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ORIGINAL ARTICLE

Artificial Intelligence-Assisted Auscultation of Heart Murmurs: Validation by Virtual Clinical Trial

W. Reid Thompson[1] · Andreas J. Reinisch[2] · Michael J. Unterberger[2] · Andreas J. Schriefl[2]

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Abstract

Artificial intelligence (AI) has potential to improve the accuracy of screening for valvular and congenital heart disease by auscultation. However, despite recent advances in signal processing and classification algorithms focused on heart sounds, clinical acceptance of this technology has been limited, in part due to lack of objective performance data. We hypothesized that a heart murmur detection algorithm could be quantitatively and objectively evaluated by virtual clinical trial. All cases from the Johns Hopkins Cardiac Auscultatory Recording Database (CARD) with either a pathologic murmur, an innocent murmur or no murmur were selected. The test algorithm, developed independently of CARD, analyzed each recording using an automated batch processing protocol. 3180 heart sound recordings from 603 outpatient visits were selected from CARD. Algorithm estimation of heart rate was similar to gold standard. Sensitivity and specificity for detection of pathologic cases were 93% (CI 90–95%) and 81% (CI 75–85%), respectively, with accuracy 88% (CI 85–91%). Performance varied according to algorithm certainty measure, age of patient, heart rate, murmur intensity, location of recording on the chest and pathologic diagnosis. This is the first reported comprehensive and objective evaluation of an AI-based murmur detection algorithm to our knowledge. The test algorithm performed well in this virtual clinical trial. This strategy can be used to efficiently compare performance of other algorithms against the same dataset and improve understanding of the potential clinical usefulness of AI-assisted auscultation.

Keywords Auscultation · Artificial intelligence · Algorithms · Physical diagnosis/cardiovascular · Congenital heart disease · Valvular heart disease

Introduction

Valvular and many forms of congenital heart disease are often first recognized by the presence of a heart murmur; however, innocent flow murmurs are common in children and young adults and may be difficult to distinguish from those due to pathology. While experienced clinicians using a simple stethoscope can distinguish innocent from pathologic murmurs with greater than 90% sensitivity and specificity [1–4], auscultation proficiency is in decline among medical trainees and primary care practitioners, making screening for heart disease by physical examination increasingly difficult [5–9]. Artificial intelligence-assisted auscultation (AIAA) has the potential to improve accuracy of screening, yet despite developments in signal processing and classification algorithms focused on heart sounds [10–15], acceptance of this technology in clinical practice is still not widespread. Clinical trials of murmur detection algorithms comparing performance to traditional auscultation and to other algorithms are needed to improve the understanding and potential role of AIAA in clinical practice. We hypothesized that a standardized, internally validated dataset of heart sound recordings could be used in a virtual clinical trial of an AI-based algorithm to quantitatively evaluate performance.

General Disclosure The algorithm discussed in this manuscript was developed by CSD Labs GmbH, Austria (http://www.emurmur.com) and is investigational, not cleared by the FDA, and not available for sale in the U.S.

✉ W. Reid Thompson
thompson@jhmi.edu

[1] Division of Pediatric Cardiology, Johns Hopkins Children's Center, Johns Hopkins University School of Medicine, 1800 Orleans Street, Baltimore, MD 21287, USA

[2] CSD Labs GmbH, Nikolaiplatz 4, 8020 Graz, Austria

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Methods

Heart sounds of patients seen in the Johns Hopkins Outpatient Center were recorded and stored in the Cardiac Auscultatory Recording Database (CARD) (http://www.murmurlab.com), which contains data from over 1200 patients, both with and without cardiac pathology [16]. For each patient, 20-s recordings were obtained with an electronic stethoscope from multiple locations on the chest, with the patient in the supine and, in some cases, standing, sitting or squatting position. Heart sounds were recorded with a simultaneous 3-lead electrocardiogram (ECG) on a separate data channel, digitized and filtered as previously described [17]. In addition to the recordings, CARD contains clinical data for each case. This includes all diagnoses from the echocardiogram done on the day of the recordings and a single cardiologist's description of the heart sounds and murmur characteristics. The dataset for this study consisted of all CARD cases meeting the following criteria. Normal cases, with or without an innocent murmur, included those with echocardiogram showing no pathology. Pathologic cases had at least one pathologic diagnosis by echocardiogram and at least one murmur considered to be caused by the pathology. Presence or absence of a murmur was determined by the study cardiologist after listening to all recordings from each case.

Prior to algorithm analysis, the following data consolidation steps were taken:

(i) Murmur intensity was scored by the study cardiologist using a grade 1 (softest) to 6 (loudest) scale for systolic and diastolic murmurs. Grades 4–6 were used only for cases in which the clinical cardiologist who actually examined the patient used these grades. In cases where the grade was listed as 1–2, 2–3, or 3–4, the lower number was used for classification.
(ii) In cases with more than one murmur, only the murmur with the highest intensity grade was considered to be present for purposes of the analysis.
(iii) The murmur intensity grade noted in the study cardiologist's description was assumed to represent the grade at the location labeled as "best heard at" (BHA).
(iv) When either a continuous or both a systolic and a diastolic murmur of equal grade were present, murmur cycle timing was considered to be "systolic and diastolic."
(v) When more than one murmur of equal intensity grade in the same phase of the cardiac cycle was present, the BHA location for the first murmur described was used.
(vi) In cases with more than one pathologic diagnosis by echocardiogram, a primary diagnosis was selected that was considered clinically most likely to be the cause of the murmur.
(vii) If the murmur cycle timing was systolic and diastolic and patent ductus arteriosus (PDA) was one of the echocardiographic diagnoses, this was considered to be the cause of the murmur. If PDA was not one of the diagnoses, the first listed diagnosis likely to be a cause of the murmur was selected.
(viii) Similar diagnoses were grouped together to create 20 primary diagnosis groups. Primary diagnoses represented less than four times in the dataset were grouped together into an "other" group.

Heart sound recordings were excluded from analysis in the following conditions. If 2 or more files were present from the same case at the same location, all but the last file recorded were excluded. If 2 or more files were present from the same location but with different patient positions (e.g., supine, squatting, standing), only the file from the supine position was used. However, if a position other than supine was indicated in the study cardiologist's description to be associated with an accentuated or better heard murmur, that recording was analyzed instead.

The murmur detection algorithm was developed by CSD Labs, Austria (http://www.emurmur.com), without the use of CARD recordings for training [14]. The algorithm's performance in this trial reflects its capabilities as of August 2016. The algorithm requires for analysis a heart sound recording in WAV format and the patient's age. It is designed to be performed on a cloud server using a record–send-analyze process. The algorithm comprises several blocks performing different functions of the overall analysis. The first block performs a signal quality check which is able to recognize and exclude from further analysis recordings with insufficient length or data quality. Next, the heart rate of the heart sound recording is determined, which is then used for segmentation of the cardiac cycle. The segmentation block determines the locations of S1, systole, S2 and diastole. Next, feature vectors are derived from the heart sound signal, using data gathered from the previous blocks. Finally, these feature vectors are used as input to non-linear artificial intelligence (AI) classifiers to label files as containing a pathologic versus innocent murmur or no murmur. Algorithm output includes a certainty measure (in %), derived from data extracted from the heart sound recording that is used during analysis.

Heart sound recordings were de-identified by changing the file name from the standard CARD name to a dataset-specific numeric name. The investigators remained blinded to clinical and echocardiographic information associated with each case throughout the study. The simultaneously recorded ECG signal was separately analyzed to obtain the gold standard average heart rate for each recording. This was used for assessing the agreement between algorithm

and ECG-derived heart rate estimates as an additional measure of algorithm performance. Algorithm analysis of all recordings was performed in a single session by automated batch processing. The clinical characteristics and echocardiographic diagnoses associated with each case were then compared to the results of the algorithm analysis to determine algorithm performance.

The primary analysis measure, predetermined prior to algorithm testing, was sensitivity and specificity of the algorithm for correct classification of each case as pathologic versus normal. Recordings from the chest location listed as BHA were used for all cases with a murmur, whether innocent or pathologic, as noted by cardiologist description. Recordings from the left mid sternal border (LMSB) were used for normal cases without a murmur. Secondary analyses included effects on sensitivity and specificity of algorithm certainty measure, recording location on the chest, patient age, heart rate, murmur intensity and primary pathologic diagnosis.

Sensitivity, specificity and accuracy with 2-sided 95% confidence intervals were calculated according to the method of Wilson: [18]

$$\frac{1}{1+\frac{1}{n}z^2}\left[\widehat{p}+\frac{1}{2n}z^2 \pm z\sqrt{\frac{1}{n}\widehat{p}(1-\widehat{p})+\frac{1}{4n^2}z^2}\right],$$

where n is the number of samples, $z = 1 - \frac{\alpha}{2}$ is the quantile of the standard normal distribution which yields for a 95% confidence level, i.e., $\alpha = 1 - 0.95 = 0.05$, $z = 1.96$, and $\widehat{p} = \frac{n_s}{n}$ is the proportion of success and n_s is the number of successes, i.e., correct estimates. The mean, standard deviation, and median of all relative deviations were computed for all files analyzed by the algorithm.

Comparison of algorithm estimate of heart rate to gold standard ECG heart rate was performed for each recording. The absolute difference between ECG (hr_{ECG}) and algorithm-derived heart rate (hr_{Alg}) was computed and the relative deviation based on the ECG heart rate was calculated:

$$\text{hrDiff}_{\text{Rel}} = \frac{\text{abs}(\text{hr}_{\text{ECG}} - \text{hr}_{\text{Alg}})}{\text{hr}_{\text{ECG}}} \times 100.$$

Results

603 cases (3180 heart sound recordings) were selected from CARD using the above criteria. Mean age at time of visit was 9.2 years (SD 8.4, median 8.8, range 0.1–80.9 years). 17% of patients were aged < 1 year, 49% 1–12 years and 34% over 12 years. 374 cases had an abnormal echocardiogram and a pathologic murmur and 229 had a normal echocardiogram and either an innocent murmur (90) or no murmur (139).

The algorithm was able to fully analyze 2823 (89%) of the recordings. Recordings not able to be analyzed were more likely to have higher heart rates and lower signal quality. There was close agreement between algorithm estimates of average heart rate by acoustic analysis and the gold standard heart rate derived from the simultaneous ECG signal. Bland–Altman analysis demonstrated a small bias of − 1.1 beats per minute (bpm) with 95% limits of agreement between − 14.2 and 11.9 bpm (Fig. 1).

The primary analysis measure for algorithm performance showed sensitivity and specificity for detection of pathologic cases to be 93% (CI 90–95%) and 81% (CI 75–85%), respectively, with accuracy 88% (CI 85–91%). When stratified by highest algorithm certainty measure (95% certainty,

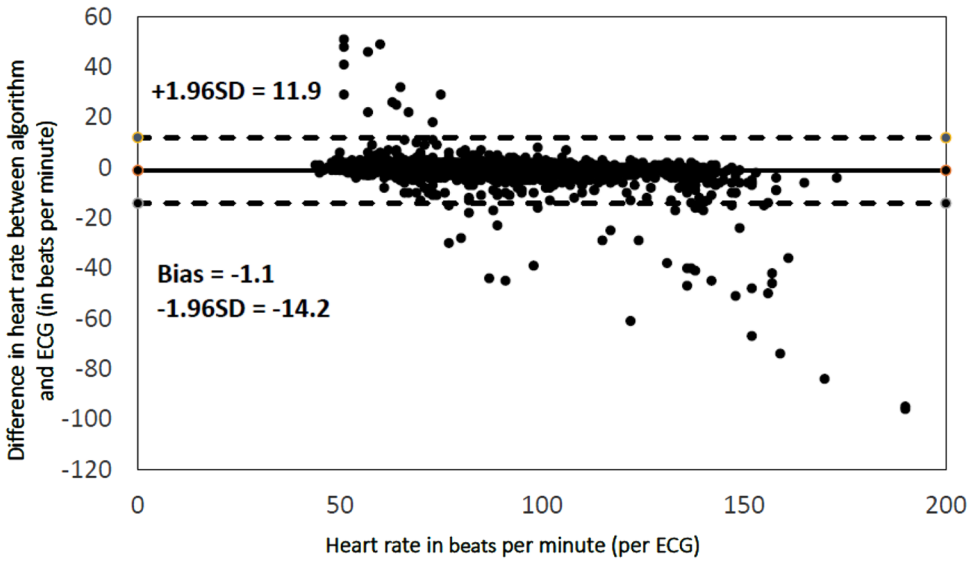

Fig. 1 Bland–Altman plot of difference in heart rate between algorithm and gold-standard ECG in bpm

Table 1 Analysis of algorithm performance by chest location at which murmur was best heard

BHA chest location	Number of cases[a]	Sensitivity (CI)	Specificity (CI)	Accuracy (CI)
APEX	182	0.77 (0.63–0.86)	0.90 (0.84–0.94)	0.87 (0.81–0.91)
LLSB	197	0.91 (0.76–0.97)	0.90 (0.85–0.94)	0.90 (0.85–0.94)
LMSB	240	0.96 (0.90–0.99)	0.84 (0.77–0.89)	0.88 (0.84–0.92)
LUSB	247	0.95 (0.89–0.98)	0.86 (0.79–0.91)	0.90 (0.85–0.93)
RUSB	177	0.98 (0.90–1.00)	0.78 (0.70–0.84)	0.84 (0.78–0.89)

BHA best heard at location on the chest, *APEX* apex of heart, *LLSB* left lower sternal border, *LMSB* left mid sternal border, *LUSB* left upper sternal border, *RUSB* right upper sternal border

[a]Using recordings from BHA chest location for cases with murmur and same location for cases without murmur, as designated

Table 2 Analysis of algorithm performance by any chest location

Any chest location[a]	Number of cases[b]	Sensitivity (CI)	Specificity (CI)	Accuracy (CI)
APEX	541	0.74 (0.69–0.78)	0.88 (0.83–0.92)	0.79 (0.75–0.82)
LLSB	558	0.77 (0.73–0.82)	0.86 (0.81–0.90)	0.82 (0.78–0.84)
LMSB	555	0.85 (0.81–0.88)	0.82 (0.77–0.87)	0.84 (0.81–0.87)
LUSB	524	0.86 (0.82–0.90)	0.80 (0.74–0.85)	0.84 (0.80–0.87)
RUSB	500	0.86 (0.82–0.89)	0.70 (0.63–0.76)	0.80 (0.76–0.83)
APEX + LLSB	511	0.84 (0.80–0.88)	0.80 (0.74–0.85)	0.83 (0.79–0.86)
APEX + LMSB	508	0.90 (0.86–0.93)	0.76 (0.70–0.82)	0.84 (0.81–0.87)
APEX + LUSB	481	0.93 (0.89–0.95)	0.74 (0.67–0.79)	0.85 (0.82–0.88)
LLSB + LUSB	501	0.91 (0.87–0.94)	0.73 (0.67–0.79)	0.84 (0.80–0.87)

APEX apex of heart, *LLSB* left lower sternal border, *LMSB* left mid sternal border, *LUSB* left upper sternal border, *RUSB* right upper sternal border

[a]Combinations (e.g., APEX + LLSB) were scored as pathologic if recording from either location was labeled pathologic by the algorithm

[b]Using recordings from chest location as designated for cases with a murmur (*not necessarily* the best heard at location) and same location for cases without murmur

64% of cases), sensitivity remained 93% (CI 89–96%) while specificity and accuracy increased to 97% (CI 93–99%) and 95% (CI 92–97%), respectively. This primary analysis used recordings from the BHA chest location for cases with either a pathologic or innocent murmur and LMSB for cases without a murmur.

When each BHA location was compared, the highest algorithm accuracy was seen using recordings from the left lower sternal border (LLSB) or left upper sternal border (LUSB) (Table 1). Comparison of recordings from any chest location regardless of whether it was designated as BHA or not found that the highest accuracy was obtained using the combination of APEX and LUSB (Table 2).

Algorithm performance was compared according to patient age group and heart rate (Tables 3, 4). Age under 1 year and heart rates greater than 120 bpm were associated with highest sensitivity but lowest specificity. Algorithm sensitivity increased and specificity decreased with increasing murmur intensity grade (Table 5).

Sensitivities for detection of pathologic murmurs associated with each primary diagnosis group are shown in Table 6. Murmurs associated with aortic stenosis and ventricular septal defect, the most common valvular and congenital lesions represented in the dataset, were detected with sensitivities > 90%.

Table 3 Analysis of algorithm performance by patient age

Patient age (years)	Number of cases[a]	Sensitivity (CI)	Specificity (CI)	Accuracy (CI)
< 1	78	0.98 (0.91–1.00)	0.53 (0.32–0.73)	0.87 (0.78–0.93)
1–12	278	0.95 (0.91–0.98)	0.76 (0.68–0.83)	0.88 (0.83–0.91)
> 12	200	0.87 (0.79–0.92)	0.91 (0.84–0.96)	0.89 (0.84–0.93)

[a]Using recordings from best heard at location as designated for cases with murmur and left mid sternal border for cases without murmur

Table 4 Analysis of algorithm performance by heart rate

Heart rate (bpm)[a]	Number of cases[b]	Sensitivity (CI)	Specificity (CI)	Accuracy (CI)
< 60	48	0.85 (0.66–0.94)	0.86 (0.67–0.95)	0.85 (0.73–0.93)
60–120	347	0.94 (0.90–0.97)	0.84 (0.77–0.89)	0.90 (0.86–0.93)
> 120	52	0.98 (0.87–1.00)	0.17 (0.05–0.45)	0.79 (0.66–0.88)

[a]Heart rate in bpm according to gold standard simultaneously recorded ECG signal

[b]Using recordings from best heard at location as designated for cases with murmur and left mid sternal border for cases without murmur

Table 5 Analysis of algorithm performance by murmur intensity grade

Murmur intensity	Number of cases[a]	Sensitivity (CI)	Number of cases[a]	Specificity (CI)
1	55	0.75 (0.62–0.84)	55	0.80 (0.68–0.88)
2	161	0.94 (0.90–0.97)	31	0.55 (0.38–0.71)
3	88	1.00 (0.96–1.00)	–	–
>= 4	31	1.00 (0.89–1.00)	–	–

[a]Using (the recording from chest location where murmur was best heard) pathologic cases for sensitivity and innocent murmur cases for specificity calculations

Table 6 Analysis of algorithm performance by primary diagnosis group

Primary diagnosis group	Number of cases	Sensitivity (CI)
AR	8	0.75 (0.41–0.93)
AS	70	0.96 (0.88–0.99)
ASD	13	0.92 (0.67–0.99)
AVSurg	6	0.83 (0.44–0.97)
AVVR	6	1.00 (0.61–1.00)
BAV	15	0.80 (0.55–0.93)
Coarc	5	1.00 (0.57–1.00)
HOCM	6	0.83 (0.44–0.97)
MR	28	0.86 (0.69–0.94)
PDA	12	1.00 (0.76–1.00)
PR	4	1.00 (0.51–1.00)
PS	35	0.97 (0.85–0.99)
RV-PAconduit	9	1.00 (0.70–1.00)
SubAS	20	0.90 (0.70–0.97)
SupraPS	4	1.00 (0.51–1.00)
TF	9	1.00 (0.70–1.00)
TFsurg	10	1.00 (0.72–1.00)
VSD	48	0.92 (0.80–0.97)
Other	23	0.96 (0.79–0.99)

AR aortic regurgitation, *AS* aortic stenosis, *ASD* atrial septal defect, *AVSurg* history of surgery on atrio-ventricular valve, *AVVR* atrio-ventricular valve regurgitation, *BAV* bicuspid aortic valve, *Coarc* coarctation of the aorta, *HOCM* hypertrophic obstructive cardiomyopathy, *MR* mitral regurgitation, *PDA* patent ductus arteriosus, *PR* pulmonary regurgitation, *PS* pulmonary stenosis, *RV-PAconduit* history of surgery to place a conduit from right ventricle to pulmonary artery, *SubAS* sub aortic stenosis, *SupraPS* supravalvar pulmonary stenosis, *TF* tetralogy of Fallot, *TFsurg* repaired TF, *VSD* ventricular septal defect, *Other* any additional diagnosis not previously listed, present in less than 4 cases in the dataset

Discussion

This is the first comprehensive evaluation of an AI-based murmur detection algorithm using recorded heart sounds. This trial represents a wide range of patient ages and cardiac pathologies and consists of recordings made from patients and equipment not used for algorithm training. These features are important positive factors in evaluating the potential generalizability of AI-based algorithms [19]. Though the recordings were made in a busy clinical environment with typical noise and patient movement, the algorithm was able to process almost 90% of the files, with overall accuracy similar to that of a cardiologist, indicative of potential clinical feasibility and usefulness. Because recordings from several chest locations per patient were used, the dataset is similar to clinical encounters where auscultation is usually done from more than one location. By analyzing algorithm performance at each chest location and for a wide range of patient ages and heart rates, these data may be useful in developing strategies to optimize clinical screening for pathologic murmurs. Since the algorithm tested is designed to run remotely from a cloud server using record–send–analyze technology, the dataset used for this trial is materially similar to that which would be collected in an actual clinical trial but has the advantage of being available for testing other algorithms to provide an efficient, objective comparison to prior art. For algorithms that rely on accurate segmentation of the cardiac cycle, a surrogate metric for assessing correct identification of each cycle is the estimate of heart rate. This was evaluated here by comparing the gold standard ECG to the algorithm estimate of heart rate and close agreement was found.

To date, no comparable validated dataset of heart sound recordings has been reported, though a smaller, multi-sourced collection without accompanying detailed clinical and echocardiographic information for each case, has recently been described [20]. With increasing use of electronic stethoscopes and linked electronic medical records, the practicality of creating even larger datasets for algorithm development and validation now exists. This approach is similar to that taken after the development of computerized electrocardiography in the 1960–1970s which led to automated ECG interpretation algorithms [21, 22]. Future algorithms are needed to detect additional abnormal acoustic features beyond murmurs. The ideal dataset for algorithm validation should not only include multiple representations of a wide range of common cardiac pathologies, but also normal subjects and uncommon pathologies across the spectrum of age ranges for which the conditions are most clinically relevant. In addition, detailed and accurate clinical and echocardiographic diagnoses for each case are required. Adherence to standardized recording techniques, instrumentation, sampling rates and filtering protocols across cases is beneficial to reduce variation in signal quality and content not related to patient or disease-specific issues, increasing the usefulness of training and validation datasets.

Advances in echocardiographic image digitization, standardization and storage have led to recent interest in using AI for automated interpretation of echocardiograms. Initial efforts in this area have been directed primarily toward detection of abnormal ventricular function and regional wall motion [23, 24]. However, the complex anatomic variation present in congenital heart disease will prove a more challenging target for image-based AI interpretation, at least in the short term. This complexity currently makes echocardiography potentially less attractive for large-scale population screening compared to acoustic-based strategies. Despite the relative advantages of AIAA, cardiac defects may have multiple acoustic signatures depending on morphologic variations, severity, and patient-related factors including physiologic state and body habitus. In addition, different defects may have similar acoustic phenotypes, and multiple defects may be present in the same patient. Thus, algorithms designed to detect valvular and congenital heart disease from acoustic features will likely remain more useful as a screening tool than as an alternative to imaging for accurate and specific morphologic diagnosis. However, the use of AIAA by the generalist to more accurately detect pathologic murmurs has potential to improve the recognition of heart disease and lower rates of unnecessary referrals to the specialist.

Study Limitations

While the virtual clinical trial format is particularly well-suited for validating and comparing algorithms requiring recorded heart sounds as input, an actual clinical trial would additionally give data on procedural aspects of AIAA not evaluated here which may have significant impact on performance. Though this is the largest trial of its kind to date, this dataset includes relatively few diastolic murmurs; thus interpretation of performance for these murmurs should be made with caution. Positive and negative predictive values associated with this or any algorithm will depend on disease prevalence in the specific clinical setting in which it is being used. Likewise, clinical use of AIAA to screen for heart disease is likely to be most effective as a decision support tool, used in combination with other clinical data.

Conclusions

The algorithm tested has high sensitivity and specificity for detection of pathologic murmurs in this dataset, similar to levels reported for specialist auscultation, making it a potentially useful screening tool for heart disease. CARD appears to be well-suited for conducting virtual clinical trials of algorithms designed to assist cardiac auscultation. It can be used to efficiently and objectively measure and compare performance of algorithms prior to expensive and time-consuming actual clinical trials. Objective comparative analysis of decision-support algorithms through use of large datasets can facilitate and accelerate understanding of the potential clinical usefulness of this technology.

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Compliance with Ethical Standards

Conflict of interest Andreas J. Reinisch is an employee and owner of CSD Labs. Michael J. Unterberger is an employee of CSD Labs. Andreas J. Schriefl is an employee and owner of CSD Labs. W. Reid Thompson declares no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors. The study dataset contained no protected health information; therefore, the study was exempted from Institutional Review Board approval.

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