CARING INTENSELY FOR TRISOMY 18 NEWBORNS, BUT LIMITING "INTENSIVE MANAGEMENT" AN ETHICAL JUSTIFICATION FOR PALLIATIVE CARE

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CARING INTENSELY FOR TRISOMY 18 NEWBORNS, BUT LIMITING
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Trisomy 18 is a rare but classic genetic disorder that occurs in approximately 1 in 8000 live births. Trisomy 18 is no longer an esoteric disease but one with modern relevance given rapidly changing approaches in medical and surgical management. Once provided comfort-measures only, babies with Trisomy 18 are beginning to be managed intensively – with full cardio-respiratory support and surgical correction of birth defects. In particular, Japan has moved from a non-intervention approach to a consistent, national intensive approach for babies with Trisomy 18. This paper investigates the outcomes of this intensive approach in order to determine an ethically-acceptable standard of care for babies with Trisomy 18. Review of the Japanese medical literature shows that intensive management of babies with Trisomy 18 results in the prolongation of short-term life without an associated increase in long-term survival or cure. Standard quality of life measures are not improved, and significant concern remains regarding treatment-associated pain and suffering. Cardiac surgery increases the risk of post-operative sudden death and is not associated with an increase in long-term survival.

This paper argues that the risk/benefit ratio for cardiac surgery is unacceptably high; therefore, such surgery should not be performed on babies with Trisomy 18. It argues that, given

families' access to prominent news stories regarding Trisomy 18 babies and reports of this Japanese experience, families need to be counseled clearly and effectively about the evidence-based outcomes of intensive management. A "child-centered" approach that seeks to minimize the child's suffering should be utilized with the goals of all treatment, including any intensive treatment, clear to all decision-making parties. Employing a Best-Interests Standard to guide decision-making supports a standard of care for neonates with Trisomy 18 that does not include cardiac surgery and that ensures provision of perinatal/neonatal palliative care. The paper argues that palliative care should be offered as the first option to families who receive a diagnosis of Trisomy 18. These conclusions have implications for U.S. hospital policy and clinician practice.

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1.0 INTRODUCTION

In 1960, Dr. Charles Edward described a neonatal syndrome with unique features: small mouth, low-set ears, clenched hands, growth retardation, congenital heart disease, and neonatal hepatitis. At that time, cytogenetic analysis, in its infancy, identified a trisomy of the 17th chromosome – "the second condition of autosomal trisomy to be reported in man". (Edwards, 1960) Later, as further cytogenetic technological advancements were gained, the condition was identified as resulting from an extra copy of the eighteenth chromosome or Trisomy 18. The full spectrum of Trisomy 18 was later refined and found to include other congenital malformations such as spina bifida, birth defects of gastrointestinal intestinal tract, kidney malformations, and brain malformations. (Thompson & Thompson, 2007) Babies were described as having failure to thrive, weak cries, and a paucity of muscle and fat. Life expectancy was observed to be significantly limited with few surviving past one year of life. Severe intellectual and physical disability was the norm in survivors. It was further determined that Trisomy 18 occurred as a result in an error in reproductive cell division, known as meiotic nondisjunction. Advancing maternal age was found to play a large role in meiotic nondisjunction.[1]

Trisomy 18 occurs in about 1 per 8000 newborn babies. (Carey, 2005) The number of total affected pregnancies increases significantly when therapeutic abortions, miscarriages, and

[1] Advanced maternal age, as a criterion for offering prenatal testing to pregnant women, refers to age 35 or older in the United States. As a medical concept, it is becoming less relevant as Non-Invasive Prenatal Screening (NIPS) becomes mainstream. Advancing age is still associated with increased risk for chromosomal anomalies.

stillbirths are included. Historically, Trisomy 18 has been treated as a lethal fetal or neonatal diagnosis. (Jones & Smith, 2006) Families were counseled that most babies died within hours or days, typically from spontaneous respiratory failure and/or cardiac arrest or morbidity related to major birth defects. Pregnancy termination was offered after a prenatal diagnosis (where and when legal and available), and family counseling focused on the high rate of stillbirth and neonatal demise. Management of live-born babies with Trisomy 18 was non-intensive and focused on comfort-care measures. (Jones & Smith, 2006) Intensive measures such as respiratory support/intubation, CPR, and surgery were not performed. The rationale behind this approach was based on the limited survival of babies with Trisomy 18 along with the likely suffering caused by these intensive interventions (as opposed to comfort-care). The severe intellectual and physical disability associated with the Trisomy 18 also likely contributed to the practice of non-intensive intervention. Thus, management of babies with Trisomy 18 was straightforward for many decades. Concomitantly, education of physicians, nurses and other healthcare providers regarding Trisomy 18 was similarly straightforward during the same time period.

Within the last decade several phenomena occurred that dramatically changed the landscape of the clinical management of babies with Trisomy 18. Reports of neonatologists in the United States "intensively managing"[2] babies with Trisomy 18—i.e., providing more than comfort care—began to emerge. (Graham et al, 2004) This practice appeared to be motivated primarily by parental wishes and respect for "parental autonomy". (McGraw & Perlman, 2007) Highlighting this change, the American Heart Association neonatal resuscitation guidelines omitted Trisomy 18 from the list of conditions for which CPR is routinely withheld. (American

[2] Intensive management refers to neonatal resuscitation, cardio-respiratory support including intubation, management in the neonatal ICU, and surgical procedures.

Heart Association, 2006) The specific reason for the AHA guideline change has not been made public.

In the spring of 2012, Trisomy 18 gained national recognition through an unusual avenue, the United States Republican Primary Presidential Campaign. One of the Republican Candidates, Rick Santorum, was found to have a two-year-old daughter with Trisomy 18. (New York Times, 2012) This daughter, Isabella, developed life-threatening pneumonia during the campaign that required her father's absence from his campaign. Mr. Santorum and his family spoke openly about their daughter and her condition, specifically, about their choices regarding her care. Isabella, as it turned out, had received intensive medical management since birth.. The Santorums claimed that their daughter deserved what any other child deserved despite her handicaps; their religious faith strongly guided their decision making. Following this publicity, American families became more aware of an alternative approach to the care of their babies with Trisomy 18: "intensive management". In addition, websites featuring live-born babies and even children with Trisomy 18 became abundant. One such website is for the Trisomy 18 Foundation (www.trisomy 18.org). Thus, the Pandora's Box of intensive management of babies with Trisomy 18 was opened. The medical and ethical landscapes changed dramatically.

At the same time, hospitals in Japan also began "intensively" managing babies with Trisomy 18. (Kosho, 2008) Japan has a national health service, and tertiary care is centralized. With time, the policy of active management became nation-wide. The extent of the policy was ground-breaking, allowing for consistent intensive management of babies with Trisomy 18, the most extreme of which was cardiac surgery. Japan quickly became the primary source of scientific publications of clinical outcomes of intensive management including cardiac surgery. The motivation to pursue intensive management of babies with Trisomy 18 seemed to reflect a

desire on behalf of neonatologists to support parental desires for more intensive management, as well as the funding available through the Japanese National Health Insurance (which covers all costs related to the care of severely disabled children). (Dr. Kosho, personal communication, 11/08/2013) There was also a general trend in attitudes of Japanese neonatologists that extending life, even if only life, was a positive outcome for babies with Trisomy 18. Furthermore, although congenital heart defects were considered not to be the primary cause of death in babies with Trisomy 18, Japanese physicians began to challenge this fact and argue that cardiac surgery may prolong survival.

Japan has moved from a non-intervention approach to a consistent, national intensive approach for babies with Trisomy 18. The United States is in flux, with some parents and organizations pushing for more intensive management. Why is this change, from non-intervention to intensive management, problematic? What lessons can we learn from Japan's experience? Respect for parental autonomy would appear to be ethically straight-forward. Patient autonomy has been a leading ethical principle for decades. (Beauchamp & Childress, 2012) Some parents have expressed a desire to have their babies with Trisomy 18 live for as long as possible. How can this be considered wrong as a matter of professional or institutional policy? Developing an ethical approach to how to care for severely disabled infants is much more complex than considering it to be solely an issue about respecting parental decisional autonomy. It has been well-established that decision-making on behalf of incompetent persons should go well beyond the wishes of the patient's family or guardians. This applies to infants and children as well.

In the context of care for persons who have never been competent, such as newborns and infants, the use of the "Best-Interest Standard" or BIS is well-accepted and recommended for

clinical decision-making.[3] (Kopelman, 2007) Loretta Kopelman provides a clear and comprehensive explanation of the BIS: "Decision-makers should use the best available information to assess the incompetent person's immediate and long-term interests and set as their prima facie duty that option that maximizes the person's overall or long term benefits and minimizes burden". (p.188) The BIS can be utilized when there are competing interests in the care of a patient who cannot advocate for him/herself and particularly when the clinical management is controversial. Originally employed to assist with decision-making for incompetent adults who had not expressed their wishes in an advance directive, it has been applied to babies with severe genetic disorders such as Trisomy 18. In terms of Trisomy 18, the BIS functions to ensure a strict "child-centered stance in all treatment decisions". (McGraw & Perlman, 2007, p.1106)

Criticisms of the BIS include that is subjective and difficult to apply. (Kopelman, 2007) How does one objectively weigh the benefit of prolonged survival against the burden of continued suffering? One can easily see how attempting to use the BIS in the context of a baby with Trisomy 18 could be mistaken for raising questions about the value of the life, such as "is the life of a baby with Trisomy 18 worth prolonging?"[4] rather than focusing on the baby's own experience of prolonged life. Therefore, it is critical to uphold a child-centered stance where all childrens' lives are considered of equal value and then apply the medical evidence to determine the appropriate risk/benefit ratio of a particular treatment for that particular child.

[3] The Best-Interest Standard has been supported by the President's Council on Bioethics, 2005, the United Nations, and the Institute of Medicine.

[4] Dominic Wilkinson, disability rights advocate, takes up this question and others in his essay, "Is it in the Best Interest of an Intellectually Disabled Infant to Die?" (2005).

Most practitioners agree that the clinical management for most conditions should be relatively uniform[5]. The fact that there are now vastly different and rapidly changing approaches to the clinical management of Trisomy 18 is a red flag indicating potentially problematic care. Consideration of the appropriate standard of care for Trisomy 18 has gained a new importance in the age of advanced medical technology and intervention.

[5] Conversely, that highly varied management of a particular disease may reflect substandard care.

2.0 PRESENTATION OF THESIS

In this paper, I argue that intensive management does not benefit babies with Trisomy 18 except in prolonging short-term life and affording the perceived benefits associated with this.[6] Furthermore, intensive management of babies with Trisomy 18 does not improve quality of life according to measures such as rates of discharge home alive.[7] Pain and suffering caused by intensive treatment must be carefully weighed against any increase in short-term survival. Finally, I will argue that cardiac surgery is not appropriate in babies with Trisomy 18 given the extreme risk/benefit ratio.[8]

My thesis will rest upon the clear presentation and understanding of the most recent morbidity and mortality statistics concerning Trisomy 18 (Section IV). This will be followed by an examination of the Japanese medical literature on the outcomes of intensive management of babies with Trisomy 18 (Section V). An in-depth ethical analysis will be provided in Section VI with a focus on the Best-Interest Standard, parental autonomy, and the implications for family decision-making. Finally, a strong case for perinatal/neonatal palliative care as the best approach for babies with Trisomy 18 will be made. A consistent, ethically-sound approach to the clinical

[6] Some families consider any extension of life an outright "good" or "benefit".
[7] Quality of life can be a subjective judgment. For example, some families will consider any time alive to be life with some degree of quality. In this paper, the definition of quality of life focuses on more concrete outcomes such as time off a ventilator, time spent at home, limitations of painful procedures and so forth.
[8] Cardiac surgery, as I will demonstrate, is associated with a very significant (approximately 50%) risk of death post-operatively.

management of babies with Trisomy 18 is imperative in the face of changing options for the clinical management of Trisomy 18 in the United States

3.0 WHY TRISOMY 18?

Trisomy 18 represents the second most common autosomal trisomy after Trisomy 21 or Down syndrome. (Niedrist et al, 2006) Therefore, there is a relatively large amount of research and literature published concerning Trisomy 18 from which to draw when compared to other rare genetic diagnoses. Although both Trisomy 21 and Trisomy 18 are associated with abnormalities in multiple organ systems, Trisomy 18 has much higher rates of fetal loss and fatality within the first year of life. (Jones & Smith, 2006) The intellectual and physical disability that is the norm for the few long-term survivors of Trisomy 18 is much more severe than with Trisomy 21. Despite the grim prognosis for Trisomy 18, the outlook is not absolutely lethal. There is a very small but predictable number of long-term survivors with Trisomy 18. There is a spectrum of fetal, neonatal, and even childhood outcomes as well as a broad spectrum of patient, family and medical management decisions concerning the management of Trisomy 18—herein lies the need for ethical analysis specific to this disorder.

4.0 REVIEW OF CURRENT MORBIDITY AND MORTALITY DATA

There are several compelling reasons to determine accurate morbidity and mortality statistics on Trisomy 18. First, outcomes of intensive management cannot be properly assessed without accurate non-intensive figures with which to compare them. Second, accurate morbidity and mortality data are necessary when counseling families so they can make informed decisions. This not only applies to decisions regarding intensive management but also to decisions about prenatal testing, therapeutic abortion, and pregnancy management. The vast majority of cases of Trisomy 18 are detected prenatally either by prenatal screening or fetal ultrasound. The ultrasound detection rate for Trisomy 18 is approximately 80%. (Callen, 2008)

The accuracy of morbidity and mortality statistics relies on several factors. First, these statistics should be derived from both congenital anomaly registrars[9] along with regional cytogenetic laboratories. Data from both of these sources should be the foundation of any analysis that seeks to avoid ascertainment bias.[10] It is important to understand the significance of ascertainment bias because differences in modes of ascertainment will affect the calculated survival rate. (Rasmussen, 2003) The review of maternity, neonatal, and pediatric records may

[9] Anomaly registrars refer to the epidemiological monitoring of the frequency, nature and outcomes of congenital anomalies for a given population by means of national, regional and disease-specific registers of congenital anomalies.

[10] In statistics, ascertainment bias is a bias in which a sample is collected in such a way that some members of the intended population are less likely to be included than others. It results in a biased sample, a non-random sample of a population in which all individuals, or instances, were not equally likely to have been selected.

be helpful in terms of developing morbidity and mortality statistics but should not be the principal source of data for any analysis. Sources with high ascertainment bias, such as support groups or families of survivors should be avoided when attempting to establish precise morbidity and mortality statistics on Trisomy 18 or other rare genetic disorders.[11] All perinatal outcomes should be included in a survival analysis: therapeutic abortion, miscarriage, stillbirth, and live-birth. It may appear counter-intuitive to include therapeutic abortions. However, the exclusion of therapeutic abortions results in over-inflation of the total fetal loss rate; it is important to take into account that some of those pregnancies that are in fact electively terminated would have resulted in miscarriage, while others would have resulted in live-born babies**.** (Morris & Savva, 2008) Overall, sophisticated statistical methods are necessary to accurately estimate perinatal survival outcomes. The morbidity and mortality data on Trisomy 18 from the current medical literature will be reviewed in the following paragraphs.

A study from Switzerland published in *The American Journal of Medical Genetics* in 2006 represents the most comprehensive Trisomy 18 publication to date in the medical literature. (Niedrist et al, 2008) It is one of the largest studies examining survival data for Trisomy 18. Records were collected from two major cytogenetic laboratories in northeastern Switzerland from 1964 to 2003. In addition, physicians and/or families were also contacted for further information. From these sources, 352 cases of Trisomy 18 were identified during that time period. Of these 352 cases, 161 babies or 47% were born alive (after miscarriages, therapeutic abortions, and stillbirths were taken into consideration). Of the live-born, 32% died within 24 hours, 40% died within the first week, and 22% of the babies died within the first month. Ten

[11] Use of family of survivors with Trisomy 18 and Trisomy 18 support groups as data sources will provide an overly optimistic prognostic picture due to the problem of ascertainment bias. Although familial/support group testimonies represent an important source of information about the experience of having a baby with Trisomy 18, they are not appropriate sources for rigorous statistical analysis.

babies (of the original 352) with Trisomy 18 were alive at one year of age (approximately 3%). Of live-born babies specifically, 6% survived to one year of age (10 of 161 live-born cases). Two children survived longer than 10 years, the oldest child was still living at 15 years of age. This represented approximately 0.5% of the total sample.

Overall, the survival data from this study showed that the greatest predictors for long-term survival were term gestational age at birth (greater than 38 weeks gestation) and female sex; both were statistically significant. The median survival time was 5 days for females but less than 24 hours for males. The median survival for Trisomy 18 neonates was 4 days (males and females together). The authors compared their results to six other published studies from 1964 to 2002, and their Trisomy 18 survival statistics were comparable. This comparability is a salient observation because it shows that the overall postnatal survival of babies with Trisomy 18 had not significantly changed over time. The authors concluded that medical interventions such as neonatal resuscitation have not influenced long-term survival in Trisomy 18. Furthermore, the authors observed that live-born babies with Trisomy 18 who had congenital heart defects, such as ventricular septal defects, did not show a different survival curve from those without congenital heart defects. This would further imply that intensive cardiac intervention is not likely to alter survival.[12]

A paper published in 2003 in *Prenatal Diagnosis* also reported statistically acceptable Trisomy 18 survival figures with a focus on prenatal outcomes. (Parker et al, 2003)[13] The data was obtained from the Trent Congenital Anomalies Register in the United Kingdom along with

[12] This makes sense when one considers that the underlying problem is a systemic chromosomal abnormality rather than an isolated congenital malformation such as a cardiac defect. The chromosomal aneuploidy is present in every cell of tissue throughout the entire body.

[13] The inclusion of prenatal outcomes is important because most pregnancies with Trisomy 18 are either terminated or end in miscarriage/stillbirth. This has implications for patient and family counseling.

three regional cytogenetic laboratories. Maternity, neonatal, and pediatric records were also reviewed for further information. Data collection took place from 1997 to 2001. There were a total of 259,009 live-births and stillbirths in the Trent region of the UK. The regional cytogenetic laboratory confirmed 88 cases of Trisomy 18, correlating to a calculated birth incidence of approximately 1 in 2943[14]. Sixty-four percent of cases were identified during an abnormal second trimester ultrasound, 16% during amniocentesis or chorionic villus sampling (CVS), and the remainder due to advanced maternal age (AMA). Seventy-five percent of patients chose pregnancy termination with 62% terminating between 14 and 26 weeks gestation. Of the continuing pregnancies, 7% ended in miscarriage, 7% were stillborn, and 11% were live-born. The median survival was five days with a range of six hours to 254 days. The authors noted that although most patients requested pregnancy termination following a prenatal diagnosis of Trisomy 18, a significant minority continued their pregnancies and delivered live-born babies (10 of 88 or 11%).

A third study from the United Kingdom investigated the risk of pregnancy loss after a prenatal diagnosis of Trisomy 18 (Morris & Savva, 2008). Information from five regional congenital anomaly registers in the United Kingdom was obtained from the years 1989 to 2003. Pregnancy loss included spontaneous abortion, stillbirth, or therapeutic abortion.[15] The authors emphasized that Kaplan-Meier survival analysis[16] had been previously established as the best way to directly estimate fetal loss rate and this was the statistical method that they used. There

[14] 95% Confidence Interval of 1 in 2383 to 1 in 3670.

[15] As stated previously, including therapeutic abortions in the category of "pregnancy loss" may seem inappropriate but is necessary from a statistical methodology stand-point. Given the high rate of pregnancy termination for Trisomy 18, by not including these figures in the calculated fetal loss rate, one would over-inflate the rates of miscarriage/stillbirth, as some of those pregnancies electively terminated would have resulted in miscarriage, stillbirth, or live-born delivery of a child. This is a widely accepted statistical methodology. See Morris & Savva, 2008 for further details.

[16]The Kaplan–Meier estimator, also known as the product limit estimator, is an estimator for estimating the survival function from lifetime data. In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment

were 475 fetuses with Trisomy 18 identified via prenatal diagnosis. There were 24 live births, 56 miscarriages/stillbirths, and 395 therapeutic abortions. Overall, eighty-three percent of fetuses with Trisomy 18 underwent therapeutic abortion. According to the survival analysis, for those fetuses with Trisomy 18 diagnosed at 12 weeks, approximately 72% (ranging 61 to 81%) would not survive to term and of those diagnosed at 18 weeks, approximately 65% (ranging 57-79%) would not survive to term. The authors concluded that their study demonstrated the importance of congenital anomaly registers in the investigation of fetal loss among rare diagnoses such as Trisomy 18, as well as the use of Kaplan-Meier survival analysis as the most accurate way to determine fetal loss rate in a given population. The authors further commented: "It is essential that women who are found to be carrying a fetus with Trisomy 18… are given reliable prognoses for their pregnancy, and that accurate epidemiological information is available to meet the demand from Healthcare Services and policymakers". (p.831)

The National Center on Birth Defects and Developmental Disabilities in Atlanta, Georgia collected data on the prevalence and characteristics of Trisomy 18 from 1994 to 2003 through the Metropolitan Atlanta Congenital Defects Program, a population-based surveillance system. (Crider, 2008) These statistics were published in the *American Journal of Medical Genetics Part A* in 2008. The authors found that the prevalence of Trisomy 18 in their population depended upon the maternal age distribution of the population, the frequency of spontaneous fetal death, the rates of prenatal diagnosis, the rates of therapeutic abortions, and the ability to ascertain these events. The overall live-birth prevalence of Trisomy 18 was 1.16 per 10,000, and approximately 4 cases per 10,000 when live-births, stillbirths, and therapeutic abortions were included. The median gestational age for live-birth for Trisomy 18 was 38 weeks. The sex ratio was again skewed towards females with 60.4% live-born babies being female and 39.6% being male.

Stillbirth occurred throughout the second and third trimester with a trend towards 34 to 37 weeks gestation. Prenatal genetic testing occurred in 76.1% of cases of Trisomy 18; 59.7% of these ended in therapeutic abortion in this study (a lower percentage than in others studies). Interestingly, therapeutic abortion rates for Trisomy 18 were lower among Hispanic and non-Hispanic blacks compared to non-Hispanic whites within Metropolitan Atlanta. Overall, the authors concluded that prenatal diagnosis data was "…critical for accurate surveillance and population-based analyses of Trisomy 18 because of the frequency of spontaneous fetal death and elective termination after prenatal diagnosis associated with these serious conditions". (p.825)

In addition to survival statistics, it is important to be able to provide patients and families with accurate data regarding the congenital malformations that complicate Trisomy 18. This particular issue was investigated in the *American Journal of Medical Genetics Part A* in 2006. (Pont & Robbins, 2006) The authors argued that there was insufficient data on the "prevalence of important co-occurring birth defects among infants with Trisomy 18". The authors obtained information from the Healthcare Cost and Utilization Project's Kids' Inpatient Database and from the Nationwide Inpatient Sample, two large current and nationally representative databases from the years 1997 to 2000. They found that 45% of newborns with Trisomy 18 had congenital heart defects: 31.2% with ventricular septal defects (VSD), 11.5% with atrial septal defects (ASD) and 4.3% with tetralogy of fallot (TOF). Of other major congenital malformations, the most common was trachea-esophageal fistula (TEF), which occurred in 7.1% of newborns. This malformation was dramatically overrepresented, appearing 300 times higher in Trisomy 18 babies than in the general population. Cleft lips, diaphragmatic hernias and neural tube defects

were also consistently seen and found at or more than 100 times greater than in the general population.

The authors also showed that approximately 30% of the live-born infants with Trisomy 18 were discharged with homecare. The remaining infants were discharged to long-term skilled nursing facilities. It was noted that infants with Trisomy 18 that had gastrointestinal malformations were more likely to die in the hospital than those who did not have these malformations (73.3 vs. 56.6%), as did infants with abdominal wall defects (71.8 vs. 56.5%). For those infants who died while hospitalized, the average length of stay was 6.7 days. The authors concluded that the statistics were important in terms of anticipating the complex medical needs as well as the home needs of infants with Trisomy 18: "It must be realized that medical placement must be identified for a substantial number of these medically complex babies. The overall goal should be to allow patients and families to make more informed healthcare decisions about their babies with trisomy 18". (p.1755)

The need for precise perinatal survival information regarding Trisomy 18 has been recognized in Japan. It also has been recognized in Japan that the prognosis of Trisomy 18 is not invariably lethal. Long-term Japanese Trisomy 18 survivors have been reported. Therefore, in 2007 authors Imataka et al. published their survival statistics in the *Journal of Genetic Counseling*. The authors collected statistics on perinatal mortality and Trisomy 18 from seven institutions in Japan by way of a retrospective literature search. Their data pool included a total of 179 cases of Trisomy 18. They found that the mortality rates within 24 hours were 14.8%, at seven days 31%, and at 28 days 56%. Approximately 9% of live-born patients were alive at one year of life. The authors concluded that their data was similar to that previously reported in the

literature. Despite the potential for ascertainment bias, these results are consistent with the other literature reviewed previously.

The morbidity and mortality statistics regarding Trisomy 18 can be summarized as follows:

1. Total prevalence: approximately 1 in 3000
2. Live-birth prevalence: approximately 1 in 10,000
3. Percentage ending in therapeutic abortion: 75-85%
4. Of pregnancies continuing, percentage ending in miscarriage or stillbirth: approximately 50%
5. Of total pregnancies, percentage resulting in live-birth: approximately 50%
6. Median survival: 4 days
7. **Of live-births**, percentage surviving one year: approximately 5%
8. **Of live-births**, percentage surviving over 10 years: approximately 3%
9. **Of total pregnancies**, percentage surviving one year: 3%
10. **Of total pregnancies**, percentage surviving 10 years: 0.5%

Greater than 90% of live-born babies with Trisomy 18 die within the first year of life. Therefore, long-term survival is rare and has not appeared to change over time. Predictors of longer survival include female sex and term gestational age at birth. The presence of a congenital heart defect did not appear to affect length of survival. These statistics represent the most accurate clinical picture of outcomes for babies with Trisomy 18. One may argue that presentation of these "cold, hard facts" to families is cruel or overly pessimistic. However, it is essential that families receive the most accurate information concerning their baby's diagnosis in order to

make well-informed decisions about medical care. It is also essential for assisting families with long-term planning.

5.0 THE JAPANESE EXPERIENCE

Although there is growing interest in the intensive treatment of babies with Trisomy 18 in the United States, limited intervention remains the standard practice. In Japan, however, the management of Trisomy 18 is significantly different. Intensive clinical management is the standard of care. (Kosho, 2006) This approach appears to be based upon multiple factors. First, there is generous national health insurance that covers the costs of the care and treatment of sick babies including those with genetic disorders. (Kosho, 2006, p.943) Second, there is increasing parental demand to prolong life despite severe, terminal disease. (Sakakihara et al, 2000) Finally, there is widespread support on behalf of Japanese physicians including neonatologists, pediatricians, and specialists to both uphold parental wishes as well as to extend life using intensive, highly technology-dependent means.[18] (Kosho, 2006, p.943) The actual length of life, even if supported by full cardio-respiratory endeavors, is considered a "good" by Japanese neonatologists. (Dr. Kosho, personal communication, 11-08-2013) The greater Japanese medical community equate quality of life with absolute length of life. (Dr. Kosho, personal communication, 11-08-2013) Within the last decade, there have been multiple medical publications from Japanese clinicians addressing both the practice and outcomes of intensive management of severely ill babies, including those with Trisomy 18. These reports allow for an

[18] Dr. Kosho has written extensively about the Japanese approach and the origins of the intensive approach in his 2006 Commentary.

in-depth analysis of the Japanese intensive clinical approach to babies with Trisomy 18 including cardiac surgery. The most pertinent of these studies will be reviewed in the following section.

In 2006, Kosho et al[19] published their detailed clinical experience with 24 patients with Trisomy 18 who received intensive treatment at Nagano Children's Hospital in Nagano, Japan. Dr. Kosho and associates argued that the policy of nonintervention for neonates with Trisomy 18 should be regarded as controversial. They questioned the appropriateness of the withdrawal or non-initiation of intensive treatment. In their neonatal intensive care unit, neonates with Trisomy 18 were managed under what they referred to as "the principle of providing intensive treatment"[20] (p.938). When deemed medically necessary, intensive treatment consisted of cesarean section, neonatal resuscitation, endotracheal intubation, respiratory support, establishment of enteral nutrition, corrective and palliative surgery for gastrointestinal malformations, and pharmacologic treatment for congenital heart defects. Their publication sought to describe the clinical course of Trisomy 18 under this principle as well as their survival statistics.

The twenty-four patients with Trisomy 18 were admitted to Nagano Children's Hospital neonatal intensive care unit from 1994 to 2003. Upon admission, the families of the neonates with Trisomy 18 were counseled about their baby's condition as well as the hospital's policy of providing intensive treatment. The authors stated that the parents could choose to accept or refuse the offer of intensive treatment. Details of the parental counseling and who provided this

[19] Authors' last names are used in this section to help with identifying references with overlapping journals and date of publications.
[20] The terms intensive management and intensive treatment are used interchangeably.

counseling were not provided, and only one family declined complete intensive treatment.[21] In their population, all patients had congenital heart defects and approximately one-third had gastrointestinal malformations (most commonly trachea-esophageal abnormalities). Mechanical ventilation for respiratory failure was performed on 21 patients or 88%. Twenty-nine percent of patients were ultimately extubated, and the median length of ventilation for these patients was 76.5 days. Cardiovascular drugs were used in 22 patients or 92%. Ninety-six percent of patients were diagnosed with "heart failure". All patients received parenteral nutritional. Twenty patients had significant thrombocytopenia (abnormally low platelets likely related to severe infection) of which three patients required platelet transfusion. Five patients had seizures requiring treatment with medication. Only 21% of patients were discharged home. The median hospital stay for these patients was 137 days. The median survival length for all patients was 152.5 days.

The authors found that the most frequent "underlying" cause of death was heart failure related to congenital heart defects, 22 patients or 96%. The second most common cause of death was pulmonary hypertension, seen in 18 patients or 78%. Finally, respiratory failure accounted for the third most common cause of death, 14 patients or 61%. The authors reported the most "frequent final mode of death" was sudden cardiac or cardiopulmonary arrest. Other causes were pneumonia, and multi-organ failure. The authors distinguished "underlying causes of death" from "final mode of death" because "most patients have complex underlying factors that were interrelated" regarding their cause of death.[22] (Kosho et al., p. 942)

[21] This patient did not undergo surgical correction of a gastrointestinal malformation but did receive mechanical ventilation, intravenous hyperalimentation, antibiotics, and blood transfusion. Interestingly, this patient was considered to be "conservatively" managed.

[22] This is not an unprecedented finding. It is well accepted that morbidity and ultimate mortality related to a chromosomal disorder, such as Trisomy 18, is a result of the underlying severe genetic abnormality.

In terms of prognosis, as stated previously, the median length of survival was 152.5 days (ranging from 0 to 1786 days).[23] Only five patients or 21% were discharged to home alive[24]. One of these patients remained alive at the time of data collection; surviving for 999 days, however, *only 30 days were spent outside of the hospital*. Interestingly, this patient did not require intubation or mechanical ventilation, surgery for gastrointestinal or other malformations, or cardiovascular support (the patient had a small heart defect – a patent ductus arteriosis that closed on its own). The remaining four who were discharged home alive died anywhere from 58 to 947 days later. There was no comparison group that received conservative treatment.

The authors stated that the causes of death in Trisomy 18 were originally thought to be related to central apnea and the withdrawal of treatment. In addition, prior studies had shown that the presence of a congenital heart defect did not appear to affect the survival of neonates with trisomy 18. The authors challenge these findings based on the results of this study. They concluded:

> In our observation under intensive treatment the major underlying factors associated with death were heart failure and pulmonary hypertension resulting from congenital heart defects, frequently accompanied by respiratory failure. The final major modes of death were sudden cardiac or cardiopulmonary arrest and possible progressive pulmonary hypertension-related events. (p.943)

[23] This can be compared to the median survival of 4 days (ranging from 0 to 254 days) shown in Section IV.
[24] Discharge days alive will be used as a quality of life measure in this paper. Survival should not only be measured in absolute number of days but also whether those days were spent within a hospital setting or if the patient was discharged home.

The authors go on to argue that medical treatments and respiratory support are effective at prolonging survival in neonates with Trisomy 18. They also raise the question of whether cardiac surgery may also be effective but admit that they could not assess this in their study.

Limitations of this study are many. Most importantly, there is no "conservative treatment" comparison group with which to compare outcomes. Furthermore, the sample size was very small.[25] Despite these limitations, this study does provide some evidence that the Japanese approach of intensive management may prolong short-term life. However, it is important to note that despite this possible prolongation of life, this extension was not associated with increased out-of-hospital survival. Furthermore, the ultimate cause of death appeared to be different in this patient population[26], likely a result of intensive therapy itself. By prolonging life with intensive treatment, the nature of death changed but not the underlying cause of disease – the trisomic condition. Intervention only prolonged short-term life and was not curative. The mode of death is important to highlight as well. Rather than dying of central apnea, patients died of conditions such as sepsis, pulmonary hemorrhage, or cardiac or respiratory arrest after resuscitation. This raises significant concerns about the pain and suffering associated with intensive management. Finally, long-term survivors, such as the patient who was still alive at the time of data collection, may have had similar outcomes regardless of intensive treatment.

It is well established that 80-100% of babies with Trisomy 18 have congenital heart defects (Saunders et al, 2002). The Koshko et al. publication raised the question whether intensive cardiac management improved survival in patients with Trisomy 18 and congenital heart defects. Intensive cardiac management specifically refers to cardiac pharmacologic

[25] Sample size will always be an issue when investigating a rare disorder like Trisomy 18. Therefore, this will be a limitation of any study.
[26] Cause of death in babies with Trisomy 18 without intensive treatment is typically related to central apnea, when babies stop breathing on their own.

therapy, palliative cardiac surgery, and corrective open heart surgery (also known as intra-cardiac repair) for congenital heart defects. It is the standard of care for babies who have overall good prognoses. Intensive cardiac management had been previously considered inappropriate for babies with Trisomy 18 due to the extremely poor prognosis. (Saunders et al, 2002)

In 2008, Kaneko et al. from the Departments of Neonatology, Pediatrics, and Cardiovascular Surgery from the Japanese Red Cross Medical Center sought to establish the impact of intensive cardiac management on babies with trisomies (specifically Trisomy 18 and Trisomy 13). This was a retrospective analysis of 31 neonates who were transferred to the Japanese Red Cross Medical Center within six hours of birth for different levels of neonatal management. The institutional management changed over time[27]; therefore, there were three groups for analysis:

A. January 2000- July 2002: Intensive cardiac management withheld
B. August 2002 – October 2003: Cardiac pharmacologic intervention only
C. November 2003- December 2005: All intensive cardiac management provided including cardiac surgery (palliative and corrective)

Statistical analysis included survival curves using the Kaplan-Meier methodology, as well as comparison via the log-rank test[28] and Cox proportional hazard models[29].

[27] According to Kaneko et al. 2008, prior to August 2002, general supportive therapy was used but not intubation/mechanical ventilation or any intensive cardiac treatment. Institutional policy changed in August 2002 where pharmacologic cardiac intervention was approved for trisomic patients. Cardiac pharmacologic therapies include closure of patent ductus arteriosis with mefenamic acid and or indomethacin and PGE1 for ductal constriction. Frequent echocardiograms were used to monitoring of these medications. The JRCMC policy changed again in November 2003 in that cardiac surgery was allowed for trisomic patients. These policies reflect the growing demand for intensive management of babies with Trisomy 18 by parents and physicians.
[28] The log-rank test is a hypothesis test to compare the survival distributions of two samples.
[29] Cox proportional hazards models are a class of survival models in statistics. Survival models relate the time that passes before some event occurs to one or more covariates that may be associated with that quantity of time.

The authors reported that 30 of 31 patients had congenital heart defects. Eighteen of the thirty were categorized into Groups B & C. The median survival in Group A was seven days; all patients in this group died within 96 days. The median survival in Group B was twenty-three days; all patients in this group died within 367 days. In Group C, four of the nine in this group were alive at the time of data acquisition. Survival ranged from 3 to 834 days (median survival in Group C could not be accurately calculated because of the ongoing survival of half of the group). It is important to note that this study included neonates with either Trisomy 18 or Trisomy 13. Only two of the seven babies with Trisomy 18 in Group C were alive at the time of data collection (versus all of the babies with Trisomy 13).

Kaplan-Meier survival curve estimates showed a statistical difference between both Groups A & C and Groups B & C (P= 0.003 and P=0.01, respectively). There was not a statistical difference in survival between Groups A & B (P=0.13). Cox proportional hazard analysis showed that both being in Group C and having a high 5-minute Apgar score were significantly related to longer survival. When combined, Groups A & B had a median survival of 14.5 days and a 4.5% survival rate at one year of life. In comparison, Group C had a calculated median survival of 243 days and a 44% survival rate at one year of life. Overall, the authors concluded that intensive cardiac management may improve survival in babies with either Trisomy 18 or Trisomy 13 (when compared to population-based studies, as reviewed in Section III of this paper). In addition, cardiac surgery appeared to have the greatest impact on extending overall survival in this patient population.

Although this study demonstrated a significant improvement in survival over time with intensive cardiac management (including cardiac surgery), there were significant limitations of this study that limit its generalizability. First, the study grouped Trisomy 18 and Trisomy 13

patients together; however, Trisomy 13 babies tended to survive longer than babies with Trisomy 18 (thus not all trisomies should be approached the same way clinically). Second, this study had an extremely small sample size. Third, the authors did not distinguish between palliative versus corrective cardiac surgery in Group C. The details of each cardiac surgery were not made explicitly clear, which further compromised the study's integrity and applicability. Finally, the authors did not address rates of discharge to home alive, out of hospital days, or other quality of life measures. Therefore, the survival rates can only be assumed to refer to survival. Because of these limitations, this study alone should not be used to justify intensive cardiac management in patients with Trisomy 18. However, this study provided enough information to encourage researchers to look more closely at the question of cardiac surgery in babies with Trisomy 18.

A study published in 2011 in the American Journal of Medical Genetics by Maeda et al. collected data on the outcomes of babies with Trisomy 18 with congenital heart disease via a nationwide network: The Japanese Society of Pediatric Cardiology and Cardiac Surgery. Between July 2005 and March 2008, questionnaires were sent to all affiliated hospitals in the network, and data on 134 patients with Trisomy 18 were collected. It was found that 94% of patients had congenital heart disease (126 of 134), and cardiac surgery was performed in 25% (32 of 126). Twenty-three patients underwent palliative surgery, five underwent corrective surgery, and two underwent palliative surgery followed by corrective surgery (also known as two-stage surgery). The authors reported that the survival estimates calculated by Kaplan-Meier estimates were statistically greater for those operated on than those not operated on (statistically significant at $P<0.01$). Nevertheless, this study suffered from significant limitations similar to the Kaneko et al. 2008 study reviewed previously. **What is especially notable about this study**

is that almost half of patients who underwent[30] cardiac surgery died suddenly post-operatively. The authors report: "It is a remarkable finding that 6 of 15 patients died suddenly after successful cardiac surgery". (Maeda et al., p.2643)

The authors did not distinguish between palliative and corrective surgery in reaching this conclusion. Therefore, although the Kaplan-Meier survival showed increased survival with cardiac surgery, there appears to be an increased risk for sudden cardiac death in these patients. The authors ultimately conclude:

The indications of cardiac surgery for these patients need to be considered electively from the individual patient's status along with continuous support for decision-making by the parents. *It is still not clear whether cardiac surgery improves long-term prognosis of patients with Trisomy 18…* (p.2646) A subsequent publication by Kaneko et al. specifically examined Trisomy 18 patient data from 2003 until 2008 with regard to cardiac surgery[31]. The decision to proceed with cardiac surgery in this patient population was "based on physician judgment and parental autonomy". (Kaneko et al., p.1374) Parents were counseled on their options and allowed to opt-out of cardiac surgery. Details of the family counseling were provided in the previously reviewed Kaneko et al. publication.

This study identified seventeen patients diagnosed with Trisomy 18 who underwent cardiac surgery for symptomatic congenital heart disease. Cardiac surgery was divided into palliative surgery versus corrective surgery. In their retrospective analysis, they identified fourteen patients who underwent palliative cardiac surgery, specifically, pulmonary artery banding. The other three patients underwent corrective surgery including the repair of ventricular

[30] Corrective or intra-cardiac surgery refers to open-heart surgery requiring cardio-pulmonary bypass.
[31] This second study was published 2009, about two years after the first Kaneko et al. study. Both studies were from the Japanese Red Cross Medical Center. It is not clear whether cases were duplicated between the studies.

septal defects as well as closure of patent ductus arteriosus. The median survival time was 324 days with a range of 12 to 1384 days for all patients. They found that female gender and palliative surgery were significantly associated with longer postoperative survival. The in-hospital mortality was 18% and the median postoperative survival was 179 days. **Five out of the six patients who underwent corrective surgery died from sudden death, sepsis, or pneumonia**. Only one patient survived corrective surgery, and this patient first underwent palliative surgery followed by second stage intra-cardiac repair of a ventricular septal defect. These two surgeries occurred at 194 days in 402 days respectively. Despite these findings, the Kaplan-Meier survival curve for operated and non-operated patients with Trisomy 18 showed significantly higher survival estimates for the cardiac surgery group ($P<0.01$).

The most frequent causes of death in the patients who underwent cardiac surgery were pneumonia and sepsis, occurring in approximately 44% of patients. Respiratory failure and heart failure accounted for several of the other deaths. Six patients were alive at the time of data collection. The authors concluded that their approach to congenital heart disease with cardiac surgery was effective at preventing congenital heart defect-related deaths. The authors reported that "82% of the patients undergoing heart surgery were discharged home with alleviated cardiac symptoms". (Kaneko et al. 2009, p.734) This is a highly questionable conclusion given the study results. The authors acknowledged that the surgery group was small, likely had simple heart defects, and likely had fewer extra-cardiac issues. Furthermore, the overall severity of each patient was not assessed. The authors concluded that initial palliative surgery results in longer survival than corrective surgery. Finally, only overall survival was analyzed, not rates of discharge home alive or other quality of life measures. The most important result from this study

was that corrective surgery was associated with an increased risk of death, thus, seriously questioning the benefit this intervention has for babies with Trisomy 18.

In a paper published in *Cardiology in the Young* in 2011, Muneuchi et al. also investigated the outcomes of cardiac surgery in patients with Trisomy 18 (data from Kyushu Koseinenkin Hospital of Japan). Their goals were to determine whether cardiac surgery reduced the morbidity and mortality of patients with Trisomy 18 and to "clarify an efficacy of cardiac surgery in trisomy 18 patients". The authors retrospectively analyzed clinical data from 34 patients with Trisomy 18 and congenital heart disease from 1985 to 2009. Data collection included preoperative assisted ventilation, palliative versus corrective cardiac surgery, time to discharge alive, weight at the time of surgery, respiratory stability, and surgeon's preference as to whether palliative or primary corrective surgery should be performed. They compared patients who underwent cardiac surgery to those who received "conservative management" (the detail of conservative management were not provided). As in the previous publication, patients were further sub-divided into palliative versus corrective surgical repair. The surgeons considered intervention when infants with Trisomy 18 reached 14 days of age and their cardiac symptomatology prevented discharged from the hospital. In addition, the authors commented that the parents "preferred aggressive treatment" but "conservative management" was also provided for those who opted to forgo cardiac surgery.

The authors identified nine patients who underwent cardiac surgery: three underwent corrective surgery and six underwent palliative surgery (pulmonary artery banding and ligation of the ductus arteriosis). Of these nine patients, two died in the hospital, two died at home after discharge, and five were discharged alive with home-care. In comparison, those patients treated conservatively experienced twenty in-hospital deaths and one death after discharge. When

comparing the two groups using Kaplan-Meier methodology, the authors concluded that there was a statistically significant difference in survival rates between the two groups (cardiac repair: 25% alive at 12 months; conservative: 9% alive at 12 months; P=0.002). Interestingly, the authors included two patients in the conservative group who were waiting for their cardiac repair.[32] If these patients were sorted to the cardiac repair group, the survival differences would no longer be statistically significant (P=0.112). Furthermore, Cox proportional hazard regression analysis showed that both cardiac surgery and pre-operative mechanical ventilation were statistically significant independent hazardous variables for survival. **In other words, both cardiac surgery and mechanical ventilation were associated with poorer survival according to this more appropriate statistical analysis.**

The authors also compared the rates of discharge home alive between the two groups and found that the difference was *not statistically significant* (P=0.80)[33]. Also of note, the median in-hospital length of stay was longer for the cardiac repair group when compared to the conservative group (5 months for cardiac repair; 3 months for conservative; P=0.009). Patient number 1, who underwent palliative cardiac surgery (pulmonary artery banding), had the longest in-hospital stay: 1996 days. It was noted that this patient (plus two others who underwent cardiac repair) stayed in the hospital because "their parents refused to raise them". (p.212)

Despite these findings, the authors concluded that cardiac surgery may increase the rate of survival in patients with Trisomy 18 although *it did not improve the chance of being discharged home alive*. The authors further wrote: "The indication of cardiac surgery should be carefully individualized to improve the quality of life in trisomy 18 individuals and concerned surrounding people".(p.215) This is an interesting conclusion given that three families whose

[32] This is inappropriate from a statistical standpoint.
[33] An important quality of life measure as is in-hospital length of stay.

babies underwent cardiac surgery "refused to raise them" during their prolonged hospital stays. (p.212) The authors acknowledged that although the patients with Trisomy 18 may have survived longer under intensive treatment, they underwent many medical procedures and had long hospital stays. It is important to note that these hospital stays could have been discharges home with palliative care. It is also important to re-emphasize that, when patients were properly assorted, the statistical difference in survival found by Kaplan-Meier analysis between the groups was no longer present.

At best, there is evidence from the review of the Japanese studies that intensive management along with intensive cardiac management (without cardiac surgery) prolongs short-term survival. However, there is no evidence that intensive cardiac management increases rates of discharge home alive or other quality of life measures[34]. Furthermore, there is insufficient evidence to conclude that cardiac surgery increases survival in any manner (short-term or long-term). Finally, corrective cardiac surgery is associated with an increased risk of sudden cardiac death post-operatively in babies with Trisomy 18. There are additional case reports of these types of catastrophic outcomes following cardiac surgery reported in the medical literature. (Paris et al, 1992) It is clear from this review that intensive clinical management of any kind does not alter the natural history of Trisomy 18. Instead, it allows for the emergence of other morbidity that would not have been encountered without intensive efforts. It is important to remember that Trisomy 18 is an incurable disorder despite medicine's most intensive efforts.

[34] Quality of life measures outside those of directly related to the child being alive as discussed in Section I.

To summarize:

1. Intensive management refers to cesarean section, neonatal resuscitation, endotracheal intubation, respiratory support, enteral nutrition, palliative/corrective surgery for GI malformations, & pharmacologic treatment of congenital heart defects
2. Median survival with intensive management – 152.5 days (range 0-1786 days)
3. Intensive management is only associated with increased short-term life
4. Most common causes of death with intensive management:
    a. Cardio-Respiratory Arrest after Resuscitation
    b. Sepsis
    c. Pulmonary Hemorrhage
5. Approximately 50% of patients undergoing cardiac surgery die suddenly immediately post-operatively
6. Patients undergoing cardiac surgery, especially those on mechanical ventilation, have poorest survival

6.0 ETHICAL ANALYSIS

In Section 4.0, a review of the population-based literature showed that the survival rate of babies with Trisomy 18 has not changed significantly over the last several decades. This is remarkable given the dramatic changes that have occurred in medicine and medical technology. Furthermore, other severe genetic syndromes or birth defects, such as cystic fibrosis or hypoplastic left heart syndrome, are associated with significant long-term survival despite their once poor prognoses. (Thompson & Thompson, 2007) Trisomy 18 continues to have an extremely poor prognosis regardless of medical intervention. The consequences of the underlying pathology in Trisomy 18, an extra copy of the eighteenth chromosome in every cell of the body, continue to be catastrophic.

In Section 5.0, a comprehensive review of the Japanese medical literature showed that intensive management of babies with Trisomy 18 led to an increase in short-term survival only, without an accompanying increase in long-term survival or in quality of life (such as discharge home alive days). The same is true with intensive cardiac management without cardiac surgery. The medical literature also demonstrated that cardiac surgery is associated with an unacceptable risk/benefit ratio due to both the significant increased risk of sudden cardiac death post-operatively and lack of increased long-term survival. Furthermore, pain and suffering remained significant concerns with all intensive management.

In total, there is a profound lack of evidence that intensive management results in substantial benefit to a baby with Trisomy 18 except in terms of the short-term prolongation of life. There have always been cases of long-term survivors with Trisomy 18. Long-term survival is not influenced by utilization of life-sustaining treatments. At this point, a return to the "Best-Interest Standard" (BIS) is required for further ethical analysis. To review, the BIS is a well-accepted principle when making clinical decisions for persons who have never been competent and able to express their own preferences, including infants. Loretta Kopelman provides an explanation of the BIS: "Decision-makers should use the best available information to assess the incompetent person's immediate and long-term interests and set as their prima facie duty that option that maximizes the person's overall or long term benefits and minimizes burdens". (p.188) Therefore, the BIS should function to assist families and physicians in making decisions that, Kopelman writes, "reasonable persons of good will would consider acceptable in similar circumstances" (p.187). The BIS has widespread international support that includes the 2005 President's Council on Bioethics, the United Kingdom's Nuffield Council on Bioethics, and the United Nations. The 2005 President's Council on Bioethics asserts:

> Ultimately, caregivers must compare the burdens, consequences, and potential complications *of the treatment itself* against the burdens, consequences, and potential complications of *non-treatment*; and they must compare the likely realities of *life after treatment* against the likely realities of *life without treatment* (p.188)

Relying on the BIS helps to avoid debates about the value of life, utilization of resources, or cost. The focus of the BIS is on the individual's experience of treatment with an emphasis on both the patient (as opposed to the experience of the family or treating physician) and the reality

of the clinical picture as depicted by the best available evidence regarding prognosis. The BIS does not aim to achieve an ideal outcome for a given clinical situation. Instead, the goal of the BIS is to arrive at the best possible option chosen from all available/realistic options. One such option is to limit intensive treatment of babies with Trisomy 18. It can be concluded by employing a BIS that there is no moral obligation to prolong life at all costs, particularly at the cost of experientially burdening the patient. (Kopelman, 2007)

Originally utilized to guide decision-making for incompetent adults who had not expressed their wishes in an advance directive, the BIS has been applied to infants and children. The BIS can be utilized whenever there are competing interests or multiple options regarding the care of a child or infant. In addition, the BIS has been employed to assist with decision-making for neonates born at the threshold of viability, it has been applied to babies with severe genetic disorders such as Trisomy 18. Overall, the BIS functions to ensure a strict "child-centered stance in all treatment decisions". (McGraw & Perlman, 2007, p.1106) In the context of infants with Trisomy 18, the BIS requires an evidence-based evaluation of the outcomes of intensive management.

One outcome that has been established from the literature review is that intensive management of babies with Trisomy (without cardiac surgery) it extends short-term life. There was not evidence for an increased long-term survival, reduced morbidity, improved quality of life, or cure. The same is true for intensive cardiac management without cardiac surgery. Cardiac surgery was associated with increased risk of sudden death and, therefore, harm. Therefore, according to the BIS, intensive management, including intensive cardiac management, should only be performed in babies with Trisomy 18 if the indication is extension of short-term survival (as is the case in Japan). This should be made explicitly clear to families who are contemplating intensive

management for their baby. After appropriate counseling, physicians may choose to pursue intensive management if it is requested by the parents out of respect for parental autonomy, but need not offer such management as part of standard of care. Assistance from a hospital ethics committee or ethical consultant may be helpful in this area of decision-making. It should be made clear that intensive management of babies with Trisomy 18 should not be performed for other indications such as to improve standard quality of life measures or to achieve long term survival. Furthermore, the benefit of increase short-term survival needs to be carefully balanced against the high potential to increase pain and suffering. Finally, cardiac surgery is associated with an unacceptably high risk to benefit ratio and *should not be performed for babies with Trisomy 18.*

Much of the ethical debate over the clinical management of babies with Trisomy 18 has focused on the value of life. For example, questions such as, "Is life with Trisomy 18 not worth living?" have been examined in the literature in the context of providing extraordinary life-sustaining treatments (Wilkinson, 2010, p.644) Long-term survivors with Trisomy 18 have profound mental retardation, physical limitations, and complex medical problems. It has been argued that prolonging such a severely debilitated life places an undue burden on society. Limited and expensive medical resources may be preserved for those with better outcomes. (Wilkinson, 2006) Assumptions or declarations about the value of a person's life ultimately lead to decisions regarding the utilization of medical resources. Not surprisingly, when a life is regarded as less valuable, negative consequences have resulted. Physician apathy, lack of compassion, and outright patient abandonment have been major criticisms by families of babies with Trisomy 18. The perception that many physicians do not value children with Trisomy 18 has led to a deep divide between families and physicians.

Alternatively, many have argued that life with Trisomy 18 should be regarded as valuable as any other life. Intellectual and physical disability should not impact negatively on how one values life. Barbara Farlow, Trisomy 18 advocate and a parent of a child with Trisomy 18, writes:

> …children with Trisomy 18 can provide something essential and important to those who love them…Resources should be considered well spent if they prolong the life of a child who lives comfortably and is loved intensely". (Janiver, Okah & Farlow, p.755, 2010)

Therefore, one would conclude that the utilization of medical resources should be no different in babies with Trisomy 18 than other babies. Websites and blogs devoted to babies and children with Trisomy 18 are a testament to this perspective. (Trisomy 18 Foundation, www.trisomy18.org, 7-15-2014)

Upholding and protecting the intrinsic value of huma life is both noble and significant. History holds many examples of discrimination against people with disabilities with the most horrific example being that of the Nazi's policy of routine extermination of disabled persons. At the same time, however, one must not confuse the management of a baby with Trisomy 18 with social reform. No child should be a "poster-child" for any movement. A child's value should not come from the amount of social change that can be gained from his/her condition. Furthermore, children with Trisomy 18 should have the same value whether or not they are loved or how much their family may love them. If a baby with Trisomy 18 is deserving of all medicine has to offer, then the resources should be available to all babies not only the ones whose families desire it. Conversely, because a life is so cherished by others does not does require that is prolonged at all cost.

It must be emphasized that the benefits of prolonging life should be for the patient and not for the family/guardians. This is an important distinction to make as clinical management should be "child-centered" just as adult care is patient-centered. Yet, the use of intensive management for babies with Trisomy 18 has been strongly fueled by parental demand. Families may demand "life at all costs" and neonatologists have acceded. (Paris et al, 1992) The problem of relying mainly on the principle of parental autonomy for guiding decisions for critically-ill babies and children has been addressed in the literature. (Paris et al, 2007) There are no established guidelines on how parental autonomy should be applied or limited in this setting. Absolute parental autonomy is essentially "normless" in the setting of decision-making for critically-ill babies and children. (Paris et al., 2007, p.429) Although the principle of autonomy has dominated the ethical landscape of Western medicine, there are limits to the application of any ethical principle as well as a need to balance competing interests. Parental autonomy should not be absolute; most importantly, the experiential welfare interests of the baby must be taken into account, particularly as these experiential interests are the only interests that can reasonably be attributed to a baby, particularly one with Trisomy 18 who has no prospect of long-term survival sufficient to develop interests beyond the avoidance of pain and the seeking of pleasure or comfort.

Furthermore, families may not be in the best position to make critical decisions about life-sustaining treatment, as "…even good and caring parents, acting out of fear, ignorance or misreading of the clinical situation, can make decisions antithetical to the child's interests" (Paris et al, 2007, p.429) . It is easy to understand why families might want "everything done" to prolong the lives of their critically-ill babies and children. To choose life-saving treatment may constitute a clear demonstration of their desire for their baby's life and thus to preserve that life.

It may represent the taking of a proactive step in a situation in which they largely feel powerless. To forgo life-sustaining treatment may feel to families like abandonment rather than like acting in the child's best interest. Unfortunately, *"Do you want everything done for your child?"* is a question often asked of families by physicians. It has many implications and multiple connotations. The answer "no" may represent more than limiting intensive treatment. It may also mean "giving up" or "being a bad parent". Furthermore, limiting treatment may result in the immediate end of their baby's life. It may be easier for families to consent to continuation of life-sustaining treatment than to face the reality that their baby or child is going to die. Imagine if the following questions were asked rather than *"Do you want everything done?"*:

1. Do you want your child to die in the ICU/hospital rather than at home, at peace in your arms?
2. Do you want your child's life to be supported only by intubation/ventilation, gastric tube-feeding, and IV medication?
3. Do you want your child to die from cardiovascular collapse, overwhelming infection or pulmonary hemorrhage while in the ICU?
4. Do you want your child to experience pain and suffering?

Although clearly inappropriate and insensitive, these questions demonstrate the impact of communication on decision-making.[35] Parents should not be put into the position of being the sole decision-makers for critical decisions regarding their baby's intensive care, especially in the setting of Trisomy 18.

[35] The questions "Do you want everything done?" is just as directive as any of the four questions listed above.

Instead, decision-making for babies with Trisomy 18 should be a team approach that follows the tenets of palliative care. The World Health Organization tenets of palliative care include the following:

1. Affirm life while accepting death as a normal process
2. Intend to neither hasten nor postpone death
3. Offer a support system to help families cope during a patient's illness and in their own bereavement
4. Interventions are aimed at comfort and quality of life
5. Apply palliative care early in the course of illness in conjunction with other therapies intended to prolong life
6. Pediatric Palliative Care begins when illness is diagnosed and continues regardless of whether or not a child receives treatment directed at the disease

The use of pediatric palliative care in the setting of the management of babies with Trisomy 18 has the potential to create a child-centered, collaborative environment for both families and physicians. Clear communication of the goals of treatment is essential. Palliative care can lay the ground work for this type of communication.

Imagine further re-framing the questions for families to as follows:

1. What are your goals at this point in your child's treatment?
2. We are concerned about your child's pain and suffering at this point, what do you think?
3. Given the very poor prognosis, what do you think is best for your child in terms of medical treatment?
4. How would you imagine a good death for your child?

Language matters. Open-ended questions like these facilitate discussion rather than forcing a parent to make yes/no decision under duress. They also allow the physicians to assess how much the parents and family understand. Do they understand what a "very poor prognosis" means for their child? Do they understand the difference between short and long-term survival? Palliative care focuses on treatments that promote comfort and symptom relief for the patient rather than extension of short-term life.

How can palliative care be tailored to the care of babies with Trisomy 18? First, palliative care should be introduced at the time of diagnosis, typically during the prenatal period. At that time, parents should be counseled about the expected complications of Trisomy 18 as well as the most up-to-date survival statistics. An example of this type of counseling using the statistics reviewed in Section IV is sketched in Appendix A, although an actual counseling process will need to take place across multiple sessions, and must be interactive and responsive to parents' questions and expressions of values, preferences, hopes, and fears. If a baby with Trisomy 18 is born alive, palliative care should continue (or commence if the condition was not diagnosed prenatally) with an emphasis on the BIS detailed above. A sketch of the content of post-natal counseling is provided in Appendix B. Ideally, through counselling sessions such as these outlined here, an optimal management of babies with Trisomy 18 can be achieved with consensus between health care providers and families.

7.0 CONCLUSION

In this paper, it was demonstrated through an extensive medical literature review that intensive management of babies with Trisomy 18 results in the prolongation of short-term life without an associated increase in long-term survival or cure. Standard quality of life measures are not increased and there is significant concern regarding heightened pain and suffering. Cardiac surgery increases the risk of post-operative sudden death and is not associated with an increase in long-term survival. The risk/benefit ratio for cardiac surgery is unacceptably high and therefore should not be performed. Families need to be counseled clearly and effectively about these evidence-based outcomes of intensive treatment. The goals of any intensive treatment should be clear to all decision-making parties with a "child-centered" approach utilized at all times. Perinatal/neonatal palliative care will help to achieve reasonable goals for all parties involved and should be available to all babies born with Trisomy 18. Furthermore, palliative care should be offered as the first option to families who receive a diagnosis of Trisomy 18. These conclusions have implications for U.S. hospital policy and for clinicians' practices in addressing the needs of their patients with Trisomy 18 and their families.

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