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RESEARCH LETTER

Misdiagnosis of trisomy 13 and trisomy 18 is more common than anticipated

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To the Editor,

Common trisomies such as trisomy 13 (T13) and trisomy 18 (T18) have been of increased interest in regards to prognosis and outcomes with multiple recent large studies suggesting patients do better than historically thought, even with major interventions (Alore et al., 2021; Cooper et al., 2019; Goel et al., 2019; Nelson et al., 2016). These studies have been well powered due to utilization of large databases and registries, which standardly identify the diagnosis of T13 and T18 based on diagnostic codes across multiple centers. These newer studies have led to thoughtful investment in identifying prognostic risk factors and approaches to clearly delineate, which of these patients will be long term survivors after interventions, how to counsel parents and families, and whether interventions are reasonable (Carvajal et al., 2020; Kochan et al., 2021; Leuthner & Acharya, 2020; Neubauer & Boss, 2020; Weaver et al., 2021). We sought to better understand our local population of patients with T13 and T18 and their outcomes in order to provide more personalized counseling for our patients' families. We found that the majority of patients identified for our study did not have T13 or T18 due to miscoding or misdiagnosis, raising significant concern that these large scale studies may misrepresent the interventional risk in this population.

We designed a retrospective chart review to look specifically at surgical outcomes for patients with T13 and T18. This was deemed to be IRB exempt by the Indiana University Human Research Protection Program (Protocol 1,908,540,907). We looked for infants and children born between 1990 and 2020 with a diagnosis of T13 or T18 treated at Riley Hospital for Children (Indianapolis, IN). We identified patients using the following International Classification of Disease (ICD) codes: 758.1-T13, unspecified, 758.2-T18, unspecified, Q91.0-T18, Nonmosiacism, Q91.1-T18, Mosaicism, Q91.2-T18, Translocation, Q91.3-T18, Unspecified, Q91.4-T13, Nonmosiacism, Q91.5-T13, Mosaicism, Q91.6-T13, Translocation, and Q91.7-T13, Unspecified. Deidentified data is available upon request.

This identified 207 unique patients with available records. These records were then manually reviewed (NH) for further information with an ultimate cohort of 117 patients documented and treated as T13 or T18 as demonstrated in Figure 1. Forty-three percent of the cohort identified by ICD coding alone had a genetic disorder other than T13 or T18 that would not have been clarified without manual chart review. These 90 patients were not clinically treated as T13 or T18, making them miscoded but not clinically misdiagnosed. These patients were excluded from our study so outcomes data is unavailable. It is worth noting that 13 (14%) of the miscoded patients had trisomy 21, which is known to have drastically different outcomes than T13 and T18. The remaining 117 patients in our cohort had complete chart review (NH) and 34 patients were identified as having a variant of T13 or T18, which included mosaicism, translocations, or "partial" trisomies. All 34 patients were treated and counseled clinically as if they had classic T13 or T18. In order to better understand this subpopulation a geneticist (GCG) reviewed these 34 charts to clarify their diagnoses.

There were a significant number of patients, 15% (18/117) of the cohort treated as T13 and T18, who were misdiagnosed. A number of these cases had the genetic testing results available and accessible in the electronic medical record. The majority of these patients had not seen medical genetics within our system. A few patients had early contact with genetics, but no follow up. The true diagnoses ranged from minor duplications to large, unbalanced translocations. Examples

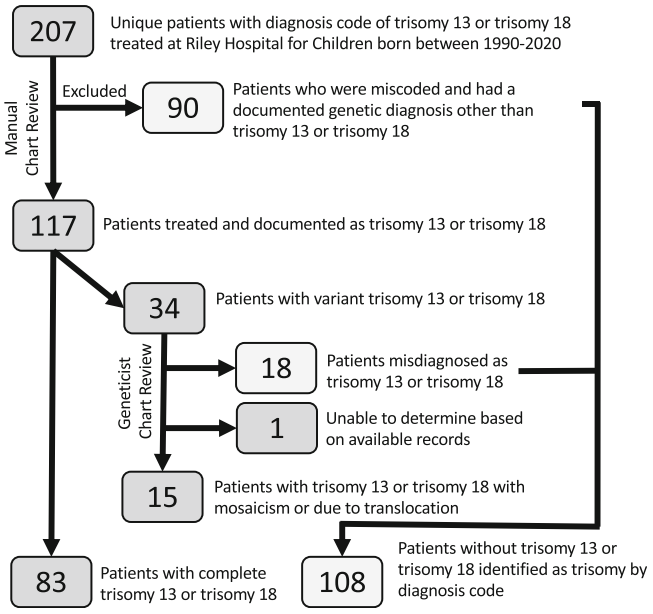

FIGURE 1 Patients identified to have trisomy 13 or trisomy 18 by ICD diagnostic code and their ultimate diagnostic category

of genetic testing results and diagnoses of patients inappropriately treated as T13 or T18 are illustrated in Table 1.

We initially theorized this confusion was likely related to genetic testing advancements and increased utilization of microarray, but as Table 2 shows there does not seem to be a pattern of increased misdiagnosis in relation to decade of birth consistent with this. These data are consistent with a systemic problem regarding misdiagnosis of T13 and T18 as it spans across decades, different care systems, and medical teams. Based on this, it is reasonable to suspect misdiagnosis of T13 and T18 is not a problem isolated to our institution. Given the majority of powered contemporary outcomes data identifies patients by diagnostic coding, where even the most dutiful and careful research teams do not have access to charts to directly view genetic testing results, this could be a major problem across the literature. Ultimately, fewer than half of the patients identified by ICD code (98/207) actually had a diagnosis of T13 or T18 between miscoding and misdiagnosis. Even a fraction of this level of inaccurate patient identification would invalidate the conclusions of these studies.

To determine what sort of effect this could have on outcomes data, we looked at the 97 patients in our cohort who were treated as T13 and T18 that had clear mortality information. These data are summarized in Table 3. We found that while the misdiagnosed group made up only 17% of this cohort, they also made up 34% of the long-term survivors who lived past 1 year. Fischer's exact testing shows 30 day, 90 day, and 1 year survival is significantly decreased in the complete T13 and T18 group compared to the misdiagnosis group at every time frame ($p = 0.0018$, 0.0002, and <0.0001, respectively). Inclusion of patients with T13 and T18 with mosaicism or due to translocation still shows significantly decreased 30 day, 90 day, and 1 year survival compared to the misdiagnosis group ($p = 0.0047$, 0.0006, and 0.0001, respectively). These data suggest that inclusion of the misdiagnosed patients in outcomes data analysis of patients with T13 and T18 likely skews favorably toward survival, making major invasive procedures seem less problematic than they may truly be in this vulnerable, complex population.

While our sample size is small, the depth and span of our data in combination with ability to directly review genetic testing results suggests that misdiagnosis of T13 and T18 is a common occurrence. This is extremely concerning as there are likely patients within this cohort who may have identifiable genetic disorders that could possibly alter treatment who are getting inappropriate information and medical management. One recommendation we have is discontinuation of the term "partial trisomy" when referring to chromosomes 13 and 18. It anecdotally seems many of these misdiagnoses were a result of calling relatively minor duplications "partial trisomy" with the eventual loss or inconsistent use of the word partial.

Diagnostic errors are unfortunately common and tend to be a "blind spot" in medicine because they are often not reported and may not even be detected (Bordini et al., 2017; Kliegman et al., 2017). We found the frequency of misdiagnosis in this population extremely surprising, as T13 and T18 are common genetic disorders many physicians trained to care for pediatric patients are familiar with. Misdiagnosis is a known concern in the setting of rare and genetic disease, but we often think of diagnostic errors resulting in missed or delayed diagnosis in this setting (Bordini et al., 2020; Kliegman et al., 2017).

While it is difficult to determine the exact type of error that led to the initial misdiagnosis in these patients, they all had continued misdiagnosis due to diagnostic momentum (Bordini et al., 2017). The diagnostic error could have been mitigated in most of our cohort by direct review of the genetic testing results and/or inclusion of the medical genetics team to review and interpret the genetic testing results. Electronic medical records make diagnostic momentum harder to overcome; however, since these patients spanned 30 years this clearly is not the main etiology for error. An area of potential intervention to prevent these errors is improving understanding among healthcare providers in regards to medical genetics, something the medical genetics field is acutely aware of, but has focused on genomics (Bordini et al., 2017; Korf et al., 2014). Our data suggests we need to focus on foundational medical genetics knowledge as well. We also suspect a source of error or perpetuated error was parents who were not clear on the diagnosis or genetic testing results. Parents often serve as expert sources of information in patients with rare or genetic diseases, but it is also known that their understanding can be limited and health care providers over rely on parents and families as a source of key information without verifying, researching independently, or discussing the diagnosis with the appropriate subspecialists (Currie & Szabo, 2019; Gallo et al., 2009).

Overall, we think these data are critically important for several reasons, the first being that it shows significant error is involved when utilizing diagnosis codes in large databases to identify genetic diseases, calling into question recent large studies suggesting favorable outcomes in T13 and T18. Second, this study reinforces the importance of verifying genetic testing results when evaluating a new

TABLE 1 Examples of genetic testing results of patients treated as trisomy 13 or trisomy 18

Patient	Genetic diagnosis	Test type	Genetic testing results
33	13 Mb Pathogenic 18p11.32p11.21 Deletion and 13.2 Mb Pathogenic 18q22.1q23 Duplication	Karyotype	46,XY,der(18)(qter?q22::p11.2?qter)
		Microarray	arr[hg19]18p11.32p11.21(136,226-13,132,968)x1, 18q22.1q23(64,802,377-78,014,123)x3
132	0.4 Mb Pathogenic 5p13.2 Duplication and a 0.5 Mb 13q31.3 Duplication of Uncertain Significance	Microarray	arr[hg19] 5p13.2(36,887,646-37,300,606)x3, 13q31.3 (93,296,561-93,862,088)x3
152	7.2 Mb Pathogenic 18q21.2q21.31 Duplication	Microarray	arr[hg19] 18q21.2q21.31(48,359,729-55,594,222)x3
159	0.5 Mb 13q14.2 Duplication of Uncertain Significance	Microarray	arr[hg19] 13q14.2(50,144,952-50,601,124)x3
167	0.3 Mb Likely Benign 18q21.1 Duplication	Microarray	arr[hg19] 18q21.1(47118528-47449144)x3

TABLE 2 Patients treated as trisomy 13 or trisomy 18 by decade of birth and ultimate diagnostic category

Year of birth	All patients	Classic trisomy 13 or 18	Trisomy 13 or 18 with mosaicism or due to translocation	Misdiagnosis of trisomy 13 or 18	Unable to determine
1990	10	5	2	3	0
2000	39	27	6	5	1
2010	67	51	7	9	0
2020	1	0	0	1	0
Total	117	83	15	18	1

TABLE 3 Outcomes for patients with available longitudinal data in patients with a clear diagnostic category

	All patients	Trisomy 13 or 18	Trisomy 13 or 18 with mosaicism or due to translocation	Misdiagnosis of trisomy 13 or 18
Total patients with available data	97	67	14	16
Alive at last follow up	35	14	7	14
Average age last follow up (days)	4157	3704	5337	4020
Median age last follow up (days)	4423	4283	5384	4442
Range age last follow up (days)	(186–10,068)	(248–6703)	(1055–10,068)	(186–7920)
Deceased	62	53	7	2
Average age of death (days)	504	417	985	1104
Median age of death (days)	41	31	52	na
Range age of death (days)	(0–6583)	(0–6583)	(8–6172)	(77–2131)
Alive at 30 days	69	41	12	16
Alive at 90 days	54	29	10	15
Alive at 365 days	42	19	9	14

Note: While 88% of misdiagnosed patients were alive at 1 year of age, only 28% of patients with trisomy 13 or trisomy 18 were alive at 1 year of age despite similar median ages at last follow up between groups. There was significantly increased survival among misdiagnosed patients compared to trisomy 13 and trisomy 18 patients of any type at all time frames.

patient and involvement of medical genetics professionals in even "straightforward" genetic diagnoses to verify information is correctly interpreted and communicated so that patients get appropriate care.

Sincerely,

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CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

Alore, E. A., Fallon, S. C., Thomas, J. A., & Vogel, A. M. (2021). Outcomes after extracorporeal life support cannulation in pediatric patients with trisomy 13 and trisomy 18. *The Journal of Surgical Research*, *257*, 260–266. https://doi.org/10.1016/j.jss.2020.07.036

Bordini, B. J., Kliegman, R. M., Basel, D., & Nocton, J. J. (2020). Undiagnosed and rare diseases in perinatal medicine: Lessons in context and cognitive diagnostic error. *Clinics in Perinatology*, *47*(1), 1–14. https://doi.org/10.1016/j.clp.2019.10.002

Bordini, B. J., Stephany, A., & Kliegman, R. (2017). Overcoming diagnostic errors in medical practice. *The Journal of Pediatrics*, *185*, 19–25. https://doi.org/10.1016/j.jpeds.2017.02.065

Carvajal, H. G., Callahan, C. P., Miller, J. R., Rensink, B. L., & Eghtesady, P. (2020). Cardiac surgery in trisomy 13 and 18: A guide to clinical decision-making. *Pediatric Cardiology*, *41*(7), 1319–1333. https://doi.org/10.1007/s00246-020-02444-6

Cooper, D. S., Riggs, K. W., Zafar, F., Jacobs, J. P., Hill, K. D., Pasquali, S. K., Swanson, S. K., Gelehrter, S. K., Wallace, A., Jacobs, M. L., Morales, D. L. S., & Bryant, R. (2019). Cardiac surgery in patients with trisomy 13 and 18: An analysis of the Society of Thoracic Surgeons congenital heart surgery database. *Journal of the American Heart Association*, *8*(13), e012349. https://doi.org/10.1161/JAHA.119.012349

Currie, G., & Szabo, J. (2019). "It is like a jungle gym, and everything is under construction": The parent's perspective of caring for a child with a rare disease. *Child: Care, Health and Development*, *45*(1), 96–103. https://doi.org/10.1111/cch.12628

Gallo, A. M., Knafl, K. A., & Angst, D. B. (2009). Information management in families who have a child with a genetic condition. *Journal of Pediatric Nursing*, *24*(3), 194–204. https://doi.org/10.1016/j.pedn.2008.07.010

Goel, N., Morris, J. K., Tucker, D., de Walle, H. E. K., Bakker, M. K., Kancherla, V., Marengo, L., Canfield, M. A., Kallen, K., Lelong, N., Camelo, J. L., Stallings, E. B., Jones, A. M., Nance, A., Huynh, M.-P., Martínez-Fernández, M.-L., Sipek, A., Pierini, A., Nembhard, W. N., … Morgan, M. (2019). Trisomy 13 and 18-prevalence and mortality-a multi-registry population based analysis. *American Journal of Medical Genetics. Part A*, *179*(12), 2382–2392. https://doi.org/10.1002/ajmg.a.61365

Kliegman, R. M., Bordini, B. J., Basel, D., & Nocton, J. J. (2017). How doctors think: Common diagnostic errors in clinical judgment-lessons from an undiagnosed and rare disease program. *Pediatric Clinics of North America*, *64*(1), 1–15. https://doi.org/10.1016/j.pcl.2016.08.002

Kochan, M., Cho, E., Mercurio, M., Greco, M., Savarese, A. M., & Falck, A. (2021). Disagreement about surgical intervention in trisomy 18. *Pediatrics*, *147*(1), e2020010686. https://doi.org/10.1542/peds.2020-010686

Korf, B. R., Berry, A. B., Limson, M., Marian, A. J., Murray, M. F., O'Rourke, P. P., Passamani, E. R., Relling, M. V., Tooker, J., Tsongalis, G. J., & Rodriguez, L. L. (2014). Framework for development of physician competencies in genomic medicine: Report of the competencies working Group of the Inter-Society Coordinating Committee for physician education in genomics. *Genetics in Medicine*, *16*(11), 804–809. https://doi.org/10.1038/gim.2014.35

Leuthner, S. R., & Acharya, K. (2020). Perinatal counseling following a diagnosis of trisomy 13 or 18: Incorporating the facts, parental values, and maintaining choices. *Advances in Neonatal Care*, *20*(3), 204–215. https://doi.org/10.1097/ANC.0000000000000704

Nelson, K. E., Rosella, L. C., Mahant, S., & Guttmann, A. (2016). Survival and surgical interventions for children with trisomy 13 and 18. *JAMA*, *316*(4), 420–428. https://doi.org/10.1001/jama.2016.9819

Neubauer, K., & Boss, R. D. (2020). Ethical considerations for cardiac surgical interventions in children with trisomy 13 and trisomy 18. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *184*(1), 187–191. https://doi.org/10.1002/ajmg.c.31767

Weaver, M. S., Lantos, J., Hauschild, K., Hammel, J., Birge, N., & Janvier, A. (2021). Communicating with parents of children with trisomy 13 or 18 who seek cardiac interventions. *Cardiology in the Young*, *31*(3), 471–475. https://doi.org/10.1017/S1047951120004023

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