Perspectives on the care and management of infants with trisomy 18 and trisomy 13: striving for balance

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Purpose of review
At the time of diagnosis of the trisomy 18 and trisomy 13, parents and care providers face difficult and challenging decisions regarding management. Because of the increased infant mortality and developmental outcome associated with both conditions, the conventional approach to management has been to withhold technological support. In recent years, an active dialogue on this topic has emerged. The purpose of this review is to summarize the literature on the outcome of infants with trisomy 18 and 13 and to discuss the key themes in this emerging dialogue.

Recent findings
In recent years, several important studies have appeared that have analyzed the issues relevant to this topic, including parental autonomy, best interest of the child standard, and quality of life. Some authorities state that in areas of ambiguity it is best to defer to parents' views, whereas others indicate concern that the best interest standard has given way to parental autonomy. Information on the actual experience of parents of children with trisomy 18 and 13 has been limited until recently.

Summary
The author recommends a balanced approach to counseling families of the newborn with trisomy 18 and 13 at the time of diagnosis. The counseling process should include presentation of accurate survival figures, avoidance of language that assumes outcome, communication of developmental outcome that does not presuppose perception of quality of life, and respect for the family's choice, whether it be comfort care or intervention.

Keywords
congenital malformations, developmental disability, infant mortality, lethal conditions, trisomy 13 syndrome, trisomy 18 syndrome

INTRODUCTION

The trisomy 18 and trisomy 13 syndromes comprise two important pediatric conditions that – despite their well-recognized neonatal mortality – deserve close attention and interest among those of us who care for children. I make this point for two reasons: after trisomy 21/Down syndrome, trisomy 18 and trisomy 13 represent the second and third most common autosomal trisomy syndromes; their combined total prevalence (elective termination of pregnancies, stillbirths, and live births), is approximately one of 1800, which makes the experience of having a baby with either a very common event (over 2000 US families annually) [1,2▪▪]; both syndromes consist of a recognizable pattern of multiple congenital anomalies with increased neonatal and infant mortality and significant intellectual disability in older children, making care challenging for the family, the primary care practitioner, and the specialist [3].

The conventional approach to management of neonates with the trisomy 18 and 13 syndromes has been a withholding of technological support and surgery with the provision of comfort care, more recently under the guidance of palliative care teams.

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KEY POINTS

- The conventional approach to management of neonates with the trisomy 18 and 13 syndromes has been a withholding of technological support and surgery with the provision of comfort care, more recently under the expert guidance of palliative care teams.
- Since 2003 and especially in the last 4 years, an active dialogue on the choices in the care and management of infants with trisomy 18 and 13 has emerged in the pediatric and bioethics literature.
- The themes that are relevant to this discourse include parent autonomy, best interest of the child standard, futility, burden of treatment, allocation of resources, and quality of life.
- The author recommends a balanced approach to counseling families of the infant with the syndromes that includes presentation of accurate figures for survival, avoidance of language that assumes outcome, accurate communication of developmental outcome that does not presuppose a family's perception of quality of life, and the recognition of the family's choice, whether it be comfort care or interventions.

Two studies in 1992 clearly advocated for this position [4,5], and a more recent survey of neonatologists documented that this view is the prevailing current attitude [6]. However, as I will expound on below, in recent years, an active dialogue on this topic is emerging in the literature. Various authors have suggested the need for a more balanced view that includes a comprehensive summary of outcome data and recognition of current knowledge of the quality of life of families and children with these conditions. This view encompasses parents being actively involved in the choice of care options and participating in the emerging dialogue.

The purpose of this review is to summarize the literature on the outcome of infants with trisomy 18 and 13 and to identify the key themes in this recent dialogue. Additionally, I will highlight the important articles of 2011 and 2012 that have informed this discourse and provide some perspective and recommendations for future directions. In this review, I will not summarize the medical and genetic aspects of the trisomy 18 and 13 syndromes and refer the reader to a recent chapter that includes this information as well as guidelines for management [3]. In order to fulfill these aims, I will pose three questions that will familiarize the reader with the most important themes. From the medical point of view, the known survival figures and developmental outcome of the children comprise the centerpiece of any discussion of the issues surrounding management of trisomy 18 and 13.

ARE TRISOMY 18 AND 13 (UNIFORMLY) LETHAL?

The trisomy 18 and 13 syndromes, also known as Edwards syndrome and Patau syndrome, respectively, were described in back-to-back studies in the same 1960 issue of *Lancet* [3]. After the initial publication of these single case reports, it soon became obvious that both conditions were relatively common and shared a similar high neonatal and infant mortality. In the large case series of Weber *et al*. [7], 28% of infants with trisomy 18 had died by 4 weeks of age, and 87% died before reaching their first birthday. The causes of this infant mortality have been remarkably understudied over the last 50 years, but include central apnea, structural heart defects, pulmonary hypertension, feeding difficulties with aspiration, and upper airway obstruction [3]. By the1990s, four population studies had been published that represented different geographical areas of the world, all showing quite similar infant mortality figures [8–11]. Interestingly, these investigations demonstrated a higher infant mortality than Weber's, likely because neonates who died in the first day of life might not have been recognized in the 1960s, and thus left out of the analysis [11]. Alternatively, the higher mortality might reflect different approaches to care and intervention in different regions: although the number of infants is small, median survival and percentage surviving to 1 year are higher in two US studies compared with European data. As is summarized in Table 1 [2▪▪,8–14], median survival ranges from 2 to 14.5 days and percentage survival to 1 year is 0–8%. Although several hospital-based series have also been published in the last 2 decades, these are not included in this analysis, as these do not accurately reflect the true incidence of death. In the last decade, four comprehensive population studies appeared in the literature [2▪▪,12–14], showing similar figures. (Because the survival figures in trisomy 13 are quite similar to trisomy 18, they will not be summarized here, and the reader is referred to the key studies [2▪▪,13,14]).

As discussed below, various articles over the last 2 decades have characterized early mortality in these syndromes as uniform. For example, Bos *et al.*'s [4] study applies the phrase 'death is imminent' as an argument for the avoidance of emergency surgery approach. In addition, the descriptors 'lethal' and 'incompatible with life' are commonly stated [11]. As suggested by Koogler *et al.* [15], the use of the term lethal in these conditions depends on the interventions applied in the care of the infant. Kosho *et al.* [16] documented that full technological interventions, including respiratory care, increased the usual 5–8% 1-year survival in trisomy 18 to 25%.

Table 1. Comparison of trisomy 18 survival studies

Age	Queensland Carter *et al.* [8] ($n=43$) % surviving	Leicester Young *et al.* [9] ($n=21$) % surviving	Denmark Goldstein and Nielsen [10] ($n=76$) % surviving	Utah Root and Carey [11] ($n=64$) % surviving	Scotland Brewer *et al.* [12] ($n=84$) % surviving	CDC Rasmussen *et al.* [13] ($n=114$) % surviving	Texas Vendola *et al.* [14] ($n=200$) % surviving	United Kingdom Irving *et al.* [2▪▪] ($n=301$) % surviving
1 week	35	32	44	45	43	50	52	36
1 month	11	18	21	34	25	38	30	27
6 months	5	NR	3	9	NR	15	NR	NR
1 year	4	0	0	5	2	8	3	6
Median survival (days)	5	2.5	6	4	6	14.5	7	NR

NR, not recorded in study.

These investigators offered families who were referred to Nagano Children's Hospital full care (except cardiac surgery), and six of 24 (25%) lived past 12 months. Although the numbers are relatively small, these authors demonstrated for the first time that intervention had an impact on infant mortality. In recent years, four series from different parts of the world report on the outcomes of cardiac surgery in infants with trisomy 18 and 13. The most recent study, by Maeda *et al.* [17▪], analyzed patients who underwent cardiac surgery and showed that patients with trisomy 18 who had cardiac surgery survived longer than those who did not have surgery. This study is an excellent source for reviewing all of the existing published data on cardiac surgery in trisomy 18 and 13.

To summarize, trisomy 18 and 13 are not uniformly lethal, as about 5–8% of infants survive to 12 months; the studies of Kosho *et al.* and Maeda *et al.* [13,17▪] support the notion that the application of the designation 'lethal' depends on level of intervention administered and demonstrate that if technological interventions, including surgery, are instituted, survival rises in supposedly lethal conditions.

WHAT IS THE DEVELOPMENTAL AND NEUROLOGICAL OUTCOME OF OLDER CHILDREN WITH TRISOMY 18 AND 13?

This query is highly important because posing it raises a crucial issue in this discussion of care of infants with trisomy 18 and 13, that is, quality of life of children and families with this disability. Few data were available on neurodevelopmental outcome of surviving children with trisomy 18 and 13 syndromes before the seminal work by Baty *et al.* [18] in 1994. Prior to this work, widely used texts such as *Recognizable Patterns of Human Malformation* ('severely mentally defective') [19] and the study cited above, Bos *et al.* [4] ('profound mental retardation'), summarized what was known about neurological outcome based on case reports/series of 1960–1990. The novelty of the Baty *et al.* study was the documentation of actual developmental data on a relatively large number of surviving children. Although the data are limited by different examiners applying different instruments in various regions, developmental quotient information on a wide age range of children with both syndromes was available for perusal. In addition, Baty *et al.* documented developmental achievements in infants and children with trisomy 18 and 13. For example, these achievements included responsive smiling at an average age of 4.7 months in trisomy 18 and 5.5 months in trisomy 13, sitting unassisted at an average age of 38.5 months in trisomy 18 and 31 months in trisomy 13, walked in a walker at an average age of 39 months (trisomy 18).

Table 2 [18] is adapted from the study and summarizes the developmental quotients for children with trisomy 18 and 13 in preschool years and those greater than 5 years of age. Although the number of children is relatively small, the number of observations is higher. These data indicate that older individuals with trisomy 18 and 13 do have significant intellectual and psychomotor disability; however, progression of milestones occurs. The average child between 3 and 5 years with trisomy 18 had skills at the 8-month level, and with trisomy 13 at the 7-month level. These scores do not reflect the observation that several children achieved milestones beyond these average developmental quotients [18]. For example, children acquired skills such as object permanence, helping with hygiene, self-feeding, understanding cause and effect, and use of signs that would surpass these average developmental quotient scores shown

Table 2. Mean chronological ages, developmental ages and developmental quotients for trisomy 18 and 13

Age (years)	Trisomy	Chronological age (months)	Developmental age (months)	Developmental quotient	Number of children
1–3	18	25.2	3.9	0.17	15
	13	26.3	7.7	0.31	5
3–5	18	46.8	8.2	0.18	7
	13	44.1	7.3	0.17	5
All ages	18	48.5	5.7	0.18	26
	13	42.9	8.4	0.25	8

Modified and adapted from [18].

in Table 2. Figure 1 depicts a girl with trisomy 18 who achieved many of these milestones. More recently, Braddock *et al.* [20] reported that persons older than 10 years of age with trisomy 18 had intentional communication skills that exceed the developmental quotient ranges of 5–8 months in the cases reported in Baty *et al.* [18] (see Table 2).

In summary, these works indicate that older children with full trisomy 18 and 13, while exhibiting significant psychomotor disability, are aware of their families, attend school, progress in their milestones, and achieve individual milestones beyond the average developmental quotient.

DISCOURSE: WHAT IS THE BASIS OF THE CONTROVERSY?

As indicated above, the articles by Bos *et al.* [4] and Paris *et al.* [5] reflect – I suggest – the prevailing approach then and now. This approach to the care of neonates with trisomy 18 includes avoidance of surgery, withholding of intervention, and/or withdrawal of treatment. The basis for the recommendation included assertions such as the 'child's prognosis is hopeless' [4] and 'groundless hopes as a means for caring or protecting the parents exposes the infant to potential pain and fruitless suffering' [5]. Prior to these studies, this widely held view was summarized concisely in the well-known compendium of syndromes mentioned above [19]. In the early editions, the entry on trisomy 18 states: 'once the diagnosis has been established, the author recommends limitation of all medical means for prolongation of life.' A similar recommendation was contained in the entry on trisomy 13. (Notably, the recent editions of this book edited by Jones [21] have changed this recommendation to the following: 'once the diagnosis has been established, limitation of extraordinary medical means for prolongation of life should be seriously considered; however, the personal feelings of the parents and the individual circumstances of each infant must be taken into consideration.' This reflects – I would suggest – some change in attitude and heralds this emerging dialogue).

In the last decade, several articles discussing the topic of management of infants with trisomy 18 and 13 have been published; by 2011, a rich dialogue on this topic had clearly emerged within the pediatric and bioethics literature. Koogler *et al.* [15] presented a contrasting view to what seemed to be the conventional wisdom in Bos *et al.* and Paris *et al.* Koogler *et al.* argue that the use of the label lethal 'is not only inaccurate, it is also dangerous.' In their article, they analyzed the three main arguments against providing medical treatment to all infants with 'lethal anomalies', which apply the themes of futility, burden of treatment, and resource allocation. Koogler *et al.* describe how all of these issues 'fail' in the argument for withholding treatment on all infants with so-called lethal anomalies. For example, the resource allocation argument focuses on whether 'it makes economic sense to treat children' with these prognoses when the money could be used elsewhere. They point out that the conditions are rare, and 'so even if these children were given maximal treatment, their care would account for a small percentage of the US healthcare budget.' Additionally, the authors demonstrate that the two arguments for a vitalistic approach that suggest providing care to all infants with 'lethal anomalies' also fail [15]. This leads them to suggest that the question must be considered 'open' and then argue for a procedural approach, which poses the question: 'Who should decide what is appropriate medical care for these children?' Koogler *et al.* go on to state: 'given this ambiguity, parental decisions to withhold or request treatment based on benefit–burden calculations should be respected' [15]. I would certainly concur. Their articulation of the arguments and issues – in my opinion – challenged the extant paradigm.

The next piece in this recent dialogue was the study by Kosho *et al.* [16] mentioned above that

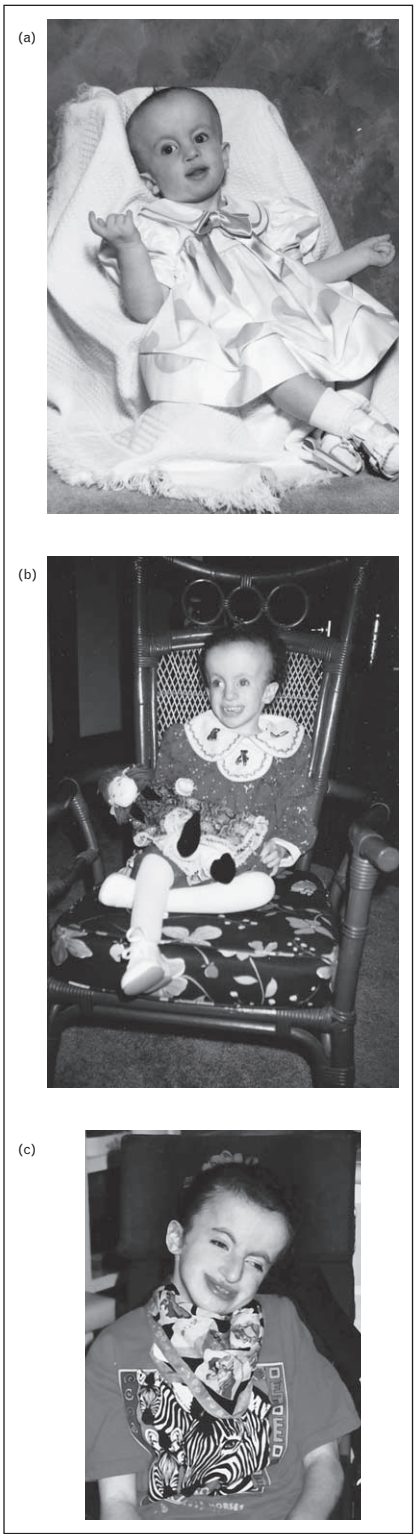

FIGURE 1. The photos show a girl with full trisomy 18 at different ages of her life. She achieved many milestones during her 19 years, including sitting up, standing, walking in a walker, knowing cause and effect, and communicating her needs. She attended school from early preschool years and enjoyed her family's activities despite her developmental challenges and severe scoliosis as an older child.

demonstrated that offering intervention did show improved survival in infants with trisomy 18. In an accompanying commentary, I pose the question: 'why have the complex and sometimes controversial issues surrounding management and care of infants with trisomy 18 (and trisomy 13) received little dialogue in the bioethics literature?' [22]. My concern was addressed by the following studies published from 2008 to 2012.

The first of these was the survey of McGraw and Perlman [6] mentioned in the introduction of this study. This article not only reports the results of their survey, in which 56% of neonatologists indicated they would not resuscitate a newborn in the delivery room with trisomy 18, but also lays the foundation for the current discourse. In their discussion, they state a concern that they suggest is a trend. The main thrust of this argument is captured in the following summary: 'These observations raise the concern that some neonatologists are abandoning the best interest standard... and instead are adopting an ''ethic of abdication'' in their approach to difficult treatment/nontreatment options.' These authors are suggesting that the factors in the decision-making pendulum have swung toward parental autonomy at the cost of the best interest standard. This study generated two letters to the editor [23,24] that discussed the challenge in deciding what is in fact the 'best interest of the child.' McGraw and Perlman characterized the issues of parent autonomy and the best interest as on a continuum; I would argue that both are elements in an equation whose goal is balance.

In the April 2011 issue of *Pediatrics*, a special article helped launch a new section of the journal, 'Ethics Rounds.' In this study, two neonatologists and a parent reflect and respond to the management of a case of an infant with trisomy 18 in which the question of offering heart surgery is raised [25▪▪]. This seminal study comprehensively discusses all of the issues that surround this topic, including futility, prolonging suffering, allocation of healthcare resources, parental choices, best interest standard, quality of life, and respectful communication. The composite of all three comments in the evolving case scenario provides singular balance. The editor's comment on this discussion closes with the statement: 'Deference to parents is generally the right course, unless the infant is clearly suffering from ongoing treatment that is not likely to be of benefit.' The point here, as suggested by Koogler *et al.*, is that in arenas of uncertainty in which answers are not clear it is most prudent to defer to the parents' wishes.

The next study in this dialogue, by Merritt *et al.* [26▪▪], provides a comprehensive topical review,

covering the key themes in the discussion of management. The authors set up the tension and the dialogue early in their study: 'many providers believe that the infant should receive purely palliative and hospice care as opposed to ''intensive technological support and surgical intervention.''' Although Merritt *et al.* present a particularly compassionate and comprehensive approach to care, I would suggest that the study lacks proper balance because of the persistent use of the term 'lethal' and the lack of discussion of quality of life of the parents and surviving children with trisomy 18 and 13.

In addition to these studies in the pediatric literature, two other relevant studies appeared in the *Journal of Clinical Ethics* in 2011 [27,28▪▪]. These articles present somewhat contrasting views on the discussion of a case of a baby with trisomy 18 and the question of withholding feeding therapy. The first study [27] uses a case of trisomy 18 to illustrate the 'facilitation model' commonly used in clinical ethics consultation throughout North America. The authors argue that, in unsettled cases, the role of the ethics consultant should be 'expanded to include a process of moral inquiry into what the allowable options should be.' The accompanying piece [28▪▪] suggests a narrative approach that allows a discussion of the values of the family in helping to provide the necessary moral grounding for decision-making. Of note, this article is one of the few published studies in which the authors indicate that infants and families of a baby with trisomy 18 may have a 'good quality of life.' They point out that 'many online testimonials and parents of children with trisomy 18 contradict the notion that these parents cannot achieve a meaningful quality of life' (see the web pages mentioned below). The authors suggest that there is absence of a clearly defined standard of care in management issues surrounding babies with trisomy 18, but by 'taking a narrative approach, including a careful thorough evaluation of the patient, family physician, and clinical situation, ethics may assist this family and medical staff in identifying a more informed and authentic range of ethically permissible option.'

The final study in this discourse is highly relevant because it addresses the understudied theme of the quality of life in families with children with trisomy 13 and 18. Janvier *et al.* [29▪▪] provide an authentic sense of the experience of parents of children with trisomy 18 and 13. They surveyed parents on the internet from various sources and obtained a remarkably high response rate; 332 questionnaires provided the data for their results. The authors showed that, despite severe disabilities, 97% of parents describe their child as a happy child; parents reported: 'these children enriched their family and the couple irrespective of the length of their lives.'

Prior to this study, few data existed on this question of quality of life of families and children with these syndromes. Baty *et al.* [18] provided input from parents about their experiences with professionals around trisomy 18 and 13 care. More recently, Bruns [30▪] reported on the medical aspects of children with trisomy 13 using parent-based data. She points out the need for more data on outcome to balance the more typical 'pessimistic' view. Additionally, I would refer the reader to the related parent support web sites [(http://www.trisomy.org, SOFT US web page), (http://www.soft.org.uk), (http://www.trisomy18.org, Trisomy 18 Foundation page), (http://www.livingwithtri13.org)] that include many pictures of older children and families enjoying what are clearly everyday experiences like any child and family. The Support Organization for Trisomy 18, 13, and Related Disorders US and UK web sites in particular provide photographs that are a striking contrast to the typical figures of neonates with these syndromes depicted in medical texts, and, I suggest, transform the traditional view of the conditions.

CONCLUSION

In the last decade, I suggest that a rich dialogue regarding the complex and multifaceted issues surrounding the care of infants and children with trisomy 18 and 13 has emerged in the literature. The conventional nonintervention approach for all neonates has been revisited and placed in some perspective. On the basis of this review, I would recommend a balanced approach to counseling families of the newborn with trisomy 18 and 13 at the time of diagnosis and at decision points in management, that is, in the delivery room, newborn nursery, and clinic. The components of this counseling process should include presentation of accurate figures for survival that take into consideration the individual clinical findings of the child, avoidance of language that assumes outcome (e.g., lethal, fatal, hopeless, incompatible with life), a realistic and balanced communication of developmental outcome that does not presuppose that one knows a family's perception of quality of life, and the recognition of the family's choice, whether it be comfort care or interventions.

Although the cited studies have identified a number of recurring themes, detailed data on the experience of families who have had a child with trisomy 18 and 13 are lacking. The recent study by Janvier *et al.* [29▪▪] begins to address this issue.

I would suggest that there needs to be more investigation on this topic that includes interviewing a broad population of parents who are rearing a child with the two syndromes. Up until recently, this discussion has lacked the input and voice of parents. Both Janvier *et al.* studies include the parents' views and voice in this dialogue. I would propose that the time has arrived for a balanced approach regarding choices in care.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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This comprehensive population study of trisomy 18 and trisomy 13 in the United Kingdom reports on total prevalence and mortality comparing two periods of time and shows a decreasing prevalence in live births with both conditions.

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This study of data from a nationwide network compares the outcome of infants with trisomy 18 and 13 who had cardiac surgery with those who did not have surgery; the study references the previous series of heart surgery in children with the syndromes.

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25. ■■ Janvier A, Okah F, Farlow B, Lantos JD. Ethics Rounds: an infant with trisomy 18 and ventricular septal defect. Pediatrics 2011; 127:754–759.

This special article represents an excellent discussion of the themes surrounding care of infants with trisomy 18 through the analysis of a case of an infant with trisomy 18 and a heart defect. Two pediatricians and a parent provide insights on the evolving chronology of events in the management of the child.

26. ■■ Merritt TA, Katlin A, Woo LC, *et al.* Trisomy 18 and trisomy 13: treatment and management decisions. NeoReviews 2012; 13:e40–e48.

This article is a thorough review of the issues of care and intervention; the authors provide guidelines for care providers in management.

27. Adams DA, Winslade WJ. Consensus, clinical decision making, and unsettled cases. J Clin Ethics 2011; 22:310–327.
28. ■■ Derrington SF, Dworetz AR. Confronting ambiguity: identifying options for infants with trisomy 18. J Clin Ethics 2011; 22:338–344.

This study comments on the accompanying study by Adams and Winslade [27] on management of an infant with trisomy 18; the authors recommend a novel narrative approach in complex cases that includes an assessment of the values of the family to help provide the necessary moral grounding for decision-making.

29. ■■ Janvier A, Wilfond B, Farlow B. The experience of families with children with trisomy 13 and 18 in social networks. Pediatrics 2012; 130:293–298.

This timely, novel, and relevant work is the first study that reports on the perceptions and experiences of quality of life in a large sample of parents of children with trisomy 18 and 13. The parent-reported data indicate that the families' experience with their children has 'enriched their lives and those of others' irrespective of the length of their lives. The work provides a uniquely positive view on how families of children with these syndromes perceive the impact of the child's condition.

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This article is a recent series that reports on older children with trisomy 13; it represents the largest group of older children with the syndrome characterized in a single study.