Circulating Tumor DNA Analysis and Functional Imaging Provide Complementary Approaches for Comprehensive Disease Monitoring in Metastatic Melanoma

Purpose Circulating tumor DNA (ctDNA) allows noninvasive disease monitoring across a range of malignancies. In metastatic melanoma, the extent to which ctDNA reflects changes in metabolic disease burden assessed by 18F-labeled fluorodeoxyglucose positron emission tomography (FDG-PET) is unknown. We assessed the role of ctDNA analysis in combination with FDG-PET to monitor tumor burden and genomic heterogeneity throughout treatment.

Patients and Methods We performed a comprehensive analysis of serial ctDNA and FDG-PET in 52 patients who received systemic therapy for metastatic melanoma. Next-generation sequencing and digital polymerase chain reaction were used to analyze plasma samples from the cohort.

Results ctDNA levels were monitored across patients with mutant BRAF, NRAS, and BRAF/NRAS wild type disease. Mutant BRAF and NRAS ctDNA levels correlated closely with changes in metabolic disease burden throughout treatment. TERT promoter mutant ctDNA levels also paralleled changes in tumor burden, which provide an alternative marker for disease monitoring. Of note, subcutaneous and cerebral disease sites were not well represented in plasma. Early changes in ctDNA and metabolic disease burden were important indicators of treatment response. Patients with an early decrease in ctDNA post-treatment had improved progression-free survival compared with patients in whom ctDNA levels remained unchanged or increased over time (hazard ratio, 2.6; \(P = .05\)). ctDNA analysis contributed key molecular information through the identification of putative resistance mechanisms to targeted therapy. A detailed comparison of the genomic architecture of plasma and multiregional tumor biopsy specimens at autopsy revealed the ability of ctDNA to comprehensively capture genomic heterogeneity across multiple disease sites.

Conclusion The findings highlight the powerful role of ctDNA in metastatic melanoma as a complementary modality to functional imaging that allows real-time monitoring of both tumor burden and genomic changes throughout therapy.

INTRODUCTION

Melanoma is an aggressive skin cancer that carries a devastating prognosis in the metastatic setting. The use of mitogen-activated protein kinase inhibitors (MAPKi) in patients with advanced BRAF mutant melanoma\(^1\) and, more recently, immune checkpoint inhibitors\(^4,5\) has led to improved overall survival. Large-scale sequencing efforts have revealed the complex mutational landscape of melanoma and established a classification that encompasses mutant BRAF, NRAS, NF1, and triple wild-type (WT) subtypes\(^6\) as well as the identification of recurrent TERT promoter mutations.\(^6,7\) Like many cancers, melanoma is heterogeneous and exhibits a branched evolutionary pattern from initiation by UV exposure to progression of...
invasive and metastatic disease. Moreover, clonal evolution of melanoma continues to occur during systemic therapy, with diverse resistance mechanisms observed at relapse.

In patients with melanoma who receive systemic therapy, tumor burden and treatment responses currently are assessed through clinical evaluation, serial lactate dehydrogenase (LDH) levels, and radiologic imaging with ¹⁸F-labeled fluorodeoxyglucose positron emission tomography (FDG-PET). FDG-PET provides unique functional information that enables an accurate assessment of changes in metabolic disease activity and tumor volume throughout treatment. Although current imaging methods are effective at monitoring treatment response, complementary strategies are needed to assess molecular alterations and capture genomic evolution in the context of therapeutic resistance to guide treatment decisions.

Circulating tumor DNA (ctDNA) has emerged as a noninvasive biomarker to track tumor burden and allow monitoring of the cancer genome in blood across several malignancies. In melanoma, the relationship between ctDNA levels and tumor burden as assessed by FDG-PET is unknown. We sought to determine whether ctDNA could accurately reflect changes in metabolic tumor burden across various molecular subtypes of metastatic melanoma as well as recapitulate the genetic heterogeneity of disease throughout treatment and progression.

PATIENTS AND METHODS

Patients and Genomic Analyses

Patients with metastatic melanoma (N = 52) who received systemic treatment consented to longitudinal monitoring with serial plasma, LDH levels, and FDG-PET between June 15, 2012, and June 30, 2015 (Data Supplement). Three of the 52 patients also consented to multiregional tumor sampling after death as part of a rapid autopsy program. Tumor material and matched normal and plasma DNA were retrospectively analyzed through targeted amplicon (TA) sequencing and digital polymerase chain reaction (dPCR) as well as through whole-exome sequencing (WES) and low-coverage whole-genome sequencing (LC-WGS) in selected cases. The limit of detection was approximately 2% and 0.1% mutant allele fraction (MAF) for TA sequencing and dPCR, respectively. The median plasma DNA input for the dPCR and TA sequencing was 640 genome copies (interquartile range, 380 to 1,120 genome copies; Data Supplement).

FDG-PET

FDG-PET was performed on combined PET-computed tomography scanners by using a low-dose noncontrast-enhanced computed tomography for attenuation correction and anatomic correlation. Whole-body metabolic tumor volume measured in milliliters was quantified on serial FDG-PET scans by adapting the PERCIST (PET Response Criteria in Solid Tumors) recommendations. Global response to treatment was qualitatively assessed for each FDG-PET scan and classified into one of five categories: progressive metabolic disease, an increase in intensity or extent of tumor metabolic activity or new sites of disease; stable metabolic disease, no visible change in metabolic activity or size of tumors; partial metabolic response, a significant reduction in FDG uptake and size of tumors; complete metabolic response, lesions revert to background of normal tissues in which they are located; and mixed metabolic response, some lesions display a reduction in FDG uptake, whereas others show no change or increase in FDG uptake. The + symbol denotes the development of new sites of disease.

Statistics

Nonparametric Spearman rank correlation was used to investigate associations between continuous variables, and the Mann-Whitney U test was used to assess associations between continuous and dichotomous variables. Progression-free survival (PFS) analysis was performed by using a Cox proportional hazards regression model. Early assessment post-treatment for all variables corresponded to measurements taken between 1 and 4 weeks after treatment commencement. Time to event was measured from the start of treatment to the first documentation of progression on FDG-PET, with the relative hazard ratio computed for each comparison.

RESULTS

cDNA Is Detectable Across Various Molecular Subtypes of Metastatic Melanoma

Fifty-two patients with a median age at diagnosis of 61 years (range, 24 to 83 years) were serially monitored with FDG-PET, LDH, and ctDNA during therapy (Data Supplement). Twenty patients (38%) received treatment with MAPKi therapy, 18 (35%) received immunotherapy, and nine (17%) received both treatments. The median follow-up was 391 days (range, 24 to 1,106 days). TA sequencing of matched tumor and plasma identified mutations in 49 patients (94%; Fig 1; Data Supplement). Canonical BRAF and NRAS mutations were found in 37 patients...
(71%) and seven patients (13%), respectively, and eight patients (15%) were BRAF/NRAS WT.

ctDNA was detected in 39 (80%) of 49 patients by TA sequencing and/or dPCR (Fig 1). Analysis of BRAF and NRAS revealed that ctDNA was detected in 34 (77%) of 44 patients known to have a BRAF or NRAS mutation. In the patients with BRAF/NRAS WT disease, alternative mutations were identified in five (60%) of eight, which allowed ctDNA detection in all five individuals.
**TERT** promoter mutations were analyzed across the cohort and identified in 36 patients (69%), in concordance with other studies24 (Data Supplement). Screening of matched plasma detected **TERT** promoter mutations in 27 (75%) of 36 patients.

**Absolute Levels of ctDNA Before Treatment Show Variation According to Sites of Disease**

Pretreatment plasma was available in 41 of 49 patients (Fig 1). Pretreatment ctDNA levels varied among patients (median, 1,112 copies/mL of plasma; range, 63 to 97,000 copies/mL of plasma), which represented between 0.1% and 82% (median, 5.4%) of total circulating DNA. Pretreatment ctDNA levels showed a stronger correlation with disease burden as measured by FDG-PET ($r = 0.61$; $P < .001$) compared with LDH ($r = 0.34$; $P = .058$; Data Supplement). Of note, although a strong correlation existed between high metastatic disease burden as assessed by FDG-PET and high levels of ctDNA before treatment, several discordant cases were observed (Fig 2). We hypothesized that discordance may relate to a differential release of ctDNA into the peripheral circulation dependent on specific anatomic sites of disease. Consistent with this premise, patients with visceral, bone, or lymph node involvement often displayed high levels of ctDNA despite at times low disease burden as detected by FDG-PET. In contrast, individuals with extensive subcutaneous disease consistently showed low levels of ctDNA despite measurable levels of disease burden as assessed by FDG-PET (Data Supplement). Similar findings were observed in patients with brain metastases where low or undetectable levels of ctDNA were commonly observed. These findings are consistent with other studies that have shown low ctDNA levels despite extensive cerebral disease.12,25

**Serial ctDNA Monitoring Correlates With Tumor Burden and Treatment Response as Assessed by FDG-PET**

We investigated whether ctDNA levels correlate with changes in disease burden throughout treatment as assessed by LDH and FDG-PET. Serial ctDNA analysis was performed on 312 plasma samples by using dPCR for selected mutations identified from TA sequencing and compared with serial LDH measurements ($n = 329$) and FDG-PET ($n = 244$) across the series. In the **BRAF** and **NRAS** mutant cohort, changes in mutant ctDNA levels throughout treatment correlated with LDH levels ($r = 0.38$; $P < .001$) and disease volume as assessed by FDG-PET ($r = 0.63$; $P < .001$; Fig 3A; Data Supplement). Of note, serial changes in mutant **BRAF** or **NRAS** ctDNA levels closely reflected metabolic responses across multiple therapies, including MAPKi and immunotherapies (Figs 3B and 3C). In the **BRAF/NRAS** WT cases, other somatic mutations were used to quantify ctDNA, and levels similarly paralleled changes in disease burden as assessed by FDG-PET (Fig 3D; Data Supplement).

Next, we aimed to compare the prognostic value of serial changes in ctDNA alongside tumor volume measurements by FDG-PET and LDH levels during treatment. By using a Cox proportional hazards regression model, we identified that patients with an early decrease in ctDNA levels (between baseline and 1 to 4 weeks on treatment) had improved PFS compared with patients where ctDNA levels remained unchanged or increased over time (Fig 3E). Similar findings were observed for patients who demonstrated an early decrease in tumor volume as assessed by FDG-PET (Fig 3E). Although baseline levels of LDH were prognostic (Data Supplement), no significant association between PFS and an early decline in LDH levels after treatment were found (Fig 3E). Consistent with these findings, individuals who had a PFS $> 3$ months were found to have a significantly greater log-fold reduction in ctDNA levels at 1 to 4 weeks after treatment initiation compared with those who had a PFS $< 3$ months ($P = .03$; Fig 3F). Rapid responses by ctDNA were most notable after MAPKi therapy in keeping with the known response kinetics of these agents.

**TERT Promoter Mutant ctDNA Provides an Alternative Marker for Disease Monitoring**

We next evaluated whether **TERT** promoter mutations could be serially monitored in ctDNA and whether levels correlated with disease burden. As identified for **BRAF** and **NRAS** mutations, absolute levels of **TERT** mutant ctDNA showed a similar strong correlation with metabolic disease burden ($r = 0.54$; $P < .001$; Fig 4A). Serial **TERT** mutant ctDNA monitoring was informative in patients with **BRAF/NRAS** WT disease ($n = 3$) in whom changes in levels of **TERT** mutant ctDNA closely correlated with treatment response (Fig 4B). **TERT** promoter mutations have been shown to occur early in the neoplastic process and to co-occur with **NRAS** mutations but after the acquisition of **BRAF** mutations.8 Therefore, we investigated whether **TERT** promoter...
mutations followed the same dynamic changes in ctDNA as \textit{BRAF} or \textit{NRAS} mutations by analyzing plasma from all \textit{BRAF} and \textit{NRAS} mutant cases that were also \textit{TERT} promoter mutant (n = 33). In these cases, absolute levels of \textit{TERT} mutant ctDNA closely correlated with levels of \textit{BRAF} or \textit{NRAS} mutant ctDNA ($r = 0.76$; $P < .001$) across the series (Figs 4C and 4D).

**Serial ctDNA Analysis Can Detect Genomic Alterations Associated With Treatment Resistance**

Twenty-nine patients were treated with a MAPKi therapy. Paired plasma (and tumor biopsy specimens where available) before treatment and at disease progression were analyzed by using TA sequencing and LC-WGS/WES in selected cases. Genomic alterations known to be associated with resistance to MAPKi therapy were identified in eight (28%) of 29 patients (Data Supplement). Acquired \textit{NRAS} mutations were the predominant genomic alteration identified through analysis of ctDNA at the time of disease progression, as illustrated in patient MEL-76 (Fig 5A). In this individual, mutant \textit{BRAF} ctDNA levels remained elevated throughout dabrafenib + trametinib treatment. TA sequencing of plasma detected the emergence of an acquired \textit{NRAS} Q61K mutation.
before a routine FDG-PET scan that confirmed progressive metabolic disease, which highlights the ability of ctDNA analysis to identify early treatment failure. Other genomic alterations associated with treatment resistance were observed in multiple patients. For example, in patient MEL-31, TA sequencing of plasma samples before and after vemurafenib + cobimetinib treatment confirmed the presence of the $\text{BRAF} \ V600E$ mutation in addition to an increasing plasma abundance of $\text{MAP2K1}$ and $\text{PTEN}$ mutations (Fig 5B). Although the $\text{MAP2K1} \ E203K$ mutation was a likely cause for resistance in this individual, $\text{PTEN}$ mutations also have been associated with diminished response to MAPKi therapy and may have contributed to the rapid emergence of the therapeutic resistance observed.26 In patient MEL-7, TA sequencing and dPCR showed that changes in ctDNA levels of two preexisting mutations ($\text{BRAF}$ and $\text{CDKN2A}$) closely paralleled the dynamics of response and progression documented on FDG-PET (Fig 5C). ctDNA analysis at progression also revealed the emergence of an activating...
AKT1 mutation that represented a potential resistance mechanism to explain the short-lived response after recommencement of vemurafenib.27 Finally, BRAF amplification is considered a common resistance mechanism to MAPKi therapy27 and may confound quantification of mutant BRAF ctDNA levels for disease monitoring. Therefore, we explored the ability of ctDNA analysis to detect the presence of copy number alterations by performing plasma LC-WGS/WES in three patients treated with MAPKi therapy. Through this analysis, BRAF amplification was identified in two individuals (Fig 5D; Data Supplement). Patient MEL-1 initially received vemurafenib treatment with ctDNA falling to undetectable levels, and FDG-PET indicated a complete metabolic response. After 12 months, isolated disease progression was observed that involved the small bowel, which was subsequently resected. ctDNA collected just after the resection revealed unexpectedly high BRAF mutant ctDNA compared with TERT mutant ctDNA levels despite the small disease volume observed on FDG-PET. LC-WGS of the corresponding plasma revealed the BRAF amplification, which was subsequently confirmed in the small bowel biopsy specimen. This BRAF amplification was not detected in an earlier pretreatment tumor biopsy specimen, which suggests that the amplification was acquired after MAPKi therapy. These findings highlight the ability of plasma analysis to detect this mode of therapeutic resistance and emphasize the advantage of tracking TERT mutations in parallel to reflect changes in tumor burden accurately.

### Plasma DNA Captures Spatial Heterogeneity Across Multiple Disease Sites

Increasing appreciation of tumor heterogeneity has revealed the importance of assessing the full spectrum of molecular alterations present across multiple disease sites to appropriately guide treatment decisions. However, multisite tissue biopsy specimens usually are not possible in patients with advanced disease, and core biopsy specimens are limited in their ability to represent intratumoral heterogeneity.28 Thus, we first sequenced multiple tumors collected at autopsy from patient MEL-99 with BRAF V600E mutant melanoma treated with vemurafenib (Data Supplement). TA sequencing of the tumors at autopsy revealed acquired NRAS Q61H and Q61K mutations in a lung and...

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**Fig 3.** (Continued). (E) Global responses to therapy indicated by a Cox proportional hazards regression model that assessed the relationship between progression-free survival (PFS) and the change in ctDNA levels, FDG-PET volumes, or LDH levels between the pretreatment and early assessment time points. (F) Relationship between PFS and the log-fold change in ctDNA levels between the pretreatment and early assessment time points. The median line for each group is shown. Statistical significance was determined by using a nonparametric Mann-Whitney U test. *P = .03, +, development of new sites of disease; CMR, complete metabolic response; HR, hazard ratio; MAPKi, mitogen-activated protein kinase inhibitor; MMR, mixed metabolic response; Nivo, nivolumab; PMD, progressive metabolic disease; PMR, partial metabolic response; SMD, stable metabolic disease.
subcutaneous metastasis, respectively, which were not detectable in either a bowel or mesenteric sample. Of note, TA sequencing of plasma taken before death detected the NRAS Q61H mutation but not the NRAS Q61K mutation from the subcutaneous metastasis. This observation not only supports our previous finding of under-representation of ctDNA from subcutaneous metastasis but also highlights the potential for ctDNA sequencing to detect specific mutations in metastatic lesions.

Fig 4. Monitoring circulating tumor DNA (ctDNA) levels through TERT promoter mutations. (A) Correlation between mutant TERT promoter ctDNA levels and disease burden as assessed by 18F-labeled fluorodeoxyglucose positron emission tomography (FDG-PET) imaging ($r = 0.54; P < .001$). Analysis was performed with Spearman rank correlation. (B) Time course of a patient with BRAF/NRAS mutant wild type disease (MEL-67) with ctDNA levels tracked through a TERT c.-124 mutation during DEDN6526A and pembrolizumab (Pembro) treatment. (C) Correlation of mutant BRAF or NRAS ctDNA copies per milliliter of plasma to mutant TERT promoter ctDNA copies per milliliter of plasma throughout treatment ($r = 0.76; P < .001$). (D) Time course of a patient with a BRAF V600E mutation (MEL-28) with ctDNA levels monitored through both a BRAF V600E and a TERT c.-124 mutation in plasma during vemurafenib (Vem) treatment and radiotherapy (RT). CMR, complete metabolic response; PMD, progressive metabolic disease; PMR, partial metabolic response; SMD, stable metabolic disease.
Fig 5. Detection of therapeutic resistance mechanisms to mitogen-activated protein kinase inhibitor (MAPKi) therapy through circulating tumor DNA (ctDNA) analysis. (A) ctDNA analysis indicated acquired resistance to MAPKi therapy in a patient with a \( \text{BRAF} \) V600K mutation (MEL-76). The patient initially presented with small-volume bone and pulmonary disease and commenced combination therapy with dabrafenib + trametinib (Dab + Tram). \( \text{BRAF} \) eDNA levels remained elevated throughout treatment, with targeted amplicon (TA) sequencing of plasma detecting the emergence of an acquired \( \text{NRAS} \) Q61K mutation 18 weeks after starting treatment. (B) ctDNA analysis indicated acquired resistance to treatment in patient MEL-31 who presented with metastatic \( \text{BRAF} \) V600E positive disease that involved left-side pelvic lymph nodes, subcutaneous deposits, and solitary bone and lung metastases. The patient commenced combination therapy with vemurafenib and cobimetinib (Vem + Cobi) after disease progression in the pelvis with single-agent Vem, which resulted in a short-lived (4 weeks) partial metabolic response (PMR); the patient died 10 weeks after starting combination therapy as a result of noncompliance. While off therapy, marked disease progression developed, with multiple new brain metastases and increasing disease over the left-side scapula. After receiving radiotherapy (RT), Vem was recommenced. While on therapy, the patient died 2 months after starting combination therapy as a result of rapid disease progression. TA sequencing of plasma samples before and after Vem + Cobi treatment confirmed the presence of the \( \text{BRAF} \) V600E mutation in addition to \( \text{MAP2K1} \) E203K and \( \text{CDKN2A} \) R80X mutations as well as an acquired \( \text{AKT1} \) E17K mutation at the time of disease progression. (C) This patient with \( \text{BRAF} \) V600K mutant disease (MEL-7) initially presented with extensive disease over the left-side scapula and multiple pulmonary metastases and commenced Vem for 2 months. A PMR was observed before the patient ceased treatment as a result of noncompliance. While off therapy, marked disease progression developed, with multiple new brain metastases and increasing disease over the left-side scapula. After receiving radiotherapy (RT), Vem was recommenced. After initial PMR+, rapid disease progression occurred within 3 months, and the patient died shortly thereafter. ctDNA analysis identified the presence of preexisting \( \text{BRAF} \) V600K and \( \text{CDKN2A} \) R80X mutations as well as an acquired \( \text{AKT1} \) E17K mutation at the time of disease progression. (D) Patient MEL-1 initially presented with bulky disease of the bowel, lung, and lymph nodes and several sites of subcutaneous disease, which were \( \text{BRAF} \) V600E mutant positive. The patient received Vem and had a complete metabolic response (CMR) before developing acquired resistance after approximately 12 months of therapy. \( \text{BRAF} \) amplification was detected by whole-exome sequencing of a post-treatment bowel metastasis and low-coverage whole-genome sequencing of the plasma sample taken at disease progression. Log2 ratio plots show the copy number alteration over \( \text{BRAF} \) in the tumor and plasma. +, development of new sites of disease; AF, allele fraction; dPCR, digital polymerase chain reaction; M, megabase; MAF, mutant allele fraction; PMD, progressive metabolic disease; Sur, surgery.
disease sites but also demonstrates the ability of ctDNA to capture genomic heterogeneity from multiple sites of disease that may be missed from a single tissue biopsy specimen.

To comprehensively assess the extent to which ctDNA was able to reflect spatial heterogeneity across various disease sites, we performed WES on multiregional tumor samples from two additional autopsy cases alongside matched plasma collected close to death (Fig 6). We assessed the representation of somatic mutations identified across the tumor and plasma samples sequenced (Data Supplement). For patient MEL-28, 307 ubiquitous mutations (present in all tumors), 36 shared mutations (present in two or more tumors), and 36 private mutations (present in only one tumor) were detected (Fig 6A). Of these, 305 (99%) ubiquitous mutations, 23 (64%) shared mutations, and five (14%) private mutations were identified in plasma. Similar findings were observed in patient MEL-10 (Fig 6B). In both patients, private mutations were the predominant type of mutation not represented in plasma. For patient MEL-28, the limited ability to detect private mutations in plasma was a result of the low MAFs (median MAF, 9% for private mutations absent in plasma). For patient MEL-10, the higher MAFs observed for private mutations not detected in the plasma (median MAF, 38%) compared with patient MEL-28 was likely a result of the limited ability to detect brain-specific private mutations (median MAF, 49% vs 22% across other sites).

DISCUSSION

Over the past decade, a major paradigm shift has occurred in the treatment of metastatic melanoma through clinical implementation of targeted therapeutics and immune checkpoint inhibitors. These treatments have changed the natural history of this aggressive disease. However, a need exists for improved strategies to monitor treatment responses through molecular approaches to guide therapy and improve patient outcomes. One potential avenue is through the use of ctDNA analysis to provide patient-specific genomic information that can be monitored in real time during clinical management.
Previous reports have provided increasing evidence that ctDNA has prognostic value in metastatic melanoma, with ctDNA levels correlating with established measures of disease burden (eg, LDH). This study provides the first correlational analysis to our knowledge that compares ctDNA and FDG-PET imaging in this disease. FDG-PET has unique advantages in monitoring treatment responses in metastatic melanoma compared with other radiologic imaging techniques because it enables whole-body imaging with high sensitivity and specificity and can provide an early functional readout of response to targeted therapies. We reveal that ctDNA levels correlate closely with changes in metabolic disease burden assessed through FDG-PET and show that an early decline in ctDNA levels provides an important alternative indicator of treatment response, which predicts patients with prolonged PFS. In contrast to FDG-PET, a key strength of ctDNA analysis is its ability to allow noninvasive sampling of the changing tumor genomic landscape under the selective pressure of therapy. In conjunction with other studies, we highlight the ability of serial ctDNA analysis to detect resistance mechanisms to MAPKi therapy to assist with the early identification of treatment failure and allow consideration of alternative therapeutic strategies.

We monitored ctDNA across all molecular subtypes of melanoma. Although our strategy allowed us to identify a trackable mutation in 94% of the cohort, the targeted sequencing approach we used could be readily expanded to include other genes, such as NF1, to allow for identification of additional somatic genomic alterations for monitoring in patients with BRAF/NRAS WT disease. Previous reports have demonstrated the ability to measure ctDNA levels through dPCR of BRAF and NRAS mutations; however, the limitation of this approach in patients with copy number alterations that involve these genes has not been previously addressed. BRAF and NRAS amplifications are known to occur frequently in melanoma (approximately 7% and 3%, respectively), and in the current study, we show the advantage of plasma analysis in assessing the emergence of copy number alterations. The data highlight that tracking TERT promoter mutations, in addition to BRAF and NRAS, offers an improved strategy for disease monitoring.

In conclusion, ctDNA can play a vital complementary role to functional imaging in metastatic melanoma because it can be used to monitor tumor response kinetics and can capture the mutational spectrum from many sites of disease. A significant limitation to ctDNA monitoring is that subcutaneous and cerebral disease sites are not well represented in the plasma, and recognition of this limitation is pivotal if ctDNA monitoring is to be integrated into routine clinical practice. For this reason, we propose that the combination of FDG-PET to monitor metabolic response and ctDNA to monitor molecular evolution has the potential to provide a powerful and complementary strategy for disease monitoring in melanoma.

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REFERENCES


