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Researcher advises translational med hubs best place for clinical phenotyping efforts

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President Barack Obama launched the "Precision Medicine Initiative" this past winter during the State of the Union address, and politicians on both sides of the aisle applauded the announcement. Broadly, precision medicine is meant to help diagnose individuals more accurately and better tailor treatment according to their physiology.

This approach has long been the goal of translational medicine, an allied field epitomized by the National Institutes of Health (NIH) Clinical and Translational Science Awards (CTSAs) program launched in 2006. The CTSAs were designed to fund the integration of basic and clinical science, so that discoveries in the laboratory could be more readily translated into new therapies, devices, or ways to predict and manage disease.

Writing this week in *Science Translational Medicine*, Garret FitzGerald, MD, FRS, director of the Institute for Translational Medicine and Therapeutics (ITMAT) and chair of the department of Systems Pharmacology and Translational Therapeutics at the University of Pennsylvania's Perelman School of Medicine, stresses that to "influence emergence of the clinic of the future, one designed to practice precision medicine," an NIH plan to establish large-scale collaborative clinical trials needs also to pay better attention to three areas of emerging practice. They include:

- the application of adaptive trial designs, in which patients' early reactions to drugs are used to modify trials' approaches

- the integration of electronic medical records (EMRs) with biobank data to pinpoint potential new disease pathways
- the pursuit of human phenomic science (HPS), the cataloging of observable, detailed, evoked responses in small numbers of patients to find the significance of molecular pathways possibly involved in disease.

FitzGerald's comments were prompted by a shift in funding strategy by the National Center for Advancing Translational Science (NCATS). Roughly 20 percent of the current CTSA funding is being removed from university hubs to be used by NCATS, mostly to foster a network capable of large-scale, multicenter trials.

"Even if a collaborative network of 62 CTSA institutes is a realistic near- or medium-term goal, it is highly unlikely to be as time or cost efficient as existing academic networks or CROs [commercial clinical research organizations] in the performance of large-scale clinical trials," he writes. For now, the focus of the President's Precision Medicine Initiative is on collecting and integrating vast amounts of clinical data from EMRs. But, this patient-record-based approach requires pairing with measures of actual physiology, pathology, or drug response, in small numbers of individuals to connect a person's genetics and phenotype.

FitzGerald calls for a leaner approach to clinical trials in a phenotyping-driven world: "Our approach to HPS must be fluid, flexible, and fast enough to interact effectively and at scale with EMR and biobank studies." And, he maintains that human phenotyping is precisely the type of endeavor that CTSAs are good at, with their individual clinical and translational research centers (CTRCs) aimed at multi-purpose, smaller trials, with specialized approaches and expertise in rare diseases, metabolomics, and pilot or proof-of-concept studies.

Human Capital

FitzGerald and ITMAT have long been at the forefront of creating a workforce of translational scientists who are adept at bridging the divide between basic research and clinical investigation. ITMAT was launched formally in January 2005, formed a basis for the CTSA program, and is the first institute of translational medicine in the world, now with close to 2,000 members and multiple educational offerings, including master's degree programs in Translational Research and in Regulatory Science.

"It is remarkable how few investigators integrate expertise in preclinical models with a sophisticated approach to quantitative phenotyping in humans," he writes. "This blend of expertise forms a discipline that has no name and yet is crucial to the interests of NIH-funded science, the pharma and biotech industries, and the U.S. Food and Drug Administration."

He holds that the reallocation of money away from the CTSA hubs will undermine their ability to pursue HPS by redirecting money from where it is performed in the CTRCs, from training and from pilot-project funding to gain proof of concept to allow investigators to pursue more substantial funding for the further pursuit of that science. The impact on training and the benefits in kind afforded by CTRCs hit young researchers the most: "These restrictions fall most heavily on young investigators and our future workforce, the element most crucial to success," FitzGerald writes.

He believes that this is an unintended consequence of the recent change in the CTSA/NCATS funding strategy but that this can be avoided. "Perhaps it is time to consider 'comprehensive' and 'specialized' CTSA hubs akin to cancer centers. Comprehensive hubs might address multiple aspects of clinical and translational science, whereas specialized hubs would have smaller budgets and focus on a particular disease or type of science. Given the current appetite for precision medicine, we should use at least some of the CTSAs to foster the development of HPS."

More information: "Evolution in translational science: Whither the CTSAs?" by G.A. FitzGerald, stm.sciencemag.org/lookup/doi/ … scitranslmed.aab1596

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