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Review Article

Paper 5: Surveillance of Multiple Congenital Anomalies: Implementation of a Computer Algorithm in European Registers for Classification of Cases†

Ester Garne,[1]* Helen Dolk,[2] Maria Loane,[2] Diana Wellesley,[3] Ingeborg Barisic,[4] Elisa Calzolari,[5] James Densem,[6] and a EUROCAT Working Group‡

[1]Hospital Lillebaelt, Kolding, Denmark
[2]University of Ulster, Belfast, United Kingdom
[3]Princess Anne Hospital, Southampton, United Kingdom
[4]Children's University Hospital, Zagreb, Croatia
[5]University of Ferrara, Italy
[6]BioMedical Computing Limited, Innovation Centre, East Sussex, United Kingdom

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BACKGROUND: Surveillance of multiple congenital anomalies is considered to be more sensitive for the detection of new teratogens than surveillance of all or isolated congenital anomalies. Current literature proposes the manual review of all cases for classification into isolated or multiple congenital anomalies. **METHODS:** Multiple anomalies were defined as two or more major congenital anomalies, excluding sequences and syndromes. A computer algorithm for classification of major congenital anomaly cases in the EUROCAT database according to International Classification of Diseases (ICD)v10 codes was programmed, further developed, and implemented for 1 year's data (2004) from 25 registries. The group of cases classified with potential multiple congenital anomalies were manually reviewed by three geneticists to reach a final agreement of classification as ''multiple congenital anomaly'' cases. **RESULTS:** A total of 17,733 cases with major congenital anomalies were reported giving an overall prevalence of major congenital anomalies at 2.17%. The computer algorithm classified 10.5% of all cases as ''potentially multiple congenital anomalies''. After manual review of these cases, 7% were agreed to have true multiple congenital anomalies. Furthermore, the algorithm classified 15% of all cases as having chromosomal anomalies, 2% as monogenic syndromes, and 76% as isolated congenital anomalies. The proportion of multiple anomalies varies by congenital anomaly subgroup with up to 35% of cases with bilateral renal agenesis. **CONCLUSIONS:** The implementation of the EUROCAT computer algorithm is a feasible, efficient, and transparent way to improve classification of congenital anomalies for surveillance and research. *Birth Defects Research (Part A) 91:S44–S50, 2011.* © 2011 Wiley-Liss, Inc.

Key words: multiple congenital anomaly; computer algorithm; classification; surveillance; etiology

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‡EUROCAT Working Group: Vera Nelen, Antwerp; Christine Verellen-Dumoulin, Hainaut-Namur, Belgium; Hanitra Randrianaivo, Ile de la Reunion, Babak Khoshnood, Paris; Annette Queisser-Luft, Mainz; Anke Rissmann, Saxony Anhalt, Germany; Mary O'Mahony, Cork and Kerry; Bob McDonnell, Dublin; Carmel Mullaney, South East, Ireland; Fabrizio Bianchi, Tuscany, Italy; Miriam Gatt, Malta; Marian Bakker, Northern Netherlands; Kari Klungsoyr Melve, Norway; Anna Latos-Bielenska, Wielkopolska, Poland; Larraitz Arriola, Basque Country, Spain; Marie-Claude Addor, Vaud, Switzerland; Elizabeth Draper, East Midlands and South Yorkshire; Judith Rankin, Northern England; Patricia Boyd, Thames Valley; David Tucker, Wales.

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*Correspondence to: Ester Garne, Paediatric Department, Hospital Lillebaelt, Skovvangen 2-6, DK-6000 Kolding, Denmark
E-mail: ester.garne@slb.regionsyddanmark.dk

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INTRODUCTION

Methods for surveillance of multiple congenital anomalies have been discussed since the thalidomide and rubella epidemics and showed the importance of public awareness of new teratogens. Surveillance of multiple congenital anomalies is considered to be more sensitive for detecting new teratogens than surveillance of all or isolated congenital anomalies (Khoury et al., 1994). There is fairly good agreement in the literature on a gross etiologic classification of congenital anomalies (Friedman, 1992, Rasmussen et al., 2003, Wellesley et al., 2005) for surveillance and epidemiologic studies to be used in combination with an anatomic approach based on organ system or an approach based on presumed pathogenesis (e.g., neural crest cell derived and vascular disruption). The proposed classifications recognize the following categories: chromosomal syndromes, monogenic syndromes, environmental syndromes, isolated congenital anomalies, and multiple congenital anomalies.

For a congenital anomaly surveillance system, a number of problems in using such a classification arise. First, the proposed classifications are based on individual case review by medical geneticists, and the resources required to review each case are beyond the capacity of a large system. Second, interpretation of the classification can vary by different medical geneticists, and it is, therefore, difficult to standardize data for comparison of prevalence rates or to pool data from registries each implementing their own review. Third, there is little existing literature on the prevalence of isolated and multiple congenital anomalies where the rules for the interpretation of the classification are explicit.

EUROCAT is a network of European registers of congenital anomalies carrying out epidemiologic surveillance of congenital anomalies. It currently covers a population of 1.7 million births per year. We developed a computer algorithm based on the International Classification of Disease v10 (ICD10) codes which gives explicit coding rules for classification and picks out a small subset of cases of potential multiple congenital anomalies for individual case review by medical geneticists. In this article, we describe the algorithm, determine the proportion of cases that require individual case review as potential multiple congenital anomalies, give the average and range of European prevalence of each of the four output categories, and describe the ratio of isolated to multiply malformed cases for different congenital anomaly subgroups.

METHODS

The EUROCAT registries are population-based and the geographically-defined populations and the methods of case ascertainment of EUROCAT have been described elsewhere (www.eurocat-network.eu; Boyd et al., submitted for publication). The registries are all based on multiple sources of information including hospital records, birth certificates, death certificates, and postmortem examinations. Cases of congenital anomalies include livebirths, fetal deaths with gestational age $\geq$20 weeks, and terminations of pregnancy for fetal anomaly after prenatal diagnosis of congenital anomalies. All structural malformations, syndromes, and chromosomal anomalies are included in the database, except minor and poorly specified anomalies found on a list of exclusions (refer to www.eurocat-network.eu).

Anonymous individual records are sent from the local registries to the Central database once per year. Cases are coded by coding experts at the local registries. Up to eight anomalies and one syndrome are coded with ICD10 and British Pediatric Association extension. Most registries also give the name of the anomaly/syndrome in text.

An ''etiologic'' classification variable designates the following groups (a case can belong to only one of these groups):

a) Chromosomal syndromes: all cases where an unbalanced chromosomal anomaly has been diagnosed (clinically and/or with a known karyotype), irrespective of types of anatomically-defined component anomalies.

b) Monogenic and environmental syndromes: all cases due to a single gene defect or a known environmental teratogen, irrespective of types of component birth defect. Further elaboration can separate out syndromes due mainly to new mutations or to environmental teratogens, depending on the purpose.

c) Isolated anomalies: all cases with one congenital anomaly or with a known sequence where multiple congenital anomalies cascade as a consequence of a single primary anomaly.

d) Multiple congenital anomalies: those babies with two or more major congenital anomalies, where the pattern of anomalies has not been recognized as part of a syndrome or sequence. Associations are included, but can be separated out when required.

Construction of the Algorithm

The ''etiologic'' classification was translated into a computer algorithm which imposes a hierarchical classification according to the ICD codes given for each case.

The final algorithm is given in the Appendix. The first category is ''chromosomal'' to which a case is allocated if it has a chromosomal ICD code. Only cases that are not allocated to ''chromosomal'' are considered for the next category, and a case is allocated to the last ''potential multiple anomaly'' category only if it does not belong to any of the preceding categories.

The algorithm has been derived iteratively since 2003. The first version was created using the existing literature (Friedman, 1992; Källén et al., 2001; Rasmussen et al., 2003; Wellesley et al., 2005) and was used to generate a list of cases of ''potential multiples'' (i.e., category M in the algorithm) from birth years 1999 to 2003. Six hundred cases (approximately 10%) were randomly chosen from the list of potential multiples for case review by a panel of three medical geneticists (E. Calzolari, I. Barisic, and D. Wellesley). The following variables were included in case review: registry, identification number, type of birth (outcome of pregnancy), birth weight, gestational age, prenatal or postnatal diagnosis, whether postmortem examination was available, karyotype, ICD10 anomaly codes, text description of the anomalies as entered by registry, and text description of anomalies as a direct translation of the ICD code. Each member of the panel reviewed all 600 case summaries and marked the cases as multiple congenital anomalies or not. Cases where all three panel members agreed were designated accordingly

(240 multiple, 173 non-multiple). A meeting was held to agree on all cases where there was initial disagreement (187 cases of 600), all of which ended in agreement. Three hundred six of the 600 cases were finally designated as multiple congenital anomalies, including 12 with a diagnosed recognized association (i.e., an association diagnosed by the child's clinician, not designated by the panel on the basis of the combination of malformations present).

Non-multiples among the potential multiples are reallocated to one of the isolated categories in the algorithm, or to the syndrome category if a syndrome diagnosis was present without a specific ICD code.

On the basis of this exercise, the flowchart was revised in several steps and new outputs of data were evaluated for each revision. The main revisions were:

1. To incorporate instances where two codes within the same organ system were commonly used which the panel agreed indicated an isolated anomaly.
2. A number of known sequences were coded into the flow chart as isolated congenital anomalies to further decrease the number of potential multiple cases for review.
3. The EUROCAT List of Minor Anomalies for Exclusion was Extended

During the first meeting, it became evident that decisions on difficult cases needed to be documented to make future work consistent with previous agreements, and these coding guidelines are available to the panel when classifying potential multiples. Examples of these decisions are:

- If the ICD code and local written text do not correspond, we will rely on the written text. If the local written text describes a minor anomaly or syndrome feature, it is considered as such.
- Balanced chromosome rearrangements are disregarded in the classification, even if there is a possibility that they may be associated with the major anomalies recorded.
- We will not apply a syndrome diagnosis to multiple congenital anomaly cases which have not been diagnosed and coded as a syndrome by the local registry.

Computerized Implementation of the Algorithm

The EUROCAT Central Database has an extensive set of associated software written in Access (Microsoft, USA) that classifies cases into EUROCAT subgroups based on ICD10 codes, and also applies the multiple congenital anomaly algorithm, outputs the short case reviews for medical geneticists, and allows the classification to be reintegrated to the dataset. This is also available in the EUROCAT Data Management Program, the compatible software used by local registries, so that the algorithm can also be applied by each registry to their own data. In addition, we proposed a new validation routine in EUROCAT Data Management Program which prompts users to enter specific ICD codes rather than generalized ICD codes. During the development of the algorithm, multiple checks were made with case samples to make sure that cases had been correctly classified by the algorithm, and that the proportion of multiples changed in the expected direction. Checking of ICD codes in registries with a high proportion of potential multiple congenital anomalies revealed that, in some instances, the registries were using major codes to describe a minor anomaly as gauged from the text information describing the anomaly. The Coding & Classification Committee provided coding advice to counteract this which is now available on the website. We considered also coding some cases in the algorithm as ''definite multiples'' on the basis of combinations of only two codes which always result in a multiple congenital anomaly classification. However, we found that there were few combinations which were frequent enough to make this exercise worthwhile at present, and felt that there was an advantage in more extensive reviewing of coding of major anomalies.

The most recent development is a web-based system where the three geneticists can review the potential multiple cases. At this final step to implement the surveillance of multiple congenital anomalies, each case is given the majority classification (two or three members of the panel designate it as multiple). However, the moderator (E. Garne) reviews the cases for disagreement to check whether there are new concerns that need discussion.

Table 1
Distribution of classification of cases with major congenital anomalies from 25 EUROCAT registries in 2004 into four groups using EUROCAT multiple congenital anomaly flowchart followed by manual review of potential multiple cases

	Number	% of total	Prevalence per 10,000 births
Chromosomal cases	2653	15	32.4
Syndromes	394	2	4.8
Isolated cases	13381	76	163.4
True multiples	1305	7	15.9
Total	17733	100	216.5

Data Analysis

The data presented here are from 25 EUROCAT Registries for births in 2004, being all full member registries which had transmitted 2004 data at the time of the analysis and had a prevalence rate above 1.5%.

The final algorithm was applied to the 2004 data to find the number and prevalence of ''potential multiples'' as well as all other hierarchical categories. All potential multiple cases were reviewed by the three geneticists. Whereas the algorithm subdivides the isolated category into neural tube defects, cardiac defects, renal, and others, we present here the entire isolated category combined.

RESULTS

From the 25 registries, 17,733 cases with major congenital anomalies were reported for 2004. The total number of births covered was 818,759, giving an overall prevalence of major congenital anomalies at 2.17%.

Table 1 presents the final classification of cases using the flow chart algorithm followed by manual review of the 1862 potential multiple cases (10.5% of all cases). Overall, 15% of all cases were classified as chromosomal

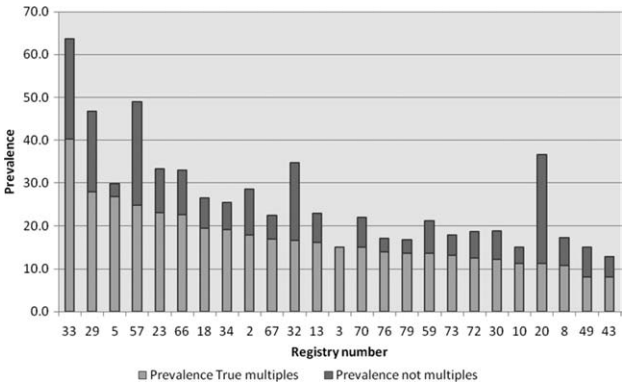

Figure 1. Prevalence per 10,000 births of potential multiple congenital anomaly cases by whether they were finally classified as true multiple congenital anomaly or non-multiple congenital anomaly cases by registry.

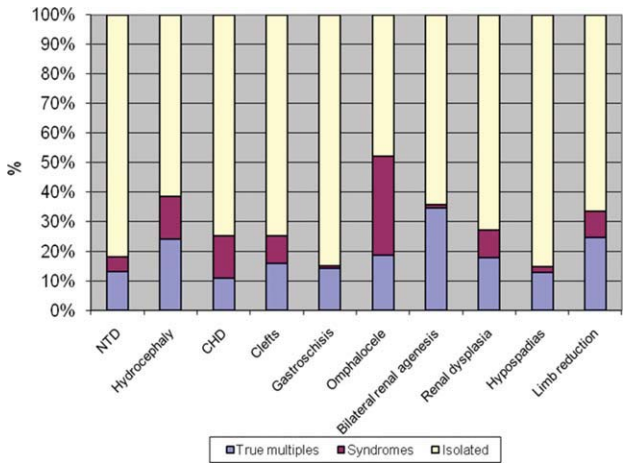

Figure 2. Proportion of cases classified as isolated, syndrome (chromosomal, monogenic, and environmental) and multiple congenital anomaly, by selected anomaly subgroup, all registries combined. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

anomalies, 2% as syndromes, 76% as isolated congenital anomalies, and 7% as multiple congenital anomalies. Prevalence of all four categories varied considerably by registry Figure 1.

Of the 1862 potential multiple cases, 1305 (70%) were agreed by the geneticists to be true multiple congenital anomaly cases. Figure 1 presents the distribution of potential multiple cases and true multiple cases by registry. The proportion of true multiples among potential multiples by registry varied from 31 to 100%.

Information on karyotyping (confirming non-chromosomal clinical diagnosis) was available in the central database for 56% of potential multiple cases and 55% of the true multiple cases.

Figure 2 presents classification of cases by anomaly subgroup for 10 selected congenital anomaly subgroups for illustration, all of these subgroups having more than the average proportion of multiple congenital anomalies. For congenital heart defects, 11% of all cases are classified as multiple congenital anomaly cases compared to the subgroups with the highest proportions –24% for hydrocephalus and 35% of cases with bilateral renal agenesis.

Examples of disagreement among the three geneticists are given in Table 2. Some disagreements were followed by written rules for future decisions.

DISCUSSION

The EUROCAT algorithm for surveillance of multiple congenital anomalies described in this article results in approximately 10% of all registered cases being selected for individual case review by medical geneticists. In our surveillance system, this is a feasible load if prospectively conducted. Potential multiple cases that are found to be isolated on review usually have a rare or unusually coded sequence, a complex malformation of the same organ system not already included in the algorithm, or

Table 2
Examples of disagreement between the 3 geneticists

Major anomaly codes	Minor anomaly codes	Written text	Geneticist 1	Geneticist 2	Geneticist 3
Q210		VSD	Isolated	Multiple	Isolated
	Q3140	Laryngomalacia			
Q788		Osteopenia			
Q0435		Hydranancephaly	Isolated	Multiple	Sequence
Q743		Arthrogryposis Multiplex			
Q057		Lumbar spina bifida	Multiple	Isolated	Multiple
Q703		Webbed toes			
Q042		Holoprosencephaly	Multiple	Sequence	Multiple
Q029		Microcephaly			
Q556					
		Micropenis			
Q660		Club feet	Multiple	Isolated	Multiple
Q650		Hip dislocation, unilateral			
Q790		Diaphragmatic hernia	Multiple	Sequence	Multiple
Q336		Lung hypoplasia			
Q4330		Malrotation of cecum and colon			

VSD, ventricular septal defects.

include minor or unspecified anomalies not obvious from their codes. Moreover, we have found it useful to review with a panel of three medical geneticists (rather than by individuals), as this clarifies further areas of contention in the designation of ''multiple congenital anomaly'' status.

There are some conceptual problems with the designation of a ''multiple congenital anomaly'' baby/fetus. One is the uncertain position of recognized associations such as VATER (vertebral anomalies, anal atresia, tracheoesophageal fistula, esophageal atresia, or renal or radial anomalies) in the classification scheme (Källén et al., 2001). Our overall approach to this was that it was important, whatever decision was made, that it should be explicit and consistent. We suspected that diagnosis of VATER would not be made consistently across Europe or over time, and we were reluctant to make paper diagnoses of VATER (and other associations) by case review of registry data. We, therefore, kept associations in the ''multiple'' category. Nevertheless, over time, the classification algorithm will need to change as associations move to the syndrome category with the discovery of genetic causes, as has occurred with the CHARGE association. A second problem is whether minor anomalies should be taken into account in designating a case as multiple congenital anomalies. We recognize that minor anomalies may be very important signs of teratogenic exposure or dysmorphic syndromes (Holmes et al., 1987). However, again we took a pragmatic approach and based our classification only on two or more major anomalies, on the basis that minor anomalies would be subject to much more diagnostic reporting and coding variation.

We found considerable variation in the population prevalence of multiple congenital anomaly cases between participating registers, both before and after case review. The main contributing factor which was resolved by case review was differences in the coding of minor anomalies, particularly where they do not have specific ICD10-BPA codes and, therefore, cannot be recognized by the computer as non-major. Case review also resolved other ''coding style'' differences, such as detailed coding of different manifestations of the same anomaly. We were perhaps more surprised by the remaining wide variation in prevalence of multiply malformed cases after conducting the case review. One reason for this may be real differences in prevalence due to geographical differences in teratogenic exposures, or due to differences in the level of diagnostic investigation leading to syndrome diagnoses. We also note that a high prevalence after case review was associated with a high proportion of ''possibly multiply malformed'' cases reclassified as isolated, which points again to differences in registration practice and the type of source medical records consulted to give detailed descriptions of each case.

The European prevalence of chromosomal syndromes of 32.4 per 10,000 births we find here is critically dependent on the maternal age distribution in the population, as well as the level of diagnostic investigation of multiple congenital anomaly cases both prenatally and postnatally. The prevalence of syndromes of 4.8 per 10,000 births refers to syndromes usually diagnosed in the first year of life (or prenatally).

The overall prevalence of isolated birth defects was 163.4 per 10,000 births. The ratio of isolated to multiple congenital anomaly cases varied by type of defect (Fig. 2). There is some debate for individual defect types whether isolated and multiple congenital anomaly cases represent etiologically distinct groupings. For example, for neural tube defects, the United Kingdom and Ireland high prevalence rate was found to pertain to both isolated and multiple congenital anomaly neural tube defects, when site of the defect was taken into account (Dolk et al., 1991), although an American study (Yen et al., 1992) had suggested etiologic differences between isolated and multiple congenital anomaly neural tube defects on the basis of differences in sex ratio. We suggest that using our algorithm to reduce workload and improve transparency of classification, it will be possible in the future to look more systematically at the epidemiologic differences between isolated and multiple congenital anomaly cases of different anatomic birth defect types.

Observations that many known teratogens (such as rubella and thalidomide) cause multiple congenital anomalies in a majority of cases have led to the practice of conducting separate surveillance over time of all cases with multiple congenital anomalies (Khoury et al., 1987), both grouped together and by individual defect combinations, to detect any changes due to new teratogens. Multiple congenital anomalies may result from a strong (high dose) or complex insult to development disrupting many processes at the time of the insult, or from a prolonged insult spanning the sensitive period for development of different organs. It is unlikely that such cases would be etiologically totally distinct from cases with isolated anomalies (and indeed the examples of rubella and thalidomide show this to be the case), but as a group, they may be more sensitive indicators of teratogenic insults for surveillance. Our algorithm makes the implementation of multiple congenital anomalies monitoring much more feasible for large populations.

We conclude that the implementation of the EUROCAT computer algorithm is a feasible, efficient, and transparent way to improve classification of congenital anomalies for surveillance and research.

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APPENDIX: MULTIPLE CONGENITAL ANOMALY FLOW-CHART FOR MONITORING OF MULTIPLE CONGENITAL ANOMALIES

Multiple Anomaly Flow-chart for Monitoring of Multiple Anomalies

At the moment, this should be for the Central Database only.

Only valid for years with ICD 10 codes.

Definition of a Multiple Anomaly Case

Two or more unrelated major structural malformations that cannot be explained by an underlying syndrome or sequence.

This means that the process of the flowchart is to find cases with two or more codes within the Q chapter, unless the case is transferred to other groups according to the steps described below.

Name for Groups

C: chromosomal.
B: genetic syndrome, skeletal dysplasia, and monogenic disorder.
N: neural tube defect isolated.
A: isolated cardiac.
R: isolated renal.
I: isolated other.
O: non-syndrome outside malformation chapter.
M: potential multiple anomalies.
T: teratogenic syndrome.

Minor, Unspecified, and Invalid Codes

The following codes are ignored in the flowchart, but appear in individual case output:

Guide 1.3 list of minors post 2005 to be used for all years.

No valid ICD code.

Group X contains cases with only the above-listed codes.

Outside Q-chapter Codes (Except the Few Codes Accepted in ''all Anomalies'')

These codes are ignored by the flowchart process but appear in the individual case output.

The Flow-chart

For three and four digit codes mentioned here, the coding also includes the codes with more digits.

Only Q-codes are valid for the process after step 2.

This is a hierarchical procedure.

Step 1

Exclude all cases with a chromosomal code.

Q90–Q93 except Q936, Q96–Q99, • Transfer to group C.

Step 2

Exclude all cases with genetic syndrome codes, skeletal dysplasia, and congenital skin disorder codes.

Q87, Q936, D821.

Q77, Q7800, Q782–788, Q7402.

Q80–Q82.

Q4471 Alagille syndrome, Q6190 Meckel–Gruber, Q7484 Larsen syndrome.

Q751 Crouzon/craniofacial dysostosis, Q754 Mandibulofacial dysostosis (Treacher Collin).

Q7581 Frontonasal dysplasia.

Excluding Q8703, Q8704, Q8706, Q8708, Q8724, Q8726 • Transfer to group B.

Step 3

Exclude all cases with a code for teratogenic syndrome code.

Q86, P350, P351, P371 • Transfer to group T.

Step 4

Exclude all cases with a heterogenous syndrome code.

Q761, Q7982, Q8581, Q8706 • Transfer to group M.

Step 5

Exclude all cases with only neural tube defect codes.

Q00–Q01, Q05 • Transfer to group N.

Step 6

Exclude all cases with codes only in cardiac chapter.

Q20–Q26 • Transfer to group A.

Step 7

Exclude all cases with codes only in renal chapter.

Q60 – Q64, Q794 • Transfer to group R.

Step 8

Exclude all cases with only one code within Q chapter.
Include known local coding variations/errors.
If Q00–Q01, Q05 • Transfer to group N.
If Q20–Q26 • Transfer to group A.
If Q60–Q64, Q794 • Transfer to group R.
If only one other Q-code • Transfer to group I.

Step 9

Exclude all cases with codes only in eye chapter.

Q10–Q15 • Transfer to group I.

Step 10

Exclude all cases with codes only with limb reduction defects.

Q71–Q73 • Transfer to group I.

Step 11

Exclude all cases with codes only for hypospadias.

Q54 • Transfer to group I.

Step 12

Exclude all cases with codes only for polydactyly.

Q69 • Transfer to group I.

Step 13

Exclude all cases with codes only for reduction defects of the brain.
Q04 • Transfer to group I.

Step 14

Exclude all cases with codes only for hip anomalies.
Q65 • Transfer to group I.

Step 15

Exclude all cases with codes only for syndactyly.
Q70 • Transfer to group I.

Step 16

Exclude all cases with codes only for syndactyly + poly dactyly.
Q69 and Q70 • Transfer to group I.

Step 17

Exclude all cases with codes only for small intestinal atresia.
Q41 • Transfer to group I.

Step 18

Exclude all cases with codes only for facial clefts.
Q35, Q36, Q37 • Transfer to group I.

Step 19

Exclude all cases with the code for balanced chromosomal rearrangements and only one Q-code.
Q95.
If Q00–Q01, Q05, and Q95 • Transfer to group N.
If Q20–Q26 and Q95 • Transfer to group A.
If Q60–Q64, Q794, and Q95 • Transfer to group R.
If only one other Q-code and Q95 • Transfer to group I.

Step 20

Exclude all cases with only outside Q chapter codes (without Q-codes).
Not beginning with Q.
D1810 accepted as outside Q-code • Transfer to group O.

Step 21

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 – talipes – hydrocephalus:
Q05 coded with Q66 and/or Q03 • Transfer to group N.
Renal aplasia/dysplasia – lung hypoplasia – talipes:
Q601/Q606 coded with Q336 and/or Q66 • Transfer to group R.
Omphalocele/gastroschisis – malrotation of gut – small intestinal atresia:
Q792/Q793 coded with Q433 and/or Q41 • Transfer to group I.
Anal atresia – rectovaginal fistula:
Q42 coded with Q522 • Transfer to group I.
Diaphragmatic hernia – lung hypoplasia:
Q790 coded with Q336 • Transfer to group I.
Anencephalus – adrenal hypoplasia:
Q000 coded with Q891 • Transfer to group N.
Unspecified hydrocephalus – reduction defect of the brain:
Q039 coded with Q04 • Transfer to group I.
Unspecified hydrocephalus – Arnold–Chiari:
Q039 coded with Q070 • Transfer to group I.
Neural tube defect – Arnold Chiari:
Q01 or Q05 coded with Q070 • Transfer to group N.
Amniotic band sequence:
All cases with the code Q7980 • Transfer to group I.
Caudal dysplasia sequence:
All cases with the code Q8980 • Transfer to group I.
Sirenomelia sequence:
All cases coded with Q8724 • Transfer to group I.
Cyclops sequence:
All cases coded with Q8703 • Transfer to group I.
Pierre Robin sequence:
All cases coded with Q8708 as only code or with Q35–Q37 • Transfer to group I.
Holoprosencephaly – median cleft lip:
All cases coded with Q042 and Q361 • Transfer to group I.

Step 22

The remaining cases are group M: potential multiple anomalies. Manual evaluation of all remaining cases before final inclusion into multiple anomaly group – or inclusion in one of the other groups.

Notes:

The need to output group M cases as individual case lists with text description of anomalies as well as codes plus variables: identification number, registry, year of birth, type of birth, twin, gestational age, birth weight, karyotype (including written text), and postmortem examination, when discovered.

For the website review of potential multiple cases, a subgroup for ''poorly specified cases'' has to be added (could go to group X).