Put It on the Board, 10/15

Neuropathologist Dr. Omalu in spotlight at CAP ’15

Bennet Omalu, MD, MBA, MPH, who gave the spotlight event speech at CAP ’15 earlier this month, says he met retired Pittsburgh Steeler Mike Webster before conducting the 2002 autopsy that would lead to the first diagnosis of chronic traumatic encephalopathy in a National Football League player.

“I met him on TV,” Dr. Omalu says. “All the channels were talking about this great NFL player who died suddenly, and talking about him in very derogatory ways. Many NFL players, when they retire, they don’t handle their money well. They become destitute and bankrupt.”

Dr. Omalu

To the Nigerian-born Dr. Omalu, fresh from completing his neuropathology fellowship at the University of Pittsburgh Medical Center, football players scrambling across the field in headgear “looked like extraterrestrials.”

As someone who did not grow up with the sport, Dr. Omalu speculated: “If they need to wear helmets, I thought that meant there must be a risk of brain injury in this game. If he [Webster] played for 17 years, and was exposed to repeated banging of the head, wouldn’t there be a probability of brain damage?”

Dr. Omalu’s instinct did not match up with what he saw when he first examined the former Pro Football Hall of Famer’s brain in his capacity as a forensic neuropathologist in the town where Webster achieved his glory days on the gridiron.

“When I opened up the skull, I expected to see a shriveled brain that looked grossly abnormal. But to my utter shock and amazement, his brain looked normal,” says Dr. Omalu, who spoke with CAP TODAY prior to his Oct. 4 speech in Nashville. Dr. Omalu did not leave the Webster matter alone, choosing to preserve the brain for further study.

About two to three months later, he pulled the case off the shelf. “I put it on the microscope mount. [Webster] was 50 years old, and yet when I looked at his brain and he had diffuse amyloid plaques everywhere and there were no neuritic plaques….I took the slides home with me. I spent six months with those slides. I saw tau randomly situated, and not reminiscent of any other dementia that I knew. My first reaction, when I went to the literature, was that I expected to find previous reports like this, but I didn’t find even one.”

Dr. Omalu presented that first case as a poster at meetings and eventually published it (*Neurosurgery*. 2005;57[1]:128–134). He later identified CTE in a second NFL player (*Neurosurgery*. 2006;59[5]:1086–1092), followed by seven more cases of CTE in former NFL players. At first, he and his colleagues encountered resistance from nonpathology physicians on the NFL’s mild traumatic brain injury committee, who asked Neurosurgery to retract the first report, on Webster, arguing that its “description of chronic traumatic encephalopathy is completely wrong.” The article was not retracted.

Dr. Omalu, 47, is now chief medical examiner for San Joaquin County, Calif., and clinical professor of pathology at the University of California, Davis. In addition to diagnosing CTE in football players, he has found the condition in a professional wrestler (*J Forensic Nurs*. 2010;6:130–136) and a 27-year-old Marine veteran of the Iraq war (*Neurosurg Focus*. 2011;31[5]:E3).

Last month, neuropathologist Ann McKee, MD, told a reporter for PBS’ Frontline website that she and her colleagues at the Boston University Center for the Study of Traumatic Encephalopathy found CTE in 87 of the 91 former NFL players’ brains they examined postmortem. In all, Dr. McKee and her colleagues have examined the brains of 165 people who played football professionally, in college, or in high school, and diagnosed CTE in 79 percent of them.

The next frontier is to spot CTE before death. Dr. Omalu, cofounder and co-director of the Brain Injury Research Institute at West Virginia University, is working with physicians at the University of California, Los Angeles, on a product called Tau Mark. That consists of a chemical marker called [F-18]FDDNP that is injected intravenously and binds to deposits of amyloid plaques and neurofibrillary tau. The research team then uses positron emission tomography to look for signs of CTE.

Their most recent study compared PET scans of 28 healthy male controls and 24 patients with Alzheimer dementia with those of 14 retired NFL players with suspected CTE. The imaging results for the players, they wrote, “suggested the presence of neuropathological patterns consistent with models of concussion wherein brainstem white matter tracts undergo early axonal damage and cumulative axonal injuries along subcortical, limbic, and cortical brain circuitries supporting mood, emotions, and behavior.” That pattern, Dr. Omalu and his colleagues found, was “distinctively different” from the neuropathology seen in the patients with Alzheimer dementia and is “primarily consistent” with the PHF-tau distribution found in autopsy-confirmed diagnoses of CTE (Barrio JR, et al. *Proc Natl Acad Sci USA*. 2015;112[16]:E2039–2047).

“Rather than disputing the pathology, we need to understand it better at every level,” Dr. Omalu says. “People should come on board. I don’t think it’s the end of the road. It’s still an open road in this process as it continues. I think 50 years from now we will understand this better at the genetic level.”
—Kevin B. O’Reilly

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Revised HER2 guidance shifts findings in practice

A revision in 2013 by the American Society of Clinical Oncology and the CAP to guidelines for evaluating the HER2 status of breast cancer has had a significant impact on women’s HER2 classification, said a study led by researchers from Dartmouth Geisel School of Medicine.

The 2013 ASCO/CAP revision of standards was the first since 2007. The updates lowered the threshold for HER2 and altered the equivocal category. The Dartmouth group’s retrospective review was based on a comparison of

one year's worth of cases prior to the guideline updates, and another year's worth of cases after the update. They found that the number of equivocal HER2 cases increased after the update, nearly half of which would have been negative by the 2007 guidelines (Muller KE, et al. *Am J Clin Pathol*. 2015;144[2]:247–252). A majority of the cases classified as equivocal with the 2007 guidelines would be reclassified as positive if using the 2013 criteria. This would have meant additional patients eligible for anti-HER2 therapy.

"With the 2013 updates, cases that fall into the equivocal category are different than those previously considered equivocal," Laura Tafe, MD, the study's senior author and assistant director of the molecular pathology laboratory at Dartmouth-Hitchcock Medical Center, said in a statement. "There is now a dilemma regarding how best to treat these patients and additional clinical studies are needed to answer this question."

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Roche's flu A/B test waived

The FDA has granted a CLIA waiver for the Roche Cobas Influenza A/B test for use on the Cobas Liat System. The company said it is the first CLIA-waived, real-time PCR test to detect influenza A and B in about 20 minutes. The test targets highly conserved regions of the influenza A and B genomes to provide broad strain coverage of more than 30 commonly found strains of influenza A and B.

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Trial finds risk-stratification value in Oncotype DX

Initial results announced from the Trial Assigning Individualized Options for Treatment (Rx) show that a group of participants with a low 21-gene recurrence score and who received hormonal therapy alone had less than a one percent chance of distant recurrence at five years. The multicenter, prospectively conducted trial known as TAILORx included more than 10,000 women with early stage breast cancer. It was sponsored by the National Cancer Institute and led by the ECOG-ACRIN Cancer Research Group with support from Genomic Health.

Second primary cancers exceeded recurrences of the original breast cancer, resulting in 93.8 percent five-year disease-free survival, the primary trial endpoint. The genetic test used in the trial is marketed as Oncotype DX Recurrence Score by Genomic Health. These results, which involve the group of 1,626 patients with a recurrence score between zero and 10, demonstrated that 99.3 percent of node-negative, ER-positive, HER2-negative patients who met accepted guidelines for recommending chemotherapy and hormonal therapy had no distant recurrence at five years after treatment with hormonal therapy alone (Sparano JA, et al. *N Engl J Med*. Epub ahead of print Sept. 28, 2015. doi:10.1056/NEJMoa1510764).

The trial used the Oncotype DX test on every patient to quantify individual risk of recurrence in order to assign them to treatment. This trial continues to evaluate the effect of chemotherapy only for those with a midrange recurrence score. In TAILORx, women with a recurrence score of 10 or less received hormonal therapy alone; women with a recurrence score greater than 25 received hormonal therapy plus chemotherapy; and those with a midrange recurrence score from 11 to 25—the primary study group—were randomized to receive hormonal therapy with or without chemotherapy.

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California registry pools pathology cancer data

The California Department of Public Health is participating in a pilot project with St. Joseph Health to better understand cancer trends in California. In this partnership, the health system is collecting and securely sending structured pathology cancer data directly to the California Cancer Registry.
"Every second we save in sharing data gives researchers more time to spend on curing cancer," department director Karen Smith, MD, MPH, said in a statement.

The project has afforded the cancer registry the opportunity to perform real-time surveillance activities on data reported via project partners. Ten hospitals within the St. Joseph Health system are sending data directly to the health department's California Cancer Registry, with other health care facilities expected to participate in the future. The pilot project is a collaboration of California's health department, St. Joseph Health, synoptic reporting solutions provider mTuitive, and the CAP.

The pathology data-capture project required the use of the CAP electronic Forms and Reporting Module. Using CAP eFRM, pathologists securely transmit complete cancer data electronically to the registry, where it can be used for patient care and cancer control efforts throughout the state. Work on this pilot program began in January 2014. St. Joseph sent the first complete data set to the state registry in March of this year.

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Precision medicine project to enroll 1 million

A National Institutes of Health advisory committee has presented NIH director Francis S. Collins, MD, PhD, with a framework for building a cohort of 1 million-plus Americans to expand the knowledge and practice of precision medicine. The NIH plans to build the infrastructure quickly so that participants can begin enrolling in the cohort in 2016; the goal is to enroll at least 1 million participants by 2020.

Of the $215 million president Obama budgeted in fiscal year 2016 for his precision medicine initiative, $130 million was allocated to the NIH to build the research cohort. Dr. Collins established the Precision Medicine Initiative Working Group of his advisory committee and asked the group to develop a plan for creating and managing a large research cohort, with data and specimens that all researchers can access.

The advisory report proposes to allow any person living in the U.S. to enroll in the study directly or through participating health care organizations. Participants would volunteer to share core data including their electronic health records, health survey information, and mobile health data on lifestyle habits and environmental exposures. They would also undergo a standard baseline exam and provide a blood sample. In return, participants will have access to their study results, along with aggregated results from all participants, and will be provided with tools to make sense of the results.