HEALTH CARE POLICY

Ten things we have to do to achieve precision medicine

Major but surmountable hurdles should be addressed now to hasten the advent of precision medicine.

By **Isaac S. Kohane**

On 30 January 2015, President Obama announced funding for an Initiative in Precision Medicine (IPM) (*1*) less than 3 years after a National Academy of Sciences (NAS) committee report (*2*) made clear just how such an initiative could accelerate progress in medical care and research. The core concept of this initiative is that by harnessing measurements of multiple modalities—not just clinical and genomic evaluations, but environmental exposures, daily activities, and many others, we can develop a much more comprehensive view of the patient's state and its trajectory over time. By understanding precisely, across all these modalities, what the distinguishing features of specific subgroups of patients are, we can better individualize therapies.

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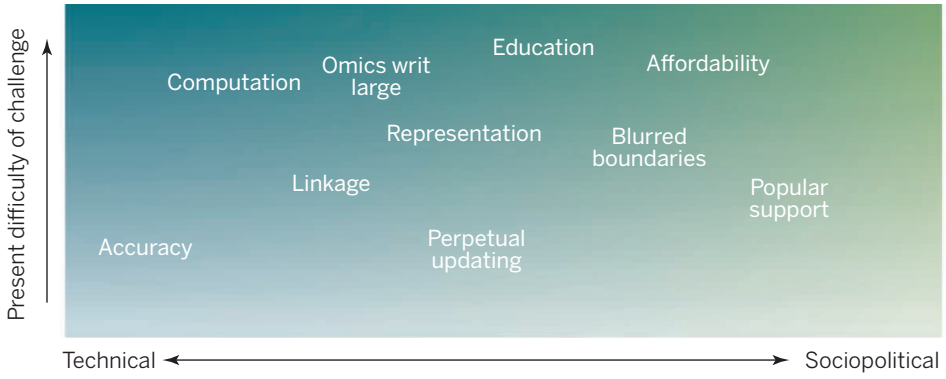
The combination of clinical findings and genomic sequencing is already resulting in life-saving cancer treatments, even though we have accumulated only a tiny fraction of the data sets envisaged by the NAS report and IPM. Today, we engage in preventative medicine—including the use of pharmaceuticals with pleiotropic, often unwanted, effects (such as statins)—on the basis of a handful of biomarkers. With more precise molecular characterizations of outcomes over time within populations, selection of primary prevention regimens can become more data driven, and unwanted effects could be minimized. What do we have to do to make the early promising results more generalizable, as well as available to clinical and public health practice? It is not merely a matter of scaling-up the molecular measures and clinical characterizations of large populations. Below are enumerated 10 large, but surmountable, challenges that will have to be addressed if precision medicine is to realize its full potential (see the figure).

1. *Linkage.* Data gathered from health care institutions, research projects, and daily events must be linked to the right individuals across their lifetimes (*3*). Even in the unlikely event that the United States would adopt a universal health identifier, many health-pertinent data types—such as diet, environmental exposure, or social Web annotations—are not linked to health care databases. Consequently, enabling the mechanism for such linkages that are both accurate and socially accepted is currently an unmet challenge.



Moving toward precision medicine. Ten challenges for achieving precision medicine are qualitatively ordered on the *x* axis by how much they are intrinsically technical versus sociopolitical challenges. The *y* axis qualitatively orders the difficulty each challenge currently presents if we are to attain the widely articulated goals for precision medicine.

2. *Accuracy.* Regardless of data type, precision medicine requires some form of ongoing assessment of the accuracy and reproducibility of the data gathered in the "information commons" envisaged in the NAS report. For example, continued methodological progress is required to overcome the current gross discordance in identification of insertions and deletions in whole-genome sequences when different technologies are used (*4*). Similarly, the bias in clinical annotations (i.e., billing codes) designed to maximize reimbursement for services must be overcome. The initiatives that many publishers have promoted in this vein (*5*) are necessary steps in this direction, but a culture and institutional mechanisms for ongoing assessment of data accuracy are still in early development.

3. *Blurred boundaries.* If there is no clear demarcation between research and clinical care, methodological and ethical problems can result (*6*). However, precision medicine often creates opportunities to benefit individual patients from the recent rapid advances in biology and high-throughput measurement. Increasingly, society as a whole and patient advocacy groups are questioning the current separation between clinical care and discovery-driven research. Yet, unlike routine clinical laboratory measurements, most omic assays are not performed in laboratories approved under the Clinical Laboratory Improvement Amendments and may be more prone to considerable variance in practice and error (*6*). Crossing the clinical care–research boundary therefore requires new models of data sharing, data verification, and vetting.

4. *Popular support.* If concerns around the privacy risk of broad data sharing and data integration are not addressed, then public concern might outweigh public support for precision medicine. The public conversation for President Obama's IPM therefore has to extend far beyond the usual community of scientists, health care providers, and technologists. Most likely, those patient advocacy groups that have seen the benefit of precision medicine or keenly experience its absence will be the most articulate and credible drivers of public support [e.g., both the Multiple Myeloma Research Foundation (www.themmrf.org/) and the Simons Foundation for autism research (http://sfari.org/) have built open-access databases of genomic and other data to promote the research effort]. Integral to this support is the development of a public consensus for appropriate procedures for consenting and clarity regarding personal control of disclosure of personal data for broader sharing (*7*).

5. *Omics writ large.* The success of high-throughput methods in capturing various personal data at the molecular level (such as genomes, transcriptomes, and proteomes) only emphasizes how much

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remains to be done in obtaining comprehensive measurements of other equally relevant health measures (*8*). Given that for many common diseases, environmental exposures are responsible for the majority of risk, how are we going to obtain systematic, comprehensive measures of these exposures over a lifetime? It may be that we require a higher level of coordination between the various agencies responsible for monitoring the relevant data (e.g., Environmental Protection Agency, Occupational Safety and Health Administration, and Health and Human Services). Here again, public support by patient advocacy groups might be the most effective in driving these agencies toward more comprehensive data acquisition and sharing.

6. *Perpetual updating*. A knowledge-diffusion process that is far more nimble and timely than the current publication process is going to be needed. For example, every year, new data (sometimes conflicting) appear regarding the pathogenicity of mutations (*9*). If timeliness matters, recomputation and reevaluation of the interpretation of these data cannot wait for investigators to add errata to their publications. Who could provide such recurrent and frequent reevaluations? It remains uncertain whether semiautomated and crowd-sourced efforts will be appropriate (*9*). A dedicated and trusted third party, akin to the National Institute of Standards and Technologies, has yet to emerge in this domain.

7. *Computation*. Computer-driven, real-time decision support at the point of care is an absolute requirement for the success of precision medicine (*10*). Even narrow specialists will not be able master all the rare and common molecular findings associated with different therapeutic subgroups and, even less, all their interdependencies. Perpetual and timely updates of this knowledge therefore requires the implementation of automated decision-support procedures that fit into the episodic and often brief encounters between patients and their care providers. Unfortunately, the capability of commercially available electronic health record systems to represent and compute with omic data is limited at best (*10*). Conversely, the genome-scale interpretations provided by direct-to-consumer or sequencing companies are not integrated with the highly relevant context provided by the clinical record. The opportunity remains sizable for innovative entrants into the market to automate decision support for precision medicine.

8. *Affordability*. Affordability of precision medicine ultimately will determine whether it is the preserve of the wealthy or the few or whether financial incentives can be made sufficient for continued discovery work. Already, there is an important debate about the cost of impressively effective but also terribly expensive targeted treatments (*11*). Similar debates about the cost of precision diagnostics also have emerged (*12*). Without large decreases in cost, precision medicine will result in a massive increase in the already large share of the overall gross national product claimed by health care in most developed countries.

9. *Representation*. Representative precision medicine is not only the expression of hope for social justice, but it is mathematically necessary if we are to avoid making gross diagnostic and therapeutic mistakes. Individuals coming from different ethnicities have different frequencies of multiple characteristics from various factors—from genomic variants to diet. Capturing these differences will be at the core of precision medicine's success in our multiethnic society. Failure to do so will result in over- and underdiagnosis in multiple populations (*13*, *14*)—the antithesis of precision medicine.

"Capturing…differences will be at the core of precision medicine's success in our multiethnic society."

10. *Education*. Education of the providers of health care merits a close reexamination so as to find the means to create a workforce that is best able to translate the knowledge gained from precision medicine to clinical care. This includes competence in quantitative reasoning (*15*) and in the ability to access just-in-time knowledge (*16*). It also requires a greater recognition that, in many instances, patients will be precision medicine experts (*17*) and, therefore, can be instrumental in collaboratively applying unique knowledge resources in precisely their own medical challenges.

Who will participate in addressing these challenges to drive precision medicine from conception to practice? At a minimum, the stakeholders must include the public, individual patients, and organizations representing patients. Then, there are (i) the health care system that will deliver precision diagnostics and therapeutics and (ii) the scientists who will develop the principles, infrastructure, and specific insights for precision medicine. Whether at the level of local institutional review boards or national regulatory authorities, as intimated above, a full implementation of precision medicine will require, at the very least, adjusting the existing oversight mechanisms. Most useful will be public examples of "information altruism" that are consistent with current regulations (*7*). Furthermore, with the entry of giants of the information age, such as Apple and Google, into healthcare (*18*), concurrent with the emergence of a new generation of profit and nonprofit biotechnology companies, industry will have a perspective on precision medicine that may not always resemble that of the other more seasoned, and perhaps more jaded, stakeholders. Even with the minimal and conservative view presented here, it is apparent that implementation of precision medicine will require an extensive national conversation. Fortunately, with IPM and the efforts of advocacy organizations, there now is a concrete program with which to productively drive the conversation. ■

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