

Artificial Intelligence-Enhanced Electrocardiography for Prediction of Cancer Therapy-Related Cardiac Dysfunction

Short title: AI-ECG Prediction of CTRCD

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1 **Abbreviations:**

2 AI-ECG: Artificial Intelligence-Electrocardiography

3 AIRE: AI-Risk Estimation

4 BIDMC: Beth Israel Deaconess Medical Center

5 BRAFi: BRAF Inhibitor

6 CI: Confidence Interval

7 CTRCD: Cancer Therapy-Related Cardiac Dysfunction

8 GLS: Global Longitudinal Strain

9 HFA-ICOS: Heart Failure Association-International Cardio-Oncology Society

10 LVEF: Left Ventricular Ejection Fraction

11 MEKi: MEK Inhibitor

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1 Targeted therapies inhibiting BRAF and MEK kinases have changed the treatment landscape of
2 *BRAF*-mutated melanoma but are associated with cardiovascular adverse events, particularly
3 cancer therapy-related cardiac dysfunction (CTRCD) and hypertension.¹ Current guidelines
4 recommend baseline risk stratification using the Heart Failure Association-International Cardio-
5 Oncology Society (HFA-ICOS) risk score to determine surveillance intensity.²⁻⁴ However, this
6 score relies on traditional clinical variables and static biomarkers, potentially missing subclinical
7 myocardial vulnerabilities. Artificial intelligence-enhanced electrocardiography (AI-ECG) has
8 demonstrated the ability to detect occult structural heart disease and predict future cardiovascular
9 events.^{5, 6}

10
11 We hypothesised that AI-ECG could outperform, or be additive to, the HFA-ICOS score and
12 improve the prediction of CTRCD in patients receiving BRAF/MEK inhibitors.

13 A prospective, longitudinal, cohort study was undertaken among patients with melanoma treated
14 with BRAF and MEK inhibitors in a regional cancer network (March 2021 to March 2023). The
15 study design and population have been described previously.⁷ Briefly, patients underwent
16 comprehensive cardiovascular phenotyping, including serial echocardiography and biomarkers at
17 baseline, 4, 12, and 24 weeks. We evaluated two endpoints in line with ICOS definitions: the
18 first occurrence of 'Any CTRCD' (defined as Grade ≥ 1) and 'Moderate/Severe asymptomatic
19 CTRCD or symptomatic CTRCD' (defined as Grade ≥ 2) at any point during the 6-month
20 follow-up. All patients were assessed prior to commencing BRAF/MEK inhibitor therapy;
21 baseline ECGs and HFA-ICOS scores were obtained before treatment initiation.

1 We used the validated AI-Risk Estimation (AIRE) platform, trained on >1.2 million ECGs from
2 189,539 patients at Beth Israel Deaconess Medical Center (BIDMC), Boston, to predict future
3 cardiovascular events⁵. ECGs were performed at each surveillance visit (baseline, 4, 12, and 24
4 weeks). For this analysis, we applied the platform's incident heart failure model to the baseline
5 ECGs of the cohort treated with BRAFi or MEKi. We compared the discriminative performance
6 (Harrell's C-statistic) with 95% confidence intervals derived from 1,000 bootstrap resamples,
7 Area under the Curve (AUC), sensitivity, and specificity of three risk stratification strategies:

8 (1) Clinical (HFA-ICOS score alone); (2) AI-ECG alone; and (3) Combined (HFA-ICOS + AI-
9 ECG). This study was designed and reported in accordance with the EHRA-AI checklist for
10 artificial intelligence in clinical electrophysiology.⁸ The additive prognostic value of AI-ECG
11 was assessed using the partial likelihood ratio test (PLRT); pairwise AUC comparisons were
12 additionally performed using the DeLong test. All analyses were performed in R (version 4.5.2).

13
14 The cohort (N=61) had a mean age 59±15 years, and 61% were male. Over a 6-month follow-up,
15 28 patients (46%) developed 'Any CTRCD', primarily mild, asymptomatic strain reductions.
16 Four patients (6.6%) developed 'Moderate/Severe CTRCD'. All four Grade ≥ 2 events were first
17 identified at 4 weeks. Two recovered LVEF to >50% and restarted treatment; one had therapy
18 discontinued for non-cardiovascular reasons (LVEF 53% at 24 weeks); and one developed severe
19 CTRCD (LVEF nadir 37%, partial recovery to 49% at 24 weeks on quadruple therapy). No
20 patient developed symptoms of heart failure.

21
22 For the broad endpoint of 'Any CTRCD' (Grade ≥ 1), discrimination was modest across all
23 modalities. The HFA-ICOS score achieved a C-statistic of 0.587 (95% CI: 0.48–0.70), which

was not significantly improved by the AI-ECG model (0.596) or the Combined model (0.611). This may reflect the transient and heterogeneous nature of Grade 1 toxicity, which often resolves without intervention and may represent hemodynamic fluctuation rather than structural injury.

In contrast, for the endpoint of ‘Moderate/Severe CTRCD’ (Grade ≥ 2), the AI-ECG model demonstrated numerically higher predictive value. The C-statistic improved from 0.814 (95% CI 0.585–1.000) with HFA-ICOS alone to 0.890 (0.751–1.000) with AI-ECG alone and 0.905 (0.783–0.963) with the Combined model (PLRT, $p=0.030$).

At the Youden-optimal threshold the AI-ECG achieved 100% sensitivity / 73.7% specificity; AUC 0.906 (0.78–1.00), versus HFA-ICOS alone (75%/86%; AUC 0.816, 0.58–1.00) and the Combined model (100%/82.5%; AUC 0.917, 0.83–1.00). Adding AI-ECG to HFA-ICOS improved predictive model fit for Moderate/Severe CTRCD; however, the DeLong test for AUC difference was non-significant (Combined vs HFA-ICOS: $p=0.27$; AI-ECG vs HFA-ICOS: $p=0.54$), indicating an overall trend towards improved discrimination.

Gradient-based saliency maps were generated using the tf-keras-vis⁹ library. Lead-level attribution was quantified by dividing each 310×868 pixel image into a 3×4 grid and computing the proportion of normalised saliency within each region. Leads I, II and aVR were identified as the primary leads of model focus (**Figure 1**).

We also evaluated an incident hypertension model from the AIRE platform, a common side effect in this cohort (46%). Neither the combination of clinical variables nor the AI-ECG model showed strong predictive capacity for this endpoint (C-statistics ~0.50–0.60). This lack of ECG

1 signal may reflect a pathophysiology driven by acute vascular toxicity rather than pre-existing
2 myocardial vulnerability.

3
4 Our findings have important implications for cardio-oncology practice. While the HFA-ICOS
5 score remains a robust tool for baseline stratification, its predictive ceiling is limited by the
6 variables currently available in the electronic health record. The addition of AI-ECG - a low-
7 cost, universally available biomarker - significantly refined risk prediction for the most severe
8 cardiac events. Specifically, the AI model successfully identified the small subset of patients
9 destined for overt LVEF decline, a group that warrants intensive surveillance (e.g.,
10 echocardiography at 4 weeks) as suggested by our prior work.¹⁰ Conversely, the lack of signal
11 for mild toxicity suggests that Grade 1 events may be stochastic or distinct from the
12 pathophysiology leading to overt failure.

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14 Limitations include the small sample size and low event rates, necessitating cautious
15 interpretation; these also precluded time-varying analyses and rendered reclassification analyses
16 unreliable. The AIRE model was trained in a US secondary care population, and while external
17 validation in a distinct Scottish cancer cohort suggests generalisability, replication in larger,
18 multicentre cardio-oncology cohorts with longer follow-up and serial AI-ECG analyses is
19 warranted.

20
21 In conclusion, AI-ECG demonstrates a trend towards additive prognostic value beyond HFA-
22 ICOS for predicting Moderate/Severe CTRCD in patients receiving BRAF/MEK inhibitors.

Integration into baseline assessment could enable more targeted surveillance of patients at highest cardiotoxicity risk.

977 words

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Conflicts of Interest: FSN reports speaker fees from GE healthcare and is on the advisory board for J&J Medtech. BZ, AS and FSN declare inventorship on a patent application relating to AI-ECG methods and hold equity shares in Cardiovolt.ai Limited.>NNL reports research grants from Roche Diagnostics, Astra Zeneca and Boehringer Ingelheim as well as consultancy/speaker's fees from Roche Diagnostics, Myokardia, Pharmacosmos, Akero Therapeutics, CV6 Therapeutics, Jazz Pharma and Novartis. All remaining authors have declared no conflicts of interest.

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Figure 1: AI-ECG Performance Predicting BRAF/MEK Inhibitor-Associated Cardiotoxicity.

The AI-ECG model trained in a secondary care US cohort was tested on a Scottish cohort of melanoma patients receiving cancer therapy. Bars display C-statistics (error bars: 95% CI) comparing HFA-ICOS (orange), AI-ECG (blue), and the combination of HFA-ICOS and AI-ECG (green). Gradient-based saliency maps (bottom) show model attention overlaid on two baseline ECGs; the top-3 leads by mean attribution across all ECGs were Lead I, aVR, and Lead II.

