Early Detection of Disease Outbreaks

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For disease outbreak detection, the public-health community has historically relied on the watchful eyes of doctors and other health-care workers, who have reported individual cases or clusters of cases of particular diseases to health-care and other authorities. The increased availability of electronic health-care data, however, raises the possibility of more automated and earlier outbreak detection and subsequent intervention. Besides diagnoses of known diseases, pre-diagnostic syndromic indicators—such as the primary complaints of patients coming to the emergency room or calling a nurse hotline—are being collected in electronic formats and could be analyzed if suitable methods existed. Martin Kulldorff and colleagues have been developing such methods, and now report a new and very flexible approach for prospective infectious disease outbreak surveillance.

Their method, which they call the “space–time permutation scan statistic,” is an extension of a method called scan statistic. All previously developed scan statistics require either (i) a uniform population at risk (with the same number of expected disease cases in every square kilometer), (ii) a control group (such as emergency visits not due to the disease of interest), or (iii) other data that provide information about the geographical and temporal distribution of the underlying population at risk, such as census numbers. The new method, because of a different probability model, can be used for the early detection of disease outbreaks when only the number of cases is available. It also corrects for missing data and makes minimal assumptions about the spatiotemporal characteristics of an outbreak. To make it widely accessible, the method has been implemented as a feature of the freely available SaTScan software.

In their article, Kulldorff and colleagues illustrate the utility of the new method by applying it to data collected from hospital emergency departments in New York City. The researchers analyzed diarrhea records from 2002, and did both a “residential analysis” (based on the home address of the patients) and a “hospital analysis” (based on hospital locations). The former has more detailed geographical information, the latter maybe be better able to detect outbreaks.

How Tumor Cells Acquire Resistance to Kinase Inhibitors

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Acquired resistance to chemotherapy is a major obstacle to successful cancer treatment. Understanding the mechanisms by which tumors become resistant to a particular agent is key to identifying new drugs or combination regimens.

Kinases are signaling molecules that control many aspects of cell behavior, including cell proliferation, i.e., whether and how fast cells divide. Abnormally active kinases promoting tumor growth are found in many cancers and are a focus of rational cancer drug design. One target for kinase inhibitors is the epidermal growth factor receptor (EGFR). Two EGFR inhibitors, gefitinib and erlotinib, showed therapeutic benefits in a subset of patients with non-small cell lung cancer. Recent work has helped us understand why some patients respond and some don’t: responsive tumors usually harbor activating mutations in the EGFR gene, which somehow make the tumors sensitive to treatment. Nearly all patients whose tumors initially respond to EGFR inhibitors, however, eventually become resistant to the drugs and progress despite continued therapy.

William Pao and colleagues examined tumors from six patients with non-small cell lung cancer who initially responded to gefitinib or erlotinib but subsequently relapsed. Tumors from all six patients carried activating mutations in the EGFR gene. In addition, in three out of the six...
to reverse, but how or why a specific individual becomes sensitized is as yet far from clear.

Verhoef A, Alexander C, Kay AB, Larché M (2005) T cell epitope immunotherapy induces a CD4+ T cell Population with regulatory activity. DOI: 10.1371/journal.pmed.0020078
Using Integrins for Tumor Imaging
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What holds cells together or connects them with the extracellular matrix—and what happens when these interactions break down—is one of the keys to determining how tumors metastasize. One group of compounds—integrins—are a central part of these interactions. Not only do integrins play a part in cell–cell and cell–matrix adhesion, but they also are involved in signal transduction (the method by which a cell relays information from receptor binding to cellular response) and in triggering cell death by linking to other molecules. One such member of this receptor family is the αvβ3 integrin, which is expressed on both the tumor cells and the new vasculature of various tumors, including melanomas. αvβ3 integrin has a role in cell migration and extravasation, which occurs during metastasis, and also in angiogenesis—the development of new blood vessels that are essential for the growth of tumors. These blood vessels are the target for one class of anti-cancer drugs—angiogenesis inhibitors. Molecules that bind to αvβ3 integrin have also been used to target therapeutic compounds to tumors: compounds that antagonize this integrin can lead to apoptosis (programmed cell death) of cells that express it.

Haubner and colleagues, the authors of a paper in this month’s PLoS Medicine, have previously developed a fluorine-labeled peptide, [18F]Galacto-RGD, that has a high affinity for αvβ3 integrin. [18F]Galacto-RGD has many of the features essential for a tracer: it is specifically accumulated by tumors that express αvβ3 integrin, it is efficiently eliminated by the kidneys, and it is stable in vitro and in vivo.

In the research paper in PLoS Medicine, Haubner and colleagues take the development of the compound further towards clinical application. First, in a mouse with human

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αvβ3 integrin expression in tumors
melanoma they used highly sensitive positron emission tomography (PET) scanning to show not only that the level of uptake of integrin was specific for the tumor, but also that the uptake was in direct proportion to the amount of αvβ3 expressed, thus potentially allowing quantification of receptor expression; however, larger tumors showed a poorer correlation, possibly because of the presence of necrotic areas that do not express the integrin.

In humans, this picture was a little less clear; in a small study of patients with tumors including melanoma, the authors found a good deal of difference between patients in the uptake of the marker by tumor cells and the corresponding tumor vasculature. However, there was good correlation between the tracer uptake and conventional staining for the integrin by immunohistochemistry—again suggesting that the marker is truly reflecting the in vivo level of the integrin.

What do these results mean for clinical applications? As well as identifying tumors that express this marker, this approach might also offer a noninvasive way to assess the degree of new vessel formation in tumors. The approach could provide important information for planning and monitoring anti-angiogenic therapies targeting this integrin and could reveal the involvement and role of this integrin in metastatic and angiogenic processes in various diseases.

Haubner R, Weber WA, Beer AJ, Vabuniene E, Reim D, et al. (2005) Noninvasive visualization of the activated αvβ3 integrin in cancer patients by positron emission tomography and [18F]Galacto-RGD. DOI: 10.1371/journal.pmed.0020070