"Vive la Différence"

I swear by Apollo the physician and Asclepius and Hygieia and Panaceia and all the gods and goddesses as my witnesses, that, according to my ability and judgment, I will keep this oath and this covenant:


Each May I listen to a modern version of this oath spoken by the 160 or so students graduating from medical school here at the University of Louisville. It is a very emotional moment, the capstone of a long and difficult journey in becoming a physician. The students stand and are joined in this oath by any physician in the audience wishing to reaffirm their commitment to the profession.

Though dressed in academic regalia and having had a part in each student’s training on their path to becoming a physician, I remain seated with my mouth shut savoring the commitment others are making to the well being and security of their patients. My lack of participation in this solemn occasion is not because I don’t agree with the words being spoken or if faced with situation where the dictums of this oath may be relevant in my life I wouldn’t try my best to live up to their standards; it is just that my training as a scientist took a far different path from the training of these graduating students, and I simply lack the skills and authority to help patients in the same way as a practicing physician.

Which brings me to this month’s Journal Club article published in the Journal of the American Medical Association as a medical news and perspectives piece [1]. The article is entitled, Exome sequencing comes to the clinic, which seems innocuous enough given the number of times the importance of various types of DNA sequencing technologies have been discussed in this forum as they pertain to gene discovery in DBA. The article, however, takes a dangerous turn in my opinion by suggesting that a patient somehow avail themselves of different resources to obtain exome sequence data and then armed with this information contact a scientist to figure out mechanisms underlying their condition and then (and only then?????) with a clinician determine a diagnosis.

I can’t help but think that the JAMA article blurs the boundaries between work being done under a physician’s lead as part of an interdisciplinary group engaged in both clinical practice and research and the idea of a patient directly contacting a researcher to obtain information for a clinical diagnosis.

As a non-physician scientist, I work with several consortiums of investigators studying various aspects of DBA. Each of these consortiums is led by one or more physicians who act as point persons for interactions with patients and their families. In the United States research studies initiated by these consortiums must be approved by Institutional Review Boards responsible for oversight of issues pertaining to patient safety and privacy. Gaining IRB approval for a study can often be a lengthy and onerous process, and yet these safeguards are in place to protect a patient and their families. My participation in these studies is made somewhat easier by the fact that the samples I receive are de-identified, which means that I am unable to trace them back to an individual patient. The fact that I receive blinded samples is also beneficial from a purely scientific point of view because I am forced to interpret the data as it stands without biases introduced by perceived notions built into the hypotheses I am testing. It is only after I have analyzed the data and my results are discussed with the larger group of investigators where additional information is revealed, perhaps a genotype or clinical phenotype linked to an otherwise anonymous sample, that conclusions are made regarding the hypotheses being tested in a research study. These discussions are distilled by the physicians in our group and when appropriate shared with patients as outlined in protocols approved by Institutional Review Boards and in accordance with information provided to a patient prior to their giving consent to participate in a study.
Sometimes the data I gather are spot on with the hypothesis being tested and other times not. In the former case, additional replicates are needed to assure the group of the significance of the observation; or in the latter case, the hypotheses need to be refined or even discarded, in which case it is back to the drawing board. This is research, performed in a research laboratory and the day-to-day results produced in such a setting are not used for making clinical decisions. It is only after data generated in this manner are validated and judgments made by experts on their relevance to disease management, that such data might find a way to clinical application. Should such research be translated to the clinic, subsequent testing moves out of a research laboratory to diagnostic laboratories, which must conform to CLIA standards. CLIA is an acronym that stands for Clinical Laboratory Improvement Amendments, which as stated at the Center for Disease Control web site: includes Federal standards applicable to all facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat human disease.

This latter point seems worthy of repeating in the context of the recent JAMA article: all facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat human disease (at least within the United States) must conform to CLIA standards. The CLIA act would seem to preclude the suggestion made in the JAMA article that patients contact researchers directly for studies on mechanisms that would then be used to make a clinical diagnosis.

More modern versions of the Hippocratic Oath acknowledge the contribution science (and presumably scientists) make to the practice of medicine, and this article is in no way intended to downplay this role.

**I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow.**

And yet, it seems imperative to emphasize the distinction between the science being performed in a research study and the science that finds its way into clinical decision-making. Exome sequencing has a critical role in gene discovery for diseases like DBA, but genes identified by exome sequencing in a research study must be validated in CLIA-approved laboratories before being applied in the clinic as physicians plan a course of action for their patients. While these steps may seem unnecessarily redundant to some, they are in place for patient safety.

If this article serves no other purpose, I am hoping that it will save time for anybody who happens to come across the JAMA article and is considering contacting me directly to perform a research-based study into the underlying basis for a patient’s condition. My response will always be the same: contact your physician, make arrangements through them to become part of an IRB-approved research study, and then with all the necessary safeguards in place, I would love to do anything within my power to shed light on the mechanisms underlying the disorder with the ultimate goal of improving the quality of life of individuals affected by DBA.