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Guest Editorial

Biomarker Research Playing an Expanded Role in Radiology

Research in radiology is expanding rapidly outside of traditional imaging studies using visual analysis alone. Studies including a biomarker component, both imaging biomarkers and biospecimen-derived biomarkers, are becoming an increasingly important part of radiology research. Biomarker identification is the foundation of “precision medicine,” in which treatments are tailored to a patient's unique variability in genes, environment, and lifestyle (Genetics Home Reference, 2019).

A biomarker is a biological characteristic that can be objectively measured as an indicator of a normal or abnormal biological process. Because there was inconsistency in the use of the term, the FDA–NIH Biomarker Working Group recently clarified usage, stating that “molecular, histologic, radiographic, or physiologic characteristics are examples of biomarkers” (O'Connor et al., 2017). Although biomarkers are used extensively in cancer staging and management and in the drug development process, they have not been commonly used to test research hypotheses in clinical trials or used as decision-making tools in clinical settings (O'Connor et al., 2017). This is changing, and one first-of-its kind study has shown that an imaging biomarker can be used to both test a research hypothesis and alter clinical care.

The recently published Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) study (Rabinovici et al., 2019) demonstrated the clinical impact of amyloid positron emission tomography (amyloid PET) imaging in dementia, using an imaging biomarker (amyloid protein plaques in the brain) as a precision medicine tool to improve evaluation of people with dementia and mild cognitive impairment.

The multicenter study of more than 11,000 Medicare beneficiaries, published on April 2, 2019, in the *Journal of the American Medical Association* (*JAMA*) (Rabinovici et al., 2019), was managed by the American College of Radiology and led by scientists at the Alzheimer's Association; University of California (UC) San Francisco; Brown University School of Public Health; Virginia Commonwealth University School of Public Health; Washington University School of Medicine in St. Louis; UC Davis, School of Medicine; and the Kaiser Permanente Division of Research.

The IDEAS study found that PET imaging that detects a specific biomarker, which in this case was Alzheimer's-related protein plaques in the brain, significantly influenced clinical management of patients with mild cognitive impairment and dementia. The study demonstrated that providing clinicians with the results of PET scans that identify amyloid plaques in the brain changed medical management—including the use of medications and counseling—in nearly two-thirds of cases, more than double what researchers predicted before the study. Amyloid PET imaging also altered the diagnosis of the cause of cognitive impairment in more than one in three study participants.

Because Alzheimer's disease is characterized by the accumulation of both amyloid protein plaques and tau protein “tangles” in the brain, the presence of one or both of these biomarkers is required for a definitive diagnosis. Until recently, amyloid plaques could only be detected by postmortem analysis of autopsied brain tissue. With the advent of amyloid PET—which involves injecting patients with tracer molecules that “stick to” amyloid plaques and can be used to visualize their location in the brain—it became possible to detect plaques with a brain scan and thus more accurately diagnose people living with the disease.

The study of biomarkers in blood and other body fluids is also having a having a major impact on radiology research. These biospecimen-derived biomarkers are not detected through imaging but in DNA, RNA, proteins and protein fragments, and cells (eg, circulating tumor cells). The hope is that once a biomarker in a biospecimen is found, a blood or other test would one day be used in conjunction with imaging tests to detect, monitor, and treat disease. Thus, there is a growing trend in radiology clinical trials to incorporate a biomarker component in which body fluid and tissue are collected from participants for future biomarker research.

One example of this is DECAMP (Detection of Early Lung Cancer Among Military Personnel), which was originally funded through a Department of Defense award to Boston University; the American College of Radiology has managed the study since 2011. The study's main goal is to discover how different types of biomarkers can help improve lung cancer screening for people who are at high risk for the disease. In the study's second phase, DECAMP-2, which is privately funded and currently under way, blood, urine, sputum, nasal brushing, buccal scraping, bronchial biopsy, bronchial brushing, and lung tissue are being collected from participants for genetic testing for lung cancer biomarkers (DECAMP-2, 2019).

The search for biomarkers in lung cancer became an especially important area of study after the landmark National Lung Screening Trial (NLST), conducted by the American College of Radiology, demonstrated that screening high-risk adults with low-dose helical computed tomography (CT) saves lives. The study results, published in the *New England Journal of Medicine* in 2011 (The National Lung Screening Trial Research Team, 2011), led to federal guidelines recommending lung cancer screening in adults aged 55-80 years, with a 30-pack a year smoking history (Lung Cancer: Screening, 2013).

Although the NLST showed that lung screening saves lives in high-risk groups, a biomarker test to guide physicians would provide a more complete picture of the disease. CT scans often detect small lung lesions that cannot be diagnosed as benign or cancerous by imaging features alone. These indeterminate nodules usually

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require follow-up with additional scans, a biopsy, or surgery. A biomarker test would help physicians better evaluate these indeterminate nodules, reducing or eliminating the need for invasive testing or additional scans.

In the coming years, biomarker discovery will be greatly enhanced by artificial intelligence (AI) algorithms. AI is expected to be more valuable than existing computational methods, both in clinical care and in drug discovery, because it has the capability to distinguish data that show up by chance from data that are connected to a disease or drug under study (Harms, 2019). Advanced AI algorithms will be able to take mammoth amounts of data and create graphical models that represent the complex molecular elements of a disease, enabling scientists to determine which biomarkers will predict treatment response, patient prognosis, or another end point (Harms, 2019).

Although both imaging and biospecimen-derived biomarkers have become an increasingly important element of radiology research studies, they are not yet widely used in clinical settings to diagnose and treat disease definitively. This will change as AI-supported and other solutions are developed. We look forward to the day when biomarkers will guide diagnosis, treatment, and management of all cancer types, Alzheimer's, and many other devastating diseases.

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