, which can be summarized, for example or used only for answers to a direct question. This means that ChatGPT's knowledge continues to grow. The paid version ChatGPT 4.0 can already perform current Internet searches. The limits are mainly on publicly accessible data. ChatGPT 4.0 is not yet able to access content that requires subscriptions or accounts.

If the knowledge of ChatGPT continues to grow and later possibly can also access all real-time data, the chatbot would be more up to date than a doctor can be. Doctors must
regularly take part in further training and keep up to date with the latest scientific developments, but the time available for this is also limited [8].

Artificial intelligence has now also learned to respond to the user in an empathetic and human way. ChatGPT, for example, shows very good emotional understanding in various situations, which was demonstrated in a study using the Levels of Emotional Awareness Scale [9]. In this study, test persons and ChatGPT are asked to imagine themselves in various predefined situations and to name their own emotional reactions and those of the people involved. The test is standardized and quantifiable, which means that ChatGPT can be compared with the normal population. ChatGPT performed significantly better than the normal population [10]. In addition, a study of another chatbot called Replika shows a lower inhibition threshold for emotional difficult topics, which helps users to address topics that are important in relation to their health [11].

One problem in regard to the treatment of patients is often is that everyone has a bias towards other people. Doctors also have these, even if they try to keep them as low as possible. The biases of doctors are the same as those which exist in the general population [12]. Even if ChatGPT has no bias about the appearance or behavior of its users, it is nevertheless still very much influenced by the Western worldview and works best in its „native language" English [13]. It can also reinforce certain user biases because, depending on the sources with which the AI has been trained with, the AI only has this information and does not know the possible opposite side. Therefore, the AI is biased if the given information is already biased [14].

Thanks to ChatGPT's ability to reply in several languages and also via speech recognition in the mobile version [15], it can be used to reduce the language barrier between doctor and patient. In hospitals and doctors' surgeries, it can always happen that patients do not speak German very well, which makes it difficult to ask them about their medical history. However, this is particularly important when it is necessary to ask which medication is being taken or
whether there are any allergies to medication, which influences future treatment [16].

An important controversial point about ChatGPT is data protection. Free ChatGPT versions use algorithms that are based on the preferences of the public, which can lead to biased or incorrect answers. In March 2023, ChatGPT was briefly blocked in Italy because not all data protection conditions were met and a data leak occurred. After the operators improved data protection in accordance with the conditions of the authority, ChatGPT was allowed to be used again [17]. According to the German Bundestag, ChatGPT is subject to the requirements of the General Data Protection Regulation (DSGVO) [18]. However, you should not enter any personal information into ChatGPT, especially if certain settings have not been changed. Entered data is used to train the AI, if you do not object [19, 20].

ChatGPT has an answer to almost every question, but is the answer always correct? Especially when using ChatGPT 3.5 it is difficult to understand the answers because no sources are given. In addition, ChatGPT can only answer with the information it has been trained with. This means that the level of knowledge only extends up to the time of the information given and therefore it does not include any current publications. With the existing knowledge ChatGPT 3.5 has in the field of medical training passed the United States Medical Licensing Examination and the German written state examinations M1 and M2. Both exams were passed with a grade of 4. However, especially in these exams, the patients are very standardized and not very comparable with patients in real life. Especially with the more complex tasks, which required not only knowledge but also logical thinking, ChatGPT did not perform well [21, 22]. But just this possibility to transfer knowledge is important in the individual treatment of patients. On the other hand, ChatGPT is very good for pure knowledge questions, as it is often needed in pharmacology.

Summary

Today's version of ChatGPT cannot provide expert advice with differentiated scientific knowledge. However, the results of systematic scientific evaluations indicate that it is a reliable source of information for the public [23]. Salas et al. published in 2023 a study in which ChatGPT was analyzed for the safety in regard to COVID-19 vaccines. They emphasized that due to its ease of understanding, AI potentially enables an increase in vaccine acceptance [24].

ChatGPT could help physicians to quickly obtain information about niche knowledge and also could help special patient groups, such as pregnant women, to better inform themselves independently about their condition and the associated particularities in dealing with medication.

However, until a better overview and expansion of data protection exists, especially for the handling of sensitive data, such as that of a patient, and the transparency of the sources has been improved, ChatGPT should only be used with caution for these topics. In addition, ChatGPT will not be able to replace a doctor's visit in the near future, as each patient is a very individual person and therefore a doctor is needed to organize the appropriate treatment. Furthermore, personal assessment of the patient by the doctor is also very important, in order to clarify possible essential questions again. However, work has also to be continued to ensure, that doctors treat their patients without bias, so that no false conclusions are drawn.

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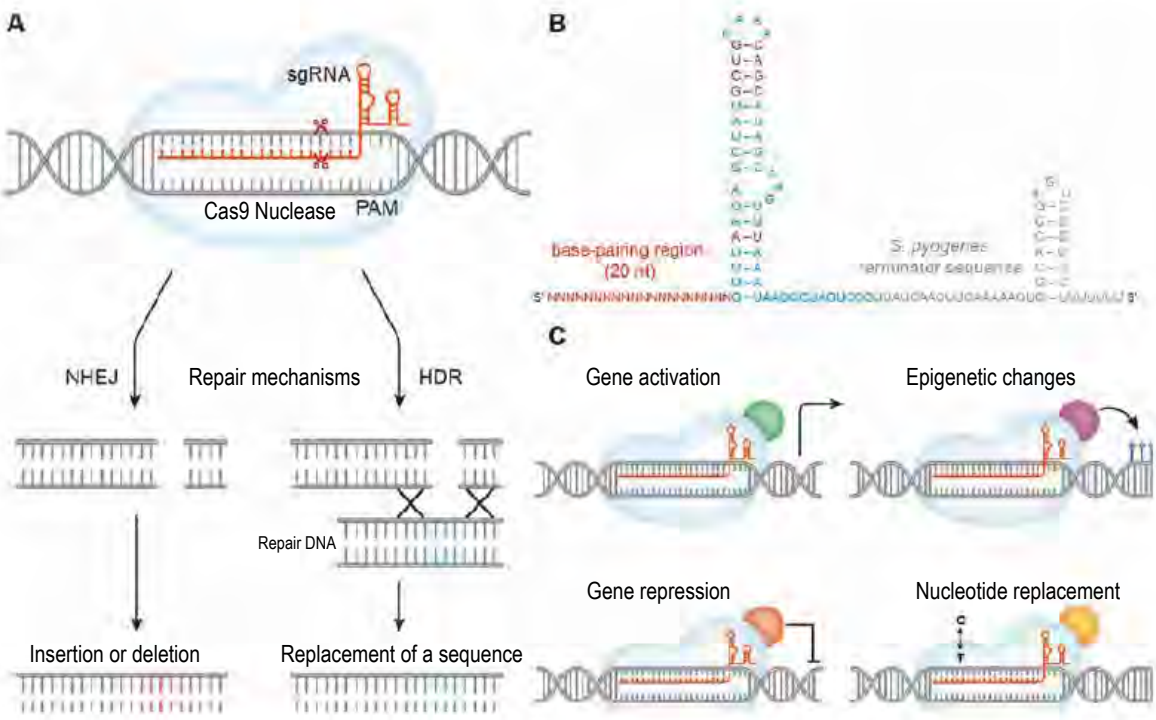
14.3 Application of CRISPR/Cas - How do gene scissors work?

Worldwide, genetic disorders and congenital anomalies occur in 2-5% of all births and cause up to 50 % of all early childhood deaths [1]. The causes of numerous genetic defects, such as
sickle cell anemia, thalassemia, muscular dystrophy and cystic fibrosis are still incurable to this day, only the transplantation of stem cells can treat individual genetically caused diseases.

For this reason, attempts are being made to develop new methods that make it possible to modify and manipulate the genome [2]. During the last few decades the CRISPR/Cas method (also known as gene scissors) has increasingly become the focus of translational research because, in theory, this technology makes it possible to repair the genetic defect by specifically modifying the defective gene or genes [1]. It is important to emphasize that the CRISPR system is not a new human invention, but a gift from Mother Nature [2]. Numerous bacteria and archaea use CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and CRISPR-associated genes (Cas genes) as an adaptive immune mechanism to efficiently protect themselves from foreign nucleic acids, such as viral genomes and plasmids [2, 3].

The CRISPR/Cas system is divided into two major categories, six types (I-VI) and further subtypes. All these defense mechanisms show remarkable overlaps. The immunological memory consists of the CRISPR array, a series of alternating repeats and spacers, whereby the spacer sequences are derived from foreign genetic elements in a process known as adaptation. The array is transcribed and processed to generate unit-sized CRISPR RNAs (crRNA) that form a complex with one (class 2, types II, V, VI) or more (class 1, types I, III, IV) CRISPR-associated (Cas) proteins [4-9]. During interference, invading nucleic acids are recognized and destroyed by complementary base pairing between the crRNA and the foreign nucleic acid [9]. Thus, the understanding of the CRISPR/Cas mechanism [8, 10-15], the simplicity and programmability of DNA-encoding, RNA-directed nucleases and the adaptation for the application to eukaryotic genome modification has led to great progress in the life sciences [9,13,15-19].

In order to use the CRISPR/Cas tools for therapeutic and diagnostic purposes, several steps must be considered. First, the specific gene or the gene sequence of the target cell is determined [1]. This is followed by the synthetic



CRISPR-Cas9 system for the modification of DNA.
(A) Structure and use of CRISPR-Cas9. (B) SStructure and example of the guide RNA.
(C) Use of CRISPR for the modification of gene sequences, repression or activation of genes and modification of epigenetic characteristics.

Fig. 50: CRISPR-Cas9 system for modifying DNA [20]

construction of the guide RNA and the Cas9 protein. Both components are combined after synthesis and introduced into the target cell. The guide RNA recognizes the specific DNA sequence by base pairing, which causes the complex to bind to the DNA, whereby the double strand is separated into single strands. At both ends of the binding site the Cas9 protein cuts the DNA, resulting in a double-strand break. The cell attempts to repair the resulting double-strand break. At this point a distinction is made between two different mechanisms: homologous and non-homologous.In the case of non-homologous repair, individual DNA nucleotides are randomly removed at the breaking point and not homologously („incorrect") reinserted. This results in the respective gene product and the therefore resulting protein is no longer formed. With homologous repair a new gene segment or a modified variant of a short DNA sequence can be inserted. For example, so-called „therapeutic DNA", which is inserted by homologous recombination can be placed at exactly the desired location. In theory, CRISPR/Cas thus offers the possibility of knocking out non-functional or overexpressed genes, but also to insert genes [1, 13].

Cas9-mediated genome modification in vivo has already been used to correct disease-associated alleles in animal models of genetic diseases, thus provided the first starting point for application in humans [15]. Sickle cell anemia (SZA) is one of the diseases where CRISPR/Cas9 is already being used as a method. SZA belongs to the autosomal recessive inherited diseases that can be treated by an amino acid substitution (Gln-Val) on the 11th chromosome. The mutation of the gene HBB (haemoglobin β) results in the characteristic sickle crescent shape of the erythrocytes and the associated symptoms, such as disruption of microcirculation and vascular occlusion crises [1, 21]. From the current point of view there are two approaches in which CRISPR/Cas9 is used for the treatment of sickle cell anemia. One is to repair the hemoglobin S gene and the other is to replace hemoglobin S with hemoglobin F. The basis of both approaches is to modify the hematopoietic progenitor stem cells from the patient's blood with CRISPR/Cas9 and transferring the modified cells back into the patients [1]. In the first approach, which means to repair the β-globin gene for hemoglobin S so that the cells produce standard hemoglobin again, the preclinical studies have been successfully completed. Furthermore this method turned out to be incredibly efficient and reproducible, which is why the first clinical trials for the introduction of this treatment method have already begun [1, 22]. The second approach, in which the elimination of the natural repressor of haemoglobin F through a mutation in the BCL11A gene takes place, is even closer to clinical application. The first drug CTX001 is already available here [23]. Antisense therapy induces a break in the BCL11A gene in transgenic mice, which in turn stops repression of hemoglobin F. This has already successfully corrected SZA in transgenic mice [1, 24].

Another congenital genetic disease for which CRISPR/Cas has been successful in researching and treating is cystic fibrosis. This monogenic autosomal recessive disease is caused by a mutation in the CFTR (cystic fibrosis transmembrane conductance regulator) gene [25, 26]. Characteristic symptoms are intestinal dysfunction, early destruction of the pancreas and inflammation associated with tissue damage and fibrosis [26]. The CRISPR/Cas9 system has been used to modify the CFTR gene using homology-based repair (HDR) in the intestinal stem cells of CF patients [27]. Using selection markers, researchers utilized CRISPR to correct induced pluripotent stem cells (iPSC) from patients with a homozygous F508 deletion on the 10th exon. Thereby, a cumulative repair efficiency of almost 90 % could be achieved [28, 29]. The CRISPR-mediated gene repair restored as expected the CFTR function in the epithelial cells and organoids, which were generated from the iPSCs [30].

The CRISPR/Cas system is not only used for autosomal inherited defects, but also for rare X-chromosome-linked diseases, such as Duchenne muscular dystrophy (DMD). In this case, mutations in the muscle protein dystrophin are present, which lead to a neuromuscular disorder [31]. The dystrophin protein is vital for the connection between the actin cytoskeleton with the extracellular matrix of the muscle cell, to ensure membrane integrity [32, 33]. Patients suffering from DMD already suffer from a steadily progressive muscle weakness from early childhood [34]. In studies by Refaey et. al. CRISPR/Cas was used to create a mutant gene in exon 23-deleted dystrophic mutant mice, and the expression of the dystrophin was restored [35]. This provided an important basis for advancing the treatment of DMD in humans as well. Furthermore, CRISPR/Cas was also used for the repair or removal of various regions of the dystrophin gene, for example DMD exon 50 and 54 [36], dystrophin exon 51 [37] and DMD exon 20 [38]. Due to the wide range of possible applications and the individual selection of the gene to be repaired, CRISPR/Cas offers a great opportunity to cure even complex diseases.

To summarize, it can be said that at the time when the two biochemists Jennifer Doudna and Emmanuelle Charpentier published the genome editing with the help of CRISPR/Cas9 (CRISPR) in the journal Science, they triggered a new genre revolution [39, 40]. An incredible opportunity was available that allowed specific gene segments to be cut and in humans and animals and to modify them. This should make it possible to cure genetic diseases. Nevertheless, the so-called off-target effects of CRISPR-Cas-mediated genome modifications should not be ignored. Off-target effects are understood to mean unexpected, undesirable or even harmful changes in the genome [41]. Nevertheless, CRISPR/Cas offers a great opportunity to treat genetic diseases in the near future.

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16 Newborn Hearing Screening 2022

Introduction

Every newborn is entitled to receive a general newborn hearing screening which belongs as from 1st January 2009 to the recommended early detection examinations after birth of a child. **Aim** of the newborn hearing screening (NHS) is to detect **congenital hearing disorders** at an **early stage (up to the 3rd month of life)** and to **initiate** the corresponding **therapies (up to the 6th month of life).**

Basis for this screening examination is the **Children's Directive of the Joint Federal Committee about the early detection of diseases at infants (Children's Directive)** with section **IV. Early detection of hearing disorders at newborns.**

The Children`s Directive determines the **process of the newborn hearing screening** in the following way:
- measurement of each ear by TEOAE or AABR up to the 3rd day of life (outside of hospital by no later than early detection examination 2 (U2))
- AABR examination is mandatory for children with increased risk
- examinations of premature infants by no later than calculated date of delivery and examinations of not healthy births by no later than 3rd month of life
- at suspicious first screening, repetition of examination on both ears by AABR preferably on the same day, but by no later than early detection examination 2 (U2)
- at suspicious finding of the follow-up AABR examination, a comprehensive
confirmation diagnostics is necessary up to the 12th week of life

According to the Children`s Directive **performance and results of the newborn hearing screening as well as** possible confirmation diagnostics have to be **recorded** in the **"yellow book of examination" of every child**. The responsible paediatrist resp. ENT physician can evaluate by reading this information if the required diagnostics resp. therapy in case of a hearing disorder was initiated.

The Monitoring of Congenital Malformations Saxony-Anhalt cooperates with the Centre for Newborn Hearing Screening Saxony-Anhalt since 2006 as **tracking centre for the newborn hearing screening** (Federal State specific screening centre).

The Newborn Hearing Screening Directive stipulates that the hearing screening should be performed via AABR at **children with an increased risk for congenital hearing disorders**. The following overview outlines in extracts possible **indications for the performance of an AABR examination** due to an increased risk of hearing disorders (modified according to JCIH 2008):

- positive family history regarding hearing disorders
- clinical suspicion of hearing disorder/ deafness
- premature birth, birth weight under 1500 g
- neonatal intensive care (> 2 days)
- hyperbilirubinemia (exchange transfusion)
- pre-, peri- or postnatal hypoxia (pH < 7.20)
- peri- and postnatal cerebral haemorrhage, oedema
- intrauterine infections
- culture positive postnatal infections associated with increased risk of hearing loss
- craniofacial anomalies
- distinctive diseases with hearing loss
- neurodegenerative diseases or sensomotoric neuropathies
- outer characteristics, which point to a distinctive disease that appears in combination with a hearing disorder (e.g. white strand of hair)
- APGAR-values of 0-4 in the first minute and 0-6 after 5 minutes

Literature:
Joint Committee on Infant Hearing: Year 2008 position statement: Principles and guidelines for early hearing detection and intervention programs. PEDIATRICS 2008; 120: 898–921

Participating institutions

20 maternity clinics existed in Saxony-Anhalt in 2022. All these clinics offer a newborn hearing screening already for several years by TEOAE or AABR. These maternity clinics all participated in the newborn hearing screening in 2022.
A screening-ID is assigned to each child - if there is no denial of this examination and /or data transmission by the parents/guardians - and the hearing screening results are forwarded to the tracking centre of newborn hearing screening Saxony-Anhalt.

The screening ID, which has to be assigned to each infant as condition to participate in the hearing screening tracking is also used by several midwifes. In this way also infants who are exclusively under care of a midwife (e.g. home births) can participate in the newborn hearing screening.

The following table on page 86 gives an overview about the single maternity clinics and number of births with a screening ID.

Maternity clinics in Saxony-Anhalt and participation in the Newborn Hearing Screening Tracking (ordered by location)

Maternity clinics	Tracking period 2022	notified live births with screening ID in this period
AMEOS Klinikum Aschersleben	01.01.-31.12.2022	403
Helios Klinik Jerichower Land Burg	01.01.-31.12.2022	352
Städtisches Klinikum Dessau	01.01.-31.12.2022	841
Altmark-Klinikum Krankenhaus Gardelegen	01.01.-31.12.2022	165
AMEOS Klinikum Halberstadt	01.01.-31.12.2022	446
Krankenhaus St. Elisabeth und St. Barbara Halle (Saale)	01.01.-31.12.2022	1,804
Universitätsklinikum Halle (Saale)	01.01.-31.12.2022	1,227
Helios Klinik Köthen	01.01.-31.12.2022	422
Krankenhaus St. Marienstift Magdeburg	01.01.-31.12.2022	950
Klinikum Magdeburg	01.01.-31.12.2022	1,408
Universitätsklinikum Magdeburg	01.01.-31.12.2022	1,268
Carl-von-Basedow-Klinikum Saalekreis Merseburg	01.01.-31.12.2022	778
SRH Klinikum Naumburg	01.01.-31.12.2022	358
Harzklinikum Dorothea Christiane Erxleben, Klinikum Quedlinburg	01.01.-11.04.2022	83
Altmark-Klinikum Krankenhaus Salzwedel	01.01.-31.12.2022	396
Helios Klinik Sangerhausen	01.01.-31.12.2022	575
Johanniter-Krankenhaus Stendal	01.01.-31.12.2022	680
Harzklinikum Dorothea Christiane Erxleben, Klinikum Wernigerode	01.01.-31.12.2022	868
Evangelisches Krankenhaus Paul Gerhardt Stift Wittenberg	01.01.-31.12.2022	668
SRH Klinikum Zeitz	01.01.-31.12.2022	281
Total live births with screening ID in clinics in Saxony-Anhalt		**13,973**

other live births with screening ID: z. e.g. home births/births in a birth center or children born outside of Saxony-Anhalt	01.01.-31.12.2022	154

Total tracking children	**14,127**

In total, **13.973 births** received a screening ID in their maternity clinic in Saxony-Anhalt in 2022. In this way data was transmitted to the tracking center and these infants could participate in the hearing screening tracking. Furthermore, **154 data records of infants** which were delivered at home or born in a birthing centre are included in our analyses. These infants received also a screening ID after birth, e.g. by their corresponding midwife.

Tracking Effort

Tracking of the newborn hearing screening requires an ample organising and personnel effort. It starts with recording the results of the hearing test in the maternity clinic and forwarding them by mail or fax to the Monitoring of Congenital Malformations. The results are entered here in a special tracking database. In total, we received results of 97 senders in 2022.

Births with screening-ID and number of incoming results

2022	Number of children with a screening ID	Number Incoming findings
january	1,182	1,605
february	1,066	1,458
march	1,124	936
april	1,096	2,000
may	1,248	1,197
june	1,181	1,471
july	1,266	1,942
august	1,303	1,744
september	1,316	993
october	1,173	2,093
november	1,081	928
december	1,091	588
total	**14,127**	**16,955**

The previous table shows how many newborns received a screening ID per month and how many results were forwarded to the Monitoring of Congenital Malformations per month.
It becomes apparent that currently per month an average of approx. 1,413 reports can be expected, however in some cases we received multiple reports for one child (e.g. from the maternity clinic, paediatric clinic, ENT clinic, ENT physician, paediatrist and from the parents).

To carry out the tracking thoroughly, 2940 letters resp. faxes were forwarded in 2022 (one up to 11 letters per infant). With reference to all infants with screening ID this corresponds to an average of 0.21 letters per infant. The tracking software also records telephone calls
with the parents/legal guardians of the infants or with the treating doctors/practices/clinics as well as processing notes are logged. For the children with screening ID, which were born in 2022, a total of 1,654 telephone calls or log notes were documented as part of the tracking measures (average 0.12 phone calls/log notes per infant).

Results (date: September 2023)

All results that were reported to the hearing screening tracking centre about infants that were born in 2022 are included in our analyses 2022 of the newborn hearing screening:

11,351 infants out of **14.127 infants** with screening ID had an **unsuspicious newborn hearing screening result**. In **2,776 cases** the **first hearing test had to be followed-up**, resp. no newborn hearing screening took place in the maternity clinic (these cases are regarded also as follow-up cases). There are numerous reasons why a hearing test did not take place, e.g. ambulant delivery, early discharge from maternity clinic, transfer of the child to another clinic or a defective hearing screening device.

The **follow-up examination** of the 2,776 infants showed in 2,062 **cases** an **unsuspicious result.** The remaining **714 infants** had again a **suspicious result.**
219 of these 714 infants received a **complete paediatric audiological confirmation diagnostic**.
According to our knowledge, **234 infants** did **not receive a confirmation diagnostic** and therefore are considered as **lost to follow-up**. In **14 cases**, the **further examinations were refused** by the parents.

157 infants did **not participate in the screening** (no reaction of parents to reminder letters or refusal of examination) and in 15 cases the **status** is still **pending**, i.e. the examinations were not finished in September 2023 or the tracking process still requires more time.
In **57 cases** the **tracking** was closed from our side **without any result,** because the parents could not be contacted, or the infant had died.

In total, the **follow up-examinations** of **244 infants** who were born in 2022 could be **completed (confirmations diagnostics)**. Among 219 infants with a suspicious result, 25 infants had an unsuspicious first screening. Maybe these infants received a follow-up-examination due to present risk factors.
Within the follow-up examination, a **hearing disorder** could be **excluded** in **206 cases.** In **38 cases** a **hearing disorder was diagnosed** (30 x bilateral and 8 x unilateral hearing disorder) and the corresponding therapy was initiated. For instance, **16 infants** received a **hearing aid** (12 x hearing aids on both sides, 4 x hearing aid on one on one side).

17 Annual Report 2022 of the Newborn Screening Centre in Saxony-Anhalt

according to §13 to § 42 inclusive attachments of the valid Children Directive of the Federal Joint Committee about early detection of diseases at infants

Cooperative direction of the screening-center:
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Kompetenznetz Neugeborenen-Screening
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Introduction

The Newborn screening is a population-based preventive measure with the aim of a complete and early detection as well as quality-assured therapy of all newborns with severe, congenital metabolic disorders (Tab. 1).
The Directive of the Joint Federal Committee about the early detection of childhood diseases (Children's Directive) stipulates the details of the newborn screening (NGS) and screening for cystic fibrosis (CF) in paragraphs 13 to 42.
The German Society of newborn screening (DGNS) compiles annually a national screening report in cooperation with the German screening laboratories (http://screening-dgns.de/reports.php). The statistical processing of the screening data is based on the quality criteria defined in the Directive for the implementation of NGS and CF screening in Germany.

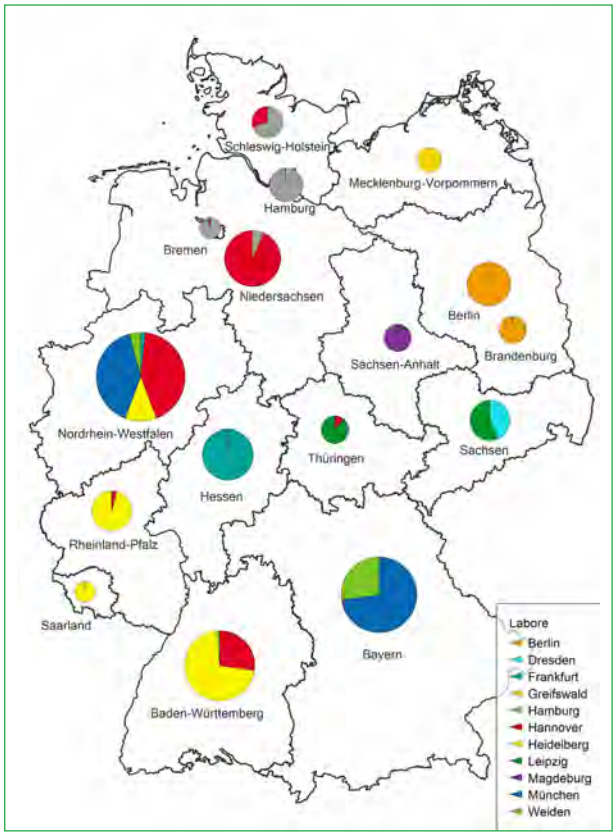

Fig. 1: Sample distribution of the screening centers in Germany 1

The report only refers to congenital metabolic and endocrinologic diseases which are defined as „target" diseases by the Directive. Furthermore, it gives a complete statistical compilation of related screening figures, recall rates and confirmed diagnoses for the current year. Additionally, data about process quality for whole Germany is presented.
Screening samples from the single Federal States are distributed to the laboratories as it is presented in figure 1 [1].
The screening laboratory in Magdeburg handles the dry blood samples of all infants born in Saxony-Anhalt.
Table 1 shows the frequencies 2020 of the screening target diseases in Germany1 for a total number of 773,144 screened births.

Tab.1: Frequency of diseases detected in screening in Germany 2020[1] (including mild forms)

Disease	Confirmed cases	Prevalence
Congenital hypothyroidism (CH)	265	1 : 2,918
Adrenogenital syndrome (AGS)	60	1 : 12,886
Biotinidase deficiency (incl. partial defects)	23	1 : 33,615
Galactosemia (classic)	19	1 : 40,692
Hyperphenylalaninemia (HPA) [of which phenylketonuria (PKU)	149 [79]	1 : 5,189 [1 : 9,787]
Maple syrup disease (MSUD)	2	1 : 386,572
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	84	1 : 9,204
Long-chain 3-OH-acyl-CoA dehydrogenase (LCHAD) deficiency	11	1 : 70,286
(Very) long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	12	1 : 64,429
Carnitine palmitoyl-CoA transferase I (CPTI) deficiency	3	1 : 257,715
Carnitine palmitoyl-CoA transferase II (CPTII) deficiency	-	
Carnitine acylcarnitine translocase (CACT) deficiency	-	
Glutarazidurie Typ I (GA I)	7	1 : 110,449
Isovaleric acidemia (IVA)	6	1 : 128,857
Tyrosinemia type I	7	1 : 110,449
Cystic fibrosis (CF) / CFSPID	146	1 : 5,296
Severe combined immunodeficiency [of which SCID]	32 [5]	1 : 24,161 [1 : 154,629]
total	**826**	**1 : 936**

Screening data 2022 of Saxony-Anhalt is outlined in the following:

Process quality

The process quality describes the process itself and its evaluation on a basis of given indicators by expert committees.
Indicators of the newborn screening are:

- complete coverage of target population
- - coverage method and rate
- - blank card systems
- completeness of control (recall)- and follow up examinations
- registration of examination parameter and standard values / cut-offs
- according to disease, laboratory and age/gestational age stratified recall rates, positive
- predictive values, prevalences
- specificity and sensitivity of test methods
- process times (here only in the preanalytic and laboratory field: age at time of blood taking, time between blood taking, arriving at laboratory and result transmission)
- individual screening results of newborns, which must be examined further on
- confirmation diagnostics
- - diagnostics type
- - diagnostics period
- final diagnosis
- start of therapy

Registration rates

Since according to §15 and §31 of the Children's Directive each newborn has a right of participation in the extended newborn screening and cystic fibrosis screening, a tracking for completeness is necessary. This can be realised for infants which are delivered in obstetric clinics by control of the respective consecutive number in the birth register and by means of a so-called blank card system in the screening laboratory. According to the Children`s Directive the obstetric clinics have to document on a blank test card the total refusal of screening, the refusal of an early blood taking within the screening, the transfer to specialised institutions or death of the newborn. These blank cards should be sent to the laboratory to support the tracking process.

The coverage rates of Saxony-Anhalt were as following for the year 2022:
According to the Federal Statistical Office 14,506 children were live births in Saxony-Anhalt
(data according to the place of maternal residence).

Tab. 2: Initial examinations according to the place of maternal residence

	Number
First screening in Magdeburg, in total	13,974
Non-resident in Saxony-Anhalt	667
Screening of children living in Saxony-Anhalt	**13,307**

The discrepancy between the number of live births and screened infants with residence in Saxony-Anhalt amounts to 1199.

Basis for the data of the State Statistical Office are the births that are reported by the birth centres to the registry offices, sorted according to the place of maternal residence. However, the number of mothers with residence in Saxony-Anhalt but who delivered their infant in another Federal State can not be recorded in our screening statistics if the screening of the infant also took place in another Federal State.

Tab. 3: Registration rates by blank cards

Blank cards in total	**527**
Blank card: infant deceased/ stillbirth	12
Blank card: refusal of early taking	403
Blank card: transfer to another hospital	48
Blank card: screening refused by parents	18
Screening took place	419

As result of follow-up (telephone calls, faxes, letters), only 1% of the blank cards sent in remained without result. All other live births participated later successfully in the newborn screening and the CF screening in our or in a neighbouring screening laboratory. Furthermore, the tracking of missing screening examinations is performed successfully according to the reasons mentioned in table 4.

Tab. 4: Completeness of control(recall)- and follow up examinations

Reason for second screening	**Suspicious first screening**	**First screening < 36h or < 32 WOG**
Requested	97	417
Received at own laboratory	92	367

WOG = weeks of gestation

Examination numbers, recall rates and assured cases

Table 5 shows recall rates of the single parameter and assured cases.

Tab. 5: Recall-rate 2022 and diagnosed patients with a metabolic disease in reference to 13,974 screening examinations (includes also early withdrawal < 36 h and preterm births < 32 WOG), prevalence 1999-2022

Target disease including all forms of the disease	Number of recalls* 2022	Assured cases 2022	Prevalence in Saxony-Anhalt 1999-2022
Hypothyroidism (CH)	51	1	1 : 4,142
Phenylketonuria (PKU/HPA)	4	3	1 : 5,376
Galactosemia (classical)	-	-	1 : 126,325
Biotinidase deficiency	4	0	1 : 95,763
Adrenogenital syndrome (AGS)[I]	30	0	1 : 16,358[I]
Medium chain acyl-CoA dehydrogenase (MCAD) deficiency[II]	1	1	1 : 11,266[II]
Long-Chain-3-OH-Acyl-CoA dehydrogenase (LCHAD) deficiency[II]	-	-	1 : 76,610[II]
(Very) long-Chain Acyl-CoA dehydrogenase (VLCAD) deficiency[II]	1	1	1 : 127,[II]
Maple syrup disease (MSUD)[II]	-	-	
Carnitine Palmitoyl-CoA Transfera-se I and II (CPTI/CPTII) deficiency[II]	-	-	
Carnitine Acylcarnitine Translocase (CACT) deficiency[II]	-	-	
Glutaric aciduria type I (GA I)[II]	-	-	
Isovaleric acidemia (IVA)[II]	11	1	
Mucoviscidosis[III]	15	4	1 : 5,361[III]
Tyrosinemia type I[IV]	1	0	1 : 78,782[IV]
Severe combined immunodeficiencies (SCID)[V]	1	-	
5q-associated spinal muscular atrophy (SMA)[VI]	-	-	1 : 30,000[VI]
Sickle cell disease (SCD)[VI]	1	1	1 : 30,000[VI]
Other[II]	4	0	

* Recall: Request of a new blood sample at suspicious screening result at first examination. Shown here the number inclusive early blood withdrawal (<36 h) or premature infant (< 32 WOG)
I Screening to detect adrenogenital syndrome (AGS) since 1997
II Enlarged screening (TMS) since 05/2001
III Screening for mucoviscidosis since 09/2016
IV Screening for tyrosinemia since 04/2017
V SCID since 08/2019
VI 5q-SMA and SCD since 10/2021

Process times

Point of taking blood samples

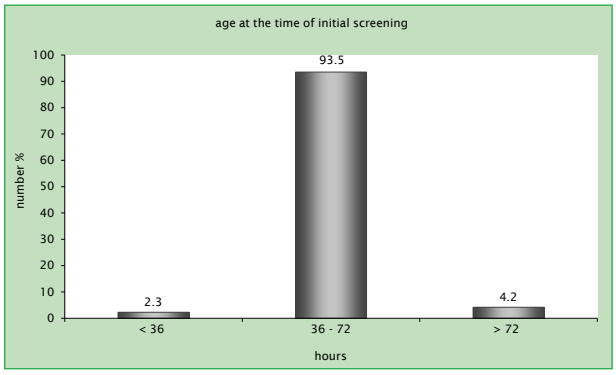

Fig. 2: Age at point of blood taking for first screening

The optimal point of taking blood samples for the newborn screening (36 –72 hours of life, §20 Children`s Directive) took place within the required period of time at 93.5 % (2021: 93.2 %) of all cases. At a total number of 6.7%, the taking of blood samples took not place within the required period of time (2021: 6.7%).

Note: Only newborns were included in the analysis if all required information was available (date and time of birth and blood collection date and time).

Transmission Time

According to §21 of the Children's Directive, the date of dispatch of the blood sample shall be
equal to the date of blood collection. The aim is to ensure that the postal route does not exceed 72 hours. Figure 3 shows that 19,6 % (2021: 20,6 %) of all transmittals reached the laboratory more than three days after the blood taking. On average, samples from 21 clinics reach the laboratory within the required time window (table 6). Postal transport times are longer than they were ten years ago, but they have not deteriorated further in the last three years.

Although there were dry blood cards that only arrived at the laboratory after more than ten days, the average transportation times were within the required range for all clinics. In 2022, there were no clinics with excessively long transportation times (< 72 hours, in 2021 this was still the case at two clinics). Since every delayed blood collection or every prolonged postal route means a potential (life) risk for the concerned infants, the laboratory tries to improve the quality of the blood collection by means of training events (letters, training events) to sensitize hospitals about this important issue. The main cause is certainly the sending of dried blood samples via private mail carriers. We urgently recommend sending the samples directly to the screening laboratory mailbox by Deutsche Post. The following instructions should also be observed:

- send blood samples on the day of collection, i.e. do not collect over several days, the letter
- should leave the hospital as soon as possible
- do not send to the hearing screening tracking center

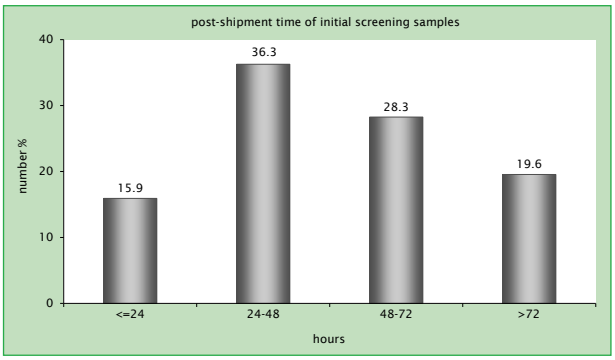

Fig. 3: Post-dispatch time of the dry blood cards (first screening)
Time from blood collection to arrival at the laboratory

Tab. 6: Post-dispatch time of dry blood cards per sending hospital (average value of all wards of a hospital), comparison 2022 to 2015

Maternity clinics	Average shipping time Shipping time (in hours)	
	2022	2015
Magdeburg St. Marienstift*	19	12
Magdeburg Universitätsklinikum*	27	29
Magdeburg Klinikum*	38	25
Zeitz	42	49
Gardelegen	45	41
Stendal	47	46
Salzwedel	48	45
Halle St. Elisabeth und St. Barbara	49	50
Naumburg	52	41
Aschersleben	54	50
Lutherstadt Wittenberg	58	56
Köthen	61	49
Merseburg	61	51
Burg	63	44
Wernigerode	63	50
Halberstadt	64	62
Sangerhausen	65	50
Halle Universitätsklinikum	67	53
Dessau-Roßlau	68	44

* Clinic with a courier service

Transmission of Results

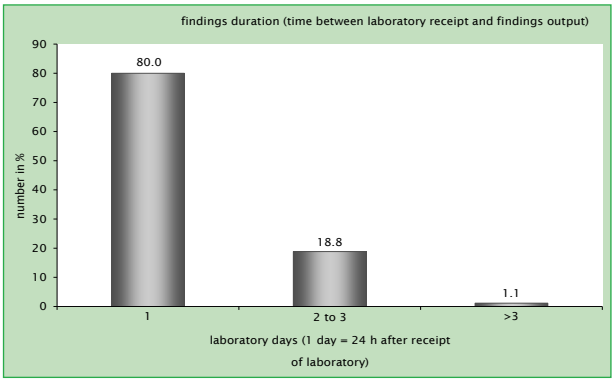

Fig.4: Duration of findings transmission

Figure 4 shows the duration of laboratory analysis of all initial screening examinations. 19,9% of all findings, that leave the laboratory after more than 24 hours, essentially reflect the prolonged duration of the findings due to the cystic fibrosis screening (3-stage screening including mutation analysis), internal repetition of analyses in case of implausibility and disruptions in the laboratory process (equipment maintenance, repairs, etc.).

In case of a highly suspicious finding, the information is immediately transmitted by telephone to the attending physician as partial finding. Due to the urgency, we do not wait for completion of all laboratory analyses in such cases.

Cystic fibrosis screening

Tab. 7: CF-Screening, participation and confirmed cases

	2022	2021
Screening, in total	13,974	15,450
CF screening included	99.8 %	99.7 %
CF screening positive	12	12
sweat test performed	12	12
CF confirmed	4	3

The screening for cystic fibrosis (CF) is offered since 09/2016 for all children throughout Germany. During the course of the 3-step laboratory analysis no control card is requested in case of a suspicious finding, but the children have to attend a CF outpatient clinic in order to exclude CF by means of a sweat test.

There is an increasing participation in the CF screening and a good acceptance of the program. In the year 2022 no parent or guardian rejected the participation in the CF screening. 0.2 % of CF analyses were not carried out due to the special fact that midwives are not allowed to take blood samples for this screening without permission from a doctor. Usually, the cooperation between midwives and paediatricians works well. All children received a sweat test after a positive CF screening. A sweat test showed highly abnormal findings in 3 children. A genetic analysis subsequently confirmed the diagnosis of severe cystic fibrosis.

Confirmation diagnostics and therapy for screening-positive patients

13 suspected screening cases could be confirmed by confirmation diagnostics and provided with a therapy:

Tab. 8: Diagnosis, confirmation diagnostics and therapy starting 2022

Diagnosis	Confirmation diagnostics	Age at start of therapy
1x Hypothyroidism	Serum-TSH sonography: athyreosis/severe dysplasia	7 days
3 x Phenylketonuria 2 x Hyperphenylalaninemia (HPA) 1 x classic PKU	Serum Phe, BH4 test, DHPR activity, pterins, partial mutation analysis	6 days HPA no therapy necessary
1 x medium chain acyl-CoA dehydrogenase (MCAD) deficiency	organic acids in urine, mutation analysis	7 days
1 x (very) long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	enzyme activity, mutation analysis	16 days
1 x isovaleric acidemia (IVA)	organic acids in urine, mutation analysis	7 days
1 x Severe combined immunodeficiency (SCID)	no feedback	no feedback
1 x sickle cell disease (SCD): SCD-S/S	Hb electrophoresis, mutation analysis	25 days
4 x cystic fibrosis 2 x classical homozygous mutation 2 x compound heterozygous mutation	sweat test mutation analysis	8-40 days

Summary

2022, there was a significant decline in the number of samples (a decrease of 1,500 samples).
There are two main reasons for this:
1. Declining number of births in Saxony-Anhalt
2. Closure of the maternity clinic in Quedlinburg

On March 2021, a new version of the Children's Directive came into force. The target diseases 5q-associated spinal muscular atrophy (SMA) and sickle cell disease (SCD) were added to the extended newborn screening. Since October 2021, every child born in Germany will be screened for SMA and SCD.
Accordingly, new information flyers were provided and senders were informed about this innovation. As before, parents have the option to have the screening for cystic fibrosis performed independently from the extended newborn screening or to decline it (checkbox on the dry blood card). CF screening can take place up to the 4th week of life of the newborn. The analysis of all target diseases of the Extended Newborn and Cystic Fibrosis Screening can be performed from one blood sample, provided that sufficient blood has been dripped. Here, new pre-analytical problems arose due to the introduction of the new laboratory method for the analysis of the SMN1 gene for SMA and haemoglobin S for SCD. The SMN1 gene is analysed by means of qPCR and tolerates no additives such as heparin or EDTA. The senders have been trained to fulfil the required criteria for the collection of dry blood samples from the heel strictly:
- Do not use EDTA, heparin or coated capillaries.
- Recommendation: use lancets with cutting blades, they provide optimal blood flow (e.g. Safety-Lancet Neonatal Blade or Safty-Heel Neonatal by Sarstedt, BD QuikHeel™ safety incision lancet)
- Disinfect heel with 70-80% alcohol and allow to dry thoroughly before puncture. Do not use hand sanitizers or similar, as they will interfere with the analysis
-Soak all 4 circles completely
The analysis of haemoglobin variants for SCD led to the following findings:
- Children with previous transfusion are in most cases not reported to the screening centre and only become apparent during Hb analysis

The Gene Diagnostics Act also applies to cystic fibrosis screening and is the overarching law with penalty paragraphs. Midwives are only allowed to take blood from newborns for the cystic fibrosis screening after permission by a paediatrician. Forms can be found on our homepage (www.stwz.ovug.de).

The Newborn Screening and Metabolism Laboratory belongs to the Institute of Clinical Chemistry and Pathobiochemistry since October 2015 (central laboratory of the University Hospital Magdeburg A.ö.R.). Nevertheless, the intensive cooperation with pediatricians for endocrinology and metabolism continues and is strongly encouraged.

The process quality of the newborn screening of Saxony-Anhalt remains very good, similar to the previous years and lies in the middle of the national average of all German screening laboratories (national screening report of the German society of newborn screening1).

We thank all materny clinics/ ambulances and midwifes for the good and smooth collaboration.

For further information about the metabolic screening centre Magdeburg, we kindly invite you to visit our website:

www.stwz.ovgu.de

We would like to inform senders, parents and interested people here about the Newborn Screening and about special metabolic diagnostics and provide downloads/ forms.
The national screening report of the DGNS1 is available on the Society's own website (http://screening-dgns.de) two years after the respective period of time.

[1] Quelle: Deutsche Gesellschaft für Neugeborenenscreening e.V. (DGNS): Nationaler Screeningreport Deutschland 2020
https://www.screening-dgns.de/Pdf/Screeningreports/DGNS-Screeningreport-d_2020.pdf