A liquid-biopsy microRNA test for invasive melanoma: Australia's 'national cancer'.

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KEY POINTS:

Question:

What are the diagnostic and prognostic performance characteristics of a microRNA-based liquid biopsy test for invasive cutaneous melanoma?

Findings:

In this observational case-control study that included 582 adults, a diagnostic 38-microRNA signature achieved 93% sensitivity and 98% specificity for invasive melanoma vs. the control group (AUC 0.98).

A complementary 12-microRNA prognostic algorithm predicted probability of 10-year melanoma-specific-survival with a hazard ratio of 7.7 (P<0.001). MEL12 is also associated with positive sentinel lymph node status (P=0.027).

Meaning:

Plasma microRNA profiling represents a non-invasive, personalized, and data-driven approach to diagnosing and risk-stratifying patients with invasive melanoma.

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IMPORTANCE:

Australia has the highest incidence of melanoma worldwide. Conventional methods of screening and diagnosis have not reduced mortality and may be contributing to the current 'epidemic' of cases here and abroad.

The potential for plasma microRNA profiling to enable early, accurate and precise melanoma diagnosis has been described previously but not independently validated.

OBJECTIVE:

To interrogate a circulating microRNA signature of invasive cutaneous melanoma ('MEL38') in a large clinically-annotated patient cohort. Secondly, to develop of a complementary microRNA signature for prognostication and treatment personalization.

PATIENTS AND METHODS:

Figure 1. 0.4ml plasma

Plasma was collected prospectively or sourced from biobanks from 582 adult patients diagnosed with Stage I-IV invasive melanoma, melanoma in-situ, non-melanoma skin cancer, or nevi.

The MEL38 microRNA signature was evaluated by NanoString® gene expression profiling of 0.4ml plasma per patient (Figures 1 & 2).

Staging, treatment and outcome data were used to develop a complementary prognostic signature to predict likelihood of 10-year melanoma-specific survival.

Table 1. Patient details for melanoma microRNA validation study

	Melanoma	Non-Melanoma
Age	Mean: 59 (range 19 to 94)	Mean: 60 (24 to 97)
Gender	F: 155 (44%), M: 199 (56%)	F: 81 (49%), M: 86 (51%)
Histological types (Top 3)	Metastatic/NOS: 152 (41%), Superficial spreading: 119 (32%), Nodular: 64 (17%)	Melanoma in-situ: 45 (22%), BCC: 35 (17%), Normal skin: 29 (14%)
Plasma type:	Archival: 314 (87%), Fresh: 49 (13%)	Fresh: 206 (100%)

RESULTS:

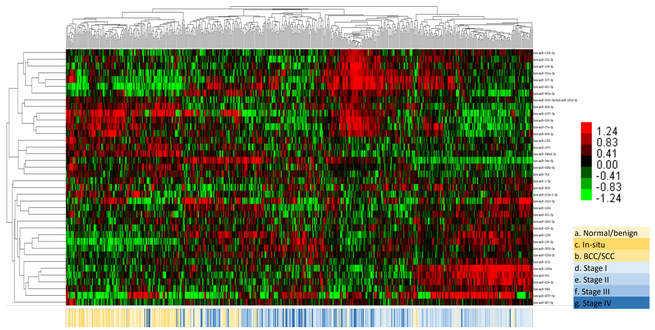

Figure 2. Hierarchical clustering of the MEL38 diagnostic microRNA signature for cutaneous melanoma in 582 plasma samples

A MEL38 score >5.5 optimally predicted the presence of invasive melanoma, correctly diagnosing 551/582 (95%) of cases and achieving 93% sensitivity and 98% specificity. The score has an area under the curve of 0.98 (95% CI 0.97 to 1.0, P<0.001 – See Figure 3).

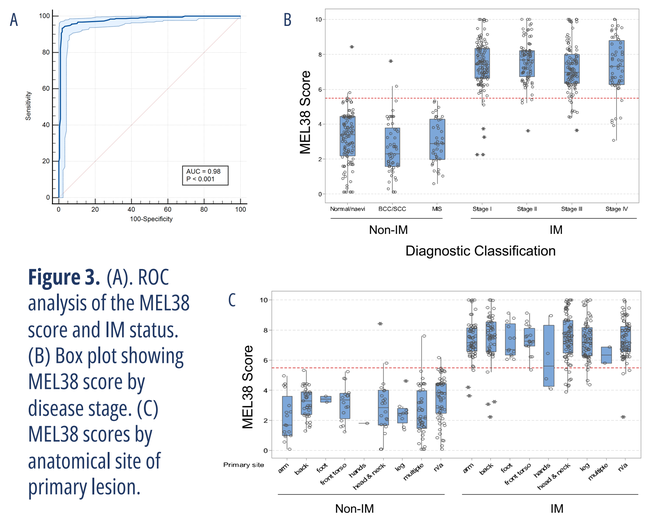

Figure 3. (A). ROC analysis of the MEL38 score and IM status. (B) Box plot showing MEL38 score by disease stage. (C) MEL38 scores by anatomical site of primary lesion.

Analysis of the Nanostring profiles generated to validate MEL38 yielded a novel 12-microRNA signature of survival risk (MEL12, Figure 4). This was used to assign patients to low, standard, or high-risk groups, which had 94%, 78% and 58% rates of 10-year survival (Log rank P<0.001).

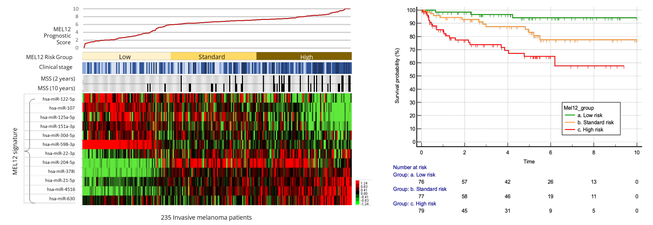

Figure 4. Hierarchical clustering of the MEL12 prognostic microRNA signature and Kaplan Meier analysis of discrete risk groups

MEL12 prognostic risk assignment was significantly associated with clinical staging (Chi square P<0.001) and sentinel lymph node status (P=0.027). 87% of patients with the high-risk MEL12 profile had melanoma detected in their sentinel lymph nodes.

CONCLUSIONS:

The MEL38 microRNA signature accurately diagnoses invasive melanoma using small volumes of plasma.

The MEL12 signature provides prognostic information and is linked to SLNB status, clinical stage, and survival, aiding treatment decisions for melanoma.

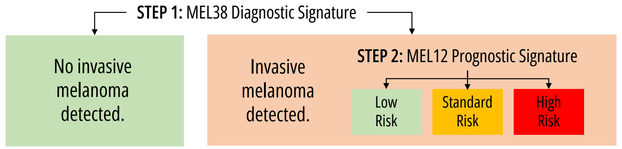

Figure 5. Clinical workflow for diagnosis and prognosis of melanoma using MEL38/MEL12 plasma microRNA profiling

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