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Prenatal assessment of congenital diaphragmatic hernia at north american fetal therapy network centers: A continued plea for standardization

Erin E. Perrone[1] | Nimrah Abbasi[2] | Magdalena Sanz Cortes[3] | Uzma Umar[1] | Greg Ryan[2] | Anthony Johnson[4] | Maria Ladino-Torres[5] | Rodrigo Ruano[6] | North American Fetal Therapy Network (NAFTNet)

[1]Department of Surgery, Section of Pediatric Surgery, Fetal Diagnosis and Treatment Center, University of Michigan, Michigan Medicine, Ann Arbor, Michigan, USA

[2]Fetal Medicine Unit, Ontario Fetal Centre, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

[3]Fetal Surgery and Intervention, Baylor College of Medicine, Houston, Texas, USA

[4]The Fetal Center, Children's Memorial Hospital, University of Texas Health Science Center, Houston, Texas, USA

[5]Department of Radiology, Division of Pediatric Radiology, Fetal Diagnosis and Treatment Center, University of Michigan, Michigan Medicine, Ann Arbor, Michigan, USA

[6]Department of Obstetrics & Gynecology, Division of Maternal-Fetal Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Correspondence
Erin E. Perrone, C.S. Mott Children's Hospital, Pediatric Surgery, 1540 E. Hospital Dr., Ann Arbor, MI 48109-4211.
Email: eperrone@med.umich.edu

Abstract

Introduction: Prenatal work-up for congenital diaphragmatic hernia (CDH) is important for risk stratification, standardization, counseling, and optimal therapeutic choice. To determine current practice patterns regarding prenatal CDH work-up, including prenatal ultrasound and magnetic resonance imaging (MRI) use, and to identify areas for standardization of such evaluation between fetal centers.

Methods: A survey regarding prenatal CDH work-up was sent to each member center of the North American Fetal Therapy Network (NAFTNet) (n = 36).

Results: All responded. Sonographic measurement of lung-to-head ratio (LHR) was determined by all, 89% (32/36) of which routinely calculate observed-to-expected LHR. The method for measuring LHR varied: 58% (21/36) used a "trace" method, 25% (9/36) used "longest axis," and 17% (6/36) used an "antero-posterior" method. Fetal MRI was routinely used in 78% (28/36) of centers, but there was significant variability in fetal lung volume measurement. Whereas all generated a total fetal lung volume, the planes, methodology and references values varied significantly. All evaluated liver position, 71% (20/28) evaluated stomach position and 54% (15/28) quantified the degree of liver herniation. More consistency in workup was seen between centers offering fetal intervention.

Conclusion: Prenatal CDH work-up and management differs considerably among North American fetal diagnostic centers, highlighting a need for its standardization.

1 | INTRODUCTION

Congenital diaphragmatic hernia (CDH) is an anomaly that affects 1 in 2500 births per year, most of which are diagnosed prenatally,[1,2] typically at the routine anatomical ultrasound (US) at 18 to 20 weeks' gestation. Prenatal prognostication of CDH relies on the US prediction of pulmonary hypoplasia (PH) by obtaining the lung-to-head ratio (LHR), with a lower LHR, that is, smaller lungs, being predictive of a worse outcome and increased mortality.[3] This has been refined as an observed-to-expected LHR (o/e LHR) which is applicable in both left and right CDHs, and is independent of gestational age and the degree of liver herniation.[4-8] LHR[3,9] and o/e LHR[4-6,10] inversely correlate with neonatal morbidity, including the duration of assisted ventilation, need for supplemental oxygen at 28 days of life, feeding challenges and the need for a prosthetic patch repair. Fetal magnetic resonance imaging (MRI) measurement of total fetal lung volume (TFLV) has also been used to guide prenatal counseling, especially since this *may* more accurately predict PH severity, compared to US.[11-16]

Despite numerous publications on these prognostic indicators, their performance has not yet been standardized. An o/e LHR <25% has been found to be predictive of a poor neonatal prognosis in left sided CDH (L-CDH) and may help select fetuses who might benefit from prenatal intervention with fetal endoluminal tracheal occlusion (FETO).[4] In practice, several methods for lung area measurement exist, including the trace, longest axis (LA), and antero-posterior (AP) methods.[17,18] The trace method has demonstrated the best reproducibility and its adoption has been urged by the North American Fetal Therapy Network (NAFTNet, https://www.naftnet.org/) and beyond.[17,19-21] Similar variability in practice surrounds fetal MRI practice: percent predicted lung volume (PPLV) and o/e TFLV have been reported from different institutions with a variety of methods to calculate the results.[11-13,22] Previous single-institution publications have attempted to identify the best formula for clinical use and have urged standardization among the fetal community.[23]

We designed a survey to evaluate current practice, including the adoption and implementation of the most recent US recommendations,[17,20,21,24] and specifically to assess the degree of variability in MRI prognostication of CDH.[25] This is particularly relevant when considering possible fetal interventions and has not been included in previous publications.[24,25]

What's already known about this topic?

- Prenatal assessment of congenital diaphragmatic hernia (CDH) is important
- Many fetal centers use a combination of ultrasound and fetal magnetic resonance imaging (MRI) in the workup to provide information to families for counseling
- There is no current standard of care or standardization

What does this study add?

- Ultrasound practices remain variable within NAFTNet centers (100% response rate) with improved standardization recognized among centers that offer fetal endoluminal tracheal occlusion (FETO)
- First study to demonstrate the practice patterns around the use of fetal MRI which is utilized in a majority of centers
- Significant variability is seen within fetal MRI use in prenatal assessment of CDH

2 | MATERIALS AND METHODS

A survey questionnaire was developed regarding the prenatal evaluation and prognostication of fetal CDH. The survey was approved by the University of Michigan Institutional Review Board (HUM00160562). All 36 NAFTNet centres were invited to participate at the biannual NAFTNet meeting, and to complete the survey. Responses were collected and analyzed via the University of Michigan Survey Platform, Qualtrics (Qualtrics, LLC: Provo, UT, 2002). Responses were not blinded, to ensure that all centers were accounted for, and follow-up e-mails were sent until the survey was completed. For any missing data points or uncertain answers, a representative at that center was contacted for clarification. Data were analyzed using descriptive statistics and presented graphically using Excel (Microsoft Corporation: Redmond, WA).

The survey consisted of 32 questions. There were six demographic and seven US questions, but its main focus was on fetal MRI practices and technique, and how such information was used clinically (n = 19) (Figure S1). To better understand potential differences in prenatal consultation across centers, we assessed which providers (radiologist, maternal fetal medicine [MFM] specialist, pediatric surgeon, neonatologist, or other) assimilated the information from the US and MRI as predictor neonatal disease severity.

3 | RESULTS

All 36 NAFTNet Centers completed the survey. Centers reported seeing a median of 12.5 (range 2-70) prenatal consults for CDH annually, with a median of 11 (range 2-25) identified as L-CDH. Centers reported similar annual volumes of postnatally diagnosed CDH, with a yearly median of 12 in total (range 2-40) and 10 (range 2-20) for L-CDH.

3.1 | Fetal US practices

All centers routinely used US to assess lung area in fetal CDH however, there was considerable variation in the methodology used to calculate and evaluate the US parameters between centers. The method used to estimate lung area varied: 21/36 (58%) used the "trace" method, 25% (9/36) used the LA and 17% (6/36) used the AP method. Although 89% (32/36) routinely calculated o/e LHR, centers varied in the frequency at which o/e LHR was assessed: 14 assessed monthly, 8 assessed every other week, 1 assessed weekly and 9 reported other frequencies (e.g. every 2–3 weeks, "arbitrarily," "periodically" etc). All fetal centers assessed liver position, 81% (29/36) evaluated stomach position, and 72% (26/36) included a fetal echocardiogram as part of their routine prenatal evaluation of CDH.

A variety of references were used to predict the neonatal prognosis (Table 1). Of 36 centers, 20 (56%) categorized severity utilizing TOTAL trial criteria with answers ranging as "mild," "moderate," or "severe" (n = 11), based on o/e LHR and liver position ("up" or "down") (n = 6), or specifically stating the use of TOTAL trial criteria (n = 3).[4,26,27] Five centers (14%) used LHR[28] and 2 (6%) used liver position plus LHR when counseling parents.[29] Complete list of references and results are listed in Table 1.

TABLE 1 Sonographic prognosticators used across NAFTNet centers

Category	References	Number of centers (n = 36)
o/e LHR (or TOTAL trial) criteria: *Mild*: >45% (regardless of liver position) or 35–44.9% with liver "down" *Moderate*: 25–34.9% (regardless of liver position) or 35–44.9% with liver "up" *Severe*: <25%	Jani et al[4] Deprest et al[26] Deprest et al[27]	20 (56%)
LHR: <1 = lethal 1–1.4 = equivalent >1.4 = better	Lipshultz et al[28]	5 (14%)
Liver position (in addition to LHR): "up" vs "down"	Hedrick et al[29]	2 (6%)
US- LiTR (in addition to o/e LHR): US derived liver-to-thoracic area ratio	Werneck Britto et al[30]	1 (3%)
None or non-specific to US	n/a	11 (31%)

Abbreviations: ECMO, extra-corporeal membrane oxygenation; LHR, lung-head ratio; o/e, observed/expected; TOTAL, Tracheal Occlusion To Accelerate Lung growth.

3.2 | Fetal MRI practices

Fetal MRI was routinely used in 28 of 36 centers (78%). Most used a 3-5 mm slice thickness (26/28, 93%) and 2 (7%) used 5 to 7 mm slice thickness. However, magnetic field strength was variable: 54% (15/28) used 1.5 Tesla (T) exclusively, 32% (9/28) used either 1.5 or 3.0T and 14% (4/28) only used 3T. Similarly, the plane used to routinely calculate TFLV varied: 50% (14/28) used "any plane which has the better/best image quality," 29% (8/28) used a coronal plane and 21% (6/28) used an axial plane. When asked about their use of diffusion weighted imaging (DWI), 39% (11/28) used it "sometimes," 36% (10/28) "never" and 25% (7/28) "always." One center (4%) also reported lung to liver signal intensity ratio (LLSIR) routinely. The time for MRI completion was <30 minutes in 11% (3/28), 30 to 45 minutes in 64% (18/28) and >45 minutes in 25% (7/28).

Gestational age at the initial MRI in a (theoretical) patient presenting at 20 weeks' gestation also varied and spanned from the second to the third trimester (Figure 1). Only 32% (9/28) of centers reported routinely getting a second fetal MRI later in pregnancy and these all aimed for 32–36 weeks' gestation. Similar to the US workup, all 28 centers assessed liver position and 71% (20/28) evaluated stomach position on fetal MRI. Prenatal lung volumes were measured using planimetric analysis in 68% (19/28), 3D reconstruction in 25% (7/28), one center (4%) used both and one (4%) did not use either. Twenty-seven centers reported on the regions of interest (ROIs) that were used to calculate lung area: all 27 centers evaluated fetal lung parenchyma, 30% (8/27) evaluated bronchi, 15% (4/27) evaluated the pulmonary vessels, 11% (3/27) evaluated the hilum and 7% (2/27) evaluated the trachea. Centers also used different references to calculate lung volume percentages: 50% Rypens[28] only, <4% Meyers only,[29] and 14% either; 2 (7%) used Barnewolt for percent predicted lung volume (PPLV)[13]; one (<4%) used Mahieu-Caputo[11]; one (<4%) used Balassy[31]; and 18% were either uncertain or used another reference (Figure 2). Other factors evaluated on MRI included percentage of liver herniation (%LH) in 54% (15/28) of centers, PPLV in 50% (14/28), liver volume-to-thoracic ratio (LiTR) in 14% (4/28), and the McGoon index[32] in 14% (4/28).

The US and MRI were performed on the same day in 10 (36%) centers, within 1 week but not the same day in 14 (50%), at more than 1 week's interval but less than a month apart in 3 (11%), and one center (4%) did not respond. When asked which modality they felt was most

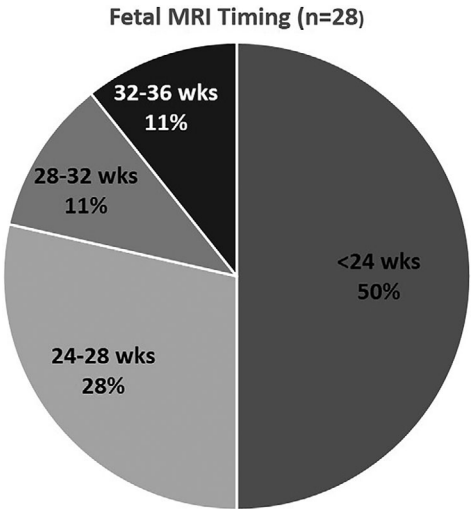

FIGURE 1 Timing of fetal magnetic resonance imaging for a patient presenting ≥20 weeks' gestation at each center

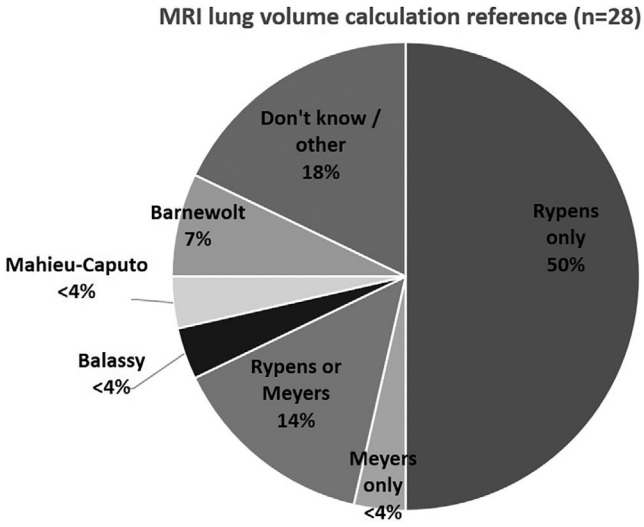

FIGURE 2 Variation in the equation used to calculate lung volumes at each center that used magnetic resonance imaging

predictive in case of discrepant results, 57% (16/28) favored MRI, 14% (4/28) favored US, 18% (5/28) used both or decided on the basis of either image quality or gestation and 11% (3/28) did not know.

3.3 | Fetal endoluminal tracheal occlusion center sub-analysis

Eleven centers (31%) were offering fetal endoluminal tracheal occlusion (FETO). Within this subset, the FETO centers reported evaluating a median of 20 (range 4-70) prenatal consults for CDH annually and having a median of 13.5 (range 4-40) total postnatal CDH cases born yearly. Nearly all centers (10/11, 91%) routinely reported o/e LHR and using the US for prognosis. The trace method was used to obtain LHR at most centers (10/11, 91%) while only one institution reported using the AP method (9%). The single center that was in the minority in each of the previous categories was different for each category.

Of the 11 FETO centers, 9 (82%) routinely used MRI in their prenatal workup of CDH and these also used a variety of techniques for measurement. All nine used 3 to 5 mm slice thickness. For magnetic field strength 33% (3/9) used 1.5T exclusively, 46% (5/9) used either 1.5T or 3T, and 11% (1/9) only used 3T. The plane used to calculate lung volumes also varied: 22% (2/9) used "any plane which has the better/best image quality" 44% (4/9) used an axial, and 33% (3/9) used a coronal plane. Forty-four percent (4/9) sometimes used DWI, 33% (3/9) used it always and 22% (2/9) never used it. Only one center (11%) routinely calculated LLSIR.

Five centers (56%) preferred to do their initial MRI at <24 weeks' gestation and while the remainder (4/9, 44%) scheduled the (theoretical) patient's study at 24 to 28 weeks. Planimetric analysis was used to measure lung volumes in 67% (6/9), while 3D reconstruction was used in 22% (2/9); one center (11%) did not know what kind of analysis was used. All centers reported the ROIs that they examined when calculating lung area: all nine evaluated lung parenchyma, 33% (3/9) evaluated the bronchi, 33% (3/9) evaluated the pulmonary vessels, 22% (2/9) evaluated the hilum and 22% (2/9) evaluated the fetal trachea. Centers also used different references to calculate lung volume percentages: most used either Rypens[33] or Meyers[34] [44% Rypens only (4/9), 11% Meyers only (1/9), and 33% used either (3/9)] and one center used Barnewolt to calculated PPLV.[13] Over half (5/9) of these centers repeated a fetal MRI at 32 to 36 weeks. When asked which modality was thought to be most predictive when discrepancies occurred, 56% (5/9) preferred MRI, 11% (1/9) preferred US and 33% (3/9) used both or decided on the basis of either image quality or gestation.

3.4 | Prenatal Counseling

Eighty-nine percent (32/36) of the centers used US findings to predict prognosis. The provider(s) who discussed prognosis with the parents varied between centers: 17 (47%) were MFMs alone, 4 (11%) were pediatric surgeons alone, 2 (6%) were radiologists, 1 (<3%) was a neonatologist and 11 (31%) were by a multidisciplinary team; one center (<3%) did not respond. Interestedly, only 58% (21/36) of centers reported that they used these data to guide their post-natal therapy. Seventy-nine percent (22/28) used the MRI results in their prognostic prediction. The health care provider(s) that counseled parents regarding prognosis again varied between centers. Six (21%) centers did not use fetal MRI in the prediction of prognosis. Different references were, however, used to guide this prognostic prediction (Table 2).

TABLE 2 MRI-based prognosticators used across NAFTNet centers

Category		References
Lung volume measurements	o/e lung volume	Rypens et al[33]
	o/e TFLV <25% = lower survival	Gorincour et al[35]
	PPLV: <15% = severe	Barnewolt et al[13]
	Mild / Moderate / Severe (o/e TFLV) Mild: >35% Moderate: 25–35% Severe: <25%	Oluyomi-Obi et al[6]
Liver measurements	Liver/Thoracic Ratio (LiTR) ≥20% liver in thoracic region = lower survival	Worley et al[36]
	Percent Liver Herniation (%LH) Combination with o/e TFLV able to better predict mortality and need for ECMO	Ruano et al[37]

Abbreviations: MRI, magnetic resonance imaging; o/e, observed/expected; PPLV, percent predicted lung volume; TFLV, total fetal lung volume.

4 | DISCUSSION

This study assessed the variability in imaging of fetuses with CDH that exists across fetal centers in NAFTNet. All centers measured the area of the contralateral lung for prenatal prognostication, with nearly 90% determining o/e LHR and the remainder measuring just LHR. This is consistent with a recent survey which evaluated US practice in fetal CDH in a subset of NAFTNet centers.[20] Although methods of lung area measurement are not uniform across NAFTNet, tracing is the preferred method of measurement (especially in centers offering FETO), rather than the longest axis method, as had previously been reported.[20,21] This shift in practice may reflect the adoption of a more standardized approach to sonographic lung area estimation as recommended by both NAFTNet[21] and ERNICA (European Reference Network on rare Inherited and Congenital Anomalies).[38] Both organizations have promoted tracing the lung, because its reproducibility has been much better both within centers and across all NAFTNet centers.[7,17,21] In our survey, 91% of NAFTNet centers offering FETO now trace the lung area, in contrast to a previous report in which only 53% of FETO centers did so.[20]

Although nearly 90% of NAFTNet centers use US information, specifically o/e LHR, to predict prognosis in fetal CDH, how this value was assigned, and which healthcare providers interpreted its prognostic significance varied across sites. Furthermore, the predictive indicators of disease severity varied (Table 1). Over 50% of centers categorized CDH severity into "mild, moderate, or severe," referencing the European CDH registry for their classification.[4,26,27] This registry has categorized CDH severity and its corresponding survival based on CDH laterality, degree of pulmonary hypoplasia (estimated by o/e LHR) and degree of liver herniation, with right sided CDH (R-CDH) and those with smaller lungs having worse outcome.[4,27,38,39] R-CDH lesions were nearly always lethal if the o/e LHR was <30%.[27,38,39] L-CDH were stratified into 4 groups: mild (o/e LHR >45% with intra-thoracic liver or 36%-45% without liver herniation), moderate (o/e LHR 36%-45% with intra-thoracic liver or 26%-35% regardless of liver herniation), severe (o/e LHR 15%-25%), and extreme (o/e LHR <15%), with survival in the range of 10% to 25% and almost no survivors in the latter two groups.[27,38] A Canadian single center retrospective review of 63 fetuses with isolated CDH also demonstrated comparable mortality in 72 fetuses based on o/e LHR, with reported survival of 21%, 50%, and 70% with o/e LHR ≤25%, 26% to 35%, and 36% to 45% respectively.[5] Our study highlights significant inconsistencies in the data that are being used to guide and inform prenatal counseling across NAFTNet. This may impact on the quality of perinatal care and may have important implications in an era of potential fetal intervention. Prenatal sonographic prognostication and counseling regarding fetal CDH should be standardized, beginning with the use of o/e LHR and prediction of survival based upon an agreed reference. At this time, the ERNICA CDH registry seems to provide the most robust dataset for this purpose.[38]

Intra-thoracic liver herniation has also been reported as an important, independent, prenatal prognosticator, as demonstrated in two large systematic reviews, showing reduced survival in fetuses with intra-thoracic liver herniation (ie, liver "up") compared to those whose liver remained intra-abdominal (ie, liver "down") as determined by MRI[40] and/or US.[41] Although all NAFTNet centers assessed liver position, only 61% incorporated this into their prenatal prognostic counseling, either as a stand-alone indicator or as part of the "mild/moderate/severe" criteria used in the TOTAL trial. Furthermore, it is unclear whether the degree of liver herniation was qualitatively or quantitatively assessed, the latter being a better predictor of neonatal mortality.[30,42] Because of the challenges in recognizing liver herniation with US, assessment of intra-thoracic stomach position has been proposed as a surrogate, and has been shown to correlate with neonatal mortality and morbidity.[43-45] In our study, although nearly 80% of centers evaluated stomach position, this was not routinely incorporated into their prenatal prognostication. Liver herniation is an important contributor in prenatal prognostication of CDH, however, standardized quantification of liver herniation and its optimal diagnostic imaging modality remain unclear. This is another assessment that should be standardized across fetal centers.

Fetal MRI volume measurements have been reported by multiple groups and have been used to guide perinatal management. There are variations in methodology, ROI, and the formulae used to calculate fetal lung volume.[22] Fetal lung measurements are reported in several different ways: PPLV, o/e FLV and o/e TFLV.[12,13,46] A 2017 systematic review showed that o/e TFLV could also be used to categorize disease severity and predict survival. The authors described three groups: "severe" (o/e TFLV <25%) with 0% to 25% survival, "moderate" (o/e TFLV 25%-35%) with 25% to 69% survival, and "mild" (o/e TFLV >35%) with 75% to 89% survival.[47] Different studies have shown how o/e TFLV and %LH are predictive of mortality, the need for ECMO and pulmonary morbidity.[37,48,49] When the predictive value of US and MRI parameters for survival have been compared, o/e TFLV was the best predictor with the most discriminatory threshold being an o/e TFLV of 25%.[6] Recent studies have suggested a potential role for 3D diaphragmatic reconstruction using MRI, to locate, classify and quantify the defect by manual segmentation.[50] Such models for prenatal CDH classification have correlated well with neonatal and post-mortem data, suggesting that this technique might help to optimize the choice of patch to be used for surgery in the neonate.[50] Although 79% of centers use fetal MRI for prognostication, there is no standardization around its role in predicting severity.

Although our study has novel findings and clarifies how fetal centers practice, it has some limitations. CDH case volume varies between institutions, which may account for some of the differences in prenatal assessment. To mitigate this, a subgroup analysis was done of the higher volume centers offering FETO, but the differences remained. Our survey was intentionally not anonymized, as our goal was to solicit responses from every NAFTNet center, to be as complete as possible in data collection. The information requested was multi-disciplinary and would usually require input from the whole team (eg, MFM, pediatric surgeon, neonatologist, radiologist, etc) to answer all the questions, but was sent to only a single representative at each site. Although respondents were encouraged to verify answers with all members of their team, we cannot be sure this happened. We also did not assess for variability within a single center as we assumed that centers followed internal protocols although we understand that institutional variability may also lead to heterogeneity in workup. Lastly, we did not directly address actual perinatal or infant outcomes in this survey and only perceived outcomes.

5 | CONCLUSION

The prenatal work-up, counseling and management of fetuses with CDH is not standardized across NAFTNet or other fetal centers. To address this, NAFTNet has developed a dedicated working group, to help standardize our prenatal prognostication and management of CDH. Such standardization is crucial to facilitate the comparison of therapeutic approaches and outcome between centers and to help identify those fetuses with CDH, which might benefit from either a prenatal intervention or specific post-natal therapeutic measures.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

E.E.P., N.A., M.S.C., G.R., A.J., and R.R. studied the conception and design. E.E.P. and U.U. data acquisition. E.E.P. analysis and data interpretation. E.E.P., N.A., and M.S.C. drafting the manuscript. G,R., A.J., R.R. critical revision.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

IRB exemption was granted by the University of Michigan Institutional Review Board (HUM00160562).

ORCID

Erin E. Perrone https://orcid.org/0000-0001-9301-0790
Magdalena Sanz Cortes https://orcid.org/0000-0002-0265-9859
Rodrigo Ruano https://orcid.org/0000-0002-3642-5858

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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