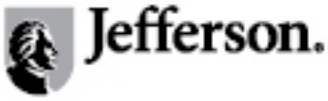

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Circulating tumor DNA to monitor metastatic breast cancer.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1305429

Circulating Tumor DNA to Monitor Metastatic Breast Cancer

TO THE EDITOR: Dawson et al. (March 28 issue)[1] suggest that the detection of circulating tumor DNA in 58% of patients with metastatic breast cancer can be used as an effective indicator of tumor load during treatment with standard systemic therapies. The study does not address the clinical utility of circulating tumor DNA. Moreover, the authors claim that circulating tumor DNA represents a more effective monitoring tool than the enumeration of circulating tumor cells. This statement is incorrect, considering that the enumeration of circulating tumor cells proved the ability to predict prognosis and monitor treatment efficacy in all patients with metastatic breast cancer, regardless of disease subtype.[2] Furthermore, new detection methods describe the molecular heterogeneity and measure dynamic phenotypic changes in circulating tumor cells during metastasis.[3,4] We propose that circulating tumor DNA provides a complementary method in the assessment of patients with detectable mutations and should be more appropriately used to select and monitor molecularly targeted therapies. Combined diagnostic methods will provide a more effective approach than each method alone to the implementation of precision medicine and improved clinical outcomes.

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No potential conflict of interest relevant to this letter was reported.

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3. Magbanua MJ, Sosa EV, Roy R, et al. Genomic profiling of isolated circulating tumor cells from metastatic breast cancer patients. Cancer Res 2013;73:30-40.
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DOI: 10.1056/NEJMc1306040

TO THE EDITOR: Dawson et al. propose circulating tumor DNA as a new biomarker for metastatic breast cancer. In our opinion, the timing of the analysis is crucial for the correct interpretation of such data obtained from samples acquired during chemotherapy.

Apoptosis leads to the augmented release of cell-free DNA,[1] so chemotherapy is expected to temporarily increase the levels of circulating tumor DNA. Thus, the assumption that such increases reflect tumor load may be incorrect, depending on the time point chosen.

We suggest a dual role for analysis with circulating tumor DNA. First, the difference between basal levels before and peak levels after the administration of chemotherapy may serve as an indicator of tumor responsiveness. Second, levels of circulating tumor DNA measured several days after the last chemotherapy cycle may serve as a surrogate marker for total tumor mass.

Analysis of the kinetics of circulating tumor DNA during the use of various chemotherapeutic drugs and regimens may pave the way for the clinical translation of analysis with circulating tumor DNA.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1306040

THE AUTHORS REPLY: We support the idea that combined methods involving circulating tumor cells and circulating tumor DNA could be used to analyze tumor status and changes. By the criterion of sensitivity for detection of disease burden, our data clearly show an advantage to the

detection of circulating tumor DNA over the enumeration of circulating tumor cells by means of the CellSearch System. Our findings provide the rationale for future studies to address the full clinical utility of analyses with circulating tumor DNA.

One apparent limitation of our work was that only two genes (*PIK3CA* and *TP53*) were analyzed for most patients. These are the two most commonly mutated genes in breast cancer, and as expected, they were informative in half the patients recruited. This does not represent a general limitation of circulating tumor DNA: as a proof of principle, we also found that we were able to monitor other somatic mutations and structural variants in a subset of patients who did not have mutations in *PIK3CA* or *TP53*. Our data indicate that any cancer-specific mutation can be monitored in circulating tumor DNA from patients with metastatic breast cancer.

The timing of blood and plasma collection is obviously an important variable. In our study, all samples were collected immediately before the administration of each treatment cycle. The possibility of measuring an increase in the release of circulating tumor DNA as an indicator of responsiveness is attractive and is supported by xenograft models.[1]

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1306040

Globalization, Climate Change, and Human Health

TO THE EDITOR: The scholarly review of globalization and climate change by McMichael (April 4 issue)[1] emphasizes the associated economic, social, demographic, and environmental threats to human health and suggests steps to mitigate these changes on a global scale. Although McMichael also mentions the effects of climate change and globalization on the geographic range of vectorborne infections, he does not alert readers to sobering examples of the emergence of tropical infections in the temperate zone (Table 1). Globalization and climate change promote the emergence of these infections synergistically. Globalization increases the number of infected travelers and the accidental importation of infected vectors. Climate change warms the environment to temperatures that permit reproduction of the vector and parasite. Increasing

Table 1. Effects of Globalization and Climate Change on the Spread of Tropical Infections to the Temperate Zone.*

Tropical Infection	Areas of Local Transmission	Comment	Reference
Dengue	Key West and elsewhere in Florida; Brownsville, Texas; France; and Croatia and other areas of southern Europe	A total of 5% of Key West residents have antibodies against dengue, and locally transmitted infections have been reported in other counties, including Miami–Dade; 39% of residents in Brownsville have antibodies against dengue	Jordan et al.,[2] Ramos et al.,[3] Butler[4]
Malaria	Greece	The CDC recommends precautions (level 1) for persons who travel to Greece, including consideration of drug prophylaxis for travel to some regions	CDC[5]
Chikungunya	Italy and France	Hundreds of persons have been infected in Italy	Butler[4]

* CDC denotes Centers for Disease Control and Prevention.