MEDICINE

Reestablishing the Researcher-Patient Compact

Well-intentioned regulations protecting privacy are denying important information to patient subjects. Advances in information technology mean that a better approach to clinical research is possible.

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In the name of privacy and protection of study subjects, the research community has, albeit with good intentions, broken the historical doctor-patient compact, distorting an ideal of information exchange that might inform subjects of health risks or benefits (*1*, *2*). To minimize privacy risks in genomic research, investigators and institutional review boards (IRBs) construe that federal regulations require anonymized data. This disallows communicating pertinent results back to subjects. Such results could help the subjects and would justify the beneficence of that research (*3*). When large cohorts are enrolled for genomic and clinical characterization (*4*–*6*), both sides agree not to reconnect findings from the aggregated data or to infer meaning or insight for a specific patient, or to make that knowledge available to the patient. The scientific motivation behind this mutual commitment never to communicate or identify has origins in the evolution of modern study design (*7*). It has coincided with the growth of grass-roots privacy concerns, the enactment of Health Insurance Portability and Accountability Act (HIPAA) (*8*), the Office of Human Research Protection (OHRP) procedures, and state laws to protect genetic information misuse (*9*–*13*). Yet this intentional failure of communication may be detrimental.

Consider the scenario: In 5000 patients with diabetes mellitus, one subject has an incidental finding of the expression of a fusion gene indicative of early malignancy. Genome-wide polymorphism studies reveal a variant in 40 others that predicts benefit from a recently approved medication. To follow up, the IRB must either sanction reidentification or notify the entire cohort, unnecessarily alarming some (*14*). This scenario will become more common as more genetic signatures are linked with pertinent phenotypes. Further, this highlights only one of several opportunities (*15*) missed because of an understandable but overreaching paternalism.

The advent of genome-scale measurements and health information technologies allows us to reconnect patient subjects and researchers in a manner respectful of regulations and privacy concerns and to maximize potential benefit to the public and the individual in the course of research. A solution must anonymize information while making discoveries available to participants who "tune in." Although seemingly paradoxical, it is comparable to UHF/VHF television. To "participate," an individual buys a television and privately decides when and what he watches. In the research analogy, a subject's "programming" is a product of her own information and the aggregated study results. Her reception of research results depends on whether she "tunes in" to the broadcast.

We propose a collaborative clinical research regime, the Informed Cohort (see figure, page 837). IC subjects are enrolled at their health-care institution through an extensive informed consent process. If they choose, subjects provide additional clinical information and biospecimens, typically a blood sample, for high-throughput measurements. In addition to the usual concerns regarding comprehension, transparency, and coercion, the consent process must mirror the dynamic quality of the subjects' changing involvement over time—contributing more information or withdrawing at will. Although IRBs may absorb the additional responsibility, we propose giving crucial oversight functions to an independent IC Oversight Board (ICOB), responsible for communicating study information back to patients. The ICOB multidisciplinary team (geneticists, statisticians, ethicists, patients, and communications experts) deals with complex issues—what information is worthy of communication and how best to communicate it, for example.

At enrollment, subjects are given a Web-based, interoperable personally controlled health record (PCHR) (*16*–*18*). In our model of PCHR design, (*16*) individual records are encrypted, preventing compelled third-party disclosures (*19*), for example, by subpoena. Only the patient can decide to whom personally identified information will be disclosed and under what circumstances (*20*–*22*). Thus, each patient owns an integrated copy of his or her traditional record data plus high-throughput genome-scale measurements made on his or her own biomaterials. For example, she may consent to share a part of her PCHR data, which is then anonymized and entered into a population database. Her data can be studied in an IRB- and HIPAA-compliant manner across topics including population genomics, public health, medication effects, and quality of care. Data can be shared with appropriate parties including biomedical researchers and public health authorities. Under no circumstances would there be an attempt to contact or to discover the identity of the patient. Anonymized data-gathering can be a dynamic process for longitudinal studies of individuals (*23*).

The IC design allows patients to be contacted as necessary and as desired by each patient. As shown in the figure, each PCHR has an "agent," the listener. The agent has a dedicated purpose: to intercept broadcasts over the Internet from the health-care system with information regarding patients with particular characteristics and to determine whether the described characteristics match the patient the agent serves. For example, does the DNA polymorphism or diagnostic category match the content of the patient's record? These broadcasts are not targeted to any specific patient, and only under two conditions does the agent notify the patient of the broadcasts: if the patient has allowed this agent listener function to be turned on at all (it can be turned off at any time), and if she has allowed further notification from the health-care system in a particular clinical or genomic domain that is available to her as an electronic checklist.

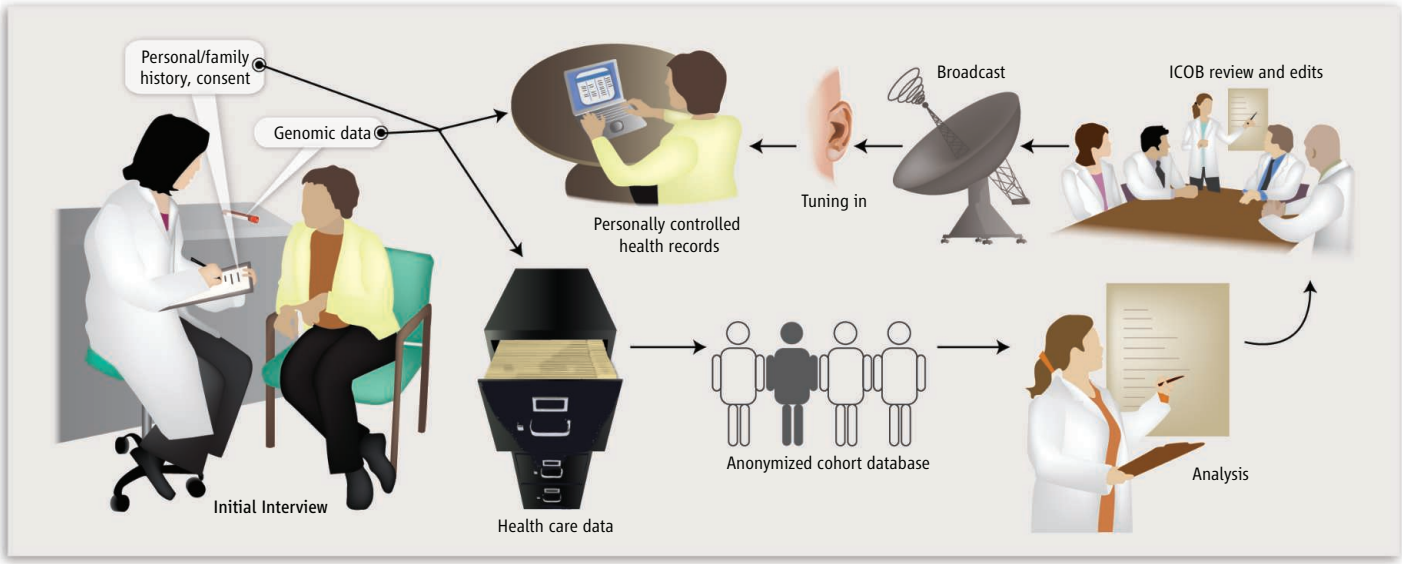
Researchers at any given time may make a discovery pertaining to a class of patients with a particular characteristic or set of genomic markers and may want to alert those patients about clinical implications, request more information, obtain more genomic material, or perform other measurements.

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However, researchers do not know who the patient is and so broadcast to the system of the IC—conditional on the ICOB editorial process and approval—a description of the kind of patients that they are seeking to contact. The agent's "decisions" are the product of the subject's stated categorical preferences for information and the ICOB's study-specific determination about what information can be effectively communicated in a manner sensitive to subjects' health literacy. All IC agents that are turned on will intercept all such broadcasts and determine whether the characteristics, of the patient, genomic or clinical, match the characteristics of the patients described in the broadcast. The agent listens for information pertaining, for example, to a particular single-nucleotide polymorphism (SNP) and scans the PCHR for the presence of that SNP. The notification appears to the patient much as an e-mail does.

Because the IC protects privacy through anonymization, but permits direct benefit to participating subjects, it is ethically superior to the status quo. It enables patients as partners in research rather than passive, disenfranchised purveyors of biomaterials and data. Further, this procedure is feasible using today's technology and does not breach current regulations. In addition, because it is built around PCHRs interacting with a national electronic health network, it could have markedly amplified research potential, offering dramatically greater accessibility for properly authorized researchers across multiple health-care institutions.

Several questions remain unanswered and require careful analysis in ways that might vary by population and geography. How can the IC work for individuals with poor health literacy? What about individuals without effective and private access to networked computers? What is the level of certainty or the expected benefit to the patient that should inform ICOB about what should be broadcast to the IC and when? Some of these questions cannot be answered in the abstract and will require detailed review by experts in each instance.

If the IC is more than a thought experiment, what will it take to realize this proposal and what are the anticipated resources required? Many of the technical hurdles have been overcome. Commodity-priced, genome-wide common variant assays are available now. Early versions of personal health records, once a futuristic concept (*24*), are in the hands of thousands of patients through diverse implementations at the Veterans Administration (*25*), hospitals (*26*), and managed-care organizations. More investment will be required in health-care settings and staffing for effective and safe support of study participants. Moreover, this investment is within the range of leading academic medical centers where this model can be debugged and made more efficient and affordable for wider adoption. Indeed, the leadership at Children's Hospital Boston has committed itself to piloting the IC in several clinics. Undoubtedly, there will be unanticipated technical, legal, and sociological challenges, and we anticipate a vigorous debate within the biomedical community.

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