# Interview

## A perspective on personalized medicine: Dr David Korn

David Korn speaks to Tarryn Greenberg, Managing Commissioning Editor

**David Korn**

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David Korn (BA, scl, MD, cl; Harvard University, MA, USA) stepped down from his position as Harvard University's inaugural Vice-Provost for Research on June 30, 2011. He is presently Consultant in Pathology and member of the medical staff at the Massachusetts General Hospital, Boston, MA, USA and Professor of Pathology at Harvard Medical School. Dr Korn has been a member of the editorial boards of the *American Journal of Pathology*, *The Journal of Biological Chemistry*, and *Human Pathology*, and for many years was an Associate Editor of the latter. He has sat on many societies, councils and boards. He has written many scientific articles, ranging from bacteriophage biochemistry and genetics to the biochemistry and molecular biology of DNA replication in human cells. During the past two decades his work, writings and lectures have focused on issues of academic values and integrity, research integrity, and health and science policy, and he is presently regarded as a national authority on matters of financial conflicts of interest in academic research.

**You are currently a Professor of pathology at Harvard Medical School (MA, USA), what led to your interest in pathology?**

During my undergraduate years at Harvard College, I majored in what was then called 'biochemical sciences' and did a laboratory thesis in microbiology (at Harvard Medical School) that convinced me that I wished to pursue basic research in my professional career. My thesis advisor strongly urged me to pursue a PhD degree, but I decided to go to medical school instead – at Harvard. In my second year, a full 9-month course in pathology sparked my interest, and I was selected as one of two in my class to be awarded US Public Health Service predoctoral fellowships to spend a full year in pathology at the Massachusetts General Hospital (MGH; MA, USA). During that year, I decided that my career would be in academic pathology, where I would be able to sustain my interest in understanding the foundations and manifestations of human disease, while also developing a cutting-edge program of fundamental biomedical research.

After spending 2 years as a pathology resident at MGH, I spent 7 years at the NIH, where I became a competitive scientist at the frontiers of biochemistry and the then still new space of molecular biology. In 1967, I was recruited by Stanford (CA, USA) to create and chair a state-of-the-art Department of Pathology, essentially from scratch, which I did. I chaired the department for 17 years, during which it became one of the top-ranked departments in the nation, and then served as Dean of Stanford Medical School for more than a decade, as well as University Vice-President for Medicine. That demanding executive leadership position made it impossible for me to keep up with the rapidly advancing sciences in which my laboratory was at the forefront, or with pathology for that matter, so I turned my interests instead to research policy and to the structure and function of US research universities.

**Are there any individuals in particular you have worked with who have had an impact on the path that your career has taken?**

I was privileged to have a number of outstanding role models and mentors. Harvard Professor, George Wald, was a magnetic and inspiring teacher, whose course, 'Introduction to Biochemistry', utterly captivated me and was very influential in the subsequent shaping of my research career. Professor Benjamin Castleman, Chief of Pathology at the MGH, was also a wonderful teacher and mentor, who took me under his wing and was instrumental in my decision to pursue academic pathology as my

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career. The research of Arthur Kornberg, Nobel Laureate and long-time chair of the Department of Biochemistry at Stanford, and his outstanding faculty initially stimulated my interest in the biochemistry of DNA replication in human cells, which became the focus of my research career. Kornberg's department was widely recognized as the best in the world, and he and his faculty became friends, colleagues and critics, whose impeccable standards inspired my research and that of my pathology research faculty colleagues.

■ What scientific policy projects you have been involved with & can you briefly discuss them?

During my Stanford Deanship, I served from 1984–1991 as Chairman of the National Cancer Advisory Board, a presidential appointment, and became deeply involved in the programs and policies of the National Cancer Institute at the NIH. Presently, I sit on the Advisory Council of the NIH's Center for Scientific Review, which oversees many aspects of the grants review process, and thus, the many policy matters relating to that vitally important process are now part of my policy agenda. As Stanford University Vice-President and Medical School Dean, I became deeply involved in the full range of federal research policies: from effort reporting to indirect cost recovery; from research ethics and research misconduct to financial conflicts of interest; from research workforce policies to the wellbeing of Stanford's graduate students and postdoctoral fellows; and to the challenges posed by the unique structure of the American biomedical research workforce, which assured its steady exponential increase independent of the state of federal research funding. This same array of research policy issues was a focus of my attention during my later tenure as Harvard University's inaugural Vice-Provost for Research. When I stepped down as Dean, I went on my very first sabbatical leave to the Association of American Medical Colleges (AAMC) in Washington, DC, USA, and during my second sabbatical year the AAMC President, Dr Jordan J Cohen, who remains a dear friend, invited me to build and lead a Biomedical and Health Sciences Research Policy Program as an AAMC Senior Vice-President. I took an early retirement from Stanford and remained at the AAMC for over a dozen years, where my colleagues and I were deeply engaged in the full spectrum of research policy issues, as well as with federal regulations and legislation, and major federal court cases that affected biomedical and health sciences research, as well as academic medicine across its full breadth of missions.

Beginning in 1999, I became a member of the Executive Committee of a new, standing National Academies of Science (NAS) committee, the Committee on Science, Technology and Law (CSTL), of which I am presently the co-chair. As its name may indicate, the Committee is composed of roughly equal numbers of members representing the full range of the sciences and of law and policy, respectively, and its agenda embraces issues that arise at the interfaces of these disciplines. The wide range of issues that the Committee has addressed, and the studies it has sponsored and reported, can readily be reviewed on the Committee's pages on the NAS website. The CSTL continues to be interested in direct-to-consumer (DTC) genetic testing and organized a 2-day workshop on the topic in the summer of 2009, from which a report has been published [1].

■ What do you think are some of the problems with DTC testing?

As described in the above mentioned CSTL report on the topic, my concerns include:

- A lack of credible oversight of the industry. Although the US FDA has the legal authority to oversee this industry (as well as homebrew genetic tests that are largely developed and deployed in academic pathology laboratories), it has so far been reluctant to exercise that authority, possibly due to lack of resources. Recently, when one of the DTC genetic testing companies made a deal with Walmart to market its 'spit cups', the FDA surprisingly announced that it would now exercise its authority and actively oversee this industry (including homebrew tests), but whether it can, or will, remains to be seen. Although the DTC genetic testing companies claim that their laboratories are compliant with Clinical Laboratory Improvement Amendments (CLIA)

requirements, those requirements have been acknowledged for years in the genetics community to be notoriously inadequate to assure the accuracy and precision of genetic tests; for one thing, CLIA does not require a 'proficiency testing regimen', as does the laboratory accreditation program of the College of American Pathologists and the genetic testing accreditation program of the American College of Medical Genetics. Thus, the CSTL workshop was informed that when a single human sample was sent by staff of the Federal Trade Commission to multiple DTC companies, reports were returned with substantially different findings and interpretations; and that when a non-human sample was submitted to multiple companies, none of them recognized that the sample was from an animal.

- It is my understanding that the companies examine a limited number of genomic sequences that have been reported to be 'associated' with certain human diseases, and their reports to their customers tend to exaggerate – often substantially – the clinical significance of their findings. Thus, these associations are often only very weakly associated with specific human phenotypes, including disease susceptibilities, perhaps in tenths of percentage points, but an increase in association from 0.2–0.6% will be communicated dramatically to the customer as a threefold increase in susceptibility to disease X. These communications are particularly problematic because there is no 'learned intermediate' in the DTC genetic testing system, as there is when genetic testing is performed in the clinical setting.
- The samples sent to the companies contain the full genomes of the senders, and thus the companies are amassing a large collection of genomes, to use as they wish, as well as actual and potential information about their customers, which may be identifying. Yet, the companies do not fall under the protective provisions of the Health Insurance Portability and Accountability Act , and it is unclear what privacy protections the companies offer or can assure. There are legally unresolved questions, for example, who owns these genomic materials? How much license do the companies have to use these materials as they wish for further testing or research? What kind of informed consent, if any, is required or obtained by the companies with respect to subsequent usage of their genomic collections, and from whom, given kinship relationships?
- What kind of effective oversight system should be established for this industry, and how best can there be achieved international harmonization of such oversight given that the DTC genetic testing industry is already an international enterprise?

**What, in your opinion, are some of the important steps in defining the pathology's role in personalized medicine?**

The traditional clinical role of the pathologist has been to interpret human specimens in the context of a patient's clinical presentation, and based on their interpretations and diagnoses, to produce a report that advises and informs healthcare providers' subsequent palliative, remedial or curative interactions with their patients. When I was in training as a pathology resident, half a century ago, pathologists were not uncommonly described as 'the doctors' doctors'. During the past two decades, spurred by the Human Genome Project and its subsequent international consortial activities (SNIPS, HapMap and so on), an enormous amount of genomic information has been accrued, more and more of which is being demonstrated to have some strength of association with a wide array of human disorders. We live in an era of 'genomic data deluge', and keeping up with this rapidly expanding database is a serious challenge for all biomedical and clinical scientists, and for practitioners. Pathologists have been actively involved in this research, but the research spans all medical specialties. The threshold question is, when do the data suggesting the association of a particular genomic change (mutation or variation) with a disease become sufficiently predictive of a disease phenotype (diagnosis, prognosis, responsiveness, or not, to particular therapeutic regimens) to warrant its incorporation into medical practice? Pathologists must participate in answering this question, and when convinced of the clinical

utility of the specific genomic change(s) must decide, based on the complexity, expense, and likely volume of requests for the genomic test, whether to establish the test in the institution's clinical laboratory or send the specimens out to a reference laboratory. In order to avoid circumvention of pathology in making these decisions, it is essential that pathologists be knowledgeable and involved at every stage of the decision-making process.

■ **What do you think are some of the biggest challenges that laboratory physicians have now in dealing with personalized medicine?**

As I suggested above, the biggest challenges are to ensure the involvement of pathology in the generation and integration of genomic information, and in interpreting its relevance to understanding and treating human disease; to incorporate into all pathology residency training programs exposure of all trainees to the fundamentals of human genomics and genomic testing; and to offer in academic medical center training programs, a specialty track in genomics and genomic testing. The history of pathology is replete with examples of what began as pathology specialties breaking away to become their own separate disciplines (microbiology, immunology, blood banking and transfusion medicine, some pathology subspecialties – cardiac, renal, hepatic, neural and so on). The centrality of genomics to 21st century medical practice is such that I believe pathology must prepare and position itself to ensure that 'genomic pathology,' in all its manifestations, remains squarely within the discipline.

■ **Where do you see personalized medicine developing towards in the next 10 years?**

This is a difficult question because the advent of personalized medicine was predicted in the rationale for proceeding with the Human Genome Project 20 years ago and undoubtedly raised overly optimistic expectations. In its idealization, personalized medicine envisions each person carrying a complete sequence of his or her genome, and each healthcare provider sufficiently knowledgeable and able to use that genomic information to decide what disease susceptibilities the person may have and what ameliorative measures that person should embrace to mitigate those susceptibilities – for example, exercise, strict weight and blood pressure control, avoidance of potentially exacerbating substances and behaviors (smoking, excess alcohol or carbohydrate consumption, lack of exercise and so on). Given the distressing amount of cigarette smoking that I observed in my dozen years in Washington, DC, USA and now, in Boston and Cambridge, MA, USA – much of it involving young people of both sexes; considering that the Surgeon General's Report was published in 1964 and all the measures the government has taken since, from progressively higher cigarette taxes to ever more vivid and scarier advertising and symbolism on cigarette packages; and the considerable amount of research funding that has been committed to identify successful antismoking educational and behavioral modification strategies – all to discourage, especially young people, from taking up smoking, my admittedly nonscientific observations are discouraging about our ability to sustainably modify human behaviors. I believe that much greater investment in the foundational behavioral sciences is needed to improve our understanding of and ability to influence human choices and decisions, and ultimately, human behaviors.

Most immediately promising, in my view, are:

- Pharmacogenomics, which is already demonstrating its ability to discriminate therapeutic responders from hyperresponders from nonresponders, thereby promising to revolutionize the biopharmaceutical industry, as well as the design and conduct of clinical trials by adding critical genomic information to inclusion and exclusion criteria, making the trials far more targeted, efficient and much less costly;
- Cancer diagnostics, where the bold National Cancer Institute decision about 15 years ago to launch its Cancer Genomics Atlas Program has spurred the identification of a sometimes bewildering array of key pathways of neoplasia, is enabling the development of new,

precisely targeted drugs, and is teaching us that morphologically different neoplasms arising in different organs and anatomic sites may seem to share the same critical pathways, and *vice versa*. It is likely that genomic diagnosis will supplement morphological categorization in an increasing variety of human neoplasms (and increasingly, in non-neoplastic disorders) and will play a key role in determining therapeutic options and prognosis. An interesting question that for the while must remain unanswered is, will genomic diagnosis in certain categories of neoplasia (and perhaps other disorders) entirely supplant the need for histopathological diagnosis? The possibility that it may, no matter how likely or unlikely, underscores the imperative of assuring that genomic testing and interpretation of disease, the integration of genomic data with clinical phenotypes, and the expert interpretation of that mass of information to inform therapeutics and prognosis remain squarely within the discipline of pathology.

**Financial & competing interests disclosure**

*D Korn is a Consultant in Pathology in the Pathology Department of the Massachusetts General Hospital (MA, USA) and Professor of Pathology at Harvard Medical School (MA, USA), but is not, and has not for nearly three decades, actively engaged in the practice of pathology. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

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## Reference

1 Committee on Science Technology *et al.* Direct-to-Consumer Genetic Testing: Summary of a Workshop. The National Academies Press, Washington, DC, USA (2010).