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RESEARCH ARTICLE

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The heart of the matter: Right heart imaging indicators for treatment escalation in pulmonary arterial hypertension

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Abstract

Right heart (RH) structure and function are major determinants of symptoms and prognosis in pulmonary arterial hypertension (PAH). RH imaging provides detailed information, but evidence and guidelines on the use of RH imaging in treatment decisions are limited. We conducted a Delphi study to

gather expert opinion on the role of RH imaging in decision-making for treatment escalation in PAH. A panel of 17 physicians with expertise in PAH and RH imaging used three surveys in a modified Delphi process to reach consensus on the role of RH imaging in PAH. Survey 1 used open-ended questions to gather information. Survey 2 contained Likert scale and other questions intended to identify consensus on topics identified in Survey 1. Survey 3 contained Likert scale questions derived from Survey 2 and summary information on the results of Survey 2. The Delphi panel reached consensus that RH imaging is likely to improve the current risk stratification algorithms and help differentiate risk levels in patients at intermediate risk. Tricuspid annular plane systolic excursion, right ventricular fractional area change, right atrial area, tricuspid regurgitation, inferior venae cavae diameter, and pericardial effusion should be part of routine echocardiography in PAH. Cardiac magnetic resonance imaging is valuable but limited by cost and access. A pattern of abnormal RH imaging results should prompt consideration of hemodynamic evaluation and possible treatment escalation. RH imaging is an important tool for decisions about treatment escalation in PAH, but systematically collected evidence is needed to clarify its role.

KEYWORDS

clinical guidelines, echocardiography, magnetic resonance imaging, pulmonary arterial hypertension, risk stratification

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic, progressive disorder driven by remodeling and proliferation in the pulmonary vasculature, which increase pulmonary vascular resistance and afterload of the right ventricle (RV).[1] Eventually, the right heart (RH) cannot compensate, uncoupling the RV from the pulmonary arterial tree and leading to morbidity and mortality as RV overload and failure occur.[2,3] Declining RV function and ability to compensate for pulmonary vascular changes are primary determinants of symptoms, clinical status, and survival in patients with PAH.[1,4]

RH imaging can provide detailed information on the structure and function of the RH and its coupling with the pulmonary arterial system.[3] In particular, measurements of RH function such as tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (RVFAC) reflect changes in ventriculo-arterial coupling and RV function.[5] Measurements of geometry, such as RV area, right atrial (RA) area, and eccentricity, reflect RV dilation.[5]

Many studies of RH imaging in PAH have identified echocardiography parameters with potential prognostic significance.[5–33] Of the at least 20 parameters studied, only RA area, the ratio of TAPSE with pulmonary artery systolic pressure (TAPSE/PASP), and pericardial effusion are cited in guidelines.[5,34,35] Additionally, significant gaps exist in the literature due to nonstandardized imaging variables and algorithms and a lack of large multicenter studies or systematic data collection across studies,[36] rendering evidence related to the use of RH imaging relatively weak and limited. There is little consensus on which RH imaging variables are appropriate, how objective imaging should be incorporated into the standard of care, whether imaging provides value beyond standard assessments of risk, and how imaging should be used in treatment decision-making.[1,4,34]

Recent evidence-based guidelines include RH imaging in risk assessment algorithms.[5,37] The 2022 European Society of Cardiology/European Respiratory Society guideline includes RH imaging in the three-strata risk assessment for the initial evaluation, but not in the simplified four-strata risk assessment for follow-up.[5,35] The REVEAL 2.0 risk score, widely used in North America, includes an echocardiographic assessment of pericardial effusion.[35] Inclusion of RH imaging information in follow-up evaluations may fill a gap by providing additional information to improve treatment decisions and, potentially, patient care.

RH echocardiography is non-invasive, relatively inexpensive, used routinely, and provides important information about structure and function. It seems reasonable to explore the potential role of RH imaging in PAH for decisions about treatment escalation, differentiating risk levels for patients in the intermediate-risk group, and monitoring improvement, stability, or deterioration. RH imaging may be useful in conjunction with other clinical evaluations for risk assessment and differentiating risk levels in patients in the broad intermediate-risk category.[4,5,34,38] In the absence of clear evidence on the appropriate role of RH imaging, expert opinion may benefit clinicians and patients by providing useful empirical recommendations on RH imaging, and may benefit the field in general by producing information on the role and status of RH imaging and better defining needs for future research and analysis.

The Delphi method is a widely used systematic, qualitative, structured technique to generate group consensus when there is not enough data to develop evidence-based recommendations. The method was developed and first described by Delbecq et al. in 1975 and is now widely used in medicine.[39–47] We conducted a Delphi study to gather information from expert cardiologists and pulmonologists to clarify the role of RH imaging in the management of PAH.

METHODS

In this Delphi study, a panel of 17 physicians with expertise in PAH and RH imaging responded to a series of three surveys, and their responses were used to identify points of consensus. The study was conceived by a PAH treatment escalation working group convened by the study sponsor (United Therapeutics Corporation). The Delphi panel was formed by (1) inviting all members of the working group, and (2) asking each member of the working group to nominate one or two additional candidates. Nominations were reviewed by the lead and senior authors, who selected candidates based on their expertise and to ensure a diversity of viewpoints. Selected candidates were invited to join the panel. All panelists were invited to be authors if they completed all three surveys and contributed to, reviewed, and approved the manuscript. Margaret R. Sketch and Meredith Broderick contributed to the design of the study, reviewed and revised the three surveys, and participated in development of the manuscript but did not respond to the surveys.

The Delphi panel was moderated by the lead and senior authors. The surveys were developed by the moderators with input and support provided by the study sponsor. Each survey was circulated by email, and panelists were asked to respond to the surveys independently and anonymously. A graphical overview of the study design is provided in the supplementary materials (Figure S1).

Survey 1 was an open-ended, qualitative questionnaire intended to elicit panelists' opinions on and practices in RH imaging in the assessment of PAH. The survey was developed by the moderators based on a literature search and their clinical knowledge and experience.

Survey 2 was developed by consolidating answers from Survey 1, pruning outliers, and adding new questions as suggested by responses to Survey 1. For most items, panelists were asked to rate their agreement, neutrality, or disagreement with statements about the role of RH imaging in PAH management, on a Likert scale ranging from −5 (strongly disagree) to +5 (strongly agree) (Figure S2). When this format would have been unduly burdensome to the panelists, the items were presented as multiple-choice or select-all-that-apply questions; each included an "Other" choice with an open-text answer section. Each broad topic area included a final open-text question for panelists to provide additional information at their discretion.

Survey 3 was similar to Survey 2, with the following exceptions: multiple-choice and select-all-that-apply items from Survey 2 were replaced with Likert scale statements based on the two responses given most frequently by panelists; open-answer items were removed; and panelists received a separate document containing their responses from Survey 2 and the aggregated results for the entire panel (mean and standard deviation of the Likert scale scores). The goal of revealing the aggregated Survey 2 responses was to encourage consensus by allowing individual panelists to compare their ratings against those of the overall group.

Consensus was predefined as a Likert scale mean ≥2.5 or ≤−2.5 with a standard deviation less than the absolute value of the mean (Figure S2). Near consensus was defined post hoc as a Likert scale score ≥2.25 or ≤−2.25. Authors reviewed each near consensus result to seek an informal consensus (defined as unanimous agreement to the result during a follow-up meeting) based on the group's clinical experience and judgment. This Delphi study was conducted and reported according to Guidance on Conducting and REporting DElphi Studies (CREDES).[48]

RESULTS

All 17 panelists specialized in pulmonology ($n = 6$) and/or cardiology ($n = 12$). Panelists had a median of 20 years' experience treating PAH (range, 13–32) and

9/17 (53%) had treated more than 1000 patients during their career. All panelists completed all three surveys.

The final survey comprised 14 broad categories, including 264 total statements which panelists rated on the Likert scale. Panelists reached consensus on 92 items (38.4%) and near consensus on eight items (3%). The results that follow focus on questions that reached consensus or near consensus and show consensus scores as (mean ± standard deviation) of the panelist's Likert scale ratings. The complete survey is presented in the supplementary material.

Role of RH imaging in PAH

The panel considered the overall role of RH imaging in PAH (Figure 1). They reached consensus that RH imaging most likely provides additive prognostic value beyond conventional tools for risk stratification, may be useful for the evaluation of treatment response, and may help differentiate various levels of intermediate risk. Panelists considered multiple RH imaging parameters, particularly measures of RV function. They agreed that RH imaging results may prompt invasive hemodynamic studies and possible treatment escalation even if risk status is stable, e.g., when RH imaging results are deteriorating, not improving, or mismatched with other parameters, such as risk stratification scores, clinical status, biomarkers, or hemodynamics.

Echocardiographic imaging

Panelists reached consensus that RH structure and function should be evaluated by echocardiography for all patients with PAH (4.76 ± 0.73), and that imaging must be done consistently and serially, with relevant parameters reported systematically (4.59 ± 0.77). Panelists were asked whether various echocardiographic parameters should be part of routine echocardiography evaluations of PAH. They reached consensus on the evaluation of pericardial effusion, tricuspid regurgitation severity, inferior vena cava diameter, TAPSE, RA area, and RVFAC. Parameters on which they did not reach consensus were eccentricity index, RV area, tissue Doppler (S′), TAPSE/systolic pulmonary artery pressure ratio, RV ejection fraction, and RV free wall strain. In a post hoc analysis comparing consensus levels for cardiologists and pulmonologists, levels of consensus were concordant for all parameters except eccentricity, RV area, and S'. Cardiologists reached consensus on eccentricity and near consensus on RV area and S', while pulmonologists did not reach consensus on any of these parameters. Figure 2 shows consensus levels for each echocardiographic parameter evaluated. Changes in TAPSE and RVFAC were considered early signs of PAH improvement or deterioration.

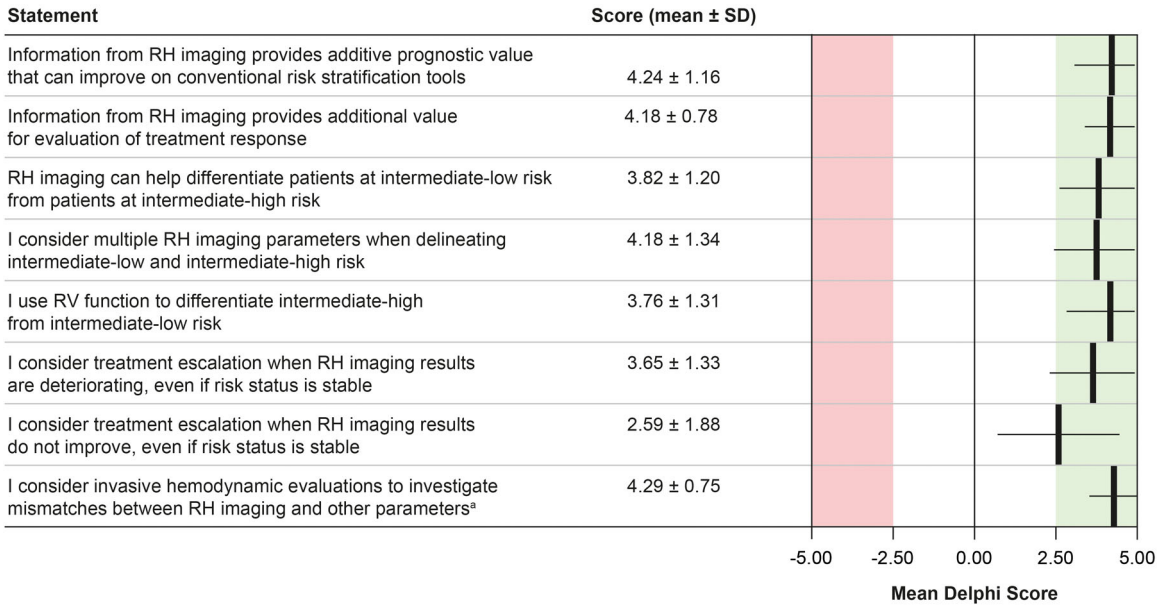


FIGURE 1 Questions on the role of RH imaging in PAH that reached consensus. Error bars indicate standard deviation. PAH, pulmonary arterial hypertension; RH, right heart; RV, right ventricle; SD, standard deviation. [a]For example, risk stratification scores, clinical status, biomarkers, hemodynamics.

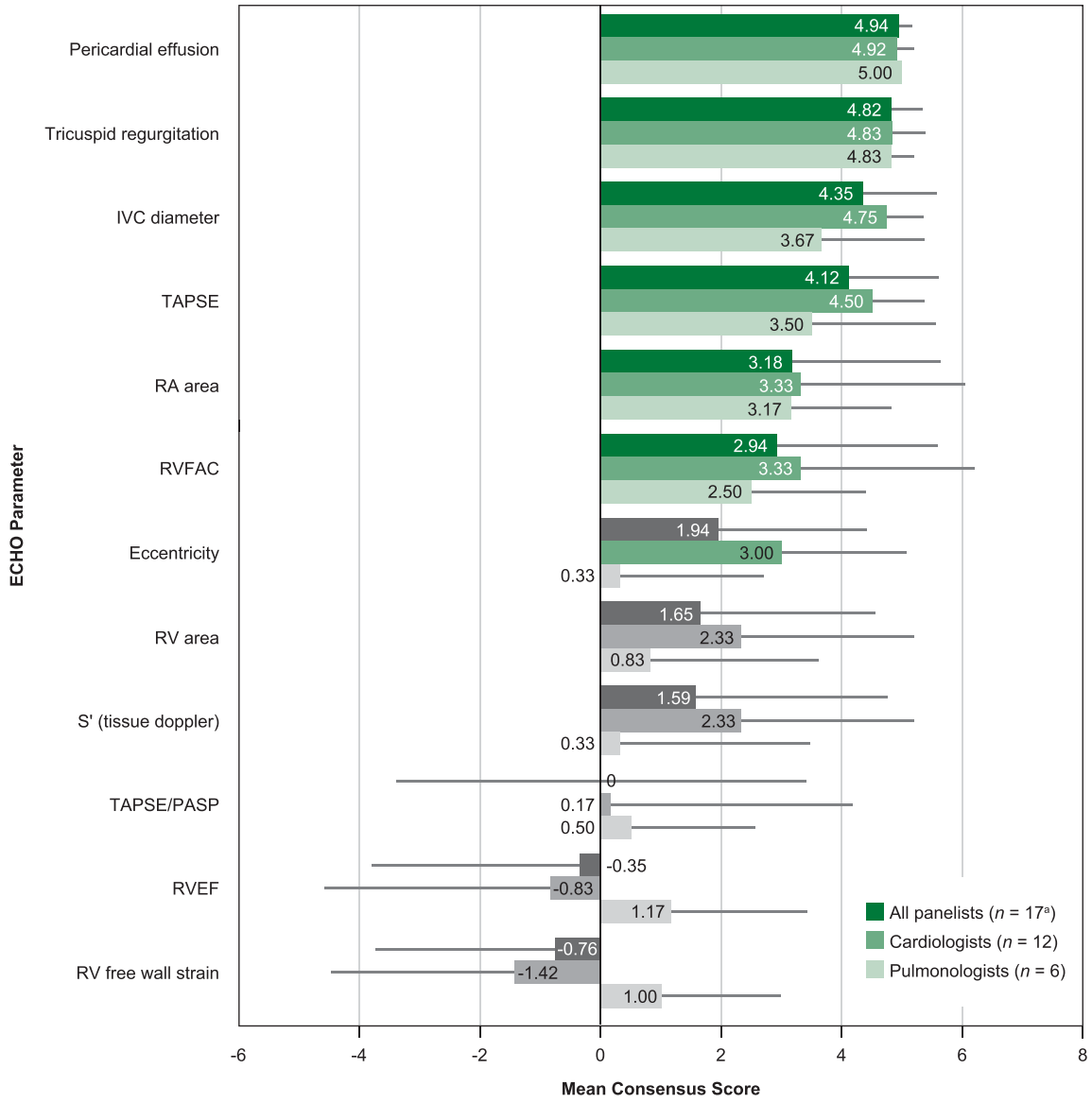


FIGURE 2 Consensus ratings for the routine use of echocardiographic imaging parameters in the monitoring of patients with PAH. Error bars indicate standard deviation. IVC, inferior vena cava; PASP, pulmonary artery systolic pressure; RA, right atrium; RV, right ventricle; RVEF, right ventricular ejection fraction; RVFAC, right ventricular fractional area change; S', tissue doppler; TAPSE, tricuspid annular plane systolic excursion. [a]One panelist is board certified in both cardiology and pulmonology and is included in both specialties.

Cardiac magnetic resonance imaging (cMRI) parameters

Panelists reached consensus that cMRI is an option if it is available and economically feasible (3.88 ± 1.41); however, 8/17 (47%) panelists expressed concerns about cost and access constraints on cMRI. The panel did not reach consensus on any cMRI parameters, possibly because of concerns about routine use of cMRI and the detailed wording of the questions (see Discussion); however, there was a near consensus that RV ejection fraction, RV end-diastolic volume, and stroke volume should be part of routine cMRI imaging (consensus scores 2.46 ± 3.39, 2.31 ± 2.92, and 2.31 ± 3.43 respectively). In post hoc review, panelists unanimously agreed that these parameters should be evaluated in cMRI. Changes in RV ejection fraction and stroke volume were considered early signs of changing PAH status (deterioration or improvement).

RH imaging parameters as goals of therapy

Panelists reached consensus that improvement in RH imaging parameters is an appropriate goal of PAH therapy (Figure 3) and that trends in RH imaging parameters are more clinically useful than any single

RH imaging measurement, are valuable for monitoring treatment response, and are a good indication of the patient's trajectory. They also agreed that RH imaging can clarify discordance between the patient's risk status and clinical symptoms/features.

Use of RH imaging for treatment decisions

Figure 4 summarizes consensus findings on the role of RH imaging in treatment escalation decisions. Panelists reached near consensus for considering treatment escalation for patients at low risk and intermediate-low risk on dual oral therapy who have abnormal RH imaging that is not improving. Panelists reached consensus for considering treatment escalation for patients at intermediate-low risk on triple therapy with a non-parenteral prostacyclin who have worsening imaging parameters and for those who are not improving and have abnormal imaging. For patients at intermediate-high risk, panelists reached consensus that treatment escalation should be considered if RH imaging shows no improvement or worsening. For these patients, sufficiently abnormal RH imaging parameters could drive treatment escalation independently of clinical, laboratory, or hemodynamic parameters (consensus score 2.59 ± 2.12). At all risk levels, abnormalities in multiple RH imaging parameters would prompt invasive hemodynamic assessment, which could lead to treatment escalation (Figure 5).

For treatment-naive patients, panelists reached consensus for considering RH imaging results when using parenteral prostacyclins for those at intermediate-high risk (3.59 ± 0.91). They did not reach consensus for up-front treatment in other clinical situations (Figure 6).

Measures of improvement/stability/deterioration

Panelists reached consensus that the following measures were part of their standard evaluation of improvement/stability/deterioration in patients with PAH: TAPSE (3.00 ± 1.85), RV function generally (no specific parameter) (4.53 ± 0.61), RA area (2.71 ± 1.93), measures of RH chamber geometry (3.35 ± 2.00), and tricuspid regurgitation (2.82 ± 1.58). Panelists also reached consensus that stability is an acceptable goal if RH imaging parameters and other measures are normal or near normal, or if medical therapy is already maximized (3.59 ± 0.84).

Timing of RH imaging studies

Panelists were asked about the frequency of routine echocardiography in incident patients (in the first year after initial diagnosis) and prevalent patients (on therapy and stable for >1 year after initial diagnosis) at low, intermediate-low, intermediate-high, and high risk. Panelists' practice for repeating routine echocardiography ranged from every 3 months to annually depending on the situation, with an increased frequency in case of hospitalization for PAH; signs of RH failure; worsening risk status, brain natriuretic peptide (BNP), or N terminal-pro-BNP; or mismatch between RH imaging and clinical status (Figure 7).

Timing of response to treatment

Panelists were asked how long they would wait to reach imaging goals to escalate treatment for incident and prevalent patients at low, intermediate-low,

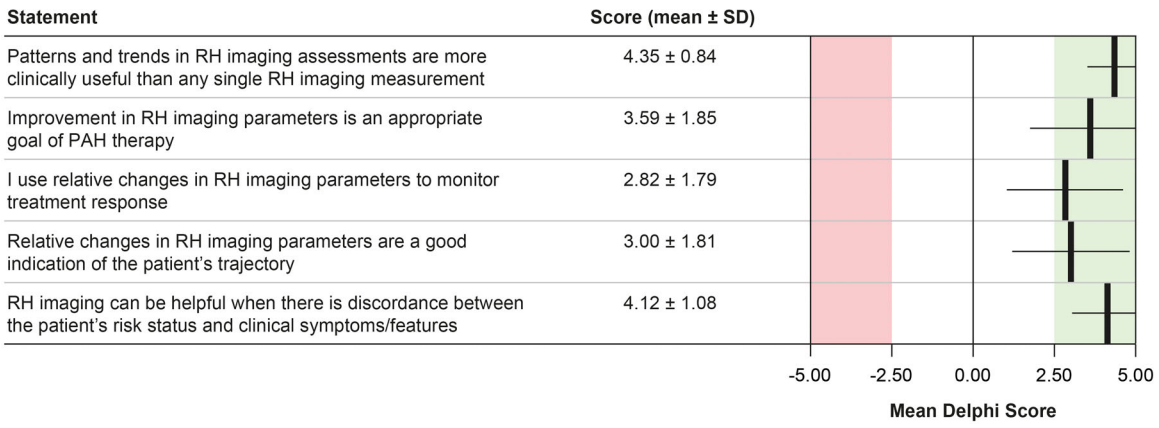


FIGURE 3 Questions on RH imaging parameters as goals of therapy that reached consensus. Error bars indicate standard deviation. PAH, pulmonary arterial hypertension; RH, right heart; SD, standard deviation.

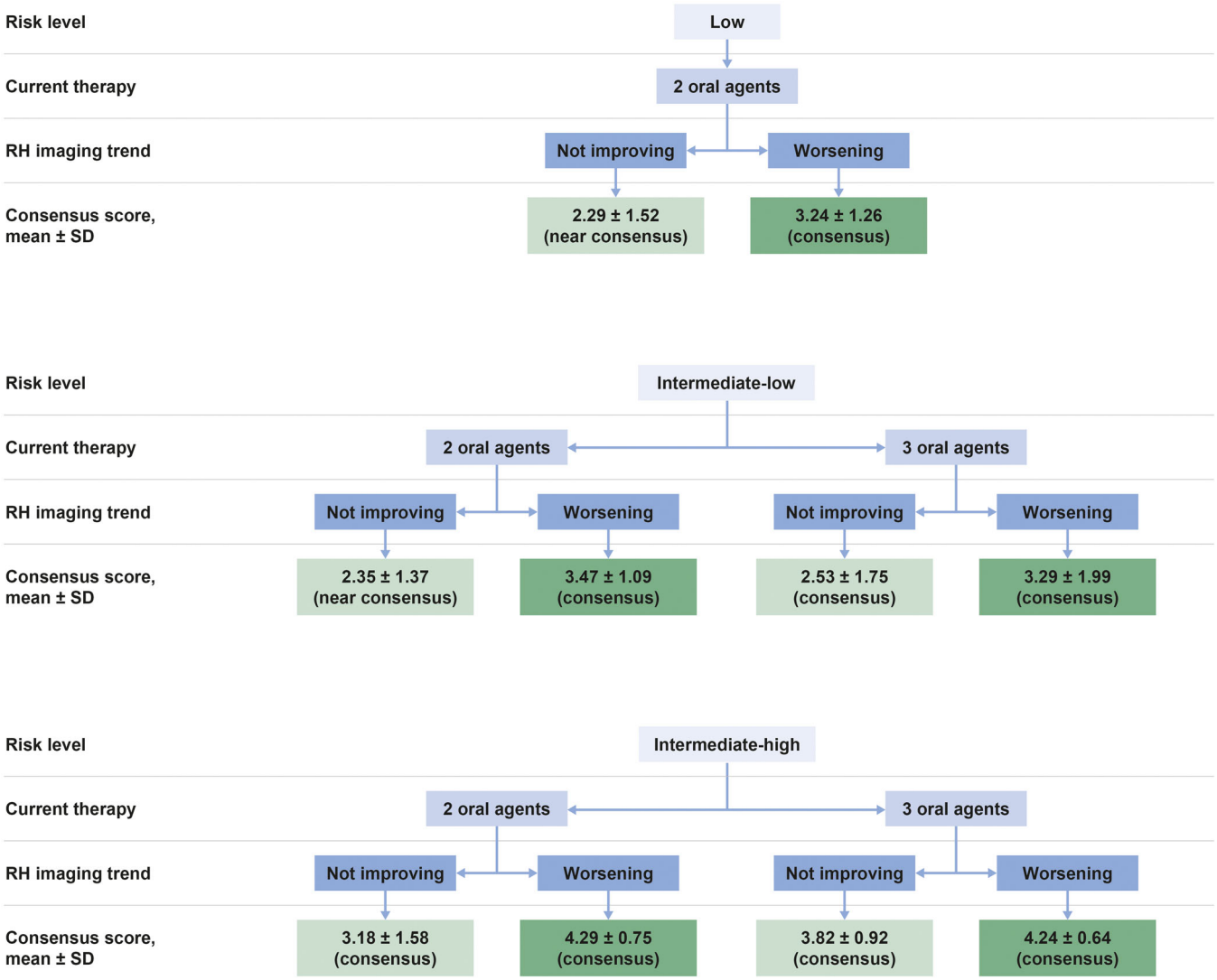
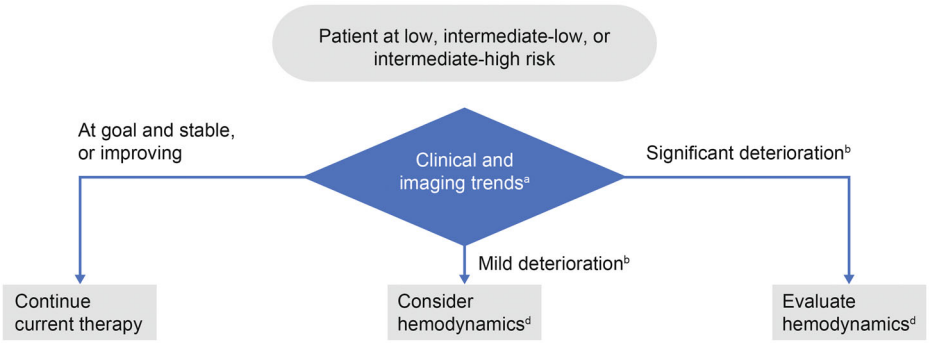


FIGURE 4 Consensus scores for considering treatment escalation by risk level, current therapy, and RH imaging trends. RH, right heart; SD, standard deviation.

and intermediate-high risk. By consensus, a 3- to 6-month trial would be appropriate in incident patients at low risk (3.00 ± 1.46) or intermediate-low risk (3.00 ± 1.28) and in prevalent patients at low risk (3.12 ± 1.23) or intermediate-low risk (2.94 ± 1.16). No consensus was reached on patients who are at intermediate-high or high risk. Treatment escalation would be considered in <3–6 months in case of disease progression, high risk in severe disease, parenteral prostanoids, pericardial effusion, or substantial worsening in N terminal-pro-BNP, WHO functional class, or 6 min walk distance test (Figure 7). A faster response was expected for parenteral prostacyclin regimens than for non-prostacyclin regimens (3.53 ± 1.33).

DISCUSSION

RH imaging encompasses a multitude of parameters across several modalities and provides valuable information on RH structural and functional status. Moreover, RH dysfunction is a key determinant of symptoms, morbidity, and mortality in PAH.[1] These observations indicate an important role for RH imaging in the evaluation and monitoring of patients with PAH, and align with several studies that support incorporation of imaging parameters in risk assessment.[1,8,10,18,19,49] In particular, echocardiography is routinely used in PAH because it is non-invasive and relatively inexpensive. However, echocardiography measures are not well integrated into current algorithms for risk assessment



Statement	Mean Delphi score by patient risk assessment group		
	Low	Intermediate-low	Intermediate-high
Abnormal RH imaging parameters would trigger hemodynamics and possible escalation	2.53 ± 1.91	2.94 ± 1.63	3.59 ± 1.29
Abnormal RH imaging parameters would trigger hemodynamics and possible escalation	2.94 ± 1.47	3.06 ± 1.16	3.29 ± 1.13
Abnormalities in multiple parameters would be required	3.82 ± 0.62	3.71 ± 0.96	3.53 ± 0.92

FIGURE 5 Suggested strategies for treatment monitoring and escalation based on clinical risk and RH imaging. Mean Delphi scores ≥2.5 indicate consensus was reached. RH, right heart. [a]If clinical and imaging trends are discordant, use whichever is worse. [b]Significant deterioration: significant clinical deterioration, significant deterioration in at least a few RH imaging parameters, or a consistent pattern of deterioration in multiple RH imaging parameters. [c]Mild deterioration: minor clinical deterioration and/or minor deterioration in a few RH imaging parameters. [d]If hemodynamic evaluation confirms deterioration, escalate treatment as appropriate based on hemodynamic, imaging, and clinical status and trends.

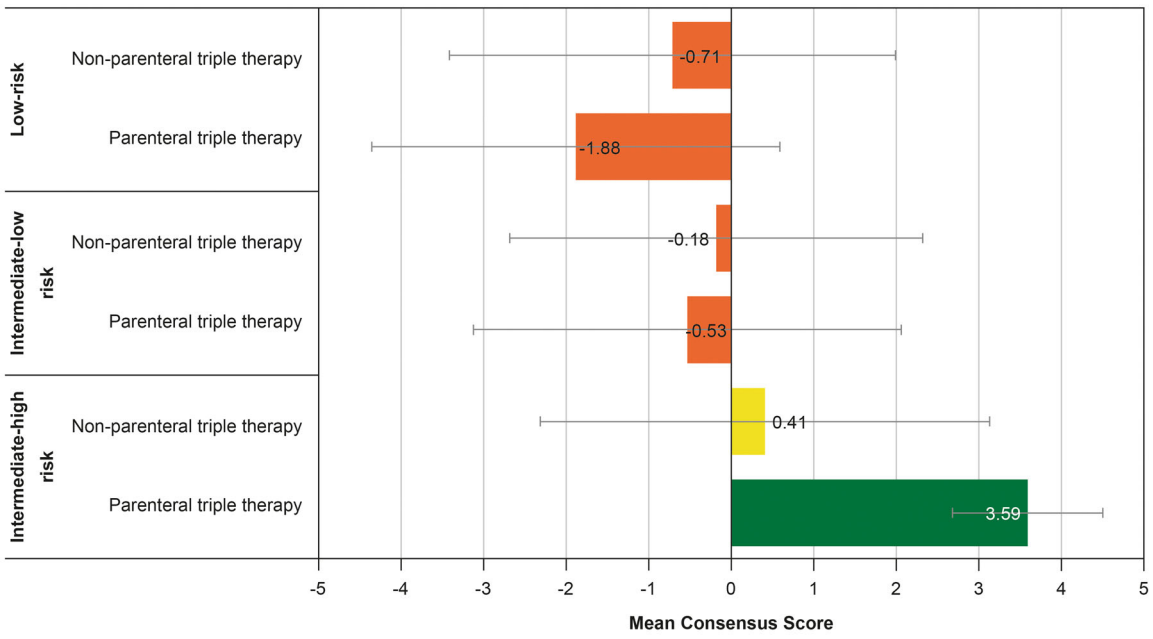


FIGURE 6 Abnormal RH imaging could prompt consideration of either non-parenteral or parenteral triple therapy as up-front therapy. Error bars indicate standard deviation. RH, right heart.

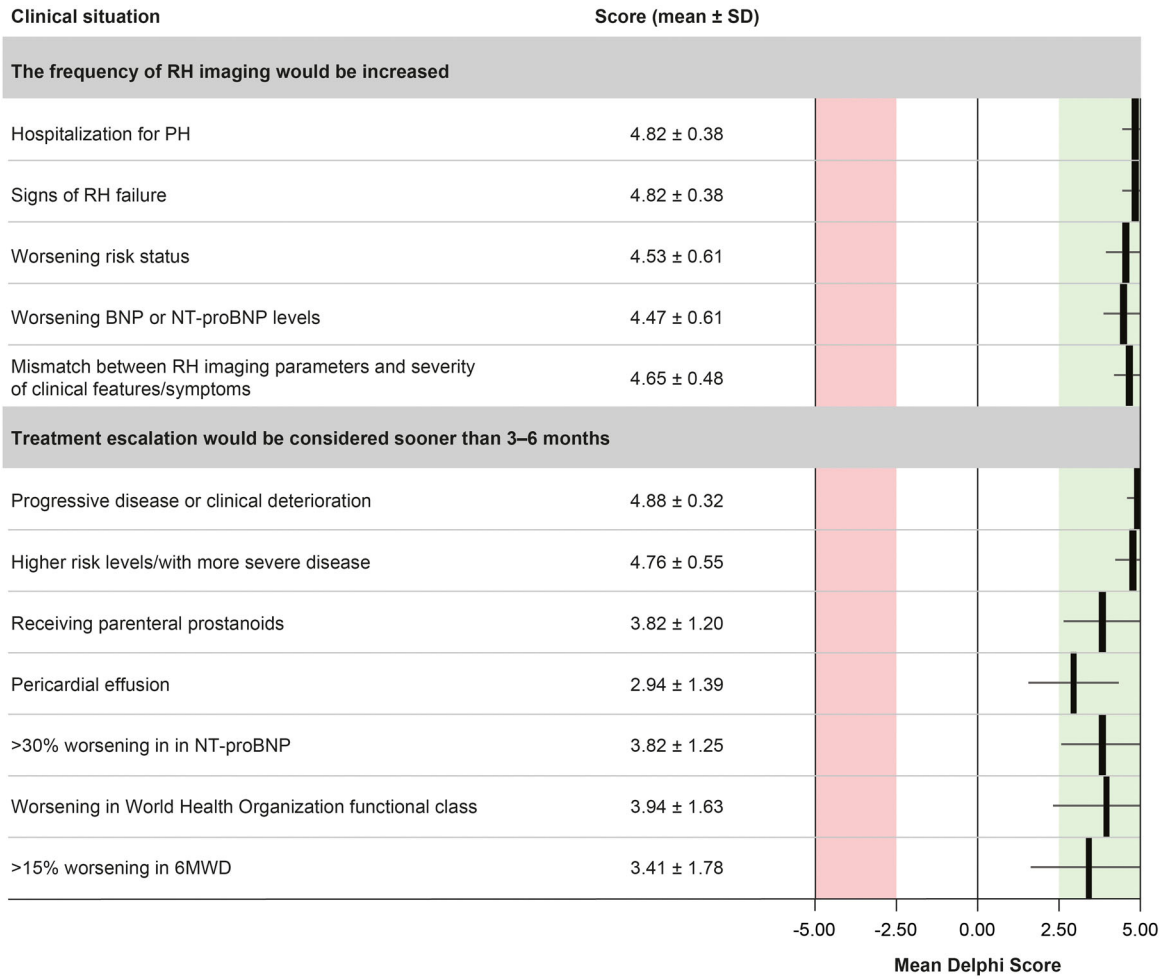


FIGURE 7 Consensus ratings on situations in which more frequent RH imaging and earlier treatment escalation would be considered. 6MWD, 6 min walk distance; BNP, brain natriuretic peptide; NT-proBNP, N terminal-pro brain natriuretic peptide; PH, pulmonary hypertension; RH, right heart, SD, standard deviation.

- RH imaging should use an integrated approach that considers multiple parameters and their trends over time
- Routine echocardiography should include assessment of pericardial effusion, tricuspid regurgitation, IVC diameter, TAPSE, RA area, and RVFAC
- Imaging methods should be standardized and included in registries and major multicenter randomized controlled trials
- RH imaging can have an important role in risk estimation, both for up-front therapy and during follow-up monitoring
- Deterioration in RH imaging parameters and/or discordance between RH imaging and clinical risk assessment should prompt consideration of an invasive hemodynamic evaluation with treatment escalation if needed

FIGURE 8 Summary of key points of consensus from the study. IVC, inferior vena cava; RA, right atrial; RH, right heart; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.

during follow-up evaluations due to the lack of standardization and collection of RH imaging parameters in major randomized controlled trials in PAH. The absence of imaging parameters may be a limitation in the four-strata European Society of Cardiology/European Respiratory Society risk assessment algorithm for monitoring PAH after diagnosis, and may contribute to the improved risk discrimination obtained with the REVEAL 2.0 risk score.

Figure 8 summarizes key consensus results from this Delphi study. Panelists agreed that RH imaging is a valuable tool that can be beneficial for risk stratification,

longitudinal monitoring, and decisions about treatment escalation. Improvement or normalization of RH imaging parameters may be a useful goal of therapy that provides earlier evaluation of patients' trajectory than clinical assessments. Panelists reached consensus on the use of multiple RH imaging parameters and systematic serial evaluations in combination with risk assessments, and on several imaging parameters that should be included in routine echocardiography, but they did not reach consensus on any specific parameters or algorithms for risk assessment.

Panelists' responses indicated that abnormal RH imaging results should prompt consideration for hemodynamic evaluation and possible treatment escalation in several situations (Figure 5): deteriorating RH imaging, lack of improvement in RH imaging when baseline RH function is poor, and when there is substantial discordance between RH imaging and clinical parameters, such as in a young patient with good clinical performance but significantly abnormal imaging results. Panelists agreed that, in general, for patients with poor or deteriorating RV function, hemodynamic evaluation and possibly treatment escalation should be strongly considered, regardless of risk level. This means escalation to triple therapy for patients at low risk on dual therapy, or escalation to parenteral prostacyclins for patients anywhere in the intermediate risk category.

There is wide variation in the use of RH imaging.[50] This study demonstrates variability even among our panel of experienced PAH specialists. One reason for this variation is the lack of standardization, systemization, and use of echocardiographic imaging in data registries and large multicenter trials. These factors reduce the feasibility of using existing echocardiographic parameters in routine practice, and also affect emerging methods and parameters such as speckle tracking, RV longitudinal strain, and incorporation of LV-related parameters in assessment of RV structure and function. For instance, several trials have shown that RV longitudinal strain has prognostic value, but as a potentially sensitive and clinically useful assessment of RH function. Inter-vendor variability, uncertainty about the optimal views and algorithms, and the lack of established reference ranges has limited the use of RV strain in PAH.[34,51–53] This is reflected in the lack of consensus and wide variability (-0.76 ± 2.98) in Likert scores for RV strain in this study. Another contributing factor may be differences between cardiologists and pulmonologists in training, experience, and familiarity with echocardiography, as reflected in the different levels of consensus reached for the use of eccentricity, RV area, and S′ in echocardiography. Differences in training and experience presumably underlie other areas of discrepancy in consensus (Table S1). The panel agreed that standardized measures, methods, and protocols for RH imaging are needed, and should be used in randomized controlled trials and registries.

The study had several limitations. The potential for bias in panelist selection and survey development is inherent to the Delphi technique, although anonymity and quantitative evaluation of responses may compensate to some degree for possible bias. Another inherent limitation is that the Delphi technique is designed to use expert opinion when clinical evidence is lacking. Study-specific limitations were related to the structure and wording of some of the survey items. Many items related to cMRI measures were worded as if cMRI is a routine measurement. Given difficulties with cost and access, this probably caused confusion between routine use of cMRI and value of cMRI when it is used. Items on RH imaging showing no improvement lacked important information on the patient's baseline status and did not provide enough information for a definitive answer. Selection of individual RH imaging parameters was problematic given that many RH imaging parameters are closely inter-related and should be considered together.

This study was conducted before release of the 2022 revision of the European Society of Cardiology/European Respiratory Society guidelines, which recommended use of RH imaging in the three-strata risk assessment model used for initial evaluation.[5] The parameters suggested for routine use by this Delphi survey align reasonably well with the guideline recommendations: this study suggests TAPSE rather than TAPSE/systolic pulmonary artery pressure for echocardiography, and stroke volume and RV end-diastolic volume rather than stroke volume index or RV end-systolic volume index for cMRI. These differences may reflect the lack of evidence on RH imaging parameters. Guidelines do not specifically consider RH imaging in the simplified four-strata module for ongoing monitoring, although they do recommend that "additional variables should be considered as needed, especially right heart imaging and hemodynamics."[5] Figure 2 may suggest appropriate variables.

In conclusion, this survey confirms the fundamental role of RH imaging in the monitoring and care of patients with PAH, highlights variability in the use of echocardiography in practice, provides consensus on which echocardiographic parameters should be included in the echocardiographic assessment of PAH patients, and indicates which parameters play a role in clinical decision-making. The remaining ambiguity regarding use of RH imaging is somewhat addressed by the 2022 European Society of Cardiology/European Respiratory Society guidelines and the REVEAL 2.0 score, but systematic, large-scale collection of RH imaging data is

needed to strengthen the evidence base for use of RH imaging. Incorporation of RH imaging into current risk assessment strategies could potentially move the needle toward improved quality and quantity of life in patients affected by PAH.

AUTHOR CONTRIBUTIONS

All panelists completed all three surveys and contributed to, reviewed, and approved the manuscript. Margaret R. Sketch and Meredith Broderick contributed to the design of the study, reviewed and revised the three surveys, participated in development of the manuscript, and approved the manuscript but did not respond to the surveys. The Delphi panel was moderated by Paul Forfia and Vallerie McLaughlin. The surveys were developed by the moderators with input and support provided by the study sponsor.

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CONFLICTS OF INTEREST STATEMENT

Paul Forfia has served on a speaker's bureau and consulted for Bayer, Janssen, and United Therapeutics. Raymond Benza has received consulting fees from Bayer, Janssen, United Therapeutics, Acceleron, CERENO, Abbott, and Gossamer; and advisory board fees from Acceleron. Michele D'Alto has received consulting fees from Janssen, MSD, Dompè, Ferrer, and AOP. Teresa De Marco has received research funding from Acceleron; and has served as a consultant for Action/Janssen, United Therapeutics, BIAL, Merck, NXT, Aerovate, and Pulnovo. Jean M. Elwing has served as a consultant for United Therapeutics, Altavant, Aerovate, Bayer, Gossamer Bio, Acceleron, Janssen, Liquid, and Insmed; and has participated in clinical research funded by Janssen, United Therapeutics, Liquidia, Phase Bio, Gossamer Bio, Bayer, Acceleron, Altavant, and Aerovate. Robert Frantz has received consulting fees from Altavant, Gossamer Bio, Insmed, Liquidia, ShouTi, and Tenax; serves on DSMB for IQVIA; and has received research grants from Bayer and United Therapeutics. Francois Haddad has received research funding from Janssen. Ronald Oudiz has received research funding, advisory board honoraria, and speaker fees from United Therapeutics. Ioana R. Preston has received research funding from Acceleron/Merck, Janssen, United Therapeutics, and PhaseBio; and consulting fees from Acceleron/Merck, Janssen, United Therapeutics, Aerovate, Gossamer Bio, and Respira. Stephan Rosenkranz has received fees for lectures and/or consultations from Abbott, Acceleron, Actelion, Aerovate, Altavant, AOP Orphan, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards, Ferrer, Gossamer, Janssen, MSD, United Therapeutics, and Vifor; and his institution has received research grants from Actelion, AstraZeneca, Bayer, and Janssen. John Ryan has received consulting fees and payment or honoraria from lectures, presentations, speakers' bureaus, manuscript writing, or education events from Bayer, Merck, United Therapeutics, Kiniksa, and Janssen PH. Robert Schilz has received research funding from Acceleron/Merck, United Therapeutics, Respira, and Bellerophon; consulting fees from Janssen, United Therapeutics, and Acceleron; and currently serves on speakers' bureaus for Bayer, Janssen, and United Therapeutics. Oksana A. Shlobin has received consulting fees from United Therapeutics and Janssen; has received honoraria from Medscape, Total CME, and Bayer; and has participated in a Data Safety Monitoring Board or Advisory Board for Janssen and Altavant. Jean-Luc Vachiery has received consulting fees from Acceleron, Actelion Pharmaceuticals (now Janssen), Altavant, Bayer HealthCare, Boehringer Ingelheim, GlaxoSmithKline, Gossamer Bio, MSD, Novartis, and Shouti. Carmine Dario Vizza has received consulting fees from Acceleron, Janssen, Altavant, Bayer HealthCare, Ferrer, GlaxoSmithKline, Gossamer Bio, and MSD. Anton Vonk Noordegraaf has served as a member of the scientific advisory board of Morphogen-X, Ferrer, Gosamer Bio, and Johnson & Johnson. The institute of Anton Vonk Noordegraaf has received consulting fees from a speakers' bureau for Johnson & Johnson, MSD, Actelion, Bayer, and Ferrer. Margaret R. Sketch and Meredith Broderick are employees and shareholders of United Therapeutics Corporation. Vallerie McLaughlin has received research funding from Acceleron, Janssen, Sonovie, and United Therapeutics; and consulting fees from Acceleron, Aerovate, Altavant, Bayer, Caremark LLC, CiVi Biopharma Inc., Corvista, Gossamer Bio, Janssen, Merck, and United Therapeutics.

DATA AVAILABILITY STATEMENT

The results of Survey 3 in its entirety are available in the supplementary materials.

ETHICS STATEMENT

None declared.

GUARANTOR

Vallerie McLaughlin is the guarantor of this manuscript.

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SUPPORTING INFORMATION

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

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