Organizational challenges in clinical genomic research

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Genome sequence data are enabling clinical genomic investigation, in which the characteristics of human patients are explored using comprehensive inventories of biomolecules. Successful investigators must navigate rapid technological change, collect and analyse large volumes of data, and engage systems of clinical care. Such projects will increasingly rely on fully integrated multidisciplinary teams, demanding new organizational models in academic biomedical research.

Until recently, genome science and human clinical research were independent fields, each with distinct intellectual traditions and communities of investigators. With the completion of the Human Genome Project, there is great interest in combining these disciplines to study disease mechanisms and improve patient care, an endeavour that we term 'clinical genomic investigation'. Whereas other reviews in this issue consider scientific approaches to this goal, we discuss the substantial organizational challenges inherent in combining these two fields.

The challenges

The field of genomics is built on two core capabilities: collecting comprehensive data sets using technologically advanced laboratory tools, and searching for subtle relationships within them using computationally sophisticated analytical methods. Previously, neither was required for success in biomedicine, and yet both are now indispensable for investigation aiming to connect genomic information with human disease.

Genomics has experienced a rapid pace of technological change, requiring that scientists keep up with emerging technologies, and skillfully integrate complex laboratory and information systems. The potential advantages of each new technology must be balanced against a typically short half-life and substantial cost, and this calculation endows the management of technology with considerable strategic importance. The process of collecting, storing and distributing large data sets places an emphasis on management skill and software engineering. Computational analysis of these large data sets draws on expertise from mathematics, statistics and computer science. Although computational scientists have long been valued in fields as diverse as physics, finance and telecommunications, they have been relatively few in biomedicine.

Research involving human subjects poses a unique set of challenges, largely attributable to the complexity of the human population, the need to respect patient autonomy, and pressure on highly distributed systems of clinical care. Human studies require careful attention to informed consent, and the Health Insurance Portability and Accountability Act of 1996 (HIPAA) codifies even greater attentiveness to privacy and security of individual patient information. The demands of informed consent and data protection compete with financial pressures that have left clinicians barely enough time for patient care, let alone research. The local jurisdiction of institutional review boards, and the lack of universal information technologies for managing patient information (much of which is still on paper, or in legacy computer systems) make it difficult to compare data across institutions even after HIPAA regulations have been met.

If both genomics and clinical investigation are complex in isolation, combining them multiplies the challenge. Human genetic research places greater demands on privacy protection, because a single DNA sample contains a complete set of genes, and thus could be misused to study hypotheses beyond the initial consent. Variations in DNA sequence provide a unique DNA 'fingerprint', which in theory could be used to identify individual study participants, or related to societal concepts of race, ethnicity and group identity. Genomic studies of human populations require larger sample sizes than do genomic investigations of well-controlled model systems, because variation in genotypic background, environment and behaviour all introduce noise. This is particularly problematic in unbiased genome-wide studies that consider 25,000 or so genes, each of which has a correspondingly low chance of being involved in the process of interest (see review in this issue by Carlson, page 446). The increased statistical significance required to distinguish the signal from the noise can be achieved by increasing the sample size. But collecting large samples requires many investigators and coordination across multiple institutions, with all the logistical challenges mentioned above.

Organizational implications

Most biomedical research is well served by the traditional model of individual laboratories led by a single principal investigator, but clinical genomic research often requires multiple investigators. This has focused attention on the importance of teamwork in biomedical science. (It is a core feature of the recently announced NIH Roadmap; see http://nihroadmap.nih.gov and Box 1.) But teams can be constructed in many different ways, each with its own capabilities and requirements for success (see Box 2). We think that clinical genomic research will most successfully be conducted by mission-focused, interdisciplinary teams that are fully integrated (rather than virtual) and work together over a sustained period to solve specified research questions.

A review of large-scale multidisciplinary research efforts suggests three common characteristics of successful, integrated teams. Chief among these is a clear and compelling

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Attention to teamwork has secured wins for the New England Patriots.

mission — a grand challenge that attracts, motivates and unites a set of disparate researchers and inspires them to subjugate their individual needs and egos in the interest of a common goal. The mission must be larger than that achievable by an individual, and yet narrow enough to have specific meaning. Crafted well, a mission provides a subtle form of guidance for consistent decision making across a distributed leadership, minimizing the need for a rigid hierarchical structure that would limit creativity and motivation.

For example, in the 1970s, Xerox PARC in Palo Alto, California, articulated its mission: to create the 'office of the future'. Attracting a body of like-minded researchers from fields as diverse as organizational behaviour, computer science and physics, PARC created the computer mouse, the 'what you see is what you get' (WYSIWYG) computer environment, personal computers and the laser printer. An example from within biomedicine is the Human Genome Project, in which a large number of investigators from different disciplines (biology, mathematics and engineering) together tackled a daunting scientific challenge, created new technologies and organizational structures, shared data to an unprecedented degree, and as the project matured, analysed and published the results collaboratively. Other instances include the synthesis of bioactive steroid hormones (discussed, along with other examples, in ref. 1) and the development of protease inhibitors to treat HIV[2].

The second requirement for success is the selection of team members — people who commit to the success of the group even at the expense of individual achievement. The field of high-energy physics has institutionalized this notion by requiring — and placing high value on — service roles. At Fermilab (Batavia, Illinois), for instance, all physicists commit a substantial fraction of their time to fulfilling core support functions, such as creating and maintaining shared equipment, managing data collection, and providing computational support. In recruiting for such teams, disciplinary excellence is not the sole criterion: individuals must be flexible and open-minded, have good communication and social skills, and be willing to work with others in pursuit of a common goal. The National Football League's New England Patriots are a striking example of such a human resource strategy: they won the Super Bowl (league championship) twice in three years by jettisoning individual superstars, identifying undervalued players who would thrive in a particular role and system, and distributing credit over the entire team.

Third, leaders of multidisciplinary teams must be skilled at motivating and facilitating the work of others, inspiring people with different backgrounds and career goals without necessarily having formal authority over their careers. Given a potentially fragile mix of skills and perspectives, team leaders must guide individuals to contributions that advance the shared goal, manage communication and group dynamics, and promote the good of the team. This can be achieved through the rare combination of charisma and selflessness. As a physicist who had a high-ranking position at Bell Labs in the 1970s told one of us, the most effective leaders play "almost a service role", with an uncanny ability to lead despite a manner that communicates "nobody works for me; I work for them".

How well do these characteristics map onto the organizational model typically encountered in academic biomedical research? Unfortunately, not very well. The notion of a mission uniting multiple investigators may be viewed suspiciously by a community that celebrates academic freedom and creativity, as well as individual success. More importantly, the current incentive structure actively reinforces individualism over teamwork. In biomedicine, individuals tend to be rewarded rather than teams: successful faculty members enjoy tenure, space and resources to advance their ideas and substantial salaries, but team members (typically trainees and transient technical staff) have little in the way of status, control, job security or financial rewards. Systems for publication reinforce a 'winner takes all' mindset, allowing only two prominent roles on publications, that of first and senior authors. In multi-investigator groups, only a few contributors can be highlighted on any given paper.

Box 1

The NIH Roadmap

In September 2003, Elias Zerhouni, director of the National Institutes of Health (NIH) in Bethesda, Maryland, announced that the agency would begin a series of new initiatives that constitute a new 'NIH Roadmap'. The Roadmap initiatives are the product of a series of meetings Zerhouni initiated with scientists, academics, business leaders and members of the public after he was appointed NIH director in May 2002. Zerhouni says the plans lay the groundwork for the future of biomedical research, which will be conducted by teams of interdisciplinary researchers who will need new tools to transform basic discoveries into new treatments. The Roadmap aims to provide those tools and spur the development of new types of scientific team.

In its first year, the NIH will spend US$130 million on Roadmap initiatives; by 2009, Zerhouni hopes that the NIH will have spent about US$2.1 billion on the initiatives. Roadmap initiatives fall into three themes: New Pathways to Discovery, Research Teams of the Future, and Re-Engineering the Clinical Research Enterprise. The Roadmap initiatives focus mainly on the development of tools, technologies, networks and resources, instead of funding individual projects.

For instance, some of the first projects announced under the Roadmap were grants to fund extramural biomedical computing centres, small-molecule repositories and screening centres, and proteomics-technology development centres.

Another main focus of the Roadmap is on high-risk research, and one new project — the Director's Pioneer Award — will award up to ten grants of half a million dollars each for five years to individuals who have "exceptionally creative abilities and diligence", according to the award announcement.

Finally, the Roadmap envisions a revamping of the nation's clinical research infrastructure by linking doctors in private offices with community and patient groups and large health care networks. The Roadmap would create a group of new clinical research associates, in an effort to establish an infrastructure that can be used for many different clinical studies.

More information on the Roadmap, including funding opportunities, can be found at http://nihroadmap.nih.gov.

Erika Check

Box 2
Models of teamwork in science

When the demands of a research question exceed the ability of a single lab to pursue them, there are at least three strategies for obtaining additional expertise and capabilities, each of which can be construed as a team-based approach: outsourcing, insourcing and integration.

Outsourcing
The simplest (and traditional) approach is to increase the scale and disciplinary focus of individual labs by collaborating with other research groups. This model deliberately *outsources* such capabilities and requires little organizational change, but reaches its limitations with larger-scale, sustained projects. Large, interdisciplinary projects require coordination, which can be difficult to achieve if each lab and participant is guided by personal interest (and rewarded according to individual accomplishment), rather than by an explicit and shared goal. Substantial investment of time and effort may be required before rewards (for example, results and publications) can be realized, a barrier that will not be overcome without commitment to a sustained and defined relationship among collaborators.

Insourcing
A second model retains the disciplinary focus of labs led by individual principal investigators, but brings new capabilities in-house through 'core labs'. This can be viewed as a decision to *insource* an otherwise unavailable, expensive and technically sophisticated capability. Core labs involve the creation of discrete entities whose goal is to assist other researchers (rather than to pursue specific questions), and are most often run by staff scientists, rather than by faculty and trainees. Valuable in the right setting, core labs are generally most successful when the service they offer is a commodity — well defined and technologically mature. In cases such as genomics, where technology is rapidly evolving and demand for practitioners is high, it can be difficult to recruit and retain the few scientists who have experience of establishing and running such capabilities — particularly to a purely service role. The idea of core labs for statistical support and computation is a particularly poor fit in the area of genomics, where analytical methods are nascent, often must be customized for each application, and represent one of the more intellectually sophisticated (and limiting) contributions to success.

Integration
A third model pays less attention to traditional barriers between individual labs and disciplines, instead creating an interdisciplinary team united in pursuit. Members of this team interact as partners rather than being under the sole leadership of a single faculty member or operating in a client-service model. Rather than isolating staff with specialized knowledge in core labs, separate from the scientific questions that motivate them, the goal here would be to fully *integrate* a range of capabilities and disciplines to solve a particular set of problems. There is a crucial element of scale, however. Such teams must be large enough to encompass the required range of capabilities, disciplines and efficiencies, yet small enough to remain focused on a single mission, communicate and respond to new information, and maintain a sense of shared purpose. Others, notably Brown and Goldstein, have written about the catalytic value of long-term collaborations that bring together like-minded investigators with discrete and complementary capabilities[1]. The teams we envision are similar in spirit, if somewhat larger in scale and broader in disciplinary focus.

Institutional change

Allowing sustained, multidisciplinary teamwork to become a viable and attractive option for biomedical research demands cultural and structural change — change that will only be brought about by academic institutions and the faculty who work in them. We focus on two areas of particular importance: education and career development.

First, scientific training for clinical genomics should involve team-based learning and greater efforts should be made to break down disciplinary barriers. Learning in groups, as well as working together on specific projects, might help young doctors and scientists to become accustomed to teamwork — not to mention to the notion that they are part of one biomedical research culture, not two. Moreover, shared activities and language promote mutual respect and understanding, which is essential for effective, sustained collaboration. (Note that training specialists with distinct skills to work together is a different goal from that of training individuals such as MD/PhDs to have dual competency.) For example, in one Boston programme, biomedically oriented physics and engineering PhD students undertake clinical rotations: on a recent programme review, alumni felt that this clinical exposure was an essential element of the programme and had deeply influenced their careers[5]. Such a curriculum will be effective only if offered to a receptive student body. In addition to the usual measures of academic potential, admissions committees may want to evaluate communication skills, ability to work in teams, and the capacity to synthesize information across disciplines.

Second, to develop the careers of people who work in teams, institutions must implement improved methods to evaluate contributions to collective accomplishments. This must start with a thorough rethinking of authorship — how it is assigned and the role it has in the selection and promotion of scientists. One way to avoid the distortions of the current first author/last author model would be to emulate physics, listing authors alphabetically. Although this model has a certain egalitarian appeal, it seems to us a missed opportunity to provide more, rather than less, information about individual contributions. (Instead it places an unrealistic burden on tenure committees to unearth the particular roles of the scientist under review, and may perhaps invite self-promotion.) We would rather see a deconstruction of the author list, where the particular contributions of each author are specified by the team itself. Such a system increases opportunities for recognition. For example, it would allow individual contributions to be acknowledged, be it patient sample collection, genomic technology, statistical analysis or biological follow-up. Each scientist or clinician would be highlighted for his or her disciplinary contributions. Consider the credits of a feature film: although the stars get top billing and the director comes last, the cinematographer and costume designer get their due. Such credits make it possible to evaluate and recognize specific contributions in the context of an ensemble project.

Evolution in the recording of authorship would be an important step towards revamping scientific career development. Committees that select and promote faculty staff often place weight on quantitative authorship-related measures (such as impact ratios and the number of papers published) and outside appraisal, but in future they will need to seek out and incorporate new assessments of scientific contribution for both their faculty and their non-faculty professional staff. But how can senior faculty, already stretched thin, be expected to take on this added responsibility? One answer may be to look at the way professional service firms work, such as law and consulting firms, where — similar to academia — people are the most valued assets, and career development is thought to be sufficiently important that senior professional staff directly oversee it themselves. In such firms, dedicated administrative staff devote substantial effort to designing procedures for evaluation, gathering input from co-workers and clients, and managing the process to ensure that the time of senior staff is efficiently used. Although the details may differ, it would appear wise to invest in better procedures for evaluating academic contributions, rather than allowing the

existing system, with its well-documented shortcomings, to dictate the meaning of success in universities[3,4].

A move towards team-based working raises a set of challenges that academic institutions will have to address. As well as providing a fair means of evaluating team members, managers need to ensure that teams don't succumb to 'groupthink', where ideas from outside the team are devalued or viewed suspiciously. Poorly managed teams can suffer from diffusion of responsibility and accountability. Even the most highly motivated and functional team may outlive its mission, which illustrates the need for mechanisms to disband the team and transfer personnel. Addressing these and other challenges will require attention, creativity and good management.

A key to success

Team-based science is not simply a fad, but a reasoned response to the fundamental challenges of combining clinical investigation with genome-wide hypothesis generation. Although many different organizational models can and should be explored, we believe that a subset of clearly articulated and important problems can effectively be studied through sustained, goal-orientated, multidisciplinary teams. Creating and nurturing these teams will require open-mindedness and imagination in considering new approaches to recruitment, education, evaluation and rewarding of success in academia. □

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