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Precision Medicine: Look to the mice

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By all accounts, President Obama's Precision Medicine Initiative (PMI) promising molecular-guided diagnostics, therapeutics, and prevention strategies is eliciting enthusiasm and excitement among clinicians, translational researchers, and patients ("NIH plots million-person megastudy," J. Kaiser, In Depth, 20 February, p. 817). To make this hope reality, the PMI Working Group of the Advisory Committee to the Director (ACD) of the National Institutes of Health (NIH) is holding workshops with stakeholders to discuss and resolve critical issues and challenges before launching NIH's $200 million in funding initiatives later this year. Key to the PMI's success is how to gather, manage, and interpret for clinical benefit the unprecedented amounts of genomic, metabolomic, and other –omic data generated by the planned 1 million plus–person research cohort (1). There are many facets to this question, including: the advantages and disadvantages of holding patient data in federated and/or centralized databases; standardization of data generated by multiple testing regimens; deriving data both from electronic health records as well as metadata pertaining to environmental influences; ensuring access to and availability of patient data and information that is sufficiently de-identified to uphold privacy rights; curation and other data manipulation to ensure that data is organized and assembled into a format conducive to secondary and tertiary analyses; and sharing of data with national and international research groups.

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Many of the issues regarding data management, accessibility, and interpretation first confronted the mouse research community in the Knockout Mouse Production and Phenotyping (KOMP2) project. KOMP2 was established as part of an international consortium [International Mouse Phenotyping Consortium (IMPC)] to provide a comprehensive description of function for each of the more than 21,000 protein coding genes in the mouse genome. Approaching 4 years into a planned 10-year NIH Common Fund timeline, KOMP2 and its global partners are using a common set of phenotyping tests covering 10 organ systems on sex-balanced cohorts of knockout mice (2). This process is similar to how the PMI will examine multiple cohorts of male and female patients according to an agreed-upon set of clinical assays across a broad spectrum of organ systems and disease phenotypes.

From a data management perspective, KOMP2 is now accomplishing in mice what the PMI seeks to accomplish in people. KOMP2 is successfully implementing collaborative solutions to address challenges with phenotyping data from globally distributed cohorts of mice. Biologists, software engineers, and research staff are working together to standardize data through harmonization of test protocols and identification of critical metadata. Access to results is facilitated by central curation of data, transparent statistical analysis, and real-time public posting of curated data from a central Web site (www.mousephenotype.org) (3). Granted, the absence of privacy concerns and need for informed consent makes this process simpler for mice than for human studies. Furthermore, our data meet guidelines for reproducibility of biomedical animal studies (4), and our statistical analysis platform is freely available for others to use (5).

In addition to data management, results from KOMP2 can provide substantial insight to inform the PMI's effort to define a new molecular taxonomy (6). Because we remain largely ignorant of the multiple functions of genes within the mammalian genome, revealing pleiotropy (one gene affecting multiple seemingly unrelated traits) will generate vital new information on genes and disease (7). Undoubtedly, many variants of unknown significance will be identified in the PMI 1 million–person cohort. As a majority of genes to be studied by KOMP2 have little or no functional data, our ongoing studies are enabling discoveries beyond what we already know (8), revealing essential new knowledge to guide interpretation of the PMI studies planned in humans. As we journey together into this brave new world of precision medicine, we encourage and welcome cooperation of the PMI with KOMP2/IMPC.

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