ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

Caption Guidance to Guide Image Acquisition in Point-of-Care Echocardiography for Patients with Cardiovascular Disease

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Summary of Key Points

- Cardiovascular diseases are mainly a consequence of abnormal cardiac structure, function, or hemodynamic parameters that can be determined by echocardiography, which are conventionally performed in echocardiography laboratories with dedicated ultrasound machines.
- Advances in the miniaturisation of ultrasound equipment allow for cardiac point-of-care ultrasound (POCUS), where bedside echocardiography can be performed by users with varying competency in image acquisition, limiting its reliability for optimal clinical decisions to be made.
- Caption Guidance (Caption Health, Inc.) is an artificial intelligence (AI) software that provides real-time prescriptive guidance to medical professionals or novice operators to obtain limited two-dimensional transthoracic echocardiography images (10 standard views) for diagnostic assessment of cardiac chambers in the point-of-care settings. This can increase the reproducibility and standardisation of image acquisition.
- Caption Guidance was found to be safe and effective in guiding trained sonographers and novice operators to acquire echocardiographic clips of diagnostic quality for clinical assessments.
    - One adverse event (0.4%) unrelated to the software was reported. Potential risks may arise from device failure or user error.
    - 92.5% to 98.8% of AI-guided scans obtained by nurses without ultrasound experience were of diagnostic quality for the visual assessment of core cardiac parameters by expert cardiologists, indicating clinical utility of the software.
    - The proportion of nurse scans of sufficient diagnostic quality for the visual assessment of cardiac parameters were similar to those obtained by sonographers using the same ultrasound equipment without AI guidance, except for inferior vena cava size (nurse *vs.* sonographer, 57.4% *vs.* 91.5%).
    - There was a high agreement in diagnostic decisions for each cardiac parameter between the nurse and sonographer scans (range, 83.2% to 99.6%), further supporting the clinical usability and utility of the software.
    - Similar ejection fraction measurements were found between the AI-guided scans acquired by novice operators and conventional scans obtained by experts.
    - Real-world integration of Caption Guidance into the intensive care unit (ICU) workflow impacted clinical decisions and patient management.
    - The software may bring potential healthcare system benefits, including improved clinical workflow, resource utilisation and care delivery.
- However, the relatively small sample size and lack of patients recruited from clinical settings such as the emergency department or ICU in the pivotal study may limit the generalisability of the results, although the real-world ICU use may allay some concerns.
- No studies reported on cost-effectiveness of the Caption Guidance software.
- Key implementation considerations include understanding the place of the AI software in current clinical workflows, risk assessment, performance tracking, assessing cybersecurity vulnerabilities and staff training. Long-term monitoring and review of the AI performance, while ensuring it continues to be of clinical relevance and fulfil organisational needs may be required post-implementation.

I. Background

Cardiovascular disease (CVD) refers to a group of multifactorial disease that includes both congenital and acquired disorders.[1] Common CVD includes coronary artery disease, which arises from reduced myocardial perfusion due to ischemia that can lead to myocardial infarction or heart failure.[2] Other types of CVD include valvular heart disease, cardiomyopathies and congenital heart disease.[1] These conditions are mainly a consequence of abnormal structural, functional or hemodynamic changes due to underlying insults to the heart and the vasculature.[1] These abnormalities can be determined by echocardiography, which is a non-invasive imaging modality commonly used in cardiology. Typically performed in echocardiography laboratories using dedicated ultrasound machines, echocardiography allows the evaluation of cardiac anatomy and structure, size and function of the cardiac chambers, morphology and function of the heart valves, and intracardiac hemodynamic parameters.[3,4] Transthoracic echocardiography (TTE), where a probe is placed on the chest to obtain views of the heart, is the most common type of echocardiography for the diagnosis, follow-up and management of CVD.[5]

Globally, CVD is the leading cause of mortality and morbidity.[6,7] In Singapore, CVD accounted for 31.7% of all deaths in 2020, mostly due to ischemic heart disease.[8] It remained as one of the leading causes of disease burden locally, responsible for 14% of all disability-adjusted life years in 2019.[9] Furthermore, CVD burden attributable to modifiable risk factors such as hypertension, hyperlipidemia, obesity and diabetes has been rising globally.[10] It also incurs substantial economic burden in Singapore, with an estimated annual direct and indirect costs of US$7.6 billion for ischemic heart disease and stroke.[11]

The ability to perform echocardiography outside the conventional laboratory setting is limited by the lack of trained sonographers and cardiologists to acquire images. Recent advances in echocardiography include the miniaturisation of ultrasound equipment, allowing cardiac point-of-care ultrasound (POCUS) for bedside examination of patients in emergency or critical care settings.[3,12] Cardiac POCUS, which is increasingly performed by medical professionals of other disciplines with varying experience in ultrasound imaging,[13] has been gaining recognition as an important tool alongside conventional physical examination, allowing for prompt clinical decisions to be made.[14,15] The lack of user experience and time sensitivity in the point-of-care setting may result in varying image quality owing to a lack of standardisation, which consequentially may result in sub-optimal clinical decisions.[12,16] Further, the use of cardiac POCUS in diverse clinical settings may lead to limited reliability compared to high-end echocardiography.[15] A better standardisation in the acquisition of cardiac POCUS images would allow a greater degree of diagnostic quality for appropriate clinical assessments and decisions to be made. To this end, artificial intelligence (AI) technologies have been proposed as a promising solution to assist and standardise image acquisition in cardiac POCUS.

II. Technology

Caption Guidance (Caption Health, Inc.) is a novel AI software developed using deep learning technology to emulate the expertise of sonographers. It is based on a convolutional neural network that was trained with more than five million hand movements by cardiac sonographers, allowing it to recognise the impact of probe position and movement on image appearance.[17] It provides real-time prescriptive guidance to medical professionals or novice operators to steer their transducer position and hand movements to acquire cardiac ultrasound images that represent standard echocardiographic diagnostic views and orientations, while displaying the current image quality and automatically capturing images of diagnostic quality.[17,18] It is intended for the acquisition of limited two-dimensional TTE (2D-TTE) in adult patients for the diagnostic assessment of cardiac chambers based on the 10 standard views as summarised in Table A1 (Appendix A).[18] These views are typically used in the diagnosis of various cardiac conditions. Additionally, Caption Guidance is targeted for use in the point-of-care setting, where it is labelled for use with the Terason uSmart 3200t Plus ultrasound system. The user has access to both the native Terason or Caption Guidance interface and is able to switch between the two.[18] Key features of the Caption Guidance software includes (Figure 1):

- Quality Meter: Provides real-time feedback that show users how close they are to capturing a diagnostic-quality TTE image. It rises as the users get closer to the optimal view, turning green to indicate that the image is of diagnostic quality.
- Prescriptive Guidance: Provides real-time guidance to direct to the user to manipulate the transducer to acquire the optimal view.
- Auto-Capture: Automatically captures clips deemed to be of diagnostic quality.
- Save Best Clip: Continuous assessment of clip quality during the scanning process and allows the user to retrospectively record the highest quality clip if the user is not able to obtain a clip sufficient for Auto-Capture.

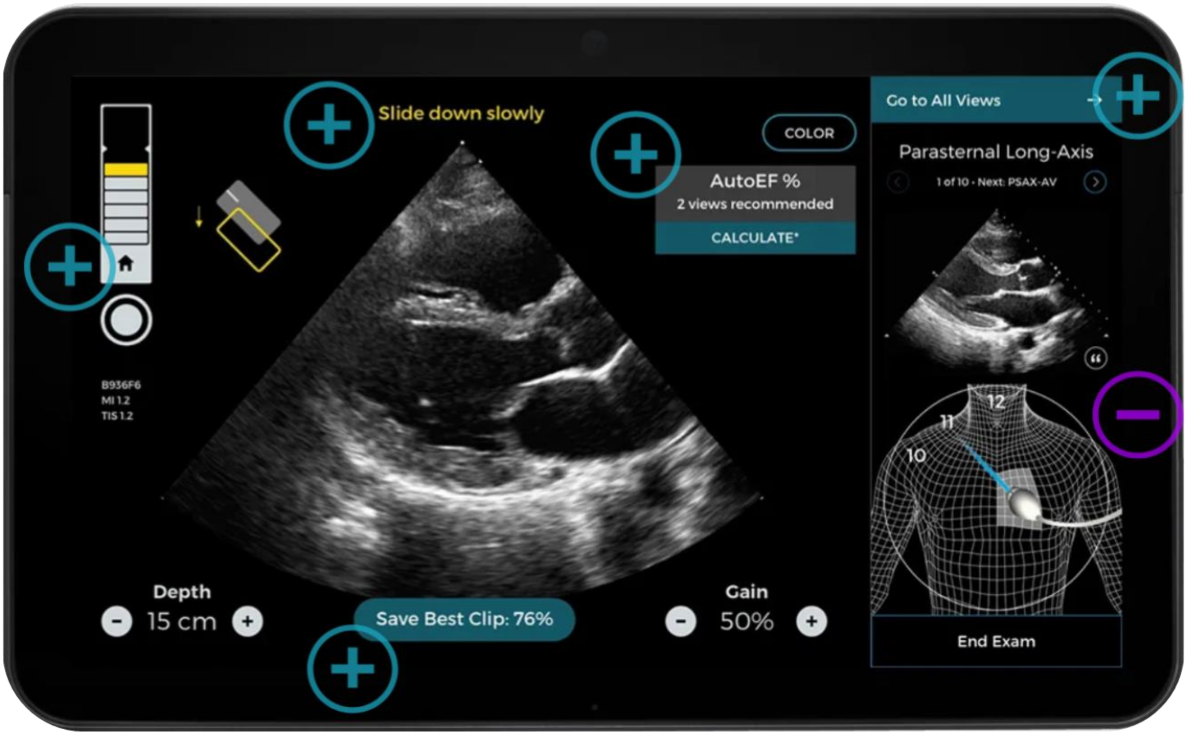

Figure 1: User interface of the Caption Guidance software, highlighting the key features to help users in obtaining TTE images. Image adapted from *https://www.captionhealth.com/technology*.

Caption Guidance works in tandem with the US Food and Drug Administration (FDA) cleared (K200621) Caption Interpretation software as part of the Caption AI platform. Caption Interpretation provides automated calculation of left ventricular ejection fraction by analysing echocardiography images acquired with assistance from Caption Guidance.

The application of AI to cardiac POCUS may bridge the gap between new technological capabilities and the wide variation in ultrasound competency of medical professionals.[19] Caption Guidance can alleviate some of the key challenges of cardiac POCUS by increasing reproducibility and standardisation of image acquisition and reporting, which may improve clinical workflows and decision-making.[16]

III. Regulatory and Subsidy Status

The Caption Guidance software was granted the Breakthrough Device Designation by the FDA and received a De Novo approval (DEN190040) on 7th February 2020 for the acquisition of cardiac ultrasound images.[18] Following this, additional 510(k) clearances were issued by the FDA for an update to the software usability and performance in April 2020,[20] and to address changes to the anticipated modifications of the software and methods to ensure safe implementation of these modifications in September 2020.[21]

In the United States, reimbursement was granted by the Centers for Medicare and Medicaid Services for Medicare patients receiving in-patient care involving Caption Guidance guided ultrasound acquisition for a variety of cardiac conditions.[22]

IV. Stage of Development in Singapore

☒	Yet to emerge	☐	Established
☐	Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☐	Established *but* modification in indication or technique
☐	Nearly established	☐	Established *but* should consider for reassessment (due to perceived no/low value)

V. Treatment Pathway

For patients who are clinically indicated for TTE, the scan is performed by a trained sonographer or doctor in an echocardiography laboratory and is reviewed by a cardiologist trained in echocardiography.[23] These patients may include those presenting with heart murmurs, valvular stenosis or regurgitation, ischemic heart disease, cardiomyopathy, aortic disease or pericardial disease, where TTE allows for the assessment of ventricular function and cardiac morphology.[24] Similar clinical information may also be obtained by nuclear cardiology, cardiovascular magnetic resonance imaging, transesophageal echocardiography and cardiac computed tomography, although its use vary based on an individual basis as well as service availability.[24] However, unlike TTE which can be performed at the point-of-care settings for a variety of cardiac conditions, these tests are often performed in specialty centres by trained experts or only for certain cardiac conditions.

In acute settings such as the emergency department (ED) where urgent triage and patient evaluation is required, cardiac POCUS has been gaining traction and is embedded in emergency medicine practice.[25] In the United States, cardiac POCUS is usually performed by emergency physicians or other medical professionals under their supervision in the ED, which are interpreted and incorporated into treatment plans.[26] The American College of Emergency Physicians outlined the scope of cardiac POCUS in the ED to include diagnosis, management of the critically ill, procedural guidance and physiological monitoring.[26] Besides the ED, cardiac POCUS may also be practiced in other point-of-care settings such as critical care or out-of-hospital settings by medical professionals of various disciplines.[26]

When incorporated into clinical workflows, Caption Guidance can be used to work alongside and support medical professionals currently performing cardiac POCUS, ensuring standardised image acquisition for better clinical decision-making and patient management. Additionally, it may also allow any healthcare professionals with no prior experience in ultrasonography to obtain echocardiographic images of relatively standardised diagnostic quality, increasing the availability of echocardiography to settings where urgent investigation into the cardiac structure and function is required, as well as in resource-constrained settings. As a result, this may potentially increase patient's access to echocardiography and lead to an improvement in time to diagnosis.

VI. Summary of Evidence

This assessment was conducted based on the Population, Intervention, Comparison and Outcome (PICO) criteria presented in Table 1. The evidence base, the inclusion and exclusion criteria were listed in Table B1 (Appendix B). Three studies[17,27,28] and a FDA decision summary[18] accompanying the De Novo approval of Caption Guidance were included in this brief. The FDA decision summary[18] comprised of two independent studies, one of which was a pivotal study.[29] The study design and characteristics of the included studies were summarised in Table B2 (Appendix B).

Table 1. Summary of PICO criteria

Population	Adult patients who are indicated for two-dimensional transthoracic echocardiography (2D-TTE)
Intervention	2D-TTE image acquisition guided by Caption Guidance
Comparison	Conventional 2D-TTE performed without guidance for automated probe adjustments
Outcome	Safety, clinical effectiveness (diagnostic quality of 2D-TTE views captured), cost effectiveness

Safety

The Caption Guidance software was found to be safe, with one (0.4%) adverse event (AE) reported in the pivotal study due to pain at the skin site owing to elevated temperature of the transducer that was determined to be unrelated to the software.[18,29] However, there may be potential health risks arising from the use of the software including algorithm, software or hardware failure, or user error, that may impede the acquisition of diagnostic quality images and delay clinical care.[18]

Effectiveness

Impact on patients

Across two studies[27,28] and the FDA decision summary[18], it was reported that Caption Guidance enabled medical professionals with no prior experience in ultrasound to obtain echocardiographic clips, where the proportion of clips with diagnostic quality ranged from 55.2% to 92.9% across the 10 standard views (Table C1 in Appendix C). Particularly in the pivotal study, 46.2% of the echocardiographic clips were acquired by nurses without ultrasound experience using the Auto-Capture feature and 93.8% of the auto-captured clips were rated diagnostic by a panel of expert cardiologists, indicating high effectiveness of the feature.[18] Moreover, in a separate study evaluated by the FDA, trained sonographers were able to obtain a high proportion of diagnostic quality images with and without Caption Guidance using the same ultrasound equipment, indicating that the software did not hinder image acquisition by trained sonographers.[18] These findings support the use of Caption Guidance by users trained in echocardiography in addition to those with no prior experience.[18]

In addition, the echocardiographic clips obtained with Caption Guidance by novice medical professionals were clinically useful, where it allowed for clinical assessments of cardiac function and structure as demonstrated across three studies[17,27,28] and the FDA decision summary[18]. In the prospective pivotal study[18], the AI-guided image acquisition by nurses without ultrasound experience met the FDA pre-specified primary effectiveness endpoints (more than 80% of scans with sufficient quality for visual assessment of cardiac parameters), where it achieved adequate quality for a panel of expert cardiologists to make qualitative visual assessment of left ventricular (LV) size, LV function and pericardial effusion in 98.8% (237 out of 240) of scans and right ventricular (RV) size in 92.5% (222 out of 240) of scans (Table 2).[18,29] In addition, more than 90% of the nurse scans were found to be satisfactory for the visual assessment of secondary endpoint parameters (RV function, left atrial size, aortic and mitral valve structure) except for tricuspid valve structure (83.3%) and inferior vena cava (IVC) size (57.5%).[29] Of note, the performance of the nurse scans was not significantly different across patients with different body mass index (BMI) categories and cardiac pathology, and was also unaffected by the presence of cardiac implants such as pacemakers and prosthetic valves (Table C2 in Appendix C).[29]

Table 2: Proportion of AI-guided echocardiography image acquisition by nurses without ultrasound experience that were of sufficient diagnostic quality to assess cardiac clinical parameters as reported by Narang et al. (2021)[29]

Endpoint	Clinical parameter examined by qualitative visual assessment	Total number of scans performed	Scans of sufficient quality, n (%, 95% CI)
Primary	Left ventricular size	240	237 (98.8%, 96.7% to 100%)
	Global left ventricular function	240	237 (98.8%, 96.7% to 100%)
	Right ventricular size	240	222 (92.5%, 88.1% to 96.9%)
	Nontrivial pericardial effusion	240	237 (98.8%, 96.7% to 100%)
Secondary	Right ventricular function	240	219 (91.3%, 85.7% to 96.8%)
	Left atrial size	240	227 (94.6%, 90.7% to 98.5%)
	Aortic valve structure	240	220 (91.7%, 88.0% to 95.3%)
	Mitral valve structure	240	231 (96.3%, 93.9% to 98.6%)

	Tricuspid valve structure	240	200 (83.3%, 77.0% to 89.7%)
	Inferior vena cava size	240	138 (57.5%, 41.5% to 73.5%)

Furthermore, the proportion of diagnostic quality scans acquired by the nurses were not significantly different to those obtained by trained sonographers using the same hardware without AI assistance for the visual assessment of the cardiac parameters by expert cardiologists who were blinded, except for IVC size (nurse *vs.* sonographer, 57.4% *vs.* 91.5%; Table 3).[29] This was postulated to the close proximity of the IVC with the descending aorta and would require further algorithm development.[29] Notably, there was a high proportion of scans with similar diagnostic decisions for each cardiac parameter between the nurse and sonographer scans as ascertained by the blinded expert cardiologists (range of diagnostic agreement across all 10 cardiac parameters, 83.2% to 99.6%), further validating the clinical utility of Caption Guidance (Table C3 in Appendix C).[18,29]

Table 3: Comparison of the diagnostic quality between the nurse- and sonographer-acquired scans as reported by Narang et al. (2021)[29]

Clinical parameter examined by qualitative visual assessment	Scans of sufficient quality				Nurse-sonographer difference, % point
	Nurse scan		Sonographer scan		
	n	% (95% CI)	n	% (95% CI)	
Nontrivial pericardial effusion	232	98.7% (96.3% to 99.7%)	234	99.6% (97.7% to 100.0%)	-0.9
Left ventricular size	232	98.7% (96.3% to 99.7%)	235	100% (98.4% to 100.0%)	-1.3
Global left ventricular function	232	98.7% (96.3% to 99.7%)	235	100% (98.4% to 100.0%)	-1.3
Mitral valve structure	226	96.2% (92.9% to 98.2%)	233	99.1% (97.0% to 99.9%)	-2.9
Right ventricular size	217	92.3% (88.2% to 95.4%)	226	96.2% (92.9% to 98.2%)	-3.9
Right ventricular function	214	91.1% (86.7% to 94.4%)	226	96.2% (92.9% to 98.2%)	-5.1
Left atrial size	222	94.5% (90.7% to 97.0%)	234	99.6% (97.7% to 100.0%)	-5.1
Aortic valve structure	215	91.5% (87.2% to 94.7%)	228	97.0% (94.0% to 98.8%)	-5.5
Tricuspid valve structure	195	83.0% (77.6% to 87.6%)	217	92.3% (88.2% to 95.4%)	-9.3
Inferior vena cava size	135	57.4% (50.9% to 63.9%)	215	91.5% (87.2% to 94.7%)	-34.1

Notes:
1. The nurse scans were obtained with the Terason ultrasound system with assistance from Caption Guidance while the sonographer scans were obtained with the same ultrasound system unassisted by Caption Guidance.
2. The study population consisted of 235 patients who had scans performed by both the nurse and sonographer.

Aside from visual assessment of the cardiac parameters by expert cardiologists, the echocardiographic clips obtained by nurses and sonographers in the pivotal study were objectively assessed by the quantification of LV ejection fraction (EF) with an AI-based software (AutoEF, Bay Labs Inc.). An absolute EF deviation of 3.96 EF% between the nurse and sonographer scans were reported which was within the inter-physician variability of EF computation.[18] Similar findings were reported by Schneider et al. (2021)[27] and Asch et al. (2021)[28], including early results from an abstract[30], where AI-based EF measurement using images acquired with Caption Guidance by novice users had good agreement with the reference EF values obtain by experts using conventional methodology (Table C4 in Appendix C). Additionally, linear measurement of the parasternal long-axis (PLAX) echocardiographic view acquired by the nurses and sonographers in the pivotal study for septal and posterior wall thickness, LV internal diameter and aortic root reported variability that was comparable to inter-sonographer measurement.[18] These quantitative assessments of the AI-guided scans corroborated the qualitative visual assessment by expert cardiologists, which affirmed similar diagnostic value of the AI-guided image acquisition compared to scans performed by trained experts, further pointing to the clinical utility of Caption Guidance.

The real-world clinical utility of Caption Guidance was also demonstrated in the COVID-19 intensive care unit (ICU), where it was used by critical care physicians with no formal ultrasound training to obtain cardiac POCUS images. In a series of five case reports, Cheema et al. (2021)[17] demonstrated that the software guided critical care physicians to acquire echocardiographic images for the diagnosis of various cardiac conditions, which was integrated into patient management and treatment plans.[17] A brief summary of the five case reports were detailed in Table C5 (Appendix C). Similarly, early evidence from an abstract reported that image acquisition guided by Caption Guidance in real-world COVID-19 units was reported to result in at least 70% of changes in patient management.[31]

Taken together, Caption Guidance appeared to be effective in guiding healthcare professionals without ultrasound experience to obtain echocardiographic clips of similar diagnostic quality and value with those obtained by trained sonographers for the clinical assessment of cardiac parameters, demonstrating good clinical utility. Further, its use in the ICU validated its integration into clinical workflows and its impact on decision-making and patient management in the real-world conditions.

Impact on healthcare system

Besides benefiting patients, Caption Guidance may improve clinical workflow, resource utilisation and delivery of patient care. It may reduce the barrier for the adoption and usage of cardiac POCUS by various healthcare professionals, which can improve patient access to echocardiography while alleviating resource constraints associated with the shortage of trained sonographers. Furthermore, the potential of the software to provide a relatively standardised image acquisition may improve echocardiographic interpretation and reduce diagnostic delays arising from unsatisfactory images, allowing timely diagnosis for better management of cardiac conditions to improve care delivery. In addition, AI technologies such as Caption Guidance, together with technological advancements of cart-based ultrasound systems to handheld devices, would serve as potential enablers for ultrasound imaging in community care where access to advanced imaging may be limited.

Cost effectiveness

No studies were identified that informed on the cost-effectiveness of the Caption Guidance software. However, the use of POCUS in the ED was found to result in significant cost savings from reduced additional testing and better clinical decision.[32]

Ongoing clinical trials

One study investigating the Caption Guidance software was identified from the ScanMedicine database (NIHR Innovation Observatory). However, the current status of the study is unknown (Table 4).

Table 4: Ongoing clinical trial of the Caption Guidance software

Study (Trial ID)	Estimated enrolment	Study design and aim	Estimated study completion date	Recruitment Status
Evaluation of TTE Utilization in Medical Surgery Step-Down Unit: Use of AI Assisted Point-of-Care Echo With Guidance Technology (NCT04203251)	100	A non-randomized, unblinded study to evaluate Caption Health guidance software in patients in the medical surgery step-down unit. Patients will be scanned by a trained hospitalist and up to 4 standard views will be obtained per participant.	May 2020	Unknown*
* As of December 2019, the recruitment status was 'not yet recruiting'. The study has passed its completion date and the recruitment status has not been verified in more than two years.				

Summary

Overall, Caption Guidance was found to be safe and effective for use by trained sonographers and novice operators and may bring potential healthcare system benefits. There were no major safety issues related to the software. The software demonstrated clinical utility, where the proportion of AI-guided nurse scans of diagnostic quality for the visual assessment of cardiac parameters were high and comparable to those obtained by sonographers, except for IVC size (nurse *vs.* sonographer, 57.4% *vs.* 91.5%), and had a high rate of agreement in diagnostic decisions made by blinded expert cardiologists (range across 10 cardiac parameters, 83.2% to 99.6%). Objective EF quantification and PLAX measurements further corroborated the diagnostic quality and clinical usefulness of the AI-guided scans acquired by novice medical professionals. Integration of the software in the ICU setting demonstrated its real-world clinical utility, where it informed clinical decisions and patient management. The software may potentially benefit the healthcare system by reducing the barrier for cardiac POCUS utilisation and improving patient access to echocardiography services, alleviating the shortage of trained sonographers, improving care delivery through a relatively standardised image acquisition, and serving as a potential enabler for ultrasound imaging in community care. The cost-effectiveness of Caption Guidance remains to be determined.

Nevertheless, the results present some limitations. Although the sample size was adequately powered for the endpoints in the pivotal study, the relatively small number of patients (n=240) and nurses (n=8) in the pivotal study may limit its generalisability. This may be further exacerbated by the non-consecutive patient recruitment to include patients of a wide BMI range and varying cardiac pathology. In addition, patients in the pivotal study were not recruited from the ED or ICU settings which can further limit the generalisability of Caption Guidance in these settings, although real-world use in the ICU setting reported by Cheema et al. (2021)[17] may alleviate some of these concerns. Time lag bias may also limit the results in the pivotal study as patients received a sonographer scan within two weeks of the nurse scan where changes in cardiac morphology or function may have occurred, although both scans were generally performed on the same day.

VII. Estimated Costs

The cost of the Caption Guidance software was not available.

VIII. Implementation Considerations

The implementation of AI medical devices (AI-MDs) such as Caption Guidance in the public healthcare institutions may bring about certain considerations as outlined in the Ministry of Health (MOH) Artificial Intelligence in Healthcare Guidelines (AIHGle).[33] As Caption Guidance is an off-the-shelf AI product, it may be imperative to exercise clinical governance and oversight over the use of the software to ensure safe and responsible implementation. This can include seeking the relevant organisational approvals and proper documentation of the decision to implement the AI-MD, proposed implementation plans and understanding the place of the AI-MD in current clinical workflows, risk assessment to anticipate software failure and its mitigation measures such as reverting back to manual image acquisition without AI guidance, performance tracking to ensure similar performance as indicated by the developer ("ground-truthing"), assessing cybersecurity vulnerabilities, staff training and transparency in end-user communications.[33] Additionally, there may also be a need for long-term monitoring and review of the AI performance and ensuring that it continues to have clinical relevance and meet organisational needs post-implementation.[33] It is worthwhile to note that even though developers are responsible for the proper design of algorithms used in the Caption Guidance software, this does not change the accountability of the implementing institution or the individual medical professional in their decision to use the AI software in delivering safe and appropriate care.

In particular, a local expert deemed that the Caption Guidance software would be more clinically useful for medical professionals with a basic understanding of TTE and cardiology. As the software allows non-specialised medical professionals without a formal background or training in ultrasound to acquire cardiac POCUS images, a set of training framework and guidelines governing its appropriate use and limitations may be useful to ensure patient safety and proper care delivery. Additionally, further consideration on credentialling may be warranted. In the pivotal trial, the nurses underwent a one-hour didactic training session to be familiarised with the ultrasonography machine and the Caption Guidance software followed by hands-on practise scans. Similarly, a tailored curriculum may be appropriate for those using cardiac POCUS as an extension of physical examination in contrast to a more intensive training targeted at users who use cardiac POCUS for bedside diagnosis, decision-making and triage.[25] Likewise, the software may also reduce the learning curve for a novice in echocardiography. Additional considerations may include cost of the additional training required and further trials of the software in the local clinical setting, especially in a fast-paced environment like the ED where time taken for image acquisition is a key consideration.

It should also be noted that the Caption Guidance software is currently labelled for use with the Terason uSmart 3200t Plus cart-based ultrasound system, with plans to also include the Butterfly iQ+ (Butterfly Network, Inc.) handheld system. Although these ultrasound devices are not currently registered with the Health Sciences Authority (HSA) in Singapore, its predicate devices (Terason uSmart 3200t and Butterfly iQ) have received HSA approval. Medical professionals or healthcare institutions who wish to use the Caption Guidance software and corresponding ultrasound devices in Singapore should ensure that the appropriate regulatory approval from HSA is obtained. In particular, the Butterfly iQ+ system is currently available in 20 countries and is in the process of obtaining regulatory approvals in other jurisdictions. Future local availability of these updated models may be anticipated.

Furthermore, telemedicine support may be required with the implementation of the Caption Guidance software in settings where cardiology expertise may not be readily available, such as primary or community care. This would allow downstream clinical interpretation and diagnosis for the images obtained. To this end, a store-and-forward approach may be adopted to allow images captured with the software to be transmitted and reviewed by qualified medical professionals.

IX. Concurrent Developments

The application of AI in echocardiography is largely limited to the analysis of acquired echocardiographic images and clips. However, AI solutions to guide image acquisition in echocardiography are becoming increasingly available. While Caption Guidance remains the only commercially available device to provide probe alignment guidance, one other similar AI technology is in ongoing development (Table 5).

Additionally, further development of the Caption Guidance algorithm may be anticipated to allow for colour, pulsed-wave and continuous-wave Doppler acquisitions that can be used to assess hemodynamic and cardiac valve functions.[29] Furthermore, the software is undergoing development to provide real-time guidance for the acquisition of diagnostic quality images for lung ultrasound.

Table 5: Similar AI technology for probe alignment guidance in POCUS

Technology (Manufacturer)	Brief description	Status
Trio (EchoNous, Inc.)	Trio is a set of algorithms for the Kosmos handheld ultrasound device that help doctors guide the probe into position, grade image quality and label cardiac structures in real-time.	Plans to file for FDA clearance

X. Additional Information

Two studies[28,29] included in this assessment were funded by Caption Health, while conflict of interest was reported in three studies[17,28,29] where some of the authors were affiliated with Caption Health.

In July 2020, the American Society of Echocardiography (ASE) issued a statement supporting the use of AI to assist guidance of optimal image acquisition for cardiovascular ultrasound to meet the increasing demand of patients requiring cardiovascular care worldwide.[34] ASE further cited Caption Health as one of the industry innovators leading the development of AI in echocardiography for better patient-centric care.[34]

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Appendix

Appendix A: Additional information regarding Caption Guidance

Table A1: Standard 2D-TTE views indicated for use

S/N	Standard 2D-TTE views indicated for acquisition with Caption Guidance
1	Parasternal Long-Axis (PLAX)
2	Parasternal Short-Axis at the Aortic Valve (PSAX-AV)
3	Parasternal Short-Axis at the Mitral Valve (PSAX-MV)
4	Parasternal Short-Axis at the Papillary Muscle (PSAX-PM)
5	Apical 4-Chamber (AP4)
6	Apical 5-Chamber (AP5)
7	Apical 2-Chamber (AP2)
8	Apical 3-Chamber (AP3)
9	Subcostal 4-Chamber (SubC4)
10	Subcostal Inferior Vena Cava (SC-IVC)

Appendix B: Studies included and study design

Table B1: List of included studies

Type of study	Number of studies included
Published studies	3
FDA decision summary	1
Note: 1. Inclusion criteria a. Studies that fulfil the PICO criteria listed in Table 1. 2. Exclusion criteria a. Studies only available in the abstract form. b. Duplicate studies.	

Table B2: Characteristics of the included studies

Author (year)	Number of patients	Study design	Population	Intervention	Comparison
FDA decision summary[18]	50	Prospective, descriptive study	Not reported	Caption Guidance guided image acquisition by trained sonographers	Scans conducted by sonographers with the same ultrasound equipment unassisted by Caption Guidance
	240	Prospective, two-centre pivotal trial; Narang et al. (2021)[29]	Patients at least 18 years old who were scheduled to undergo a clinically indicated echocardiogram	Caption Guidance guided image acquisition by 8 nurses with no prior scanning experience with the Terason machine	Image acquisition by sonographers with the Terason machine unassisted by Caption Guidance
Schneider et al. (2021)[27]	14	Prospective pilot study	Inpatients in the general cardiology ward who had sinus rhythm	Caption Guidance guided image acquisition by 19 echo-naïve first semester	Scans conducted by expert with GE S70 (General Electric Healthcare)

				medical students with the Terason machine	
Asch et al. (2021)[28]	67*	Prospective study	Patients who are clinically indicated for echocardiography	Caption Guidance guided image acquisition by 8 nurses with no prior scanning experience with the Terason machine	Scans conducted by expert with conventional methodology
Cheema et al. (2021)[17]	5	Prospective, real-world study	Patients admitted to the COVID-19 intensive care unit	Caption Guidance guided image acquisition by critical care physicians with no formal training in ultrasound	–
* Number of patients in Protocol 2 of the study which involves image acquisition by novice nurses.					

Appendix C: List of supplementary tables

Table C1: Percentage of novice-acquired clips that were of diagnostic quality for each view

Echocardiographic view	Percentage of novice-acquired clips of diagnostic quality, n (%, 95% CI)		
	FDA decision summary[18] (n=240)	Schneider et al. (2021)[27] (n=57)*	Asch et al. (2021)[28] (n=67)
Parasternal Long-Axis (PLAX)	92.1% (87.9% to 96.3%)	58.0%	55.2%
Parasternal Short-Axis at the Aortic Valve (PSAX-AV)	66.3% (59.0% to 73.5%)	–	–
Parasternal Short-Axis at the Mitral Valve (PSAX-MV)	75.8% (70.7% to 80.9%)	–	–
Parasternal Short-Axis at the Papillary Muscle (PSAX-PM)	92.9% (89.1% to 96.7%)	–	–
Apical 4-Chamber (AP4)	88.8% (81.5% to 96.0%)	86.0%	88.1%
Apical 5-Chamber (AP5)	78.8% (66.9% to 90.6%)	–	–
Apical 2-Chamber (AP2)	80.0% (70.4% to 89.7%)	68.0%	56.7%
Apical 3-Chamber (AP3)	71.3% (61.6% to 80.9%)	–	–
Subcostal 4-Chamber (SubC4)	76.3% (70.2% to 82.3%)	–	–
Subcostal Inferior Vena Cava (SC-IVC)	59.2% (43.1% to 75.2%)	–	–
* Based on the total number of echocardiographic scans performed, where 19 medical students each scanned three patients. Note: The diagnostic quality of the echocardiographic clips (PLAX, AP2 and AP4) reported by Schneider *et al.* (2021)[27] and Asch *et al.* (2021)[28] were based on sufficient image quality to produce an automated left ventricular ejection fraction estimate.			

Table C2: Performance of nurse scans in the qualitative visual assessment of the clinical parameters stratified by BMI and cardiac pathology as reported by Narang et al. (2021)[29]

Endpoint	Clinical parameter examined by qualitative visual assessment	Scans of sufficient quality, n (%)					
		BMI Category			Presence of known cardiac abnormality		Total (n=240)
		<25 (n=85)	25 to <30 (n=76)	≥30 (n=79)	Present (n=153)	Absent (n=87)	
Primary	Left ventricular size	84 (98.8%)	76 (100%)	77 (97.5%)	151 (98.7%)	86 (98.9%)	237 (98.8%, 96.7% to 100%)
	Global left ventricular function	84 (98.8%)	76 (100%)	77 (97.5%)	151 (98.7%)	86 (98.9%)	237 (98.8%, 96.7% to 100%)
	Right ventricular size	85 (100%)	70 (92.1%)	67 (84.8%)	138 (90.2%)	84 (96.6%)	222 (92.5%, 88.1% to 96.9%)
	Nontrivial pericardial effusion	84 (98.8%)	76 (100%)	77 (97.5%)	152 (99.3%)	85 (97.7%)	237 (98.8%, 96.7% to 100%)
Secondary	Right ventricular function	85 (100%)	70 (92.1%)	64 (81.0%)	135 (88.2%)	84 (96.6%)	219 (91.3%, 85.7% to 96.8%)
	Left atrial size	82 (96.5%)	73 (96.1%)	72 (91.1%)	143 (93.5%)	84 (96.6%)	227 (94.6%, 90.7% to 98.5%)
	Aortic valve structure	80 (94.1%)	73 (96.1%)	67 (84.8%)	137 (89.5%)	83 (95.4%)	220 (91.7%, 88.0% to 95.3%)
	Mitral valve structure	82 (96.5%)	74 (97.4%)	75 (94.9%)	146 (95.4%)	85 (97.7%)	231 (96.3%, 93.9% to 98.6%)
	Tricuspid valve structure	83 (97.6%)	62 (81.6%)	55 (69.6%)	123 (80.4%)	77 (88.5%)	200 (83.3%, 77.0% to 89.7%)
	Inferior vena cava size	62 (72.9%)	34 (44.7%)	42 (53.2%)	82 (53.6%)	56 (64.4%)	138 (57.5%, 41.5% to 73.5%)

Table C3: Overall agreement of nurse- and sonographer-acquired scans in the clinical assessment of the clinical parameters comparing normal and abnormal conditions based on a blinded evaluation by expert cardiologists as reported by Narang et al. (2021)[29]

Endpoint	Clinical parameter	Total number of scans*	Overall agreement between nurse- and sonographer-acquired scans, % (95% CI)
Primary	Left ventricular size	232	95.7% (92.2% to 97.6%)
	Global left ventricular function	232	96.6% (93.3% to 98.2%)
	Right ventricular size	213	92.5% (88.1% to 95.3%)
	Nontrivial pericardial effusion	231	99.6% (97.6% to 99.9%)
Secondary	Right ventricular function	212	92.9% (88.7% to 95.7%)
	Left atrial size	222	86.9% (91.9% to 90.7%)
	Aortic valve structure	213	90.6% (85.9% to 93.8%)
	Mitral valve structure	225	93.3% (89.3% to 95.9%)

	Tricuspid valve structure	186	95.2% (91.1% to 97.4%)
	Inferior vena cava size	131	83.2% (75.9% to 88.6%)
* Based on the number of patients whom a qualitative visual assessment can be made in both the nurse and sonographer scan populations.			

Table C4: Agreement of EF values between AI-guided image acquisition by novice users and those obtained by experts

Outcomes based on multi-views for EF computation	Agreement between automated EF measurements obtained by AI-guided image acquisition by novice users with reference EF values determined by experts	
	Schneider et al. (2021)[27] (n=14)	**Asch et al. (2021)[28] (n=67)**
Correlation value* (95% CI)	0.92	0.84 (0.75 to 0.90)
Bias, mean ± S.D.	3.02% ± 5.7%	2.5% ± 6.4%
* Determined by Pearson correlation coefficient for Schneider et al. (2021)[27] and by intraclass correlation for Asch et al. (2021)[28].		

Table C5: Clinical utility of Caption Guidance as demonstrated by real-world utilisation in the intensive care unit across five case reports as reported by Cheema et al. (2021)[17]

Case	Clinical assessments guided by Caption Guidance	Impact on clinical decision or patient management
#1	In a 65-year-old woman, AI-guided POCUS demonstrated a severely dilated and dysfunctional right ventricle which was a new finding from a previous echocardiography study, hyperdynamic left ventricle, a mitral valve prosthesis and a dilated inferior vena cava.	• Allowed determination of progressive pulmonary hypertension with subsequent right ventricular failure as the primary insult. • Patient improved with heart failure management.
#2	In a 76-year-old woman, AI-guided POCUS revealed normal right ventricular function, but new severe left ventricular dysfunction with a non-collapsible inferior vena cava.	• Attending physicians changed the treatment strategy to a regimen for acute heart failure.
#3	In a 72-year-old man, AI-guided POCUS revealed preserved left ventricular function, a dilated right ventricle with severely reduced function and a moderate pericardial effusion.	• Started on dobutamine for cardiogenic shock.
#4	In a 72-year-old man, AI-guided POCUS revealed acute biventricular heart failure with apical and midventricular akinesis that was suggestive of severe stress-induced cardiomyopathy.	• The patient had improved respiratory failure and shock state with diuresis and inotropic support from predominantly noncatecholamine vasopressors.
#5	In a 52-year-old man, AI-guided POCUS revealed severely dilated and dysfunctional right ventricle with a hyperdynamic left ventricle, in addition to a dilated, non-collapsible inferior vena cava.	• The patient was urgently converted to venoarterial extracorporeal membrane oxygenation (ECMO) for five days and was later successfully converted back to venovenous ECMO but was unable to be weaned from it.

Appendix D: Other supporting information relating to the Caption Guidance software

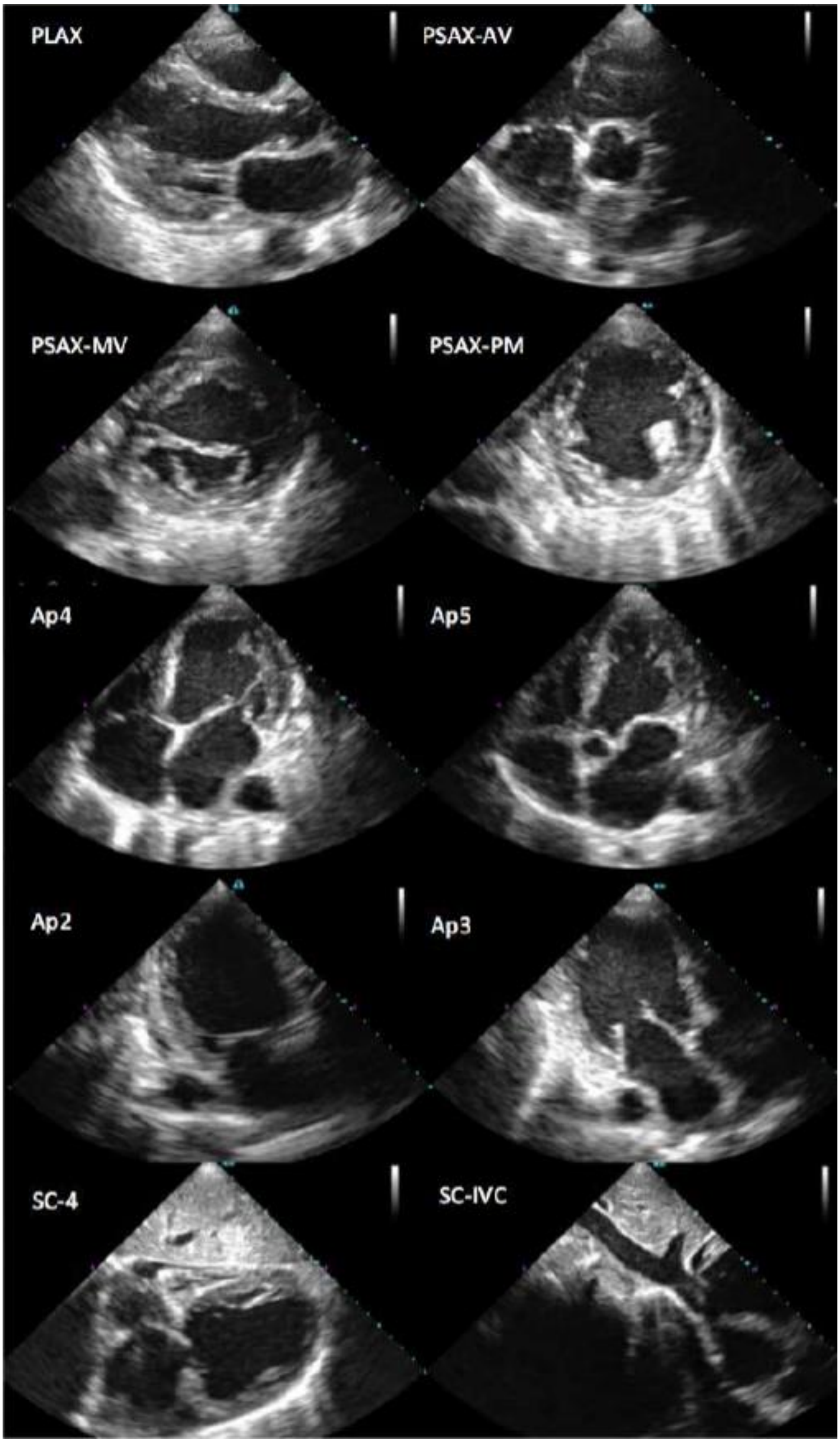

Figure D1: Representative still images of 10 standard TTE views acquired by a nurse with Caption Guidance that were judged to be of diagnostic quality. Image adapted from Narang et al. (2021)[29].