ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

EchoGo Heart Failure to Aid in the Diagnosis of Heart Failure with Preserved Ejection Fraction

Document Number: HSB-M 01/2025

Date: Mar 2025



This briefing presents independent research by the ACE. It reflects the evidence available at the time of writing based on a limited literature search. It does not involve critical appraisal and is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered. The views expressed are those of the author and not necessarily those of the ACE, or the Ministry of Health.

Contents

Summary of Key Points 2
I. Background 3
II. Technology 3
III. Regulatory and Subsidy Status 4
IV. Stage of Development in Singapore 5
V. Treatment Pathway 5
VI. Summary of Evidence 5
Safety 6
Effectiveness 6
Cost-effectiveness 8
Ongoing trials 8
Summary 9
VII. Estimated Costs 9
VIII. Implementation Considerations 9
IX. Concurrent Developments 10
X. Additional Information 10
References 11
Appendix 13

Summary of Key Points

- Heart failure (HF) is characterised by symptoms and signs caused by a structural or functional heart abnormality, with diagnosis corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. Heart failure with preserved ejection fraction (HFpEF) (i.e. left ventricular ejection fraction of at least 50 percent) accounts for about half of all HF cases worldwide.
- Transthoracic echocardiography (TTE) is routinely used to confirm the diagnosis of HF but there is considerable variability in the performance and interpretation of TTE findings, often leading to uncertainty and delay in diagnosis.
- EchoGo Heart Failure (Ultromics Ltd.) is a software-only device that allows for the automated detection of HF with preserved ejection fraction using artificial intelligence. It is indicated for use in patients suspected of HF with an ejection fraction of at least 50 percent. The device produces a binary classification result in a report to the physician workstations through a secure cloud-based server within 20 minutes. It is intended for use by an interpreting clinician as an adjunct to standard diagnostic pathways to highlight HFpEF suspicion.
- Based on three retrospective case-control studies (one of which is a conference abstract) and one retrospective real-world study, EchoGo Heart Failure appeared to be safe and accurate, with limited clinical utility data.
    - The artificial intelligence (AI) model's sensitivity ranges from 87.8% to 89.8% while its specificity varies between 55.6% and 86.3%. Where reported, its positive and negative predictive values were 83.6% and 86.5%, respectively.
    - The model was shown to be able to reclassify indeterminate cases from clinical algorithms, successfully reclassifying 73.5% of HFA-PEFF indeterminate cases (with 87.3% sensitivity and 71.3% specificity) and 73.6% of H_2FPEF indeterminate cases (with 84.0% sensitivity and 78.3% specificity).
    - The positive outputs from the AI model were significantly associated with worse clinical outcomes, including HF hospitalisation (hazard ratio 3.76; 95% confidence interval (CI): 2.71 to 5.21) and cardiac mortality (hazard ratio 5.55; 95% CI: 3.28 to 9.37).
    - No literature on the cost-effectiveness of HFpEF was identified.
- Key uncertainties surrounding EchoGo Heart Failure include a lack of prospective, multi-centre validation, making its real-world effectiveness uncertain. The underrepresentation of diverse populations in its training data raises concerns about bias and performance in minorities or patients with comorbidities.
- There are multiple other technologies with similar functioning that are FDA or HSA approved. HSA-approved technologies include GE HealthCare Vivid E95 and Us2.ai.
- The adoption of EchoGo Heart Failure faces potential challenges related to regulatory compliance with Singapore's PDPA for data transfer and with MOH Artificial Intelligence in Healthcare Guidelines. There are also ethical concerns about patient consent for AI diagnostics. Clinician acceptance is crucial, with concerns over AI reliability and accountability in diagnostic decisions.

I. Background

Heart failure (HF) is defined as a clinical syndrome with current or prior symptoms (e.g. breathlessness, swollen ankles, fatigue) and signs (e.g. S3 heart sound, lung crackles, jugular venous distension, peripheral oedema) caused by a structural or functional cardiac abnormality, and corroborated by elevated natriuretic peptide levels or objective evidence of pulmonary or systemic congestion.[1]

HF can be classified based on the measurement of left ventricular ejection fraction (LVEF): [1]

- HF with reduced ejection fraction (HFrEF): LVEF ≤40%
- HF with mildly reduced ejection fraction (HFmrEF): LVEF 41 to 49%
- HF with preserved ejection fraction (HFpEF): LVEF ≥50%
- HF with improved ejection fraction (HFimpEF): baseline LVEF ≤40%, a ≥10-point increase from baseline LVEF, and a second measurement of LVEF >40%

In Singapore, 4.5% of the population live with HF, compared to 1 to 2% in the United States and Europe.[2] HFpEF accounts for about half of heart failure cases worldwide,[3] and has overtaken HFrEF as the most prevalent form of the disease.[4] With Singapore's aging population and the rising prevalence of diabetes, obesity, and hypertension, the incidence of HF is expected to increase.[5] Generally, people with HFpEF experience similar morbidity and mortality rates as those with HFrEF.[3]

The diagnosis of HFpEF is challenging due to the heterogeneous nature of the syndrome, reliance on integration of imaging, clinical, and biomarker data, and variability in diagnostic accuracy. While traditional clinical diagnostic algorithms such as HFA-PEFF (Heart Failure Association pretest assessment, echocardiography and natriuretic peptide score, functional testing, and final aetiology) and H_2FPEF (heavy, hypertensive medicines, atrial fibrillation, pulmonary hypertension, elder, and filling pressure) scores are valuable,[6,7] a significant proportion of cases remain indeterminate. Moreover, as these clinical algorithms employ multiple sources of patient information, they are often limited by conflicting or inadequate data.[8] Transthoracic echocardiography (TTE) is routinely used to confirm the diagnosis of HFpEF.[1] However, the test imposes a burden on skills, time, and expertise of the assessor, and there is considerable variability in the performance and interpretation of TTE findings. This can in turn lead to delay in diagnosis and the use of invasive tests such as right heart catheterisation for confirmation. Artificial intelligence (AI) models represent a promising innovation in this landscape, leveraging computational methods to automate and aid in the diagnosis of HFpEF detection.

II. Technology

EchoGo Heart Failure (Ultromics Ltd) is an automated machine learning-based decision support system, indicated as a diagnostic aid for patients undergoing transthoracic echocardiographic examination due to suspicion of heart failure. When utilised by an interpreting clinician, this device provides information that may be useful in detecting HFpEF. It is indicated for use in adults over 25 years of age. The artificial intelligence (AI) model uses

a single routinely acquired apical four-chamber video clip from a standard TTE examination that has been assessed to demonstrate LVEF of at least 50% as input. It reports within 20 minutes a classification decision suggestive of the presence or absence of HFpEF.

The second iteration of the technology (i.e. EchoGo Heart Failure 2.0) released in 2024 also includes an EchoGo Score ranging from 0 to 100% to support the classification. To aid in the interpretation of the EchoGo Score, a comparative visual analysis using the software's independent testing dataset displays the reported EchoGo Score output against that of the diseased population with confirmed HFpEF (see Figure 1). This allows the user to interpret the EchoGo Score relative to the 50% decision threshold.

It is intended that an interpreting clinician would use the report from either version of EchoGo Heart Failure as an adjunct to standard diagnostic pathways, to highlight HFpEF suspicion. The software-only technology seeks to tackle the challenges of HFpEF detection.

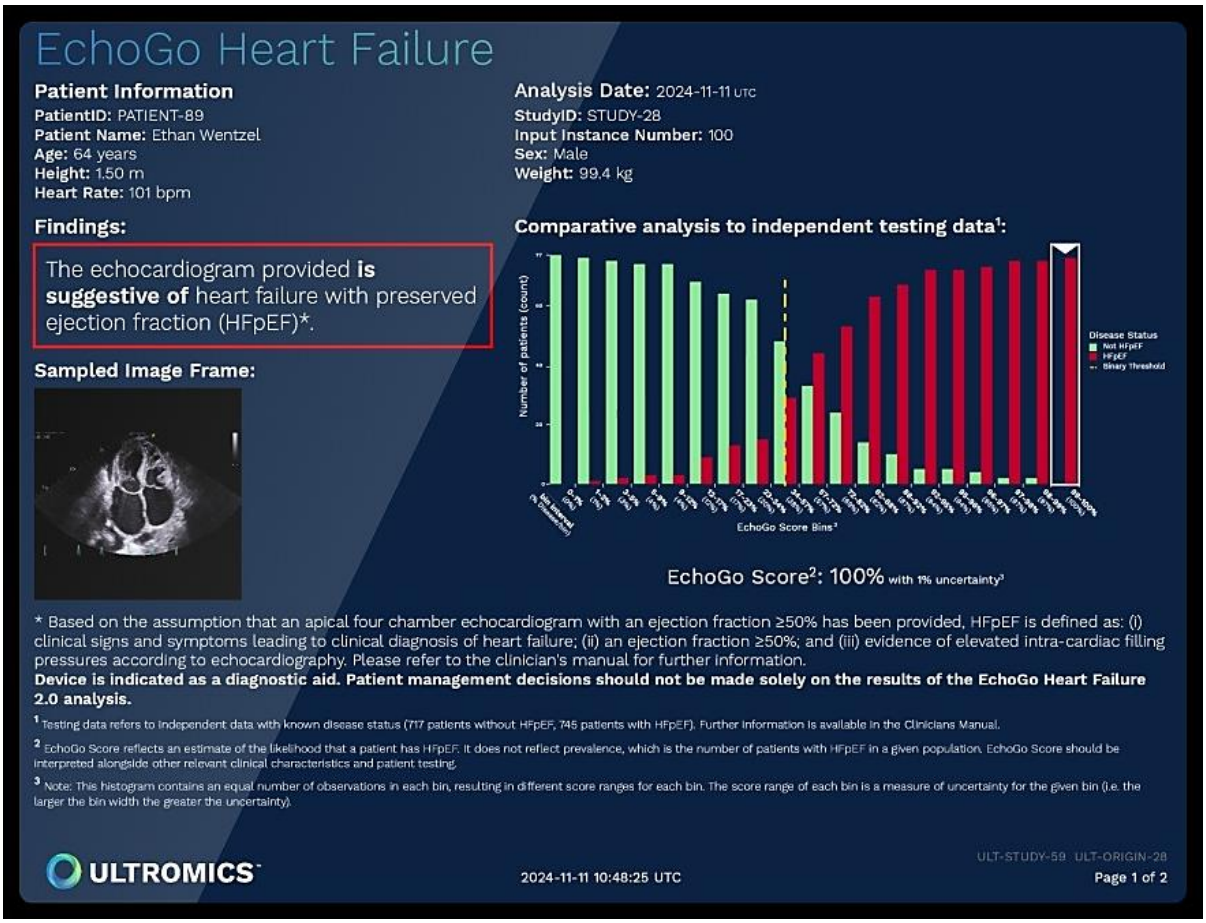


Figure 1: EchoGo Heart Failure 2.0 interface. Taken from https://www.ultromics.com.

III. Regulatory and Subsidy Status

EchoGo Heart Failure 1.0 received United States (US) Food and Drug Administration (FDA) Breakthrough Device Designation and FDA 510(k) clearance in 2022.

In the US, EchoGo Heart Failure is eligible for reimbursement in outpatient and inpatient settings. For inpatients, Medicare provides reimbursement (to a max of $1023.75 per analysis) through the NTAP code ICD-10: XXE2X19. From 1 January 2025, reimbursement for

outpatient technical component will be paid through Cat III CPT code 0932T ($299.91 on average).

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

The European Society of Cardiology (ESC) diagnostic algorithm for HF is outlined in Figure A1, and is well-regarded locally. Briefly, the diagnostic algorithm begins with a clinical assessment of risk factors, symptoms, and signs, which are corroborated by ECG findings. If HF is suspected, biomarkers such as natriuretic peptide levels are measured. Elevated levels or unavailable testing would indicate the need for TTE to confirm a diagnosis of HF by identifying structural or functional abnormalities and to evaluate LVEF to classify HF. The aetiology is then determined before commencing treatment.

Local clinicians generally agreed with the ESC diagnostic algorithm. However, they pointed out that laboratory assessment with natriuretic peptide may not be available in primary care or have low uptake in the outpatient setting. Thus it is likely to be conducted at the same time as TTE. Furthermore, they stressed that TTE should incorporate an assessment of LVEF, left ventricular mass, left atrial size, and valvular disease, if any.

Figure A2 demonstrates the proposed integration of EchoGo Heart Failure into the current ESC diagnostic algorithm. Most local clinicians opined that the AI tool should be applied to all clinically suspicious cases of HF undergoing TTE evaluation, to aid the detection of HFpEF. It is noteworthy that in Singapore EchoGo Heart Failure is not intended for use as a standalone diagnostic device, as outlined by the FDA.

VI. Summary of Evidence

The assessment was conducted based on the Population, Intervention, Comparator and Outcome (PICO) criteria outlined in Table 1. Literature searches were conducted in health technology assessment (HTA) databases, Cochrane Library, PubMed and Embase. Handsearching for published studies on Ultromics Ltd. official website was also conducted. The key evidence consists of three studies including: (i) the key training and validation study with a retrospective, multisite, and multinational cohort from the US and United Kingdom (UK), and tested with independent multisite data from the US,[9] (ii) a retrospective, multisite study using an updated version of the AI model to reassess accuracy and clinical outcomes,[10] and (iii) a retrospective, real-world study.[11] A conference abstract (retrospective case-control study) was also included as supplementary evidence. The study was conducted amongst

individuals at high risk for HFpEF, with high rates of hypertension, atrial fibrillation, diabetes, coronary artery, kidney, and pulmonary disease.[12] The study design and characteristics of the key and supplementary evidence are presented in Tables B1 and B2 (Appendix B).

Table 1: Summary of PICO criteria

Population	Patients suspected of heart failure undergoing TTE evaluation
Intervention	EchoGo Heart Failure (Ultromics Ltd) in addition to conventional diagnosis of HFpEF
Comparator	Conventional diagnosis of HFpEF without AI assistance, such as TTE and clinical algorithms (i.e. H_2FPEF, HFA-PEFF)
Outcome	Safety, clinical effectiveness (e.g. diagnostic accuracy, heart failure hospitalisation, cardiac mortality), cost and cost-effectiveness
Abbreviations: H_2FPEF, heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, and filling pressure; HFA-PEFF, Heart Failure Association pretest assessment, echocardiography and natriuretic peptide score, functional testing, and final aetiology; HFpEF, heart failure with preserved ejection fraction; TTE, transthoracic echocardiography	

Safety

Included studies did not report direct safety data,[9-11] and no major safety issues are expected as the non-invasive AI-automated detection relies on routine echocardiographic data. Akerman et al. (2023) opined that the use of EchoGo Heart Failure may reduce the need for other invasive diagnostics, such as right heart catheterisation.[9]

Effectiveness

Classification Accuracy

The classification performance of the final model training and validation data sets (n=6,756 patients) was good, with an area under receiver-operating characteristic curve (AUROC) of 0.97 and 0.95, respectively.[9] At a classification threshold of 0.50, this corresponded to a sensitivity of 88.7% and specificity of 85.4% in the validation data set (see Table B3 in the appendix).[9]

Independent testing was conducted using retrospective, multicentre data from the US (n=1,284), out of which 94 (7.3%) was nondiagnostic. Compared to a clinical diagnosis of HF (based on an International Classification of Diseases 9 or 10 code and elevated intracardiac filling pressure), the testing dataset reported a sensitivity of 87.8% and a specificity of 81.9% for HFpEF.[9] These improved to 89.8% and 86.3%, respectively, in the updated AI model (see Table 2).[10] The authors reported that further analyses did not identify any factors meaningfully impacting the performance of HFpEF, with sensitivity and specificity maintained across subgroups.

Table 2: Classification accuracy of EchoGo Heart Failure

Study (year) & type	Population (n)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUROC (95% CI)
Key evidence						
Akerman et al. (2023)[9] Multicentre, retrospective	n = 1284; 646 cases and 638 controls	87.8% (84.5% - 90.9%)	81.9% (78.2% - 85.6%)	83.6% (80.2% - 87.0%)	86.5% (83.0% - 90.0%)	0.91 (0.90 – 0.93)
Akerman et al. (2024)[10]	n = 1284; 646 cases	89.8% (87.5% - 92.5%)	86.3% (83.6% - 89.7%)	87.2% (84.7% - 89.8%)	89.0% (87.0% - 91.7%)	—

Multicentre, retrospective	and 638 controls					
Supplementary evidence						
Akerman et al. (2023)[12] Single-centre, retrospective	n = 439; 213 cases and 226 controls	88.8% (84.0% - 93.4%)	55.6% (47.7% - 64.0%)	—	—	—

In the key training and validation study, the conventional HFA-PEFF clinical algorithm demonstrated a high sensitivity and specificity, while the H_2FPEF algorithm had high sensitivity (98.2%) and a specificity of 74%, (Table 3). However, both algorithms had high proportions of non-diagnostic outcomes, 54.6% and 60.4%, respectively, compared to 7.3% in EchoGo HF testing data (see in Table 3). In Akerman et al. (2023), the AI model successfully reclassified 73.5% of HFA-PEFF indeterminate cases (with 87.3% sensitivity and 71.3% specificity) and 73.6% of H_2FPEF indeterminate cases (with 84.0% sensitivity and 78.3% specificity).[9]

Karnik et al. found that out of the 117 patients screened positive for HFpEF by the AI model, 11 of them had incomplete H_2FPEF scores.[11] This also demonstrated the model's ability to reclassify non-diagnostic outcomes from clinical algorithms.

Table 3: Performance difference between EchoGo Heart Failure and clinical algorithms

Study (year)	Intervention/ Comparator	Sensitivity	Specificity	% Non-diagnostic outputs
Akerman et al. (2023)[9]	EchoGo Heart Failure	87.8%	81.9%	7.3%
	H_2FPEF	98.2%	74.0%	60.4%
	HFA-PEFF	95.0%	97.0%	54.6%
Abbreviations: H2FPEF – heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, and filling pressure, HFA-PEFF – Heart Failure Association pretest assessment, echocardiography and natriuretic peptide score, functional testing, and final aetiology				

According to supplementary evidence from the conference abstract in high-risk patients (n=439), EchoGo demonstrated similarly high sensitivity (88.8%). However, it had a low specificity of 55.6% (see Table 2), albeit a slight improvement over the H_2FPEF specificity score of 38.1%. The AI model only managed to reclassify 54.3% of non-diagnostic H_2FPEF scores in high-risk patients.[12]

Clinical Utility

Patient management decisions

Akerman et al. (2023) juxtaposed the implication of traditional clinical algorithms against that of the AI model on patient management decisions. They found that the combined use of information from the model and existing clinical scores facilitated the correct management of up to 30.0% more patients, compared to using clinical scores alone.[9]

Mortality

Akerman et al. (2023) showed that the model successfully identified patients with worse 5-year survival (hazard rate (HR) of 1.9; 95% CI: 1.5 to 2.4) (see Figure C1).[9] Similarly, in the

updated AI model study, positive AI outputs were significantly associated with higher cardiac mortality (HR: 5.55; 95% CI: 3.28 to 9.37) compared to negative outputs.[10]

Hospitalisation

Akerman et al. (2023) demonstrated that, at a median of 3.4 years (inter-quartile range, 1.7 to 6.5 years), positive AI outputs were significantly associated with higher risk of HF hospitalisation (HR: 3.76; 95% CI: 2.71 - 5.21) compared to negative outputs (see Figure C2).[10] In the supplementary evidence with high-risk patients, the AI model using H_2FPEF score also identified more HFpEF patients who were hospitalised within one year of TTE (78.9% vs. 54.5%).[12]

The updated AI model also reclassified HF hospitalisation risk in non-diagnostic clinical scores, including 92% of HFA-PEFF outputs and 91% for H_2FPEF, reinforcing the model's potential value in addressing one of the primary limitations of traditional diagnostic scores.[10]

Cost-effectiveness

No cost-effectiveness studies for EchoGo Heart Failure were identified.

Key uncertainties

EchoGo Heart Failure presents several uncertainties that warrant further exploration. One major concern is the lack of prospective, multi-centre validation. Most studies rely on retrospective data or controlled settings, leaving its real-world effectiveness in diverse clinical workflows uncertain.

Another critical issue is the potential for bias due to underrepresentation of certain populations in the training dataset. It remains unclear how well the tool performs in ethnic minorities, or for patients with multiple comorbidities. Additionally, the AI tool focuses on distinguishing HFpEF from non-HFpEF cases. The studies do not explicitly evaluate the tool's ability to differentiate HFpEF from other overlapping cardiac or systemic conditions, such as diastolic dysfunction due to comorbidities like obesity or chronic kidney disease.

Moreover, most studies reported conflict of interest (COI). They either were supported by grants from Ultromics Ltd or stated that the authors were employed by the company.

Ongoing trials

One ongoing trial was identified from the Cochrane Library and ScanMedicine databases. Funded by the University of Texas Southwestern Medical Center, the study is a randomised trial to evaluate the impact of integrating Ultromics EchoGo analysis and HF prevention recommendations into clinical decision support tools. The trial status is currently "Not yet recruiting" as of January 2025.

Table 4: Ongoing clinical trial

Study (Trial ID)	Population & estimated enrolment	Brief description	Estimated study completion date
Using Ultromics EchoGo HFpEF Algorithm to Identify and Treat High	Providers of patients that have a positive	A pragmatic EHR-based randomized controlled trial to evaluate the utility of providing Ultromics EchoGo analysis results	June 2027

Heart Failure Risk in Patients With Type 2 Diabetes (NCT06593314)	EchoGO result i.e. HFpEF detected n=50	and recommendations for heart failure risk prevention therapies using an EHR embedded clinical decision support tool.	
Abbreviations: EHR, electronic health record; HFpEF, heart failure with preserved ejection fraction			

Summary

Overall, evidence is limited and mostly from the US and UK. EchoGo Heart Failure is safe and has acceptable classification accuracy (with good sensitivity ranging from 87.8% to 88.8% but lower specificity ranging from 55.6% to 86.3%) to aid in the diagnosis of HFpEF. Although it appears to be less accurate than traditional clinical scores, it can reclassify indeterminate cases resulting from them. Limited evidence also showed that the AI model may identify patients with higher mortality and higher risk of HF hospitalisation.

However, as the published studies lack Asian representation, its local applicability is unclear. Future studies should evaluate the generalisability and effectiveness on diverse patient populations, as well as the long-term impacts and cost-effectiveness in diverse healthcare settings.

VII. Estimated Costs

No public information on the cost of EchoGo Heart Failure was identified, apart from the reimbursement information from the USA (see Regulatory and Subsidy Status Section for details).

VIII. Implementation Considerations

The adoption of EchoGo Heart Failure presents several critical considerations across regulatory, ethical, cost, infrastructural, and clinical factors.

Firstly, the tool's reliance on cloud-based data processing raises concerns about compliance with Singapore's Personal Data Protection Act (PDPA). Any transfer of sensitive patient data across borders would require robust safeguards to protect confidentiality. Ethical considerations, such as obtaining informed consent from patients for AI-driven diagnostics, could also slow adoption. Many patients may be unfamiliar with the technology and hesitant about its use. Additionally, EchoGo Heart Failure will need to be compliant with the MOH Artificial Intelligence in Healthcare Guidelines (AIHGle).

Implementing EchoGo Heart Failure involves upfront expenses for licensing, staff training, and upgrading IT systems to ensure compatibility. Currently, it is unclear whether cost may be a potential barrier given the lack of cost information.

Lastly, clinician acceptance is a critical factor in adoption. Healthcare professionals may be hesitant to trust AI tools without clear evidence of their reliability and added value in local clinical settings. Concerns about over-reliance on AI for critical diagnostic decisions and accountability in cases of diagnostic errors could further deter adoption.

IX. Concurrent Developments

Besides EchoGo Heart Failure, there are several other technologies that leverage echocardiographic imaging to detect HF, including HFpEF. These systems typically utilise advanced algorithms or AI to enhance diagnostic accuracy and efficiency. Examples are summarised in Table 5. GE HealthCare Vivid E95 and Us2.ai received HSA registrations on 19 October 2022 and 28 May 2022, respectively.

Table 5: Similar technologies in development

Technology	Brief overview	Key features that aid HFpEF detection	Status
DiA Imaging Analysis	AI-based platform for automated echocardiographic parameter quantification	It automates the assessment of diastolic function, including strain and tissue Doppler imaging parameters, which are key in diagnosing HFpEF.	FDA-cleared; commercialised in the US, Europe, Asia, and the Middle East
GE HealthCare Vivid E95 with AI Tools	High-end ultrasound hardware and software system with integrated AI for quality cardiac imaging and quantification	It aids in HFpEF detection by automating diastolic function analysis and strain imaging.	FDA-cleared and HSA-registered; commercialised in North America, Europe, and Asia
Philips HeartModel	AI-enhanced cardiac imaging software integrated into Philips' ultrasound systems	It integrates AI tools for diastolic dysfunction analysis, including E/e' ratio and left atrial volume index, both crucial for HFpEF evaluation.	FDA-cleared; commercialised globally (distributed through Philips' ultrasound systems)
Us2.ai	AI decision support tool that automatically processes studies from 2D and Doppler images, providing a comprehensive report in under two minutes	It automates the generation of a full echocardiographic report, including diastolic function grading, E/e' ratio, and other metrics associated with HFpEF.	FDA-cleared and HSA-registered; commercialised in Asia, Europe, and North America

Abbreviations: AI, artificial intelligence; E/e' ratio, ratio of early mitral flow rate to early diastolic mitral annulus velocity; FDA, United States Food and Drug Administration; HFpEF, heart failure with preserved ejection fraction; HSA, Singapore Health Sciences Authority; LVEF, left ventricular ejection fraction.

X. Additional Information

The clinicians provided mixed feedback on the utility of EchoGo Heart Failure in Singapore's healthcare system. While some highlighted its potential to address diagnostic delays particularly for non-specialists, others questioned its incremental value in an already well-resourced system. EchoGo Heart Failure was seen as potentially useful for risk stratification and enhancing diagnostic efficiency by automating complex echocardiographic analyses, reducing variability, and aiding in triaging cases. However, concerns were raised about its limited utility for cardiologists, who are proficient in existing diagnostic methods, and the risk of over-reliance on AI and imaging without integrating clinical and laboratory data. The consensus was that EchoGo could be valuable for non-specialists to improve diagnostic confidence and reduce delays. However, its adoption in Singapore would depend on further validation of its applicability to the local population, and broader integration with clinical workflows. While the technology cannot currently be integrated with point-of-care ultrasonography (POCUS), such functionality would significantly enhance its future utility.

References

1. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail*. 2021;23(3):352–380. doi: 10.1002/ejhf.2115.

2. Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. *ESC Heart Fail*. 2014;1(1):4–25. doi: 10.1002/ehf2.12005.

3. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. *Prog Cardiovasc Dis*. 2005;47(5):320–332. doi: 10.1016/j.pcad.2005.02.010.

4. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev. 2017;3(1):7-11. doi: 10.15420/cfr.2016:25:2.

5. National Heart Centre Singapore Partners Medera's Novoheart to Develop Asia's First Bioengineered Human Heart-In-A-Jar With Heart Failure for Precision Medicine. [Internet] Singapore: National Heart Centre Singapore; 2023 November [cited 2024 December 13] Available from: https://www.nhcs.com.sg/news/research/national-heart-centre-singapore-partners-mederas-novoheart-to-develop-asias-first-bioengineered-human-heart-in-a-jar-with-heart-failure-for-precision-medicine

6. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019 ;40(40):3297–3317. doi: 10.1093/eurheartj/ehz641. Erratum in: *Eur Heart J*. 2021 ;42(13):1274. doi: 10.1093/eurheartj/ehaa1016.

7. Reddy YNV, Carter RE, Obokata M, et al. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. 2018 ;138(9):861-870. doi: 10.1161/CIRCULATIONAHA.118.034646.

8. Sanchis L, Andrea R, Falces C, et al. Differential Clinical Implications of Current Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography. *J Am Soc Echocardiogr*. 2018;31(11):1203–1208. doi: 10.1016/j.echo.2018.08.011.

9. Akerman AP, Porumb M, Scott CG, et al. Automated Echocardiographic Detection of Heart Failure With Preserved Ejection Fraction Using Artificial Intelligence. *JACC Adv*. 2023;2(6):100452. doi: 10.1016/j.jacadv.2023.100452.

10. Cassianni C, Huntley GD, Castrichini M, et al. Automated Echocardiographic Detection of Heart Failure With Preserved Ejection Fraction Using Artificial Intelligence Is Associated With Cardiac Mortality and Heart Failure Hospitalization. *J Am Soc Echocardiogr.* 2024;37(9):914–916. doi: 10.1016/j.echo.2024.06.016.

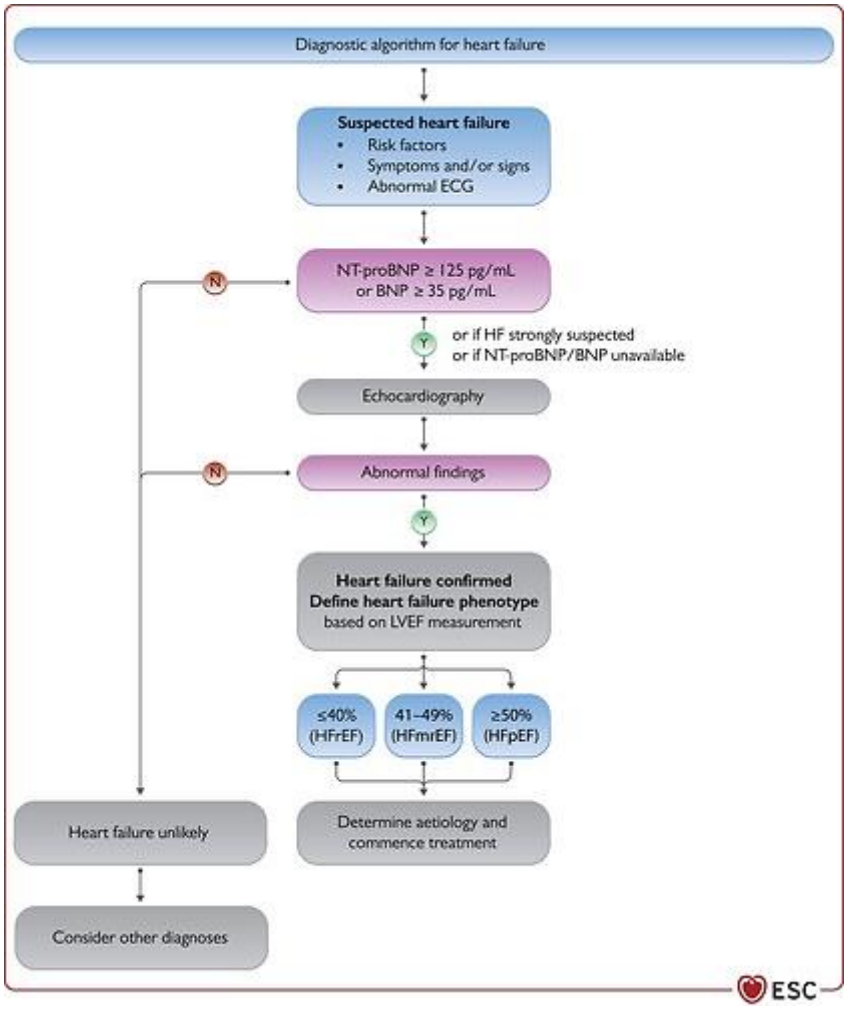
11. Karnik A, Jankowski M, Narang A. Unmasking HFpEF With Artificial Intelligence: A Disruptive Opportunity for Disease Detection. *J Card Fail*. 2024;30(11):1533–1534. doi: 10.1016/j.cardfail.2024.02.010.

12. Akerman AP, Al-Roub N, Angell-James C, et al. Abstract 18252: Comparison of an Artificial Intelligence Heart Failure Detection Model and Clinical Prediction Models in Patients With Heart Failure With Preserved Ejection Fraction (HFPEF). *Circulation. J. Am Heart Assoc.* 2023;148(Suppl_1). doi:10.1161/circ.148.suppl_1.18252

Appendix

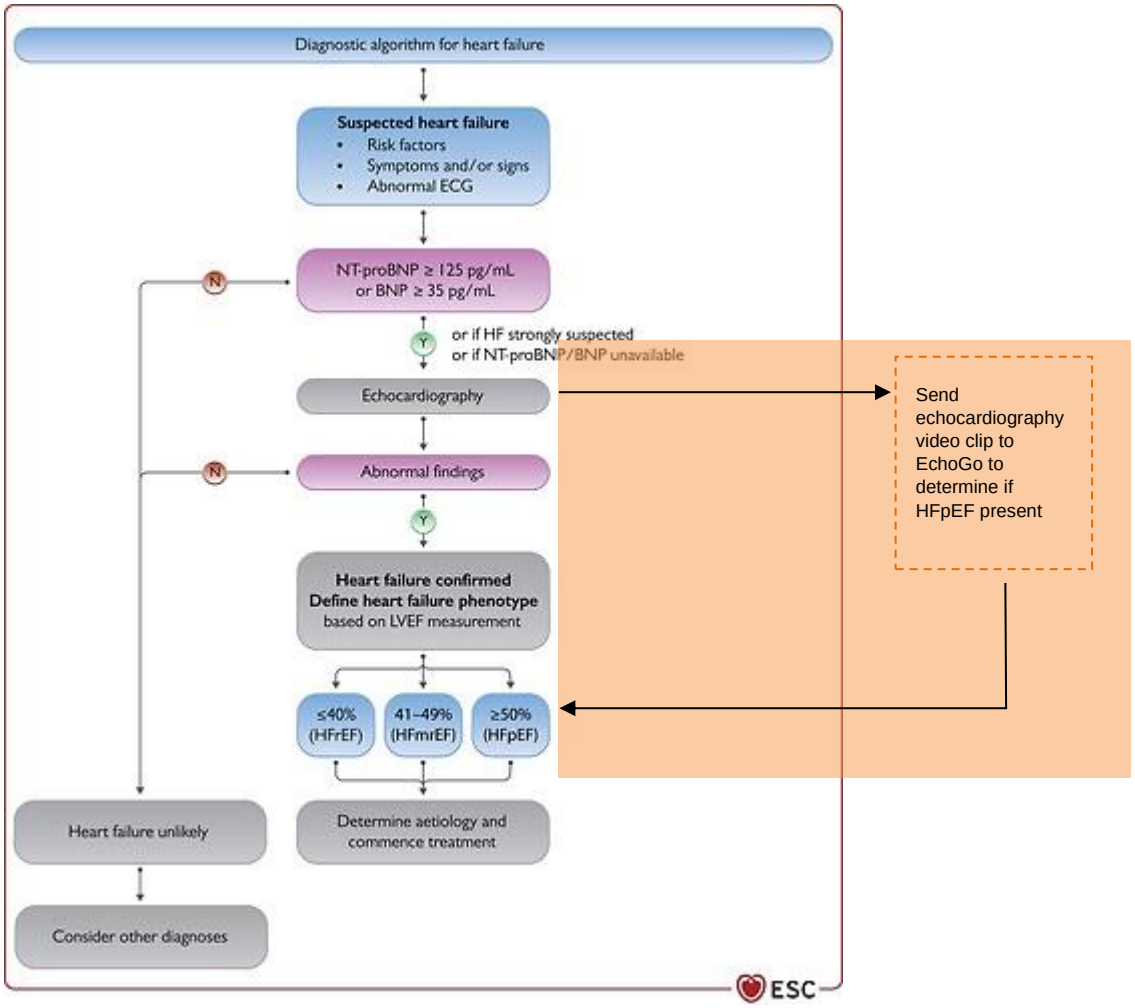
Appendix A: Clinical pathways

Figure A1: 2021 ESC's diagnostic algorithm for heart failure



Abbreviations: BNP, brain natriuretic peptide; ECG, electrocardiogram; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP; N-terminal pro-B-type natriuretic peptide

Figure A2: Proposed integration of EchoGo Heart Failure into 2021 ESC's diagnostic algorithm for heart failure



Abbreviations: BNP, brain natriuretic peptide; ECG, electrocardiogram; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP; N-terminal pro-B-type natriuretic peptide

Appendix B: Included studies

Table B1: List of included studies

Type of study	Key evidence base	Supplementary evidence base
Retrospective, case-control	2	1[a]
Real-world	1	-

Note:
Inclusion criteria: studies that fulfil the PICO criteria listed in Table 1.
[a] Although study was presented only as conference abstract, it was included as supplementary evidence as the study included a population of patients who are high-risk for HFpEF, with high rates of hypertension, atrial fibrillation, diabetes, coronary artery, kidney, and pulmonary disease.

Table B2: Design and characteristics of studies in key evidence base

Study	Study design	Population (n)	Intervention	Comparator(s)	Reference standard
Key evidence					
Akerman et al. (2023)[9]	Model training and validation	Patients from the Mayo Clinic and St George's Hospital databases who had undergone a comprehensive TTE between January 2009 and December 2020 (n = 6756; 2971 cases and 3785 controls)	EchoGo Heart Failure	-	● Clinical diagnosis of HF, based on an ICD 9 or 10 code, within one year of the associated echocardiogram (case) or lack of diagnosis (control) collected from the patient medical records ● LVEF ≥50% (cases and controls) ● Evidence of elevated intracardiac filling pressure (case) or lack thereof (control)
	Retrospective, multicentre, case-control study	Participants were selected from the Mayo Clinic Health System database (multi-sites across five different states) (n = 1284; 646 cases and 638 controls)		H_2FPEF HFA-PEFF	
Akerman et al. (2024)[10]	Retrospective, multicentre, case-control study	As above in the case-control study by Akerman et al. (2023)	EchoGo Heart Failure (updated model)	H_2FPEF HFA-PEFF	
Karnik et al. (2024)[11]	Retrospective, real-world study	Consecutive clinical echocardiograms from unique patients from the Bluhm Cardiovascular Institute, Northwestern University, Illinois (n = 532)	EchoGo Heart Failure	H2FPEF	Clinical interpretations of echocardiograms with a manual chart review (including calculating H2FPEF) to ascertain clinical risk factors that corroborated diagnosis
Supplementary evidence					
Akerman et al. (2023) –	Retrospective, single-	Patients who received routine TTE at Beth Israel	EchoGo Heart Failure	H_2FPEF	● Presence of ICD-10 codes for HF (I50.X), LVEF ≥50%, and

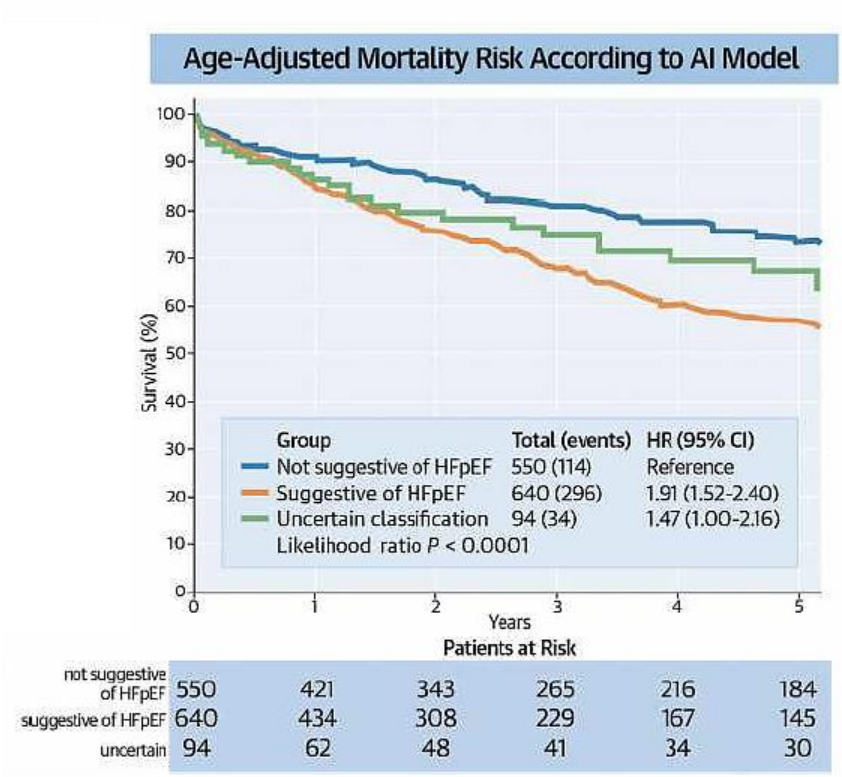
conference abstract[12]	centre, case-control study	Deaconess Medical Centre, Harvard Medical School (n = 439; 213 cases and 226 controls)			grade II or III diastolic dysfunction (case) ● Absence of HF within one year of the index TTE (control)
Abbreviations: HF, heart failure; H2FPEF, heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, and filling pressure, HFA-PEFF, Heart Failure Association pretest assessment, echocardiography and natriuretic peptide score, functional testing, and final aetiology; ICD, International Classification of Diseases; LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiography					

Table B3: Classification accuracy of EchoGo Heart Failure in training and validation

Study (year) & type	Population (n)	Sensitivity	Specificity	AUROC (95% CI)
Akerman et al. (2023)[9] Model training and validation	n = 6,765; 2,971 cases and 3,785 controls	Validation: 88.7%	Validation: 85.4%	Training: 0.97 (0.96 – 0.97) Validation: 0.95 (0.93 – 0.96)
Abbreviation: CI, confidence interval				

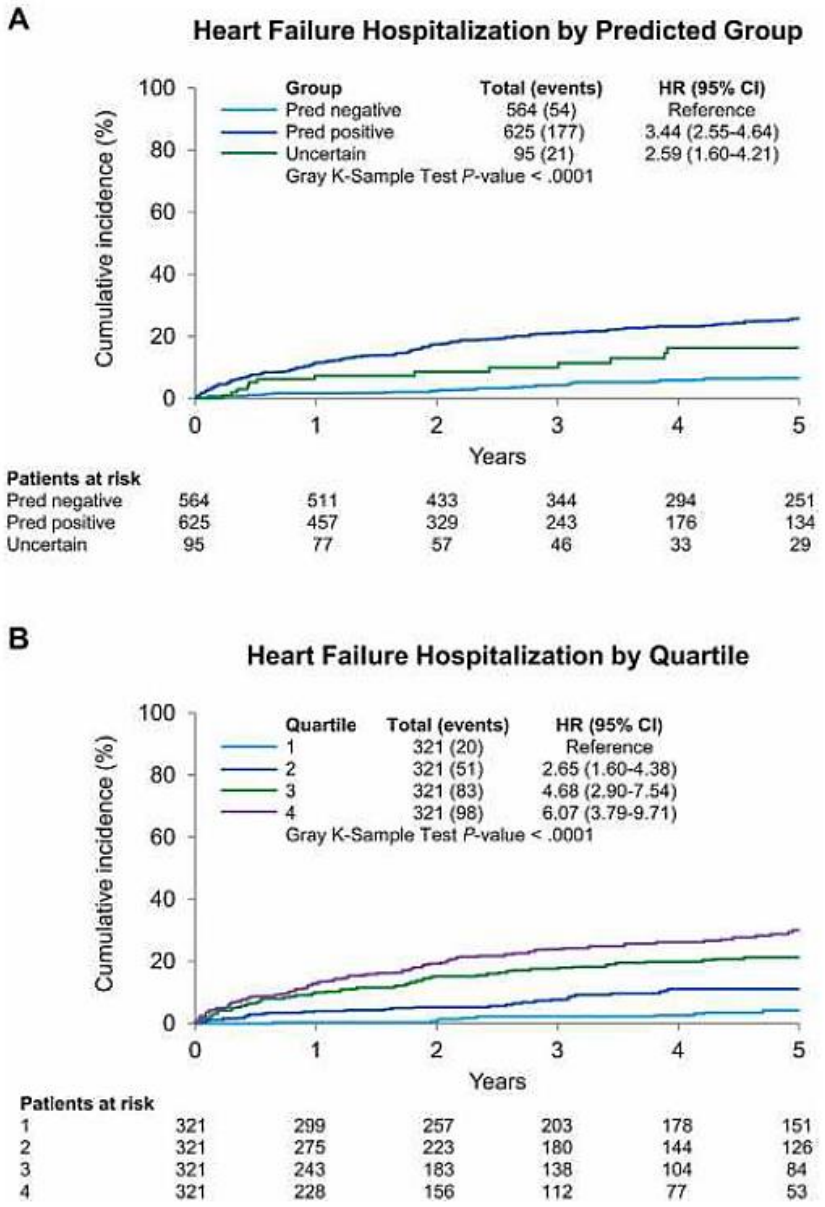
Appendix C: Figures adapted from included studies

Figure C1: Age-adjusted five-year mortality risk according to EchoGo Heart Failure



Abbreviations: AI, artificial intelligence; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio.

Figure C2: Risk for heart failure hospitalisation based on heart failure categorical output (A) and quartiles of continuous probability output (B)



Abbreviations: CI, confidence interval; HR, hazard ratio; pred, predicted