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PRACTICE AND POLICY

Updated EUROCAT guidelines for classification of cases with congenital anomalies

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Abstract

Background: Precise and correct classification of congenital anomalies is important in epidemiological studies, not only to classify according to etiology but also to group similar congenital anomalies together, to create homogeneous subgroups for surveillance and research. This paper presents the updated EUROCAT (European surveillance of congenital anomalies) subgroups of congenital anomalies and the updated multiple congenital anomaly (MCA) algorithm and provides the underlying arguments for the revisions.

Methods: The EUROCAT methodology is described. In addition, we show how we validated the revised EUROCAT subgroups and MCA algorithm, which are both based on the International Classification of Diseases (ICD10/ICD9) codes.

Results: The updated EUROCAT subgroups and the updated MCA algorithm are described in detail and the updated version is compared to the previous versions.

Conclusion: The EUROCAT subgroups and MCA algorithm provide a standardized and clear methodology for congenital anomaly research and epidemiological surveillance of congenital anomalies in order to facilitate the identification of teratogenic exposures and to assess the impact of primary prevention and prenatal screening policies. The EUROCAT subgroups and MCA algorithm are made freely available for other researchers via the EUROCAT Database Management Software.

KEYWORDS

birth defects, CAKUT, heart defects, multiple congenital anomalies, neural tube defects, orofacial clefts, syndrome

1 | INTRODUCTION

Congenital anomalies occur in 2%–3% of births (EUROCAT, 2022b) and lead to significant morbidity and mortality (Glinianaia et al., 2020; WHO, 2020). They also have a large impact on families, health care systems, and society as a whole (WHO, 2020). The cause of congenital anomalies is often unknown or multifactorial, but in some cases, a genetic or teratogenic cause can be identified. Also, one type of congenital anomaly can have different etiologies. For example, a coarctation of the aorta can be due to a chromosome anomaly (e.g., Turner syndrome), a monogenic disorder (e.g., NOTCH1 mutation), exposure to a teratogenic agent (e.g., valproic acid), or its cause may be multifactorial/unknown. It is also important to know whether anomalies in other organ systems are present. The different anomalies can be part of a sequence; "a pattern of multiple anomalies derived from a single known or presumed prior anomaly or mechanical factor" (Spranger et al., 1982). An example of a sequence is the Potter sequence: bilateral renal agenesis or dysplasia leads to oligohydramnios and this in turn leads to pes equinovarus (clubfoot) and lung hypoplasia. The pes equinovarus in the Potter sequence will have a different etiology than isolated pes equinovarus. A case with pes equinovarus and another unrelated anomaly in another organ system, for example, an atrial septum defect, is considered an MCA case and will probably have a different etiology. Precise and correct classification of congenital anomalies is therefore important in epidemiological studies, not only to classify as syndromic, MCA, or an isolated anomaly, but also to group similar congenital anomalies together, to create homogeneous subgroups for surveillance and research.

EUROCAT has created subgroups of congenital anomalies from the beginning, which were published in EUROCAT Guide 1 (EUROCAT, 1984). The subgroups have been revised several times. The latest revision was started for several reasons. First, new developments in genetic diagnostics prompted the revision of the genetic syndromes and microdeletions subgroup. Second, while working with the data in the surveillance (cluster and trend analysis), the EUROCAT Coding and Classification Committee found that several subgroups needed updating (e.g., gastroschisis and omphalocele were added as an exclusion criterion for the atresia or stenosis of other parts of small intestine subgroup as they are considered to be secondary to the abdominal wall defect). Third, the recent developments in prenatal screening programs in Europe have led to increased prenatal detection of certain congenital anomalies (e.g., agenesis of corpus callosum, unilateral renal agenesis), which prompted the addition of new subgroups. Finally, in specific studies, it became clear that some subgroups were not homogeneous enough to be of practical use (e.g., mitral insufficiency is no longer included in the mitral valve anomalies subgroup). The revision of the EUROCAT subgroups also triggered the revision of the MCA algorithm, which is partially based on the subgroups.

The aim of this paper is to present the updated EUROCAT subgroups of congenital anomalies and the updated MCA algorithm and to provide the underlying arguments for the revisions. The standardized EUROCAT subgroups are based on the International Classification of Diseases version 10 British Paediatric Association Extension codes (ICD10/BPA) and ICD9/BPA codes and we hope these will be used by other researchers.

2 | METHODS

2.1 | EUROCAT—European surveillance of congenital anomalies

The EUROCAT network was established in 1979 and at present comprises 43 population-based congenital anomaly registries surveying close to 1.5 million births per year (EUROCAT, 2022a). It is dedicated to the epidemiological surveillance of congenital anomalies in order to facilitate the identification of teratogenic exposures and to assess the impact of primary prevention and prenatal screening policies (Dolk, 2005). All registries submit their data once or twice a year to the JRC-EUROCAT Central Registry, which has been located at the European Commission Joint Research Centre (JRC) in Ispra, Italy, since 2015 (Kinsner-Ovaskainen et al., 2018). On the February 9, 2023, data on 540,556 cases were held in the central database for birth years 1980–2020 (EUROCAT, 2022c). All registries submit their data in a standardized fashion, according to the instructions defined in EUROCAT Guide 1.5, and using the EUROCAT Data Management Software and the EUROCAT data portal for data exchange (EUROCAT, 2023a). All pregnancy outcomes are reported to EUROCAT: live births, stillbirths, fetal deaths from 20 weeks of gestation, and elective terminations of pregnancy for fetal anomaly at any gestational age. The recommended follow-up for cases after birth is one year, but this varies between registries. More information about the specifics of the different EUROCAT local registries is available on the EUROCAT network website (EUROCAT, 2022d). Only cases with major congenital anomalies, which are defined as structural changes that have significant medical, social, or cosmetic consequences for the affected individual (EUROCAT, 2023a; WHO, 2020), should be submitted. Major anomalies should be congenital in origin and be structural, not solely functional

(e.g., cerebral palsy, developmental delay/intellectual disability, hearing loss and autism are not registered, unless seen in association with major structural congenital anomalies). All major anomalies occurring should be specified. EUROCAT has defined a list of anomalies, which are classified as minor congenital anomalies because they pose no significant health problem and tend to have limited social or cosmetic consequences for the affected individual (EUROCAT, 2023a; WHO, 2020). Cases with only minor anomalies are excluded in the central database. In addition, the most common genetic syndromes and chromosomal anomalies which have their own ICD10/BPA code are registered in the JRC-EUROCAT Central Registry (EUROCAT, 2017).

The major anomalies are allocated to EUROCAT subgroups, which group anomalies together because of shared etiological mechanisms or clinical characteristics. There is a balance to be found between lumping and splitting, to create homogeneous groups of not too few cases, also taking into account what can be realistically found in medical records or databases and can be processed by all registries. Also, specific ICD10/BPA codes (EUROCAT, 2008) need to be available for the anomalies and the subgroups should be consistent with the hierarchical classification of the ICD10. If a case has MCA, it will be allocated to several EUROCAT subgroups based on the ICD10/BPA codes for the case.

Within EUROCAT, potential MCA cases are identified via the EUROCAT MCA algorithm (EUROCAT, 2023a; Garne et al., 2011). These potential MCA cases are manually reviewed by three clinical geneticists from the EUROCAT Coding and Classification Committee to ensure their correct classification and facilitate the identification of teratogenic exposures that cause patterns of multiple malformations (Morris et al., 2023).

The EUROCAT methodology is published on the EUROCAT website (EUROCAT, 2023a) and the EUROCAT definitions and classification of congenital anomalies have been used in many studies and publications outside EUROCAT (Byrne et al., 2020; Gildestad et al., 2020; Klungsøyr et al., 2019; Sass et al., 2017; Taylor et al., 2021). The validated algorithm used for the classification of congenital anomalies into subgroups and the MCA algorithm have been implemented in the EUROCAT Data Management Software (DMS, EUROCAT, 2022e). The software is available to any researcher free of charge, upon request. It can be used, provided that the data is collected according to EUROCAT specifications (EUROCAT Guide 1.5), reported using ICD10/BPA or ICD9/BPA codes and include all pregnancy outcomes.

2.2 | Validation of new subgroups and MCA algorithm

Prior to the implementation of the new subgroups and MCA algorithm, the text descriptions of changed ICD10/BPA codes were checked to make sure that the codes were correctly used. For all revised subgroups, we subsequently checked whether the exclusion or inclusion of new codes was correctly assigned to the respective subgroups, based on the ICD10/BPA codes. We also compared the number of cases obtained for each subgroup with automated reports to ad hoc extractions focused on the ICD10/BPA codes added or excluded from the subgroups. For the new subgroups, we checked the total number of cases per registry per year to see whether there were sufficient cases to warrant a new subgroup. Although the subgroups were checked on the whole JRC-EUROCAT Central Database (1980–2020), to include ICD9/BPA codes, the final validation focused on the most recent birth years 2015–2020. It relied upon a data extraction from the JRC-EUROCAT Central Database of all registries contributing with anonymous data on individual case level (EUROCAT full member registries, $n = 36$) with all cases coded in ICD10/BPA. In total, 119,955 cases were registered with the total population coverage being 4.6 million births. The final data extractions were done on February 9, 2023.

The output of the MCA algorithm was also checked both on the whole Central Database and the recent subset of data. The cases that were classified differently by the old and the new MCA flowchart were examined on individual case level to see whether the new algorithm performed as intended. In addition, ad hoc extracts were done for specific anomalies (e.g., anencephaly, cyclopia, holoprosencephaly, polycystic kidneys, and teratogenic syndromes) to check whether the classification of the new MCA algorithm was correct.

3 | RESULTS

3.1 | Revised EUROCAT subgroups

The updated EUROCAT subgroups are presented in Table 1 and can also be found at the EUROCAT website (EUROCAT, 2023a). The subgroups are based on ICD10/BPA codes, which have been a requirement for EUROCAT since 2005. To permit analysis of older EUROCAT data and for other registries that still use ICD9/BPA, the subgroups are also specified for ICD9/BPA codes. The new version of the subgroups (2023) is compared to the previous version of the subgroups (2021) in Table S1,

TABLE 1 Updated EUROCAT subgroups, version November 17, 2022.

EUROCAT subgroups	ICD10-BPA	ICD9-BPA	Comments
All anomalies[a,b]	Q-chapter, D215, D821, D1810[c], P350, P351, P354, P358, P371	74, 75, 2377, 27910, 2281[c], 7607, 7608, 76280, 7710, 7711, 77121	No ICD9-BPA code for sacral teratoma Q code of major malformation must be present for P350, P351, P354, P358, P371, Q86, Q7980, 7607, 7608, 76280, 7710, 7711, 77121
Nervous system anomalies[b]	Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07, Q8703	740, 741, 742, 759801	
Neural tube defects	Q00, Q01, Q05	740, 741, 7420	
Anencephaly and similar	Q00	740	
Encephalocele and meningocele	Q01	7420	Exclude if associated with anencephaly subgroup
Spina Bifida	Q05	741	Exclude if associated with anencephaly or encephalocele subgroups
Hydrocephaly	Q03	7423	Exclude hydranencephaly 74232. Exclude if associated with NTD subgroup
Severe microcephaly	Q02	7421	Exclude if associated with NTD subgroup
Arhinencephaly / holoprosencephaly[b]	Q041, Q042, Q8703	74226, 759801	Exclude if associated with NTD subgroup
Agenesis of corpus callosum[b]	Q0400	742211	Exclude if associated with NTD subgroup
Eye anomalies	Q10-Q15	743	
Anophthalmos / microphthalmos	Q110, Q111, Q112	7430, 7431	
Anophthalmos	Q110, Q111	7430	
Congenital cataract	Q120	74332	
Congenital glaucoma	Q150	74320	
Ear, face, and neck anomalies	Q16, Q17, Q18	744	
Anotia and atresia / stenosis / stricture of external auditory canal[b]	Q160, Q161	74400, 74401	
Congenital heart defects (CHD)	Q20-Q26	745, 746, 7470–7474	Exclude PDA with GA <37 weeks Exclude peripheral pulmonary artery stenosis with GA < 37 weeks
Severe congenital heart defects[b,d]	Q200, Q201, Q202, Q203, Q204, Q205, Q206, Q212, Q213, Q214, Q2182, Q220, Q224, Q225, Q226, *Q230*[e], *Q232*[e], Q234, Q242, *Q244*[e], *Q245*[e], Q251, Q252, *Q253*[e], Q262, Q263	7450, 7451, 7452, 7453, 7456, 7461, 7462, 74600, *7463*[e], 7465[e], 7467, 74682, 7471, 74720, 74722[e], 74742, 74743	No ICD9-BPA code for double outlet left ventricle, hypoplastic right heart, Ivemark atrial isomerism, subaortic valve stenosis, and malformations of coronary arteries
Common arterial truncus	Q200	74500	
Double outlet right ventricle	Q201	745111	
Double outlet left ventricle[b]	Q202	No code	

TABLE 1 (Continued)

EUROCAT subgroups	ICD10-BPA	ICD9-BPA	Comments
Complete transposition of great arteries (D-TGA)	Q203	74510	
Single ventricle	Q204	7453	
Corrected transposition of great arteries (L-TGA)[b]	Q205	74512	
Ventricular septal defect (VSD)	Q210	7454	
Atrial septal defect (ASD)	Q211	7455	ICD10-BPA code includes common atrium
Atrioventricular septal defect (AVSD)	Q212	7456	ICD9-BPA code includes common atrium
Tetralogy and pentalogy of Fallot[b]	Q213, Q2182	7452	
Tricuspid atresia and stenosis	Q224	7461	
Ebstein's anomaly	Q225	7462	
Pulmonary valve stenosis	Q221	74601	
Pulmonary valve atresia	Q220	74600	
Aortic valve atresia/stenosis	Q230	7463	No ICD9-BPA code for aortic valve atresia
Mitral valve atresia/ stenosis[b]	Q232	7465	No ICD9-BPA code for mitral valve atresia
Hypoplastic left heart (HLH/HLHS)	Q234	7467	
Hypoplastic right heart (HRH/HRHS)	Q226	No code	
Coarctation of aorta	Q251	7471	
Aortic atresia / interrupted aortic arch	Q252	74720	
Total anomalous pulmonary venous return	Q262	74742	
Patent ductus arteriosus (PDA) as only CHD in term infants (GA +37 weeks)	Q250	7470	Livebirths only
Respiratory anomalies[b]	Q300, Q32-Q34	7480, 74833–74835, 7484, 74850, 74852, 74858, 7486, 7488	Exclude lung hypoplasia Q336
Choanal stenosis or atresia	Q300	7480	
Congenital pulmonary airway malformations (CPAM)	Q3380	No code	
Oro-facial clefts[b]	Q35-Q37	7490, 7491, 7492	Exclude if associated with holoprosencephaly subgroup
Cleft lip with or without cleft palate[b]	Q36, Q37	7491, 7492	Exclude if associated with holoprosencephaly subgroup
Cleft palate[b]	Q35	7490	Exclude if associated with cleft lip with or without cleft palate subgroup. Exclude if associated with holoprosencephaly subgroup

(Continues)

TABLE 1 (Continued)

EUROCAT subgroups	ICD10-BPA	ICD9-BPA	Comments
Gastro-intestinal anomalies[b]	Q38-Q45, Q790	750, 751, 75661	Exclude Q411-Q418 or 75111–75112 if associated with gastroschisis or omphalocele subgroup. Exclude Q433 or 7514 if associated with gastroschisis or omphalocele subgroup.
Esophageal atresia with or without tracheo-esophageal fistula	Q390-Q391	75030–75031	
Duodenal atresia or stenosis	Q410	75110	Exclude if associated with annular pancreas subgroup
Atresia or stenosis of other parts of small intestine[b]	Q411-Q418	75111–75112	Exclude if associated with gastroschisis or omphalocele subgroup
Ano-rectal atresia or stenosis	Q420-Q423	75121–75124	
Hirschsprung's disease	Q431	75130–75133	
Atresia of bile ducts	Q442	75165	
Annular pancreas	Q451	75172	
Anomalies of intestinal fixation[b]	Q433	7514	Exclude if associated with gastroschisis or omphalocele subgroup
Diaphragmatic hernia	Q790	75661	
Abdominal wall defects	Q792, Q793, Q795	75671, 75670, 75679	
Gastroschisis	Q793	75671	
Omphalocele	Q792	75670	
Congenital anomalies of kidney and urinary tract (CAKUT)[b]	Q60-Q64, Q794	75261, 753, 75672	Exclude Q620, 75320 if associated with VUR (Q627, 75324) or with NTD subgroup
Unilateral renal agenesis[b]	Q600	75301	ICD9-BPA code includes unilateral hypoplasia and dysplasia of kidney
Bilateral renal agenesis including Potter sequence	Q601, Q606	75300	ICD9-BPA code includes bilateral hypoplasia and dysplasia of kidney
Multicystic renal dysplasia	Q6140, Q6141	75316	
Congenital hydronephrosis including ureter obstruction[b]	Q620, Q621, Q623	75320, 75321, 75329	Exclude hydronephrosis (Q620, 75320) if associated with vesico-uretero-renal reflux (VUR, Q627, 75324) or with NTD subgroup
Lobulated, fused and horseshoe kidney and ectopic kidney[b]	Q631, Q632	75332, 75333	
Bladder exstrophy and / or epispadias	Q640, Q641	75261, 7535	
Posterior urethral valves[b]	Q6420	75360	
Prune belly syndrome[b]	Q794	75672	
Genital anomalies[b]	Q50-Q52, Q54-Q56	7520–7524, 75260, 7527–7529	

TABLE 1 (Continued)

EUROCAT subgroups	ICD10-BPA	ICD9-BPA	Comments
Hypospadias	Q54	75260	
Indeterminate sex	Q56	7527	
Limb anomalies	Q65-Q74	7543–7548, 755	Exclude Q660 or 75450 if associated with NTD or bilateral renal agenesis/Potter subgroup Exclude Q650-Q652 or 75430 if associated with NTD subgroup
Limb reduction defects (LRD)[b]	Q71-Q73	7552–7554, 75551	
Transverse LRD[b]	Q710, Q712, Q7180, Q720, Q722, Q7280, Q730		
Longitudinal preaxial LRD[b]	Q7131, Q714, Q7231, Q725		
Longitudinal postaxial LRD[b]	Q715, Q726		
Longitudinal central LRD[b]	Q716, Q727		
Intercalary LRD[b]	Q711, Q721, Q731		
Club foot—talipes equinovarus[b]	Q660	75450	Exclude if associated with NTD or bilateral renal agenesis/ Potter subgroup
Hip dislocation[b]	Q650-Q652	75430	Exclude if associated with NTD subgroup Hip dysplasia might be included in the ICD9 cases
Polydactyly	Q69	7550	
Syndactyly	Q70	7551	
Other anomalies / syndromes			
Craniosynostosis	Q750	75600	
Congenital constriction bands / amniotic band sequence resulting in major malformations[b]	Q7980	76280	Q code of major malformation must be present
Situs inversus	Q893	7593	
Conjoined twins	Q894	7594	
VATER/VACTERL association	Q8726	759895	
Pierre–Robin sequence[b]	Q8708	75603	
Caudal regression sequence[b]	Q8980	No code	
Sirenomelia[b]	Q8724	No code	
Septo-optic dysplasia[b]	Q044	74284	
Vascular disruption anomalies[b]	Q0435, Q411, Q412, Q418, Q710, Q712, Q7180, Q720, Q722, Q7280, Q730, Q793, Q7980, Q7982, Q8706		Q code of major malformation must be present for Q7980
Laterality anomalies[b]	Q206, Q240, Q3381, Q890, Q893		
Teratogenic syndromes resulting in major malformations[b]	Q86, P350, P351, P354, P358, P371	7607, 7608, 7710, 7711, 77121	Q code of major malformation must be present

(Continues)

TABLE 1 (Continued)

EUROCAT subgroups	ICD10-BPA	ICD9-BPA	Comments
Valproate syndrome[b]	Q8680	No code	Q code of major malformation must be present
Maternal infections resulting in major malformations[b]	P350, P351, P354, P358, P371	7710, 7711, 77121	Q code of major malformation must be present
Genetic disorders[b] (genetic syndromes, hereditary skin disorders, skeletal dysplasias, and chromosomal anomalies)	D821, Q4471, Q6190, Q7402, Q7484, Q751, Q754, Q7581, Q77, Q780-Q789, Q796, Q800-Q824, Q8282, Q8283, Q850, Q851, Q8581, Q87, Q8934, Q90-Q93, Q96-Q99	2377, 27910, 751653, 755551, 75581, 75601, 75604, 7564, 75650–75659, 75685, 7571, 75730, 75732–75736, 7580–7583, 7585–7589, 75934, 7595, 75961, 7598	Exclude associations and sequences: Q8703, Q8704, Q8706, Q8708, Q8724, Q8726, 75862, 759801, 759844, 759895
Skeletal dysplasias[b]	Q7402, Q77, Q780-Q789	755551, 7564, 75650–75659	
Down syndrome / trisomy 21	Q90	7580	
Patau syndrome / trisomy 13	Q914-Q917	7581	
Edwards syndrome / trisomy 18	Q910-Q913	7582	
Turner syndrome[b]	Q96	75860, 75861, 75869	
Triploidy and polyploidy[b]	Q927		

Note: The EUROCAT subgroups are published in EUROCAT guide 1.5, chapter 3.3, https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en.

[a]All anomalies = all cases with a major structural congenital anomaly, excluding cases with only minor anomalies as defined in Section 3.2 in EUROCAT guide 1.5. Cases with more than one anomaly are only counted once in the "All Anomalies" subgroup.

[b]New subgroup created in 2022 or existing subgroup which changed in 2022.

[c]ICD10 code D1810 (ICD9 code 2281) is the code for cystic hygroma.

[d]The severe CHD subgroup was based on the paper by Dolk H, Loane M, Garne E and EUROCAT working group. Congenital heart defects in Europe: prevalence and perinatal mortality, 2000–2005. Circulation. 2011; 123: 841–849. The following CHDs are included: single ventricle, hypoplastic right heart, hypoplastic left heart, tricuspid valve atresia, Ebstein anomaly, common arterial truncus, double outlet right ventricle, double outlet left ventricle, complete and corrected transposition of the great arteries, atrioventricular septal defect, tetra- and pentalogy of Fallot, pulmonary valve atresia, tricuspid valve stenosis, aortic valve atresia/stenosis, mitral valve atresia/stenosis, coarctation of aorta, aortic atresia/interrupted aortic arch, total and partial anomalous pulmonary venous return, Ivemark atrial isomerism, aortopulmonary window, cor triatriatum, subaortic valve stenosis, supravalvular aortic stenosis and malformations of the coronary arteries.

[e]Severe CHD with codes shown in *italics* should only be included in specific studies when diagnosed in the first year of life.

where the number of cases, prevalence, and proportion per subgroups are shown. The subgroups of the previous and the new version of the subgroups are quite similar, but the new classification has led to more homogeneous subgroups. In addition, the genetic disorders subgroup is now more accurate, which is very important for surveillance (as genetic conditions are excluded). The largest differences were seen in the severe congenital heart defects, mitral valve atresia/stenosis, hydronephrosis, clubfoot, vascular disruption anomalies, and skeletal dysplasias subgroups.

3.2 | All anomalies

The EUROCAT "all anomalies" subgroup includes all major anomalies with an ICD10/BPA code in the Q chapter and seven conditions with a code outside the Q chapter of the ICD10/BPA: sacral teratoma (D215), 22q11 deletion syndrome (D821), cystic hygroma (D1810), congenital rubella syndrome (P350), congenital CMV syndrome (P351), congenital zika virus disease (P354), other congenital viral diseases (P358, e.g., congenital varicella), and congenital toxoplasmosis (P371). For the teratogenic syndromes and congenital constriction bands / amniotic band sequence, it is specified that a major congenital malformation must be present.

3.3 | Nervous system anomalies

The "nervous system anomalies" subgroup is divided into five subgroups. First are the neural tube defects (NTDs), which are further subdivided into anencephaly and similar (including craniorachischisis and iniencephaly), encephalocele and meningocele, and spina bifida. When other brain anomalies are seen together with an NTD, they are excluded from their respective subgroups, as the anomaly is thought to be secondary to the NTD. The second subgroup is hydrocephaly, defined as the dilation of the

ventricular system with impaired circulation and absorption. The third subgroup is severe microcephaly, which is defined as a head circumference below −3 standard deviations at birth for gestational age and gender (see also the EUROCAT detailed congenital anomaly coding guidelines, EUROCAT, 2023a). The fourth subgroup is arhinencephaly / holoprosencephaly, which in the updated version also includes cyclopia (the most severe form of holoprosencephaly, Q8703). The last subgroup is new and comprises cases with complete agenesis of corpus callosum. In the last decade, prenatal screening has been implemented in all European countries, leading to increased prenatal detection of brain anomalies, among which is corpus callosum agenesis, which otherwise might have been detected much later in life. There were 1112 cases with corpus callosum agenesis present in the data extraction of the JRC-EUROCAT Central Database, of which 28 also had an NTD and were therefore excluded from the corpus callosum agenesis subgroup. In total, 366 cases had the corpus callosum agenesis code only.

3.4 | Eye anomalies

Four subgroups of eye anomalies were defined. The first combines anophthalmos with microphthalmos as both anomalies are rare and manifestations of the same spectrum. Anophthalmos also has its own subgroup. The third subgroup comprises congenital cataract, and the fourth subgroup consists of congenital glaucoma.

3.5 | Ear, face, and neck anomalies

Many of the anomalies of the ear, face, and neck are considered minor anomalies, but one new subgroup was created which combines anotia (absence of the ear) with atresia, stenosis, or stricture of the external auditory canal. These anomalies often occur together (Abdel-Aziz, 2013) and are thought to share the same etiology and develop in the same embryonic time period (Czeizel, 2008). There were 275 cases with atresia, stenosis, or stricture of the external auditory canal present in the data extraction, of which 33 cases also had anotia and 40 cases had only the code for atresia, stenosis or stricture of the external auditory canal reported. There were 112 cases with anotia in the data extraction, of which 23 cases had only the anotia code.

3.6 | Congenital heart defects

The overarching "congenital heart defects (CHD)" subgroup comprises all CHD, except the ones that are considered minor, a consequence of preterm birth or functional anomalies (e.g., patent ductus arteriosus or stenosis of the peripheral pulmonary artery in children with a gestational age less than 37 weeks, patent foramen ovale, congenital heart block, persistent right aortic arch, persistent left superior vena cava). The subgroup "severe CHD" includes heart defects that result in a functional univentricular heart: single ventricle, hypoplastic right heart, hypoplastic left heart, tricuspid valve atresia, Ebstein anomaly and those who commonly require surgery: common arterial truncus, double outlet right ventricle (DORV), double outlet left ventricle, complete and corrected transposition of the great arteries (TGA), atrioventricular septal defect (AVSD), tetra- and pentalogy of Fallot, pulmonary valve atresia, tricuspid valve stenosis, aortic valve atresia/stenosis, mitral valve atresia/stenosis, coarctation of aorta, aortic atresia/interrupted aortic arch, total and partial anomalous pulmonary venous return, Ivemark atrial isomerism, aortopulmonary window, cor triatriatum, subaortic valve stenosis, supravalvular aortic stenosis, and malformations of the coronary arteries. The severe CHDs classification has been extended and is based on a previous paper (Dolk et al., 2011), which showed that EUROCAT cases with severe CHD were more uniformly ascertained and were often diagnosed early (prenatally or in the first week of life). The severe CHD cases often needed surgery (80%, with an additional 7% too severe for surgery). The nonsevere CHD cases (ventricular septal defect (VSD), atrial septal defect (ASD), pulmonary valve stenosis, patent ductus arteriosus in term babies, and valve insufficiencies) are often milder, although in large septal defects or severe stenosis surgery can also be necessary.

In addition to the severe CHD subgroup, there are 22 other heart defect subgroups (Table 1). Two subgroups were updated. The tetralogy of Fallot (Q213) subgroup now also includes pentalogy of Fallot (Q2182). The mitral valve atresia/stenosis (Q232) subgroup no longer includes mitral valve insufficiency (Q233), because the valve insufficiency may be secondary to dilatation of the left ventricle. Double outlet left ventricle and corrected TGA (L-TGA) were added as new subgroups. In the data extraction, there were 25 cases with double outlet left ventricle, of which 1 had only this code reported and there were 154 cases with corrected TGA, of which 18 had only this code reported.

3.7 | Respiratory anomalies

The respiratory anomalies subgroup is subdivided into two subgroups: choanal atresia and congenital pulmonary airway malformations (CPAM, formerly called

congenital cystic adenomatous malformation of the lung). Lung hypoplasia is excluded from the respiratory anomalies subgroup, as this is mainly secondary (due to other causes), and some registries have used the lung hypoplasia code to report preterm babies with bronchopulmonary dysplasia. No major updates were done.

3.8 | Oro-facial clefts

The oro-facial clefts (OFC) subgroup is subdivided into two subgroups: cleft lip with or without cleft palate and cleft palate. If a case has an OFC in combination with holoprosencephaly, it is excluded from the OFC subgroup, because the OFC is thought to be secondary to the holoprosencephaly. A case with an anencephaly and an OFC, however, is considered a MCA case in the EUROCAT multiples surveillance.

3.9 | Gastrointestinal anomalies

The gastrointestinal anomalies subgroup is subdivided into nine subgroups: esophageal atresia with or without tracheo-esophageal fistula, duodenal atresia or stenosis, atresia or stenosis of other parts of small intestine, anorectal atresia or stenosis, Hirschsprung's disease, atresia of bile ducts, annular pancreas, anomalies of intestinal fixation, and diaphragmatic hernia. Cases with duodenal atresia or stenosis due to an annular pancreas are excluded from the duodenal atresia or stenosis subgroup because the atresia/stenosis is secondary to the annular pancreas. The subgroup "anomalies of intestinal fixation" was added as a new subgroup. In the data extraction, there were 797 cases of which 237 had only this code reported. In total, 30 cases were excluded from the subgroup "anomalies of intestinal fixation," because a gastroschisis or omphalocele was also present. The same exclusion is applied to cases from the atresia or stenosis of other parts of the small intestine subgroup, as the atresia/stenosis is very likely secondary to the abdominal wall defect (Frolov et al., 2010).

3.10 | Abdominal wall defects

There are two subgroups within the abdominal wall defects: gastroschisis and omphalocele. These abdominal wall defects are very different in etiology with gastroschisis occurring more often in young mothers and omphalocele which can have a genetic origin (Frolov et al., 2010).

3.11 | Congenital anomalies of kidney and urinary tract (CAKUT)

This subgroup was previously named "urinary," but is now named CAKUT, which is consistent with the term used in literature (Kohl et al., 2021). Eight CAKUT subgroups were defined, including three new subgroups. Unilateral renal agenesis was added, because this anomaly is often detected on prenatal ultrasound scan and with the implementation of prenatal screening programs in Europe, the ascertainment has increased. In the data extraction, there were 1955 cases with unilateral renal agenesis, of which 1086 had only this code reported. The subgroup "bilateral renal agenesis including Potter sequence" was not changed, because the underlying kidney anomaly was often not specified in EUROCAT cases with Potter sequence. The congenital hydronephrosis subgroup was extended and now also includes ureter obstruction (atresia/stenosis of ureter and other obstructive defects of renal pelvis and ureter), which results in hydronephrosis. If cases have hydronephrosis and vesico-uretero-renal reflux (defined in EUROCAT as a minor anomaly) or an NTD, they are excluded from this subgroup, as the hydronephrosis is likely a secondary effect. The subgroup "lobulated, fused, and horseshoe kidney and ectopic kidney" was added, which includes anomalies of renal embryonic migration, that is, fusion anomalies and renal ectopia (Rosenblum, 2022). In the data extraction, 569 cases were present with a lobulated, fused or horseshoe kidney (Q631), of which 159 had only this anomaly reported and 1032 cases were registered with an ectopic kidney (Q632), of which 513 had only this anomaly reported. There were 25 cases with both Q631 and Q632 coded, leading to a total of 1576 cases in the subgroup "lobulated, fused and horseshoe kidney and ectopic kidney." Prune belly syndrome now has its own subgroup. In the data extraction, 47 cases with prune belly syndrome were present, of which three had the prune belly code as the only reported code. Cases with codes for both prune belly syndrome and posterior urethral valves are included in both the posterior urethral valves and prune belly syndrome subgroup.

3.12 | Genital anomalies

Two subgroups fall within the genital anomalies subgroup: hypospadias and indeterminate sex. No updates were needed for these subgroups.

3.13 | Limb anomalies

The limb anomalies subgroup is divided into limb reduction defects (LRD), talipes equinovarus, hip dislocation,

polydactyly, and syndactyly. New subgroups were added to subdivide the LRD subgroup into five smaller groups with different etiology: transverse LRD, longitudinal preaxial LRD, longitudinal postaxial LRD, longitudinal central LRD, and intercalary LRD according to the LRD classification described in Bergman et al., 2020 (Bergman et al., 2020). Ten ICD10/BPA codes could not be classified as they are not specific for the LRD subcategories (Q713, Q7130, Q718, Q719, Q723, Q7230, Q724, Q728, Q729, and Q738), but these are included in the overarching LRD and limb anomalies subgroups. The data extraction from the JRC-EUROCAT Central Database showed that all LRD subgroups had more than 100 cases, except for the intercalary group (51 cases). For the pes equinovarus subgroup, an exclusion criterion was added. The reason for this is that the pes equinovarus is considered to be a secondary anomaly when an NTD or Potter sequence is also present. The hip dysplasia subgroup was changed, because EUROCAT now regards hip dysplasia as a minor anomaly: the hip dysplasia code was removed and the subgroup was renamed "hip dislocation." Hip dislocation cases with an NTD are excluded from this subgroup. There were no changes in the polydactyly and syndactyly subgroups.

3.14 | Other anomalies/syndromes

There are fourteen subgroups specified that fall under the other anomalies/syndromes subgroup. No changes were made to the craniosynostosis, situs inversus, conjoined twins, and VATER/VACTERL association subgroup. For the congenital constriction bands / amniotic band sequence, teratogenic syndromes, and maternal infections, it was specified that a major congenital anomaly must be present for cases to be submitted to the JRC-EUROCAT Central Registry. The teratogenic syndromes subgroup includes cases with a congenital infection and a major congenital anomaly (e.g., rubella, CMV, zika, varicella, and toxoplasmosis) and cases with major congenital anomalies due to exposure to known teratogenic agents (e.g., alcohol, medications, heavy metals, and radiation). The fetal alcohol syndrome (FAS) subgroup no longer has its own subgroup for several reasons. First of all, this entity is difficult to diagnose in the neonatal period and is best done later by a multidisciplinary team including clinical geneticists (to rule out genetic disorders and for dysmorphology evaluation) and psychologists (for neuropsychological assessment). In addition, major congenital anomalies are not frequently present in FAS (Hoyme et al., 2016). Lastly, the number of FAS cases was lower than expected for all EUROCAT registries, except Ukraine and Reunion.

The vascular disruption subgroup at present contains the following anomalies: hydranencephaly (Q0435), small intestinal atresia (Q411, Q412, Q418), transverse LRDs (Q710, Q712, Q7180, Q720, Q722, Q7280, Q730), gastroschisis (Q793), amniotic band sequence (Q7980), Poland anomaly (Q7982), and Moebius syndrome (Q8706) (Gold et al., 2011; Harbord et al., 1989; Holmes et al., 2018; Husain et al., 2008; Lubinsky, 2014; Pavone et al., 2014; Pedersen et al., 2017; Ruschkowski et al., 2021; Van Allen et al., 1987; van Gelder et al., 2014). The limb body wall complex (LBWC, body stalk anomaly) was not added to the vascular disruption subgroup as there is no specific ICD10/BPA code for this entity. It must be noted that there is no consensus in the literature about which anomalies are due to vascular disruption. Based on the current literature, the EUROCAT Coding and Classification Committee has decided to include the above mentioned anomalies, but will review the literature regularly to see whether updates can be made. In the laterality anomalies subgroup the following anomalies are present: isomerism of atrial appendages/Ivemark syndrome (Q206), dextrocardia (Q240), bronchopulmonary isomerism (Q3381), congenital spleen anomalies (Q890), and situs inversus (Q893) (Soofi et al., 2021).

The following subgroups were newly added: Pierre Robin sequence, caudal regression sequence, sirenomelia and septo-optic dysplasia. Pierre Robin sequence consists of the triad of micrognathia, glossoptosis and airway obstruction, often accompanied by a cleft palate (Hsieh & Woo, 2019). It can be isolated, but can also be syndromic. In the JRC-EUROCAT data extraction there were 460 cases with Pierre Robin sequence. The other three anomalies are very rare, but have a specific ICD10/BPA code and are well described clinical conditions. Caudal regression sequence and sirenomelia are both associated with anomalies at the caudal end of the trunk, with fusion of the lower limbs in sirenomelia, but are thought to have different etiologies (Boulas, 2009). Maternal diabetes is an important risk factor for caudal regression sequence (Boulas, 2009). Septo-optic dysplasia is characterized by optic nerve hypoplasia, pituitary hormone anomalies, and midline brain anomalies and was found to be associated with low maternal age in an earlier EUROCAT study (Garne et al., 2018). In the data extraction, there were 84 cases with caudal regression sequence, 45 with sirenomelia (5 cases had codes for both caudal regression sequence and sirenomelia), and 76 with septo-optic dysplasia.

3.15 | Genetic disorders

The genetic disorders subgroup was updated and now includes genetic syndromes, hereditary skin disorders, skeletal dysplasias, and chromosomal anomalies. The

reason for this overarching genetic disorder subgroup was that the distinction between monogenic syndromes and chromosomal anomalies is disappearing with ever smaller genetic aberrations being found with new techniques. This subgroup is important for case-malformed control studies as it contains all anomalies which have a genetic origin (including point mutations, deletions or duplications, unbalanced translocations, methylation disorders, etc.). This subgroup contains the following diagnoses: 22q11 deletion syndrome (D821), Alagille syndrome (Q4471), Meckel-Gruber syndrome (Q6190), Larsen syndrome (Q7484), Crouzon syndrome / craniofacial dysostosis (Q751), mandibulofacial dysostosis including Treacher-Collins syndrome (Q754), frontonasal dysplasia (Q7581), Ehlers-Danlos syndrome (Q796), neurofibromatosis type 1 (Q850), tuberous sclerosis (Q851), Sturge–Weber syndrome (Q8581), congenital malformation syndromes (Q87, associations and sequences are excluded: Q8703, Q8704, Q8706, Q8708, Q8724, Q8726), Kartagener syndrome (Q8934), chromosomal anomalies (Q90-Q93, Q96-Q99), hereditary skin disorders (Q800-Q824, Q8282, Q8283), and skeletal dysplasias (cleidocranial dysostosis Q7402, osteochondrodysplasias Q77, Q780-Q789). Polycystic kidney disease (Q611, Q612, Q613) was not included in the genetic disorder subgroup as many cases in the JRC-EUROCAT Central Database with these codes appeared to have unilateral multicystic dysplastic kidney disease, which does not belong in the genetic disorder subgroup. There is a separate subgroup for the skeletal dysplasias and for trisomy 21 (Q90), trisomy 13 (Q914–Q917), trisomy 18 (Q910–Q913), Turner syndrome (Q96), and triploidy and polyploidy (Q927). This last subgroup is new and there were 493 cases in the data extraction with Q927 as the only code in 232 cases. The Klinefelter subgroup was removed, as cases with Klinefelter syndrome almost never have congenital anomalies and diagnosis can be delayed until puberty, leading to considerable underreporting.

The genetic disorders subgroup contains diagnoses that almost always have a genetic cause. In some cases, the genetic cause might not have been identified (e.g., clinical diagnosis of Noonan syndrome) but is presumed to be present. In addition, within this group, there will be some cases that have a genetic disorder and an unrelated major anomaly (e.g., a case with trisomy 21 and a cleft lip and palate). These cases will be classified in the genetic disorder subgroup, as it is often difficult to determine which defects are related to a certain genetic disorder and which ones are not. The defect could occur in a minority of cases with the genetic disorder or the defect might not have been described yet in a rare syndrome. For cases with a genetic anomaly or syndrome without a specific ICD10/BPA code, the EUROCAT Coding and Classification Committee recommends using Q878 (EUROCAT, 2023a). This way, the anomaly/syndrome will be allocated to the genetic disorder subgroup and will also be classified correctly by the MCA algorithm.

3.16 | Revised MCA algorithm

The EUROCAT MCA algorithm is designed to classify cases into the following mutually exclusive groups: genetic disorders, teratogenic disorders, isolated anomalies and MCA based on ICD10/BPA and ICD9/BPA codes (Garne et al., 2011). The algorithm is following the MCA definition: two or more unrelated major congenital anomalies in different organ systems that cannot be explained by an underlying syndrome or sequence (Table 2) (EUROCAT, 2023a). Almost all steps of the MCA algorithm have been updated compared to the previous version in order to be consistent with the revised EUROCAT subgroups and also more sequences have been added in step 19.

The MCA algorithm will first exclude all cases that are not eligible for inclusion in the EUROCAT database: in step 0, all cases which only have nonaccepted codes and/or minor, unspecified, or invalid codes will be excluded. In step 1, all cases with a genetic disorder code will be transferred to group G—the genetic disorder group. In step 2, all cases with a teratogenic syndrome code and at least one other accepted major anomaly code will be transferred to group T—the teratogenic syndrome group. In step 3 (newly added), cases with a code for the VACTERL association or oculo-auriculo-vertebral spectrum (OAVS, Goldenhar) will be transferred to group M. The underlying reason for transferring OAVS and VACTERL to group M is that in both conditions multiple congenital anomalies are present and the underlying cause remains unknown in the majority of cases (Bogusiak et al., 2017; Thiem et al., 2022; van de Putte et al., 2020). Group M is the group with potential MCA. In addition, cases with a code for polycystic kidneys are transferred to group M in this step, because the EUROCAT Coding and Classification Committee has decided to review all these cases manually. This way, the text description of cases can be taken into account. In steps 4–6, cases with codes only for NTDs, congenital heart defects or CAKUT will be transferred to the isolated NTD (N), isolated cardiac (A), or isolated renal (R) group, respectively. In step 7, cases with only one accepted major code will be transferred to the isolated other (I) group. In step 8, cases with cystic hygroma and one other accepted major code will be transferred to their respective groups (group N, A, R or I). In steps 9–16, cases with specified codes will be transferred to group I

TABLE 2 Updated EUROCAT multiple congenital anomaly algorithm, version 17 November 2022.

Steps[a]	Rule	ICD9-BPA codes[b]	ICD10-BPA codes[b]	Transfer to
Step 0	Exclude all cases with only nonaccepted ICD9/BPA or ICD10/BPA codes	Outside 740–759, except 2377, 27910 and 2281 which are accepted as outside malformation chapter codes	Outside Q chapter, except D215, D821 and D1810 which are accepted as outside Q-codes	**Group O**: non-syndrome outside malformation chapter (teratogenic syndromes without a major congenital anomaly are included here)
	Exclude all cases with only minor, unspecified and invalid codes[c]	Only minor codes, and/or 7584 and/or 7597 and/or 7599	Only minor codes, and/or Q95, and/or Q897 and/or Q899	**Group X**: minor, unspecified and invalid codes
Step 1	Exclude all cases with a genetic disorder code	2377, 27910, 751653, 755551, 75581, 75601, 75604, 7564, 75650–75659, 75685, 7571, 75730, 75732–75736, 7580–7583, 7585–7589, 75934, 7595, 75961, 7598, except 75862, 759801, 759844, 759895	D821, Q4471, Q6190, Q7402, Q7484, Q751, Q754, Q7581, Q77, Q780-Q789, Q796, Q800-Q824, Q8282, Q8283, Q850, Q851, Q8581, Q87, Q8934, Q90-Q93, Q96-Q99, except Q8703, Q8704, Q8706, Q8708, Q8724, Q8726	**Group G**: genetic disorders (genetic syndromes, hereditary skin disorders, skeletal dysplasias and chromosomal anomalies)
Step 2	Exclude all cases with a teratogenic syndrome code and at least one other accepted major ICD9/BPA or ICD10/BPA code	7607, 7608, 7710, 7711, 77121	Q86, P350, P351, P354, P358, P371	**Group T**: teratogenic syndromes resulting in major malformations
Step 3	Exclude all cases with the VACTERL association code	759895	Q8726	**Group M**: potential multiple congenital anomalies
	Exclude all cases with the OAVS / Goldenhar syndrome code	75606	Q8704	
	Exclude all cases with polycystic kidney codes	75311–75313	Q611-Q613	
Step 4	Exclude all cases with codes only for neural tube defects	740, 741, 7420	Q00, Q01, Q05	**Group N**: isolated NTD
Step 5	Exclude all cases with codes only for congenital heart defects	745, 746, 7470–7474	Q20-Q26	**Group A**: isolated cardiac
Step 6	Exclude all cases with codes only for congenital anomalies of kidney and urinary tract (CAKUT)	75261, 753, 75672	Q60-Q64, Q794	**Group R**: isolated renal
Step 7	Exclude all cases with only one accepted major ICD9-BPA or ICD10-BPA code			**Group I**: isolated other
Step 8	Exclude all cases with the code for cystic hygroma (2281 or D1810) and only one other accepted major ICD9/BPA or ICD10/BPA code	If (740, 741, 7420) and 2281	If (Q00, Q01, Q05) and D1810	**Group N**: isolated NTD
		If (745, 746, 7470–7474) and 2281	If (Q20-Q26) and D1810	**Group A**: isolated cardiac
		If (75261, 753, 75672) and 2281	If (Q60-Q64, Q794) and D1810	**Group R**: isolated renal

(Continues)

TABLE 2 (Continued)

Steps[a]	Rule	ICD9-BPA codes[b]	ICD10-BPA codes[b]	Transfer to
		If only 2281, or 2281 and one other accepted major ICD9/BPA code	If only D1810, or D1810 and one other accepted major ICD10/BPA code	**Group I**: isolated other
Step 9	Exclude all cases with codes only for nervous system anomalies, not NTD	7421–7429, 759801	Q02-Q04, Q06-Q07, Q8703	**Group I**: isolated other
Step 10	Exclude all cases with codes only for eye anomalies	743	Q10-Q15	**Group I**: isolated other
Step 11	Exclude all cases with codes only for ear anomalies	7440–7443	Q16-Q17	**Group I**: isolated other
Step 12	Exclude all cases with codes only for respiratory anomalies	7480, 74833–74835, 7484, 74850, 74852, 74858, 7486, 7488	Q300, Q32-Q34	**Group I**: isolated other
Step 13	Exclude all cases with codes only for oro-facial clefts	7490, 7491, 7492	Q35-Q37	**Group I**: isolated other
Step 14	Exclude all cases with codes only for small intestinal atresia	75111, 75112	Q411-Q418	**Group I**: isolated other
Step 15	Exclude all cases with codes only for genital anomalies	7520–7524, 75260, 7527–7529	Q50-Q52, Q54-Q56, except Q518	**Group I**: isolated other
Step 16	Exclude all cases with codes only for limb anomalies	7543–7548, 755	Q65-Q74	**Group I**: isolated other
Step 17	Exclude all cases with code for conjoined twins	7594	Q894	**Group I**: isolated other
	Exclude all cases with code for cyclopia	759801	Q8703	
Step 18	Exclude all cases with the code for balanced chromosomal rearrangements (7584 or Q95) and only one other accepted major ICD9/BPA or ICD10/BPA code	If (740, 741, 7420) and 7584	If (Q00, Q01, Q05) and Q95	**Group N**: isolated NTD
		If (745, 746, 7470–7474) and 7584	If (Q20-Q26) and Q95	**Group A**: isolated cardiac
		If (75261, 753, 75672) and 7584	If (Q60-Q64, Q794) and Q95	**Group R**: isolated renal
		If only one other accepted major ICD9/BPA code and 7584	If only one other accepted major ICD10/BPA code and Q95	**Group I**: isolated other
Step 19	Exclude all known sequences or combinations of anomalies without other anomaly codes (NB: Any one of these codes may be used more than once—disregard duplicate codes)			
	Spina bifida—central nervous system anomalies—talipes—hip dislocation—congenital hydronephrosis	741 coded with (7422–7429 and/or 7545 and/or 7543 and/or 75320)	Q05 coded with (Q03, Q04, Q06-Q07, and/or Q66 and/or Q65 and/or Q620)	**Group N**: isolated NTD
	Anencephaly—adrenal anomaly	740 coded with 7591	Q00 coded with Q891	**Group N:** isolated NTD
	Bilateral renal agenesis/dysplasia—lung hypoplasia—talipes	75300 coded with (74851 and/or 7545)	Q601/Q606 coded with (Q336 and/or Q66)	**Group R**: isolated renal
	Gastroschisis/omphalocele—anomalies of intestinal fixation—small intestinal atresia	75671/75670 coded with (7514 and/or 7511)	Q793/Q792 coded with (Q433 and/or Q41)	**Group I**: isolated other

TABLE 2 (Continued)

Steps[a]	Rule	ICD9-BPA codes[b]	ICD10-BPA codes[b]	Transfer to
	Ano-rectal atresia and stenosis—rectovaginal fistula	7512 coded with 75242	Q42 coded with Q522	**Group I**: isolated other
	Diaphragmatic hernia—lung hypoplasia—anomalies of intestinal fixation	75661 coded with (74851 and/or 7514)	Q790 coded with (Q336 and/or Q433)	**Group I**: isolated other
	NTD—Arnold Chiari malformation—tethered cord	No ICD9/BPA code for Arnold-Chiari malformation or tethered cord	Q01/Q05 coded with (Q070 and/or Q068)	**Group N**: isolated NTD
	Amniotic band sequence code and at least one other accepted major ICD9/BPA or ICD10/BPA code	All cases with the code 76280 and at least one other accepted major ICD9/BPA code	All cases with the code Q7980 and at least one other accepted major ICD10/BPA code	**Group I**: isolated other
	Poland anomaly—symbrachydactyly—aplasia pectoral muscle	75680 coded with (7551 and/or 76581)	Q7982 coded with (Q70 and/or Q7480 and/or Q7981)	**Group I**: isolated other
	Caudal regression sequence	No ICD9/BPA code for caudal regression sequence	All cases with the code Q8980	**Group I**: isolated other
	Sirenomelia sequence	All cases coded with 759844 (sirenomelia/caudal regression)	All cases coded with Q8724	**Group I**: isolated other
	Pierre Robin sequence	All cases coded with 75603 as the only code or with 7490	All cases coded with Q8708 as the only code or with Q35	**Group I**: isolated other
	Holoprosencephaly/arhinencephaly—oro-facial clefts—brain anomalies	74226 coded with (7490–7492 and/or 7421–7424)	Q042/Q041 coded with (Q35-Q37 and/or Q02-Q04)	**Group I**: isolated other
	Annular pancreas—atresia/stenosis of duodenum	75172 coded with 75110	Q451 coded with Q410	**Group I**: isolated other
Step 20	The remaining cases are **group M**: potential multiple congenital anomalies. Manual evaluation of all remaining cases will take place by the geneticists of the EUROCAT coding and classification committee. All cases will be manually allocated to either the multiple congenital anomaly group or one of the other groups.			**Group M:** potential multiple congenital anomalies

Note: The updated EUROCAT MCA algorithm is published in EUROCAT guide 1.5, chapter 3.4, https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en.

[a]This is a hierarchical procedure.

[b]For 3 and 4 digit codes mentioned here, the coding also includes the codes with more digits. Only accepted ICD9/BPA and ICD10/BPA codes are valid for the process after step 2.

[c]Minor, unspecified and invalid codes: Minor codes as specified in Guide 1.5 Chapter 3.2. Balanced chromosomal rearrangements (7584 or Q95). Multiple malformation code (7597 or Q897). Unspecified malformation code (7599 or Q899). No valid ICD code.

(e.g., cases with only nervous system anomalies or only eye anomalies or only oro-facial clefts). In step 17, all cases with a code for conjoined twins or cyclopia are transferred to group I. In step 18, cases with a code for balanced chromosomal rearrangements and only one other accepted major code will be transferred to their respective groups (group N, A, R, or I). In step 19, sequences are identified and transferred to the group of the primary anomaly. Spina bifida with associated anomalies is transferred to group N, Potter sequence to group R and a variety of sequences (Poland anomaly with symbrachydactyly, amniotic band sequence, caudal regression sequence, sirenomelia sequence, Pierre Robin sequence, holoprosencephaly with orofacial clefts) to group I. All remaining cases

TABLE 3 Examples of case classification.

Example	Classification MCA algorithm	Classification after manual review
Trisomy 21 and cleft lip/palate	G—genetic disorder	-
Zika virus and microcephaly	T—teratogenic syndrome	-
ASD and VSD	A—isolated heart	-
Spina bifida and pes equinovarus	N—isolated NTD (sequence)	-
Arthrogryposis multiplex congenita with limb anomalies	I—isolated other	-
Amniotic band syndrome (ABS) with associated anomalies	I—isolated other	-
Polycystic kidney code with text description multicystic dysplastic kidney disease	M—MCA	R—renal
Limb body wall complex (LBWC, body stalk anomaly) with associated anomalies	M—MCA[a]	I—isolated other, LBWC is considered a sequence as it is in the same spectrum as ABS[a]
OEIS complex	M—MCA	M—MCA
Multicystic kidney disease and hypospadias	M—MCA	M—MCA
Esophageal atresia and ano-rectal malformation	M—MCA	M—MCA (anomalies in different gut segments)
Situs inversus and a congenital heart defect	M—MCA	M –MCA[b]

[a]Because LBWC does not have a specific ICD9/BPA or ICD10/BPA code, it cannot be identified by the MCA algorithm and will be transferred to group M at the end of the flowchart.
[b]If a genetic cause has not been identified, these cases are classified as M since they are of uncertain etiology.

are transferred to group M, the potential MCA cases. All cases in group M are manually reviewed by the geneticists of the EUROCAT Coding and Classification Committee and will then be allocated to one of the groups. In Table 3, examples of case classification are given. It is important to note that the geneticists of the EUROCAT Coding and Classification Committee will not assign a syndrome diagnosis to MCA cases. Etiological diagnoses can only be made at a local level in the clinic after thorough clinical examination, extensive family history taking and genetic testing and cannot be made based on registry data. If the ICD code and written text do not correspond, the geneticists will rely on the written text.

The updated MCA algorithm was validated with several extractions from the JRC-EUROCAT Central Database. In Table 4, the new version (2023) is compared to the previous version (2021) of the MCA algorithm (the number of cases and percentages are shown per classification group). In the new MCA algorithm, the number of cases increased in the isolated cardiac, genetic disorders, isolated other, isolated neural tube defects, and teratogenic syndrome groups. This led to a decrease in the number of cases in the potential MCA group (10,773 compared to 12,296). After checking the data on individual case level, we found that the cases were classified much better overall.

4 | DISCUSSION

4.1 | Use of EUROCAT subgroups and MCA algorithm

The EUROCAT subgroups can be used for several purposes: for monitoring congenital anomaly prevalence (EUROCAT, 2022c), for trend and cluster analysis (EUROCAT, 2023b), to study environmental risk factors, for clinical purposes (e.g., gain insight into pregnancy outcome or mortality for specific congenital anomaly groups), for monitoring prenatal screening programs (EUROCAT, 2022b), and to monitor data quality (EUROCAT, 2020). In addition, large heterogeneous subgroups comprising all anomalies within a certain organ system are useful to show the relative health burden of anomalies in different organ systems. The new subgroups and the MCA algorithm have been applied to all cases reported to EUROCAT since 1980. Associate members that provide aggregate data to EUROCAT are currently in the process of adopting the new subgroups.

Statistical monitoring of congenital anomalies is performed each year by EUROCAT (EUROCAT, 2023b). The statistical monitoring can identify trends and clusters of congenital anomaly subgroups that occur in one registry, one country or throughout Europe (for rare anomalies, only pan-European trend analysis will be performed). As teratogens often give rise to a specific pattern of congenital anomalies, statistical monitoring of MCA cases is also

TABLE 4 Comparison of the new version (2023) versus the previous version (2021) of the MCA algorithm with data from all EUROCAT full member registries with birth years 2015–2020.

New MCA algorithm (2023)				Previous MCA algorithm (2021)			
Code	**Classification**	**Number of cases**	**Percentage**	**Code**	**Classification**	**Number of cases**	**Percentage**
A	Isolated cardiac	26,192	21.8%	A	Isolated cardiac	26,143	21.8%
G	Genetic disorders	27,111	22.6%	B	Genetic syndrome, skeletal dysplasia and monogenic disorder	3776	3.2%
				C	Chromosomal	23,026	19.2%
I	Isolated other	40,074	33.4%	I	Isolated other	38,854	32.4%
M	Potential multiple anomalies	10,773	9.0%	M	Potential multiple anomalies	12,296	10.3%
N	NTD isolated	3725	3.1%	N	NTD isolated	3506	2.9%
R	Isolated renal	11,684	9.7%	R	Isolated renal	11,989	10.0%
T	Teratogenic syndrome	382	0.3%	T	Teratogenic syndrome	351	0.3%
X	Minor, unspecified or invalid codes	14	0.0%	X	Minor, unspecified or invalid codes	14	0.0%
Total		119,955	100.0%	Total		119,955	100.0%

important (Howley et al., 2023; Khoury et al., 1994). Potential MCA cases in the EUROCAT dataset are identified via the MCA algorithm, after which manual evaluation by geneticists follows. Periodic evaluation of the MCA cases in EUROCAT is performed by statisticians together with clinical geneticists with results published separately (Calzolari et al., 2014; Morris et al., 2023). In risk factor studies using EUROCAT data, cases with specific congenital anomalies are often compared to malformed controls with a genetic disorder (which are specified in the genetic disorder subgroup), and cases with a genetic disorder and the congenital anomaly, which is being studied, are excluded from the analysis.

The updated EUROCAT subgroups define homogenous and etiologically similar subgroups of congenital anomalies based on ICD9/BPA and ICD10/BPA codes. It is important that the EUROCAT subgroups and MCA algorithm are regularly updated based on new research (e.g., CHARGE association was classified as MCA prior to the discovery that CHD7 mutations were causative) or new coding systems. When the ICD11 is implemented by hospitals throughout Europe, EUROCAT will need to update the subgroups and MCA algorithm to also include ICD11. As the ICD11 is quite different from the ICD10, this will take considerable time. We understand that others might disagree with some of the congenital anomaly subgroups, particularly as sometimes decisions were made by consensus after in-depth discussions that may have included opposing views. For specific studies, it might be useful to define congenital anomaly subgroups in a different way. The strength of the EUROCAT subgroups lies in the standardized and clear way in which anomalies are grouped, which was endorsed by the EUROCAT Coding and Classification Committee and supplemented with literature review and data extractions from the JRC-EUROCAT Central Database. The revised MCA algorithm was validated with several data extractions and overall performs better. The current subgroups and MCA algorithm are published in this paper and are freely available from the EUROCAT website as part of EUROCAT Guide 1.5. In addition, the software (EUROCAT DMS) will be made available to any researcher free of charge, upon request. It can be used, provided that the data is collected according to EUROCAT specifications (EUROCAT Guide 1.5), reported using ICD10/BPA or ICD9/BPA codes and include all pregnancy outcomes. We hope the EUROCAT subgroups and MCA algorithm are useful for others working in congenital anomaly research.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data analyzed during this study belong to the individual EUROCAT congenital anomaly registries. Applications to analyze these data will be considered by the JRC-EUROCAT management committee and if they are considered of high scientific merit, permissions for the sharing of the data will be sought by the JRC from the relevant registries.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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