# **Original Investigation**

# Survival and Surgical Interventions for Children With Trisomy 13 and 18

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**IMPORTANCE** Trisomy 13 and 18 are genetic diagnoses with characteristic physical features, organ anomalies, and neurodevelopmental disability. Most children with these disorders die shortly after birth, although limited data suggest some children survive longer. Surgeries are controversial, and little evidence is available about outcomes.

**OBJECTIVE** To describe survival and utilization of any type of surgery among children with trisomy 13 and 18 born over a 21-year period in Ontario, Canada.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective cohort study used linked health administrative databases to identify children born in Ontario between April 1, 1991, and March 31, 2012, with a diagnosis code for trisomy 13 or 18 on a hospital record in the first year of life. Survival was calculated from birth and death dates; children living on March 31, 2013, were censored at their last clinical encounter.

**EXPOSURES** All procedures classified as occurring in an operating room through March 31, 2013, were categorized as *major*, *intermediate*, or *minor* surgeries.

MAIN OUTCOMES AND MEASURES Survival and surgical procedure utilization.

RESULTS The cohorts included 174 children with trisomy 13 (mean [SD] birth weight, 2.5 [0.7] kg; 98 [56.3%] female); and 254 children with trisomy 18 (mean birth weight, 1.8 [0.7] kg; 157 [61.8%] female), with follow-up times of 0 to more than 7000 days. Median (interquartile range [IQR]) survival times were 12.5 (2-195) days for trisomy 13 and 9 (2-92) days for trisomy 18. One-year survival for trisomy 13 was 19.8% (95% CI, 14.2%-26.1%) and 12.6% (95% CI, 8.9%-17.1%) for trisomy 18. Ten-year survival for trisomy 13 was 12.9% (95% CI, 8.4%-18.5%) and 9.8% (95% CI, 6.4%-14.0%) for trisomy 18. Survival did not change over the study period. Forty-one children (23.6%) with trisomy 13 and 35 children (13.8%) with trisomy 18 underwent surgeries, ranging from myringotomy to complex cardiac repair. Median age at first surgery for trisomy 13 was 92 (IQR, 30.5-384.5) days and for trisomy 18, it was 205.5 (IQR, 20.0-518.0) days. Kaplan-Meier curves showed 1-year survival after first surgery of 70.7% (95% CI, 54.3%-82.2%; n = 23) for trisomy 13 and 68.6% (95% CI, 50.5%-81.2%; n = 29) for trisomy 18.

**CONCLUSIONS AND RELEVANCE** Among children born with trisomy 13 or 18 in Ontario, early mortality was the most common outcome, but 10% to 13% survived for 10 years. Among children who underwent surgical interventions, 1-year survival was high.

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risomy 13 and 18 are genetic diagnoses associated with characteristic physical features and organ anomalies, often including cardiac malformations and neurologic impairments<sup>1</sup> that occur in approximately 8 to 15 per 100 000 live births. Approximately 50% of infants with trisomy 13 and 18 die during the first weeks of life.<sup>3</sup> Survival during the first year of life is described in 12 population-based studies (sample size range, 19-8750 participants), 3,4 but survival beyond 1 year is infrequently analyzed. Case series and parent surveys have identified longer-term survivors.<sup>5,6</sup> The rarity of the diagnoses and low 1-year survival rates have meant that longer-term survivors are uncommon in population-based studies,3 although a large study conducted in 2016 found higher 5-year survival than previously described.7 Clinically, longer-term survivors with trisomy 18 are described as socially interactive with significant motor and cognitive delays (eg, verbalizing a few words); children with trisomy 13 also have severe neurologic impairment.8 Knowledge about the quality of life of children with trisomy 13 and 18 is limited. 9 Several studies have highlighted the need for better description of longer-term survivors.3,10

Lack of information about longer-term survival complicates clinical decision making. Common anomalies that may require intervention include cardiac septal defects in both trisomy 13 and 18 and cleft palate in trisomy 13. Common surgeries in this population include feeding-related (eg, Nissen fundoplication), cardiac, and orthopedic interventions. 11 However, surgical interventions for children with trisomy 13 and 18 are controversial. 8,10,12 Some clinicians argue that interventions, especially cardiac procedures, are futile, 12,13 in part because of extrapolation of early mortality statistics. More data about survival in general and after interventions are important to guide decision making. This study describes survival and surgical procedures over a 22-year period among children with trisomy 13 and 18 in Ontario, Canada's largest province, with a population of approximately 13 million.

### Methods

# **Study Data**

Children were followed-up over time in multiple health administrative and demographic data sources in the singlepayer health care system in Ontario. These data sets were linked by encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). The Registered Persons Database was used for demographic and vital statistics for Ontario residents eligible for health care; the Discharge Abstract Database for hospitalizations; Same Day Surgery records for outpatient procedures; census data for neighborhood income quintile; Ontario Health Insurance Plan billing for the most recent clinical encounter; and the Ontario Vital Statistics Death File for death data. All databases use encoded health card numbers as identifiers, except the vital statistics database, which requires probabilistic linkage (96.2% linkage rate). Ontario legislation governing ICES allows use of health administrative data without individual consent for health system research, provided strict privacy

### **Key Points**

Question What are the survival and utilization of surgery among children with trisomy 13 and 18 in Ontario between 1991 and 2013?

Findings In this population-based retrospective cohort study of 174 children with trisomy 13 and 254 children with trisomy 18, early mortality was common, but 10% to 13% survived for 10 years. Among children who underwent surgery, 1-year survival was 69%

Meaning Long-term survival is more common than previously thought, and the potential for surgical benefit should be investigated.

guidelines are met. Institutional policy requires suppression of cell sizes under 6 to ensure nonidentification. Research ethics approval was obtained from the Hospital for Sick Children and Sunnybrook Health Sciences Centre, and administrative approval from the University of Toronto.

The cohorts were constructed using diagnostic codes from hospital records. All children born in Ontario between April 1, 1991, and March 31, 2012, who had a diagnostic code (International Classification of Diseases, Ninth Revision or Tenth Revision [ICD-9 or ICD-10]) for trisomy 13 (ICD-9, 758.1 or ICD-10, Q91.4-Q91.7) or for trisomy 18 (ICD-9, 758.2 or ICD-10, Q91.0-Q91.3) on a hospital record in the first year of life were included. To ensure accurate calculation of incidence, children were excluded if they were not Ontario residents at birth or, among children missing birth records, if they were not hospitalized in the first 7 days of life. Children with irreconcilable data errors, including no valid identifier for linkage, uncertain genetic diagnosis (equal diagnosis codes for trisomy 13 and 18 or a diagnosis code for trisomy 21), and birth dates occurring after death dates were also excluded. Data are reported by fiscal year (April 1 to March 31).

### Survival

Survival was calculated using death dates from the Ontario Vital Statistics Death File (available through 2012) and the Registered Persons Database. At study end (March 31, 2013), children without death data were censored from the date of their most recent clinical encounter. To meet privacy requirements, survival curves were truncated when 6 children remained.

# Surgeries

Hospital records were evaluated for procedure codes through March 31, 2013. Procedures were classified into organ system categories according to coding system chapter (eg, codes starting with 47 in the Canadian Classification of Procedures were labeled cardiac). Surgeries, defined as procedures likely performed in an operating room, were identified using a scheme published by the US Healthcare Cost and Utilization Project.14 A published table of projected lengths of stay was used to assess anticipated surgical invasiveness. 15 Same-day surgeries were classified as minor, surgeries with 1-day projected lengths of stay as intermediate, and all others as major. Projected length

JAMA July 26, 2016 Volume 316, Number 4

421

of stay was also used to create a hierarchy of surgeries within each organ system (eAppendix in the Supplement).

To avoid double-counting complex surgeries with multiple procedure codes, children with multiple procedures in the same organ system on the same date were assessed. Using the hierarchy in eAppendix (in the Supplement), the primary surgery by organ system and date was included in the analysis. Three pediatrician authors (K.E.N., S.M., A.G.) reviewed surgery categorization and application of the hierarchy to multiple procedure codes. Details are available from the authors.

### Covariates

Birth weight and postal code were obtained from the birth record. Census-based markers of rurality and socioeconomic status were derived from postal codes. The Rurality Index of Ontario, which assesses population density and health care access, defined rural or urban residence. 16 Individuals were assigned the income quintile of their census dissemination area (400-700 people). ICD-10 trisomy codes, in use after 2002, identified children with mosaicism (Q91.1 or Q91.5) or translocation (Q91.2 or Q91.6). Children without ICD-10 codes identifying cytogenetic status (ie, children born before 2002 and children with general trisomy ICD-10 codes) were classified as not specified. Congenital anomalies were defined by diagnostic codes contained in chapter 14 of ICD-9 (Congenital Anomalies) or chapter XVII of ICD-10 (Congenital Malformations, Deformations, and Chromosomal Anomalies), excluding genetic diagnoses. Ontario birth rates were acquired from Statistics Canada.17

### **Analyses**

Comparisons of demographic characteristics of children with trisomy 13 and 18 with those of the general Ontario newborn population were made using  $\chi^2$  tests. Clinical characteristics of children surviving 7 days to 1 year were compared with those surviving more than 1 year using Wilcoxon rank-sum tests for birth weight and  $\chi^2$  tests for sex, cytogenetic status, income quintile, rurality, and type and number of organ systems affected by congenital anomalies. Kaplan-Meier survival curves were created for children with trisomy 13 and 18 and for survival after first surgery for those undergoing surgeries. To test if survival statistics were inflated by inappropriate inclusion of children in the cohorts, a sensitivity analysis evaluated a more stringent case definition, which required that children with more than 1 hospitalization have more than 1 discharge diagnosis code of trisomy 13 or 18. Survival among the full cohort was compared with survival of those meeting the stricter definition with a log-rank test. Conditional survival, which is the likelihood of surviving to the next time point among children alive at the previous time point, was calculated. Birth prevalence was graphed over time using loess curves, which are unrestricted nonparametric curves. Trends in birth prevalence were modeled using negative binomial regression, and rates were generated using Ontario live births as an offset. The association of birth year with survival time was tested with a Cox proportional hazards model, using year as an independent predictor. The Cox models did not contain timedependent covariates. The proportional hazards assumption was tested graphically and statistically and was satisfied in all models. To investigate potential bias from comparing older and newer cohorts, a sensitivity analysis using the Cox models tested short-term survival (maximum 2 years) to ensure more homogeneous populations. Negative binomial regression models were used to assess change in frequency of surgeries over time and were adjusted for age categories to account for changing age distributions. These models included data from all surgeries, including surgeries performed on the same child at different times. Median age at procedure and postoperative survival were calculated for the most common surgeries. To maximize information while meeting privacy requirements, median age and postoperative survival were assessed based on the following criteria: (1) procedures (ie, 1 child undergoing 2 surgeries would contribute separate data for each procedure); and (2) individual children. R version 3.1.2 was used to compare cohort demographics with the general Ontario newborn population and to evaluate birth prevalence over time; all other analyses were performed using SAS version 6.1. Testing was 2-sided, and P values less than .05 were considered significant.

### Results

### **Demographics and Prevalence**

In Ontario, 174 children with trisomy 13 and 254 children with trisomy 18 were liveborn between 1991 and 2012 (eFigure 1 in the Supplement). Compared with the general Ontario newborn population, infants with trisomy 13 (mean [SD] birth weight, 2.5 kg [0.7]; 98 [56.3%] female); and infants with trisomy 18 [mean [SD] birth weight 1.8 kg [0.7]; 157 [61.8%] female) had lower birth weights, and infants with trisomy 18 were more likely to be female (Table 1). eTable 1 in the Supplement shows the most common congenital anomaly diagnoses by organ system. The incidence of trisomy 13 and 18 was stable over time with mean birth rates for trisomy 13 of 6.0 (95% CI, 5.2-7.0) and for trisomy 18 of 8.8 (95% CI, 7.7-9.9) per 100 000 live births (eFigure 2 in the Supplement).

### Survival

Children with trisomy 13 and 18 were observed from 0 to more than 7000 days. At the end of follow-up, 24 children with trisomy 13 and 23 children with trisomy 18 were alive; 7 children with either trisomy (1.6%) left the province before the end of the study. The primary analysis had no missing data. Survival did not change over time. Hazard ratios for birth year were 1.00 (95% CI, 0.97-1.03) for trisomy 13 and 1.00 (95% CI, 0.98-1.03) for trisomy 18. This finding was unchanged when maximum survival was limited to 2 years. Median survival time for children with trisomy 13 was 12.5 (IQR, 2-195) days and for trisomy 18 it was 9 (IQR, 2-92) days (Figure 1). Children meeting the stricter case definition had a shorter median survival time of 7.5 (IQR, 1-94) days for trisomy 13 and 6 (IQR, 1-74) days for trisomy 18, but their overall survival was not statistically different by log-rank test (P = .14 for trisomy 13; P = .24 for trisomy 18). Early deaths were common, but fewer deaths occurred after 3 months in

Table 1. Clinical Characteristics of Children	-	P Value for Trisomy 13		P Value for Trisomy 18	
	Trisomy 13	vs Ontario Newborn Population <sup>a</sup>	Trisomy 18	vs Ontario Newborn Population <sup>a</sup>	Ontario Newborn Population
Total No.	174		254		
Fiscal year of birth, No. (%)					
1991-1995	47 (27.0)		74 (29.1)	b	741 663 (25.6) <sup>c</sup>
1996-2000	44 (25.3)		62 (24.4)		661 387 (22.8)
2001-2005	47 (27.0)	b	53 (20.9)		657 792 (22.7)
2006-2011	36 (20.7)		65 (25.6)		838 506 (28.9)
Gender, No. (%) <sup>d</sup>					
Male	76 (43.7)		97 (38.2)		71 521 (51.2)
Female	98 (56.3)	.21	157 (61.8)	<.001	67 974 (48.7)
Birth weight, kg, No. (%)d					
≥2.5	89 (51.2)		40 (15.8)		130 277 (93.4)
1.5-2.49	67 (38.5)	<.001	141 (55.5)	<.001	7746 (5.6)
<1.5	17 (9.8)		72 (28.4)		1440 (1.0)
Missing	1 (0.4)		1 (0.6)		
Neighborhood income quintile, No. (%)e			. ,		
1st (lowest)	50 (28.7)	.51	71 (28.0)		118 538 (23.1)
2nd	30 (17.2)		55 (21.7)		106 150 (20.7)
3rd	34 (19.5)		42 (16.5)	.30	99 676 (19.4)
4th	31 (17.8)		48 (18.9)		94 229 (18.4)
5th (highest)	28 (16.1)		34 (13.4)		82 385 (16.1)
Missing	1 (0.6)		4 (1.6)		02303 (10.1)
Rurality index for Ontario <sup>f</sup>	_ (:::)		. (=/		From 2003-2011 <sup>9</sup>
Rural	18 (10.3)		24 (9.5)		41 115 (7.7)
Urban	155 (89.1)	.33	228 (89.8)	.23	492 597 (92.2)
Missing	1 (0.6)		2 (0.8)		.32337 (32.2)
Cytogenetic status, No. (%) <sup>h</sup>	1 (0.0)		2 (0.0)		
Not specified	157 (90.2)		236 (92.9)		
Mosaic	6 (3.5)		6 (2.4)		
Translocation	11 (6.32)		12 (4.7)		
Congenital anomaly diagnoses, No. (%)i	11 (0.32)		12 (1.7)		
Cardiac	55 (31.6)		94 (37.0)		
Gastrointestinal	9 (5.2)		10 (3.9)		
Genitourinary	21 (12.1)		23 (9.1)		
Ear, nose, throat, and respiratory	43 (24.7)		19 (7.5)		
Neurological	25 (14.4)		20 (7.9)		
Ophthalmological	19 (10.9)		<6 (<2.4)		
Musculoskeletal and dermatological	31 (17.8)		34 (13.4)		
No. of organ systems with congenital anoma diagnoses per child, No. (%)			51 (13.7)		
0	92 (52.9)		142 (55.9)		
1	22 (12.6)		52 (20.5)		
2	23 (13.2)		39 (15.4)		
3	15 (8.6)		14 (5.5)		
	22 (12.6)		7 (2.8)		

Characteristics were defined at birth hospitalization except cytogenetic status.

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 $<sup>^{\</sup>text{a}}$  P value based on  $\chi^2$  test comparing trisomy 13 or 18 with the Ontario newborn population.

<sup>&</sup>lt;sup>b</sup> See eFigure 2 (in the Supplement) and the Results: Demographics and Prevalance section for evaluation of incidence over time.

<sup>&</sup>lt;sup>c</sup> Data from Statistics Canada.<sup>17</sup>

 $<sup>^{\</sup>rm d}$  Ontario newborn population data were from 2010 Statistics Canada  $^{\rm 18}$ 

<sup>&</sup>lt;sup>e</sup> Ontario newborn population data were from a 1996-2000 study about neighborhood income and health outcomes. <sup>19</sup>

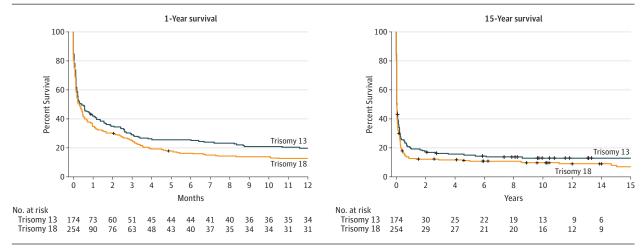
<sup>&</sup>lt;sup>f</sup> Rurality Index for Ontario based on 2008 census data.

 $<sup>^{\</sup>rm g}$  Data from study about universal bilirubin screening in Ontario newborns from 2007 to 2010.  $^{\rm 20}$ 

<sup>&</sup>lt;sup>h</sup> Cytogenetic status unavailable before 2010.

 $<sup>^{\</sup>rm i}\,$  Children may be included in more than 1 category.

Figure 1. One-Year and 15-Year Survival of Children With Trisomy 13 and 18 and Number at Risk



Black data markers indicate censored.

trisomy 13 and after 6 months in trisomy 18 (eFigure 3 in the Supplement). One-year survival was 19.8% (95% CI, 14.2%-26.1%) for children with trisomy 13, and 12.6% (95% CI, 8.9%-17.1%) for children with trisomy 18. At 10 years, 12.9% (95% CI, 8.4%-18.5% [n = 13]) of the trisomy 13 cohort was alive, and 9.8% (95% CI, 6.4%-14.0% [n = 16]) of the trisomy 18 cohort was alive (Figure 1). For 51 infants with trisomy 13 who were alive at 30 days, 1-year survival was 46.6% (95% CI, 33.3%-60.1%) and for 63 infants with trisomy 18 who were alive at 30 days, 1-year survival was 36.1% (95% CI, 24.7%-48.3%). Among 44 infants with trisomy 13 who were alive at 6 months, 50.5% (95% CI, 35.4%-65.6%) were alive at 10 years and among 40 infants with trisomy 18 who were alive at 6 months, 60.0% (95% CI, 43.7%-75.2%) were alive at 10 years (eTable 2 in the Supplement). Nearly 80% of the cohorts had cause of death on their death certificates listed as trisomy 13 or 18, an associated anomaly (eg, ventricular septal defect), or multiple congenital anomalies, with most of the remainder listed as acute infections or general diagnoses (eg, perinatal conditions). eTable 3 in the Supplement shows the characteristics of children surviving 7 days to 1 year compared with those surviving more than 1 year, and few factors were associated with longer-term survival. Among children with trisomy 13, only mosaic- or translocation-type trisomy was associated with longer survival. For children with trisomy 18, male gender, higher birth weight, and mosaic- or translocation-type trisomy were associated with longer survival. Longer-term survivors with trisomy 18 also had more neurologic diagnoses and more admissions in the first year of life. Having cardiac or neurologic diagnoses or having congenital anomalies in more organ systems was not associated with shorter survival for either trisomy 13 or 18.

# **Surgical Procedures**

Forty-one children (23.6%) with trisomy 13 underwent 135 surgical procedures (34 were major and 61 were intermediate). Thirty-five children (13.8%) with trisomy 18 underwent 92 surgeries (27 were major and 34 were intermediate). Ear, nose, and

throat procedures were the most common among children with trisomy 13, accounting for 43 procedures among 17 children. Procedures to implant medical devices were the most frequent for children with trisomy 18 (20 children underwent 26 of these procedures). Among children undergoing surgery, 16 children (39.0%) with trisomy 13 had 1 lifetime procedure and 15 children (42.8%) with trisomy 18 had 1 lifetime procedure; 15 children (36.6%) with trisomy 13 and 7 children (20.0%) with trisomy 18 had 4 or more lifetime procedures. The median age at first surgery was 92 days (IQR, 30.5-384.5) for children with trisomy 13 and 205.5 days (IQR, 20.0-518.0) for children with trisomy 18. Of children undergoing surgery, 8 (19.5%) with trisomy 13 were younger than 14 days old at time of first surgery as were 6 (17.1%) with trisomy 18.. Tables 2 and 3 display outcomes associated with surgeries by organ system, and eTable 4 in the Supplement lists the specific surgeries. Most surgeries occurred at a median age of older than 6 months except medical device placement in children with trisomy 13 and first cardiac or gastrointestinal/genitourinary procedure in trisomy 18. Median survival after first surgery was more than 1 year in all organ system categories except ophthalmic surgeries in trisomy 13 and cardiac surgeries in trisomy 18. Figure 2 is a Kaplan-Meier curve showing survival after the first surgery. Of children with trisomy 13, 87.8% (95% CI, 73.1%-94.7% [n = 36) survived 30 days and 70.7% (95% CI, 54.3%-82.2% [n = 29]) survived 1 year after their first procedure. For trisomy 18, 82.9% (95% CI, 65.8%-91.9% [n = 30]) survived 30 days and 68.6% (95% CI, 50.5%-81.2% [n = 23]) survived 1 year after their first surgery. After adjustment for age, the intervention rates increased by 4% per fiscal year for both trisomy 13 and 18; these changes were not statistically significant over time (P = .11 for both, eTable 5 in the Supplement).

# Discussion

Among children with trisomy 13 and 18 born in Ontario between 1991 and 2012, longer-term survival and use of surgi-

Table 2. Outcomes of Children With Trisomy 13 After Surgical Procedures<sup>a</sup>

Organ System and Intervention Type <sup>b</sup>	No. of Procedures	No. of Children	Trisomy 13 (n = 41), Median (Range), y				
			Outcomes Including All Procedures <sup>c</sup>		Outcomes Including Only the First Procedure per Child		
			Age at Procedure	Postoperative Survival <sup>d</sup>	Age at Procedure	Postoperative Survival <sup>d</sup>	
Cardiac							
Major	10	6	0.7 (0.1-9.8)	8.3 (0-11.3)	0.5 (0.1-0.9)	9.7 (0-11.3)	
Gastrointestinal and genitourinary							
Major/intermediate	9	7	1.5 (0-2.9)	1.8 (0-15.9)	1.1 (0-2.9)	3.6 (0-15.9)	
Minor	7	7	4.6 (0.7-11.1)	5.4 (0-14.2)	4.6 (0.7-11.1)	5.4 (0-14.2)	
Ears, nose, throat							
Major/intermediate	28	13	1.4 (0.3-13.7)	7.4 (0.4-17.1)	0.5 (0.3-6.0)	7.3 (1.2-17.1)	
Minor	15	10	2.8 (0.5-6.4)	2.9 (0.2-18.3)	1.7 (0.5-4.5)	2.0 (0.2-18.3)	
Respiratory and neurological							
Major/intermediate	13	8	2.1 (0-14.2)	3.4 (0-16.2)	1.4 (0-5.6)	2.7 (0-16.2)	
Minor	<6						
Technology							
Major/intermediate	21	16	0.3 (0-8.8)	1.8 (0-11.3)	0.2 (0-8.4)	1.8 (0-11.3)	
Minor	<6						
Musculoskeletal and dermatological							
Major/intermediate	14	12	1.4 (0-15.8)	1.1 (0-5.9)	0.5 (0-15.8)	1.1 (0-5.9)	
Minor	<6						
Ophthalmological							
Minor	12	<6					

<sup>&</sup>lt;sup>a</sup> Per institutional policy, data were suppressed for cell sizes of less than 6 children to ensure nonidentification.

cal interventions were more common than previously reported in population-based studies. eTable 6 in the Supplement describes survival findings among 12 of the largest populationbased studies. The early mortality rates in this study were similar to those in previous ones<sup>3,4,21</sup>; however, a majority of children surviving 6 months lived 10 years or longer. Many prior studies did not evaluate survival beyond 1 year.  $^{22\text{-}25}$  Four studies did not evaluate survival beyond 1 year. ies (2 studies for trisomy 18 only<sup>3,26</sup> and 2 studies for both<sup>7,27</sup>) identified individuals living beyond 5 years. The most recent study reported 5-year survival of 9.7% for children with trisomy 13 and 12.9% among children with trisomy 18.7 In this study, cardiac and neurological diagnoses were not associated with shorter survival, and children with shorter survival did not have anomalies in more organ systems. One prior study also found no association between cardiac defects and survival.3

More than 20% of children with trisomy 13 and more than 10% of children with trisomy 18 in this study underwent 1 or more interventions, ranging from minor procedures (eg, myringotomy) to major cardiac repairs (eg, hemi-Fontan). Oneyear survival after first surgery was approximately 70%. Given the debate about surgery in these populations,  $^{13,28,29}$  this survival likely reflects both careful patient selection and procedural benefit. One prior population-based study reported 2 surgeries among 30 children with trisomy 13 and none for 67 children with trisomy 18.22 Previous case series about surgeries have reported 1-year survival of 17% to 100%. 30,31 No studies have explored how quality-of-life factors into decision making around procedural benefit.32

One factor likely contributing to higher survival and intervention rates found in this study was the use of health administrative data. Ontario's single-payer health care system captures all surgical procedures and deaths, and children leaving the province were censored after their last clinical encounter. In contrast, most population-based studies use birth defect registries, which rely on case notification by hospital or laboratory personnel. Most registry-based studies use posthoc linkage to death registries to calculate survival, which creates challenges when children do not have verified dates of death at end of follow-up. Although some researchers used ancillary data to confirm vital status, other studies either excluded children without death dates or assumed children were alive at study end. eTable 6 (in the Supplement) describes study approaches to missing data. Differing strategies can substantially affect survival statistics. Two recent studies used data from the same registry over similar time periods (1985-2003 and 1985-2007). One study<sup>22</sup> reported 1-year survival of 13.8% for trisomy 13 and of 1.6% for trisomy 18; the other study<sup>33</sup> reported 1-year survival of 3.3% for trisomy 13 and of 6.0% for trisomy 18. Additionally, many registry-based studies did not have access to medical records, including surgeries. 3,4,23,24,27,34,35

<sup>&</sup>lt;sup>b</sup> Specific surgery types are detailed in eTable 4a (in the Supplement).

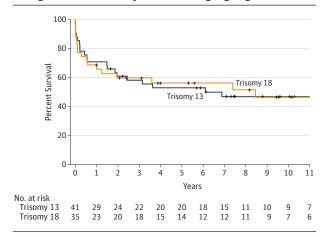
<sup>&</sup>lt;sup>d</sup> Calculated from discharge date when the intervention date was not available.

Table 3. Outcomes of Children With Trisomy 18 After Surgical Procedures<sup>a</sup>

Organ System and Intervention Type <sup>b</sup>	No. of Procedures	No. of Children	Trisomy 18 (n = 35), Median (Range), y				
			Outcomes Including All Procedures <sup>c</sup>		Outcomes Including Only the First Procedure per Child		
			Age at Procedure	Postoperative Survival <sup>d</sup>	Age at Procedure	Postoperative Survival <sup>d</sup>	
Cardiac							
Major	10	6	0.7 (0-2.6)	7.4 (0.1-15.0)	0.1 (0-0.7)	0.3 (0-15.0)	
Gastrointestinal and genitourinary							
Major	8	7	1.8 (0-6.1)	4.1 (0-10.1)	0.1 (0-5.8)	3.9 (0-10.1)	
Minor	<6						
Ears, nose, throat, respiratory, and neurological							
Major/intermediate	10	7	4.7 (0-6.4)	4.3 (0-11.4)	1.6 (0-5.8)	3.9 (0-11.4)	
Minor	15	<6					
Technology							
Major/intermediate	21	20	0.6 (0-2.6)	2.3 (0-15.5)	0.5 (0-2.6)	2.1 (0-15.5)	
Minor	<6						
Musculoskeletal							
Major/intermediate	12	8	7.7 (0.8-16.5)	9.5 (0.1-20.0)	8.2 (0.8-16.5)	7.6 (0.1-20.0)	
Minor	6	<6					
Ophthalmological							
Minor	<6						

<sup>&</sup>lt;sup>a</sup> Per institutional policy, data were suppressed for cell sizes of less than 6 children to ensure nonidentification.

Figure 2. Survival After First Surgery and Number at Risk Among Children With Trisomy 13 and 18 Undergoing Surgeries



Time O is the date of the surgical procedure. If the date of surgical procedure is unavailable, time O indicates the date of postsurgical hospital discharge. Black data markers indicate censored.

Administrative data sources have limitations, especially related to cohort creation. Unlike registry-based studies with laboratory-confirmed diagnoses, this study defined the population with diagnostic codes listed on hospital discharge records. Study population underascertainment could arise from several causes. Infants could die before diagnosis, but this would be uncommon because most trisomy 13 and 18 diagnoses are established prenatally.<sup>22</sup> When liveborn infants

die soon after birth, including in the delivery room, both a hospital discharge record and a death certificate are required. Diagnostic data and cause of death are ascertained by the same physician so the hospital record should include the presumptive diagnosis. This study's reliance on hospital records would miss home births resulting in out-of-hospital deaths; however, that scenario would be rare for 2 reasons. In Ontario, home deliveries by midwives are not currently used for palliative care or for infants with abnormal prenatal diagnoses. Also, clinical policy specifies that infants born at home with previously undiagnosed congenital anomalies are to be transferred to a hospital. The use of administrative data also means that the study cohort might include children without a laboratory-confirmed diagnosis of trisomy 13 or 18, or children whose records were mistakenly coded. However, sensitivity analyses showed no difference in survival with a stricter case definition. Additionally, the prevalence reported for trisomy 13 and 18 (6.0 and 8.8 per 100 000 live births) was on the lower end of previously described ranges of 4-13.6 for trisomy 13<sup>22,36</sup> and 8.5-90 for trisomy 18.<sup>22,37</sup> If the cohort contained a large proportion of misclassified children, the birth prevalence would likely be inflated. Also, frequencies of diagnoses for specific congenital anomalies were similar to those in other studies.<sup>38</sup> A general validity analysis of diagnostic codes in this study's data source demonstrated a positive predictive value of 0.82 (IQR, 0.74-0.89).<sup>39</sup>

The most important study limitation is the lack of quality-of-life measures to add important context to the survival data; this study alone is insufficient to support decision

Outcomes including all procedures may include the same child more than once.
 d Calculated from discharge date when intervention date was not available.

<sup>&</sup>lt;sup>a</sup> Calculated from discharge date when intervention date Calculated from discharge date Calculated from discharg

making for children with trisomy 13 and 18. The limited literature on quality of life in these populations has relied on parental report. One study of families belonging to online support groups found that "almost all parents reported a positive view of family life and the quality of life of their child," and "described surviving children as happy." <sup>40</sup> Information about neurocognitive developmental outcomes is sparse, with a few small studies describing a spectrum of disability. <sup>5,9</sup> In addition to this study's data about survival duration, measurement of quality of life in the context of major surgeries will be important to help families and clinicians balance the risks and benefits of interventions.

This study has several other limitations. First, identification of children with mosaic or translocation-type trisomy 13 and 18 was incomplete. The ICD-9 codes used before 2002 did not specify cytogenetic diagnosis. As in other studies in which cytogenetic status could not be verified, 3,7,23,33,35 children with mosaic- and translocation-type trisomy were included in this study's primary analysis. This decision likely increased rates of longer-term survival compared with studies including only children with full trisomy 13 or 18. Second, 7 children (1.6%) left the province before the end of follow-up and they may have had subsequent uncaptured surgical procedures. Third, data on prenatal diagnoses, terminations, and miscarriages were unavailable, so this study reports liveborn prevalence rather than true prevalence. Fourth, to meet privacy requirements, procedures were grouped by organ system and may include data on multiple surgeries from the same child, even though these

groupings are not homogeneous, and individual rates would be more clinically relevant. Also the number and heterogeneity of the procedures limits the analysis of surgical timing and postoperative survival trends. Further, this study cannot determine if interventions caused longer survival. However, because of the rarity of these diagnoses and variability in their presentation, it is challenging to generate definitive evidence about intervention efficacy. In particular, the randomized clinical trial necessary to test for a causal relationship between surgery and survival would be neither ethical nor feasible so the information available from administrative data, while incomplete, is useful. This study did not assess for comorbidities other than congenital anomalies because of the risk of time confounding the association between comorbidities and survival. For example, the increased number of neurologic congenital anomaly diagnoses among longer-term survivors with trisomy 18 likely reflects an increased probability of undergoing neuroimaging over time. Additionally, the study data do not include details on important demographic and clinical factors or family treatment goals.

# Conclusions

Among children born with trisomy 13 or 18 in Ontario, early mortality was the most common outcome, but 10% to 13% survived for 10 years. Among children who underwent surgical interventions, 1-year survival was high.

# ARTICLE INFORMATION

**Correction:** This article was corrected on October 20, 2016, and on May 2, 2017, because of typographical errors in the text.

Author Contributions: Drs Guttmann and Nelson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Nelson.

Critical revision of the manuscript for important intellectual content: Rosella, Mahant, Guttmann.

Statistical analysis: Nelson, Rosella.

Obtained funding: Nelson, Mahant, Guttmann.

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Study supervision: Guttmann.

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JAMA July 26, 2016 Volume 316, Number 4

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