Medical Costs of Children Admitted to the Neonatal Intensive Care Unit: the Role and Possible Economic Impact of WES in Early Diagnosis

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Abstract

Objective: The objective of this study is to provide an overview of average healthcare costs for patients admitted to the Neonatal Intensive Care Unit (NICU) and to assess possible impact of implementing Whole Exome Sequencing (WES) on these total healthcare costs.

Methods: We retrospectively collected postnatal healthcare data of all patients admitted to the level IV NICU at the Radboudumc (October 2013-October 2015) and linked unit costs to these healthcare consumptions. Average healthcare costs were calculated and a distinction between patients was made based on performance of genetic tests and the presence of congenital anomalies (CAs).

Results: Overall, €26,627 was spend per patient. Genetic costs accounted for 2.3% of all costs. Healthcare costs were higher for patients with CAs compared to patients without CAs. Patients with genetic diagnostics were also more expensive then patients without genetic diagnostics. When performing trio-WES for all patients instead of current diagnostics, overall healthcare costs will increase with 22.2%. In case only patients with CAs receive trio-WES, average per patient healthcare costs will increase with 5.3%. Performing trio-WES only for patients with multiple CAs did not result in any cost changes.

Conclusions: Genetic diagnostic testing accounted for a small fraction of total costs. By implementing trio-WES as genetic diagnostic test for all patients with CAs there is a limited increase in overall healthcare budget. Not only the diagnostic yield of this cohort will increase, but implementing trio-WES for all patients with CAs may also allow for improved personalized treatments options guided by the diagnoses made.

Summary

What is known:

- Implementing WES at an early stage during the diagnostic trajectory can result in timely diagnosis and early initiation of appropriate type of care.
- As congenital anomalies often have a genetic origin, genetic diagnostic testing in these patients may help to obtain a diagnosis.

What is new:

- An overview of average healthcare costs for patients with and without (multiple) CAs and for patients who did and who did not receive genetic diagnostic testing.
- Three different scenarios in which Whole Exome Sequencing is implemented based on the presence of (multiple) CAs.

Introduction

Genetic disorders are of great impact in the wellbeing of an individual. For instance, in Europe, 23.9 per 1,000 births between 2003 and 2007 have a congenital anomaly caused by a genetic disorder [1]. The prevalence of genetic disorders within the neonatal intensive care unit (NICU) is not exactly known and can be missed easily in a neonatal setting [2]. Earlier research has shown that a large part of patients admitted to the NICU consists of patients with a genetic disorder and 30-50% of these genetic disorders results in neonatal and infant deaths [3-9]. Earlier research has shown that 13.7% of the patients admitted to the NICU suffer from (multiple) congenital anomalies (CAs) [8, 10]. As CAs often have a genetic origin, genetic diagnostic testing in these patients may help to obtain a diagnosis. A recent study focusing on the clinical aspects of the patients included in this study indeed showed the correlation between a conclusive genetic diagnosis and the presence of (multiple) CAs [11]. This finding indicates the need for improvement of genetic diagnostic research in order to diagnose these patients, decrease the time to diagnosis with possibility of starting treatment earlier [11-12]. The introduction of genetic tests for all patients with CAs albeit clinically relevant, will have economic effects that need to be clarified.

The advent of novel genetic technologies, including Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS), have made it possible to investigate the exome or genome, without the need for a priori knowledge about a suspected underlying cause of the disease [13]. Implementing WES or WGS at an early stage during the diagnostic trajectory can result in an timely diagnosis. Once the diagnosis has been established, the appropriate type of care can be initiated. Timely genetic testing compared to “delayed” diagnostics, shows a decrease in healthcare consumption [13].

These novel genetic technologies are very promising for their clinical added value. However, implementation of novel genetic technologies also may come at high costs. Therefore, the latter impact should deliberately be discussed and adequately analyzed. Previous research stated that implementation of WES and WGS might be cost-effective in the future for critically ill newborn infants [3, 12, 14-15]. The evidence is very scarce and it is questionable whether outcomes and cost savings can be extrapolated between different patient groups and different countries.

To decide on implementing new diagnostic approaches like WES or WGS, it is essential to put additional costs into perspective. The main objective of this study is to retrospectively calculate the uptake of genetic testing and associated costs for patients admitted to the Neonatal

Intensive Care Unit (NICU). The secondary objective is to assess the possible impact of implementing WES on the total healthcare costs.

Materials And Methods

Study participants and healthcare data collection

In order to include a long follow-up period and to start before the introduction of WES as part of the diagnostic trajectory, patients were included in this retrospective study if they were admitted to the level IV NICU at the Radboud University Medical Center (Radboudumc), Nijmegen, The Netherlands, between October 2013 and October 2015. Patients were excluded from this study in case (1) the patient was admitted to the NICU due to results from the neonatal blood spot screening program; (2) genetic diagnostic testing was performed in order to investigate the presence of a known familial mutation; or (3) no healthcare data could be retrieved. We retrospectively collected all available healthcare data from hospital information systems and patient records. We collected all healthcare data until April 4th, 2019. On this date, data was collected. This study was approved by the Medical Research Ethics Committee Arnhem/Nijmegen under file number 2016-2486/NL57511.091.16.

Data analysis

In this study, the total number (and percentage) of females and males and the average age in days at the moment of data collection (including standard deviation) were calculated. Follow-up time was calculated as the number of days between the first hospital visit until the moment of data-collection (April 4th, 2019). As Marouane et al. [11] showed a correlation between a conclusive genetic diagnosis and the presence of (multiple) CAs, we also made a distinction between patients who did and those who did not receive genetic testing, and those with and without (multiple) CAs (figure 1).

The outcome measures of this study were healthcare resource use and costs related to this healthcare resource use. Healthcare data was divided into seven types of costing categories: (1) hospitalization; (2) consultations; (3) diagnostics; (4) medication; (5) genetics; (6) surgery; and (7) other, which consists of all other healthcare activities which cannot be categorized into one of the previous categories. Genetic costs consisted of costs related to both genetic counseling and genetic diagnostic testing. Unit prices were retrieved from the Dutch Healthcare Authority (Nederlandse Zorgautoriteit; NZa), the cost-manual of the National Healthcare Institute (Zorginstituut Nederland; ZiN) and literature research and linked to the corresponding healthcare activities [16-20]. All unit prices were converted to the same index year (2020). Descriptive and scenario analyses were performed in R (version 4.0.3) [17].

Descriptive analysis of current healthcare costs

1. **Average healthcare costs.** This analysis was performed with the available healthcare data, for all patients divided in the different costing categories. For all categories, the mean, median and range (minimum and maximum) of costs, total number of healthcare activities and the average unit price was calculated.
2. **Genetic diagnostic testing vs. no genetic diagnostic testing.** The average healthcare costs for patients who received genetic diagnostic testing were compared to patients who did not receive genetic diagnostic testing. For each costing category, the average costs per patient were calculated, including mean, median and range (minimum and maximum). Furthermore, for each costing category, the number of units and the average unit price was calculated. The minimum follow-up period of patients included in this study was 730 days. Therefore, in order to ensure comparability between groups, follow-up time included in the analysis for these patients was 730 days starting on the first day of admission to the NICU.
3. **(Multiple) CAs vs. no CAs.** We also compared the average healthcare costs for patients with an isolated congenital anomaly, multiple CAs and patients without CAs. We calculated average costs per patient, including mean, median and range (minimum and maximum), and the number of healthcare activities including their unit costs. For this sub-analysis, follow-up time was also limited to 730 days starting on the day of admission to the NICU to ensure comparability between groups.

Scenario analysis

The presence of (multiple) CAs is one of the most obvious reasons to suspect a genetic defect that underlies a disorder. In order to ensure comparability between groups, patients with a prenatal diagnosis were excluded from the scenario analyses. The following three scenario analyses were performed:

1. **Implementing WES as first-tier test for all patients admitted to the NICU.** The average healthcare costs and the total costs related to genetic testing in case all patients admitted to the NICU receive WES were estimated and compared to the current costs (figure 2, scenario A). For patients who did receive genetic diagnostic tests, all costs related to these genetic diagnostic costs were excluded from the results since it was assumed that performing WES would result in the same diagnosis and thus replaces the whole standard diagnostic trajectory.

Healthcare activities which were included in the WES scenario are pre-test genetic counseling, performing (trio-)WES and post-test genetic counseling. The total costs related to this WES scenario were calculated by multiplying the total number of patients admitted to the NICU by €2,892, i.e. the costs of pre- and post-test genetic counseling (€1,089 [16-20]) and per-sample costs of WES (€1,803 [16]). Costs related to performing trio-WES were €6,498 (pre- and post-test genetic counseling and 3 times the per-sample costs of WES). The current costs of genetics were compared to the costs resulting from this scenario analysis.

2. **Implementing WES as first-tier test for all patients with CAs admitted to the NICU.** The average healthcare costs and the total costs related to genetic testing in case all patients with CAs and admitted to the NICU receive WES were estimated and compared to the current costs (figure 2, scenario B). As with scenario analysis A, current costs for genetic testing were excluded from the scenario in which all patients with CAs receive (trio-)WES and total genetic costs were calculated by using the same formula. In the end, costs related to performing WES for all patients with CAs were compared to the genetic costs related to the standard and current genetic diagnostic trajectory.
3. **Implementing WES as first-tier test for all patients with multiple CAs.** In scenario C, current healthcare costs were compared to the costs in case all patients with multiple CAs received WES. The average total healthcare costs and genetic costs were calculated just like scenario A and B.

Results

Study participants

Overall, 1470 patients were admitted to the NICU of the Radboudumc between October 2013 and October 2015. In total, 27 patients were excluded from the data analysis, resulting in a study population of 1443 patients (figure 1). In de scenario analysis, another 15 patients were excluded due to a prenatal genetic diagnosis. There were 610 females (42.3%) and 833 boys (57.7%), with a mean age of 1650 (±209) days at the moment of data collection. The average follow-up time was 1614 (±209) days. An overview of follow-up time per patient is shown in supplementary table A.

Descriptive analysis of current healthcare costs

1. **Average healthcare costs.** For all 1,443 included patients, the average costs spend on healthcare were €26,627 per patient (table 1). Hospitalization accounted for the largest part (84.1%) of all healthcare costs, which was on average €22,382 per patient. An overview of all cost categories and its corresponding costs can be seen in table 1.

   Of 1,443 patients included in this study, 194 patients (13.4%) received genetic diagnostic testing. In total, 410 genetic diagnostic tests were performed, totaling to an average of €616 per patient, and accounting for 2.3% of the total costs for all 1,443 patients together.
2. **Genetic diagnostic testing vs. no genetic diagnostic testing.** Table 2 shows the costs of healthcare use for the different categories in patients who received genetic diagnostic tests and patients who did not receive genetic diagnostic tests.

   For patients who did receive genetic diagnostic testing, the average costs spend on healthcare was €43,804 per patient. 5.8% (€2,523 per patient) of these costs consisted of costs related to genetics.

   For patients who did not receive genetic diagnostic testing, the total costs spend on healthcare were €18,404 per patient. Of these costs, 0.5% (€99 per patient) were related to genetics, i.e. genetic consultation and evaluation without performing any genetic diagnostic tests.

   For both patient groups, the main part of the total healthcare costs consisted of costs related to hospitalization, 80.0% (€35,055 per patient) and 87.0% (€16,007 per patient) of all costs for patients with and without genetic diagnostic testing respectively.
3. **(Multiple) CAs vs. no CAs.** The average healthcare costs for patients with and without (multiple) CAs are shown in table 3. Total healthcare costs were €27,350 and €53,686 per patient for patients with isolated and multiple CAs respectively. For patients without CAs, these total healthcare costs were on average €15,210 per patient.

For patients with isolated CAs, costs related to hospitalization accounted for 79.7% (€21,808 per patient) and costs related to genetics accounted for 2.4% (€665 per patient) of all costs. For patients with multiple CAs, 83.4% (€44,781 per patient) of the costs was related to hospitalization and 3.8% (€2,036 per patient) to genetics. 89.1% (€13,548 per patient) of the costs and 0.7% (€104) of the costs were related to hospitalization and genetics respectively for patients without CAs.

Scenario analysis

Since trio-WES approach will be the most relevant as genetic diagnostic trajectory in this study population, only results regarding trio-WES (table 4) will be discussed in this paper. Results regarding implementing single-WES can be found in supplementary table B.

1. **Implementing WES as first-tier test for all patients admitted to the NICU.** In case trio-WES was performed for all 1,428 patients admitted to the NICU (figure 2, scenario A), total genetic costs increased to €6,498 per patient, which is an increase in costs of 949.8% (table 4). The average total healthcare costs increased 22.2% (€32,361 instead of €26,482 on average per patient).
2. **Implementing WES as first-tier test for all patients with CAs and admitted to the NICU.** 446 patients (31.2%) were admitted to the NICU with CAs and were included in this scenario analysis (figure 2, scenario B). Of these patients, 291 patients did not receive any genetic diagnostic testing (65.2%). The total healthcare costs related to genetic diagnostic testing in case trio-WES was performed for all of these patients (n = 446) were on average €2,207 per patient (n = 1,428). Compared to the regular diagnostic trajectory this was an increase in costs of 227.4% (on average €1,408 per patient extra, see table 4). The average total healthcare costs increased with 5.3% (€27,893 per patient).
3. **Implementing WES as first-tier test for patients with multiple CAs.** In total, 136 patients had multiple CAs. Replacing the traditional diagnostic trajectory by performing trio-WES for patients with multiple CAs did not result in a change in average genetic diagnostic costs and overall healthcare costs (table 4).

Discussion

We presented an overview of the average healthcare costs of patients admitted to the NICU. We estimated the economic impact of the inclusion of WES as part of the diagnostic trajectory on the resources spent on genetic testing and on the overall healthcare costs. We modelled multiple scenarios to find a balance between making maximal benefits of the use of WES in this patient population, while limiting the socio-economic impact on the healthcare system. Our results showed that care for patients who received genetic diagnostic tests (€43,804 per patient) was more expensive compared to care for patients who did not receive genetic diagnostic testing (€18,404 per patient). This has been calculated for the first two years after the patients were admitted to the NICU. Of these costs, €2,523 (5.8% of all costs) and €99 (0.5% of all costs) was spent on genetic testing, respectively. Apart from spending more budget on genetic testing for the patients with (multiple) CAs, the main difference was attributed to costs for hospitalization and consultations. This was in line with results obtained by others, showing that more complex patients often have higher healthcare costs [22]. We observed a similar trend between patients with isolated and multiple CAs: care for patients with multiple CAs was more expensive than for patients with isolated CAs (€53,686 vs. €27,350 per patient). Care for patients without CAs were the least expensive (€15,210 per patient).

Of the 57 patients that received a conclusive genetic diagnosis and were included in the scenario analyses, 52 presented CAs, highlighting that such anomalies can have a genetic origin [11]. In the total cohort, 461 patients presented with (multiple) CAs, but not all patients received genetic testing. An argument of not testing in these patients is often related to the long turnaround times. Since these have been drastically reduced by the introduction of WES, we modelled three scenarios to determine the anticipated impact on diagnostic yield and healthcare costs for wider spread implementation in a NICU setting.

In case of scenario A, all 1,428 patients would receive genetic diagnostic testing by WES. Compared to the current costs, genetic costs increased with 949.8% and overall healthcare costs with 22.2%. Although costs will increase significantly, testing all patients will allow to identify all 57 diagnoses in the cohort in one test, at the start of the diagnostic trajectory. Moreover, testing allows to identify an extrapolated number of diagnoses that currently remain undetected because patients are not subjected to diagnostic testing. Since only 5 diagnoses were made in patients without CAs, one might wonder whether clinical preselection on who should receive WES based on having CAs is not a more economically sustainable option.

We therefore modelled scenario C, where WES was only performed for patients with multiple CAs, as this clinical sub-cohort of NICU patients had relative highest diagnostic yield. Testing all 136 patients with multiple CAs by trio-WES, but refraining genetic testing in all other patients (n = 1,428), resulted in no change in healthcare costs. Whereas there may be an economic benefit when introducing trio-WES for patients with multiple CAs, this scenario seems unethical as the diagnostic yield in patients with isolated CAs in this cohort is 5.8% (18 out of 310 patients). Hence, at cohort level, this scenario would leave 40.4% of patients (23 out of 57) undiagnosed.

Scenario B, allowing to perform WES for those patients with either isolated or multiple CAs, seemed as such most beneficial. The costs related to genetic testing increased with 227.4% for trio-WES, but the average total healthcare costs increased with 5.3% (€1,411). Although the costs are higher compared to the current diagnostic trajectory, this would allow the detection of >99% of all genetic diagnoses in the cohort. This scenario includes both the diagnoses established in the current situation, but also the diagnoses of those patients who currently remain untested despite a clinical presentation suspicious to be of genetic origin. This approach would miss the genetic diagnosis in the 5 of 982 patients without CAs. They now received a conclusive genetic diagnosis after performing genetic testing well after the neonatal period because of (neuro)developmental delay. It might, however, be expected that these patients would still receive genetic testing later in life, similar to the current situation, because of developmental delay [11].

A possible limitation of this study was that the diagnostic trajectory was not completed for all patients included in the scenario analysis. Although we did not include any restrictions regarding follow-up length, total healthcare costs used in this scenario analyses are probably higher due to an increase in the amount of healthcare costs in case a longer follow-up period is included. This can also has impact on the increase in

costs when healthcare costs are compared to the WES-scenarios. The same holds for the calculated costs related to surgery and medication, which might also be underestimated. Unfortunately, it was not possible to collect all unit costs taking into account the amount of medication prescribed and unit costs related to surgery. Therefore, which is also a strength of this study, the results of this study showed the maximum increase in costs when WES is performed. If this study is repeated after a certain amount of time, results of the scenario analyses will probably be more positive (i.e. less increase in costs due to increase in current healthcare costs and decrease in costs related to WES). According to earlier research, it is very valuable that patients were followed over time for several years [23]. The genetic diagnostic trajectory can be very long and costly, so including a longer follow-up period in an economic evaluation provides a more accurate overview of the actual costs.

Another assumption made in this study was that performing WES provides the same results as the standard diagnostic trajectory. Furthermore, in this study, costs related to prenatal diagnostic testing were not taken into account. Prospective follow-up studies are needed in order to create more evidence to support these assumptions and to increase insight in the exact effects of implementing WES into diagnostic care. Ideally, a prospective follow-up study is performed, in which patients receive current diagnostics and trio-WES to see what the exact clinical and economic impact is of implementing WES.

In conclusion, genetic diagnostic testing in a NICU patient cohort accounts for a small fraction of total costs. Only half of patients whose clinical presentation is suspective of a genetic disorder, are currently being tested. We showed that with limited increase in overall healthcare budget on this cohort, all patients presenting with CAs can be tested by trio-WES. This will not only increase the overall diagnostic yield of this cohort, but may also allow for improved personalized treatments options guided by the diagnoses made.

Abbreviations

CAs; congenital anomalies, NICU; Neonatal Intensive Care Unit, WES; Whole Exome Sequencing, WGS; Whole Genome Sequencing

Declarations

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Tables

Table 1

Total healthcare costs per patient (n = 1,443)

	Mean (€)	Percentage of total (%)	Median (€)	Min (€)	Max (€)	Units (n)	Unit costs (€)
Hospitalization	22,382	84.1	7,178	0	587,353	27,084	1,192
Consultations	85	0.3	0	0	3,051	3,356	36
Diagnostics	1,476	5.5	515	0	22,600	220,165	10
Medication	127	0.5	0	0	160,961	1,464	125
Genetics[a]	616	2.3	0	0	14,064	1,269	700
Other	1,911	7.2	457	0	35,039	36,224	76
Surgery	31	0.1	0	0	15,780	896	49
Total	26,627		9,665	69	630,689	290,458	132

[a]Includes all costs related to genetics (i.e. genetic counseling, genetic diagnostic tests)

Table 2

Average healthcare costs per child per category for patients who did or did not receive genetic diagnostic tests (n = 1,443)[a]

	Mean (€)	Percentage of total (%)	Median (€)	Min (€)	Max (€)	Units (n)	Unit costs (€)
Patients without genetic diagnostics (n = 1,249)							
Hospitalization	16,007	87.0	5,556	0	501,834	16,760	1,193
Consultations	35	0.2	0	0	1,760	1,156	38
Diagnostics	984	5.3	334	0	20,325	133,654	9
Medication	144	0.8	0	0	160,961	1,117	160
Genetics[b]	99	0.5	0	0	6,449	323	384
Other	1,123	6.1	211	0	31,100	15,376	91
Surgery	11	0.1	0	0	1,565	452	32
Total	18,404		6,606	0	527,393	168,838	136
Patients who received genetic diagnostics (n = 194)							
Hospitalization	35,055	80.0	16,125	0	471,572	5,499	1,237
Consultations	249	0.6	117	0	2,073	1,264	38
Diagnostics	2,505	5.7	1,501	0	16,024	45,304	11
Medication	2	0.0	0	0	302	233	2
Genetics[b]	2,523	5.8	1,745	0	12,692	589	831
Other	3,342	7.6	2,409	0	25,534	9,697	67
Surgery	127	0.3	0	0	15,643	254	97
Total	43,804		24,230	569	501,537	62,840	135

[a] From date of admission to the NICU until 730 days after this admission date; [b]Includes all costs related to genetics (i.e. genetic counseling, genetic diagnostic tests)

Table 3

Average healthcare costs per child per category for patients with isolated, multiple or without congenital anomalies (n = 1,443)[a]

	Mean (€)	Percentage of total (%)	Median (€)	Min (€)	Max (€)	Units (n)	Unit costs (€)
Patients without congenital anomalies (n = 982)							
Hospitalization	13,548	89.1	4,400	0	242,384	10,987	1,212
Consultations	19	0.1	0	0	900	484	38
Diagnostics	781	5.1	277	0	14,230	88,235	9
Medication	2	0.0	0	0	1,095	325	7
Genetics[b]	104	0.7	0	0	9,601	233	439
Other	751	4.9	136	0	24,746	9,488	78
Surgery	4	0.0	0	0	936	176	24
Total	15,210		5,418	0	267,073	109,928	136
Patients with an isolated congenital anomaly (n = 312)							
Hospitalization	21,808	79.7	11,461	0	501,834	6,000	1,134
Consultations	116	0.4	39	0	2,073	946	38
Diagnostics	1,694	6.2	948	0	15,503	49,308	11
Medication	568	2.1	0	0	160,961	685	259
Genetics[b]	665	2.4	0	0	11,888	287	723
Other	2,486	9.1	1,059	0	25,534	6,949	112
Surgery	14	0.1	0	0	914	269	16
Total	27,350		15,481	10	527,393	64,444	132
Patients with multiple congenital anomalies (n = 149)							
Hospitalization	44,781	83.4	18,987	298	471,572	5,272	1,266
Consultations	252	0.5	98	0	1,838	990	38
Diagnostics	2,808	5.2	1,543	0	20,325	41,415	10
Medication	3	0.0	0	0	302	340	1
Genetics[b]	2,036	3.8	872	0	12,692	392	774
Other	3,601	6.7	2,441	0	31,100	8,636	62
Surgery	204	0.4	0	0	15,643	261	116
Total	53,686		25,870	2,200	501,537	57,306	140

[a] From date of admission to the NICU until 730 days after this admission date; [b]Includes all costs related to genetics (i.e. genetic counseling, genetic diagnostic tests)

Table 4

Average costs per patient for scenario A, B and C, implementing trio-WES

	Current costs[a] (€)	**Scenario A (€)** Trio-WES[b]	**Scenario B (€)** Trio-WES[b]	**Scenario C (€)** Trio-WES[b]
Costs related to genetic testing				
Patients with multiple congenital anomalies (n = 136)	2,816	6,498	6,498	6,498
Patients with isolated congenital anomaly (n = 310)	954	6,498	6,498	0
Patients without congenital anomalies (n = 982)	208	6,498	0	0
Total (n = 1,428)	**619**	**6,498 (+949.8%)**	**2,027 (+227.4%)**	**619 (+0.0%)**
Overall healthcare costs				
Patients with multiple congenital anomalies (n = 136)	69,170	72,852	72,852	72,852
Patients with isolated congenital anomaly (n = 310)	33,414	38,958	38,958	32,460
Patients without congenital anomalies (n = 982)	18,382	24,671	18,173	18,173
Total (n = 1,428)	**26,482**	**32,361 (+22.2%)**	**27,893 (+5.3%)**	**26,482 (+0.0%)**

WES; Whole Exome Sequencing; [a]Without taking into account the differences in follow-up time and excluding patients with a prenatal diagnosis; [b]Costs include pre-test genetic counseling, trio-WES and post-test genetic counseling

Figures

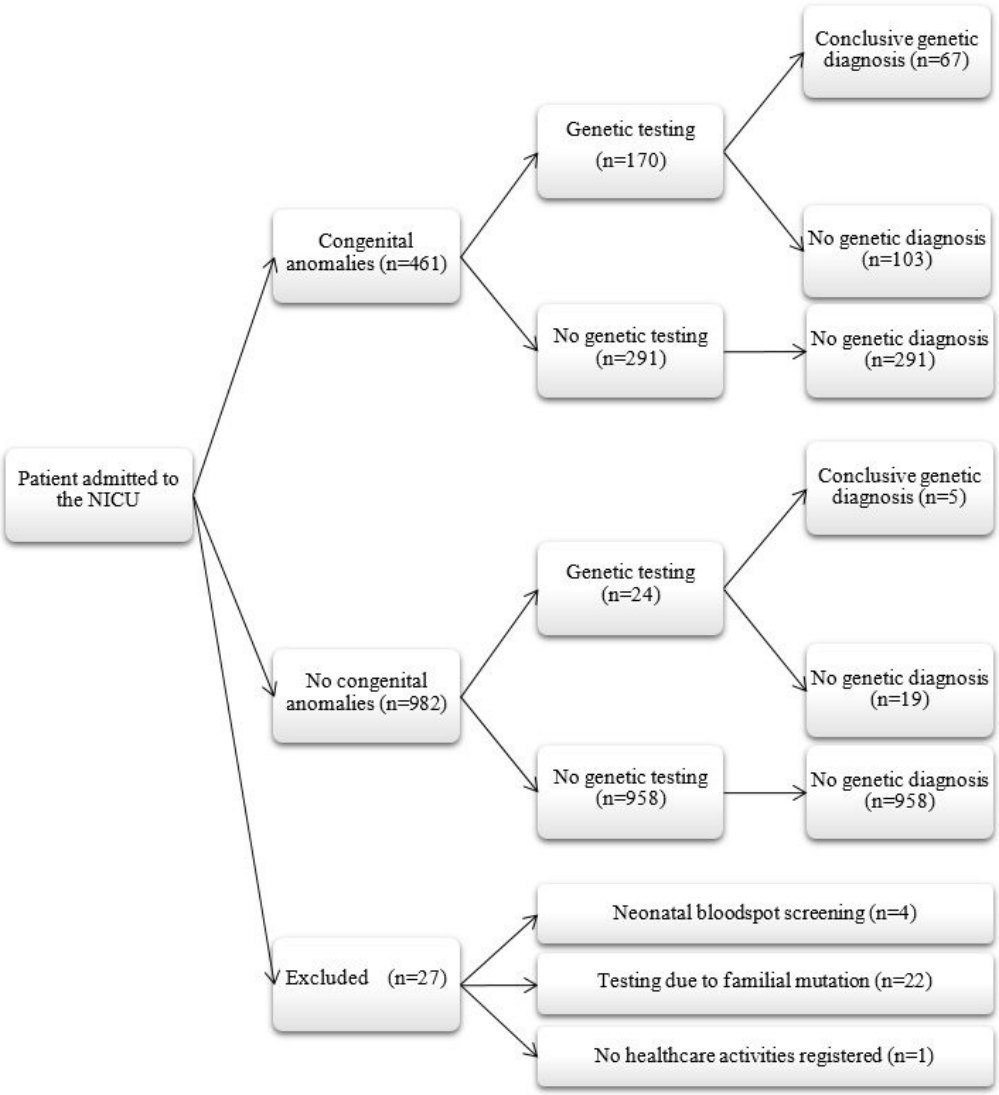

Figure 1

Patients included in this study

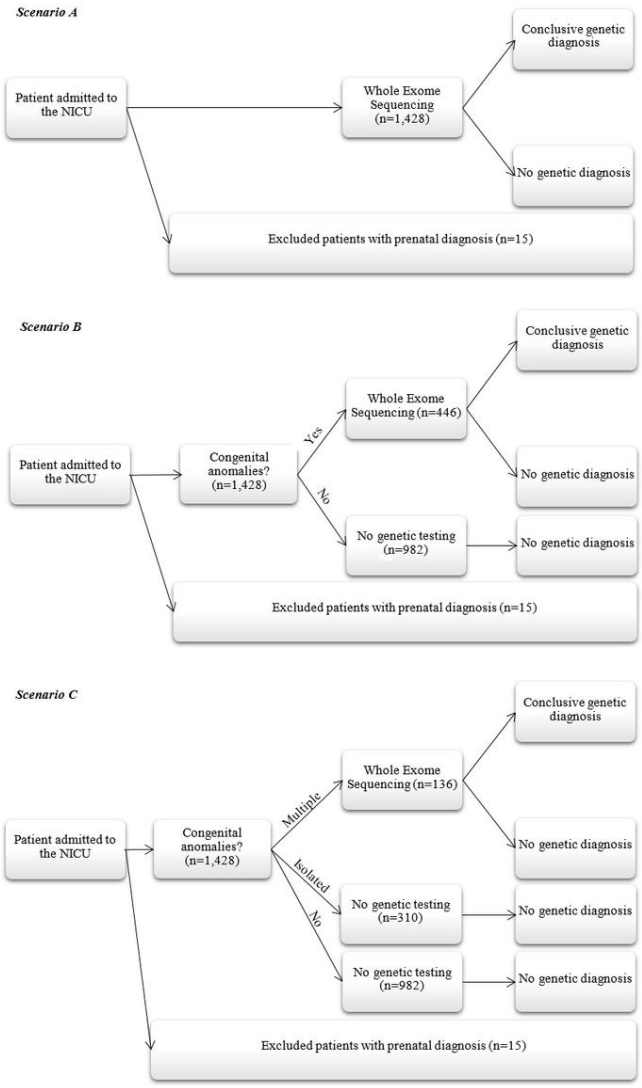

Figure 2

Scenario analyses

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableA.xlsx
- SupplementaryTableB.pdf