FEATURE

The UBC Medical Curriculum and the Genomic Revolution

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GENOMIC MEDICINE IS HERE—WHERE ARE WE?

A man with a seizure disorder has obtained cytochrome P450 genotyping through a direct–to–consumer laboratory in the United States. He brings the result to his neurologist, asking that this information be used to improve his anticonvulsant therapy.

- A woman who is 19 weeks pregnant asks her family doctor for advice about whether she should have a genetic amniocentesis. Her routine serum screen indicated a 1 in 6 risk for trisomy 18 in the fetus, but a subsequent test that measured cell–free DNA in her blood gave a risk of 1 in 10,000.

- A healthy middle–aged man has just received the results of a genomic analysis he purchased for $99 over the Internet. The report provides information on more than 200 health–related risks and traits, and the man asks his physician for advice about what he can do to reduce his risks for developing several problems that have been raised in the report.

Each of these situations has occurred in British Columbia in the past year. The genomic revolution in medicine has arrived, but few physicians are prepared for it. In a recent survey of 329 B.C. physicians, 67.7 % believed that genomic knowledge was of great or very great importance to clinical practice (4 or 5 on a 5–point scale).[1] Nevertheless, 67.8 % assessed their own knowledge of genomic technologies as very poor or poor (1 or 2 on a 5–point scale), and 64.6 % rated their own knowledge about how to incorporate genomics into clinical practice as very poor or poor.[1]

This lack of knowledge about genomics is certainly not indicative of a general lack of clinical knowledge among B.C. physicians but instead reflects the rapid growth in our understanding of human genome science during the past few years. Substantial completion of the human genome sequence did not occur until 2003, long after most B.C. physicians finished their medical school and residency training.[2]

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GENOMICS IN THE CURRENT UBC MEDICAL CURRICULUM

The current University of British Columbia (UBC) medical curriculum is almost completely devoid of content related to genomics, and even the coverage of conventional medical genetics is deficient. The present curriculum includes only parts of five or six of 21 major competencies listed in the Association of Professors of Human and Medical Genetics Medical School Core Curriculum in Genetics.[3] This is of particular concern because these medical genetics competencies provide the conceptual framework needed to understand future clinical developments in genomics.

The need to prepare physicians for the growing importance of genomics in medical practice has been widely recognized.[4,5] For example, a 2004 report by the Association of American Medical Colleges (AAMC) recommends that, before graduating, a medical student should demonstrate an understanding of the molecular biology of the human genome and the integration of genetics into medical practice.[6] An authoritative 2009 report entitled, "Scientific Foundations for Future Physicians" includes, *inter alia*, the following specific learning objectives:

- Describe the functional elements in the human genome, their evolutionary origins, their interactions, and the consequences of genetic and epigenetic changes on adaptation and health (M3-1).

- Describe the major forms and frequencies of genetic variation and their consequences on health in different human populations (M3-2).

- Explain how genetic and environmental factors interact to produce phenotypes and provide the basis for individual variation in response to toxic, pharmacological, or other exposures (M3-5).[7]

Our knowledge of genomics and genetics is improving rapidly, and mastering the conceptual framework of genomics is necessary to use it appropriately in patient care.

GENOMICS AND CURRICULUM RENEWAL

The MD Undergraduate Curriculum Renewal process within the UBC Faculty of Medicine offers an opportunity to improve the ability of future physicians to use genomics appropriately in

their medical practices. The concept of a spiral curriculum with increased focus on the scientific basis of medical practice during the clinical years and integration of teaching across organ systems will provide many opportunities to illustrate clinical applications of genomic medicine. Similarly, as students progress from basic to complex patient presentations, there will be many opportunities to incorporate concepts that are central to genomic medicine, such as individual variation in disease susceptibility, response, and treatment.

Unfortunately, however, the renewed curriculum could turn out to be even less effective than the current curriculum in teaching the fundamental principles and conceptual framework of genomics. The same factors that have impaired the current curriculum, namely poor integration of foundational science with clinical medicine and variability in the learning experience among students,[8] could hamstring the new curriculum. The renewed curriculum will teach structural biology, physiology, biochemistry, pharmacology, and pathology almost entirely in the context of clinical presentations, and there will be little opportunity to discuss transcendent basic science principles apart from their relationship to the pathophysiology of particular diseases. This change in the curriculum is concerning, especially for the study of genomics where the underlying mechanisms, which need to be understood to apply the principles to other situations, are frequently not apparent at the level of the phenotype. Focusing only on the applied end of genomic knowledge is likely to produce rote learning of "factoids," rather than a deep understanding of the principles that provide a framework for appropriate use of genomics in future clinical situations.

In addition, while the incorporation of "scholarship & science/academics"[9] as an ongoing activity throughout clerkship offers the possibility of improving students' understanding of the basic science that underlies particular clinical problems, the presentation of this stream as a separate component of the curriculum could make it largely irrelevant for most students. It will be challenging to maintain the engagement of students in "scholarship & science/academics"[9] when it competes with their time for clinical learning at the bedside.

The best solution, of course, would be to eliminate the distinction between clinical and science/academic learning by assuring that all clinical teaching is based on and used to illustrate contemporary scientific knowledge. This could easily account for 20% of learners' time on the wards, in clinics, or in physician's offices, but it would be very difficult to implement, maintain, and monitor in a widely distributed medical curriculum. It would pose a particular challenge at UBC, where most clinical teaching is performed by busy clinicians whose first concern is, and must be, providing care to their patients. The problem is even greater with respect to genomic medicine because most B.C. physicians have limited knowledge of genomic technologies or how to incorporate them into clinical practice.[1]

A MADE-IN-BRITISH COLUMBIA SOLUTION?

Preparing physicians to practice genomic medicine means including learning materials in the curriculum that will enable students to understand the principles of genomics and to achieve the competencies needed to apply these principles clinically. The renewed curriculum must contain a comprehensive set of specific genetic and genomic competencies, not just a few adventitious objectives that may fit into an occasional presentation focused on other issues.

If genomic medicine is integrated throughout the curriculum, as it should be, evaluation of these competencies will need to be ongoing and cumulative throughout the entire medical school experience. Students should be expected to demonstrate their understanding of fundamental genetic and genomic principles explicitly, as well as the clinical competencies that derive from them.

British Columbia has very strong resources in genetics and genomics. The Michael Smith Genome Sciences Centre is a world–leading site for genomics and bioinformatics research. The B.C. Provincial Medical Genetics Program is among the largest and most comprehensive clinical genetics services in North America, and the UBC Department of Medical Genetics includes one of the most distinguished groups of human geneticists in Canada. These faculty members could provide outstanding curricular materials and learning support in genetics and genomics for the undergraduate medical curriculum.

Integrating genomic learning throughout the renewed curriculum will not be effective without initially providing students with an opportunity to master the fundamental principles of genetics and genomics. Clinical problems that focus on fostering a deeper understanding of genetic and genomic principles could be used in the early portion of the curriculum to provide students with the conceptual framework needed to address specific clinical applications later in their medical education. This might require some flexibility in the presentation–based curriculum as currently envisioned, but would be consistent with the concept of a spiral curriculum. It would not be easy for clinical faculty throughout the province to teach or guide students in learning material that is unfamiliar to the faculty members themselves, but the renewed curriculum will provide opportunities for many other kinds of distributed learning for both students and faculty.

In 2009, Genome British Columbia presented a bold vision of British Columbia as a "Personalized Medicine Province."[10] The goal was to provide British Columbians with access to the best healthcare in the world and optimize the use of available economic resources. Personalized medicine was seen as the key to more accurate individualized diagnoses, which would in turn assure that the right patient receives the right treatment at the right time. Making genomics a central organizing principle of the UBC medical curriculum by spiraling from an understanding of the conceptual framework through increasingly complex clinical applications throughout the four years would be a giant step toward making this vision a reality.

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Integrating Genomics into Clinical Practice

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INTRODUCTION

There are two main clinical scenarios in which genomic analyses will be pursued. The first is to support the making of a diagnosis. This is usually, but not always, done in the context of presenting symptoms or signs. Second, genomics can be applied to obtain probabilistic assessments. The concept is to apply genomic information to guide anticipatory health care and/or optimize the use of "pharma" products. The interpretations of some of these assessments are complex, and there can be ethical considerations regarding their integration into a public health system.

MAKING THE DIAGNOSIS

Copy number variants

Chromosomes are vulnerable to rearrangements involving deletions and duplications. The resulting variations in the copy number of the genes are a common cause of developmental/intellectual differences, often with accompanying minor or major malformations. The traditional karyotype has limited resolution. The introduction several years ago of array comparative genomic hybridization (aCGH) technologies, for identification of submicroscopic chromosomal deletions and duplications, increased our ability to offer a specific diagnosis to individuals with developmental differences by about 20%.[1]

Mendelian diseases

Until recently, we had limited abilities to confirm diagnoses of many conditions that were suspected to be genetic. This was both because the majority of the genes for the Mendelian conditions had not been identified, and because when there were implicated genes, testing was too labour intensive. Genomics researchers have addressed the first problem with genomic sequencing. One approach is to identify a few patients with a similar diagnosis and figure out what gene to implicate by determining what gene is commonly mutated among the patients. Newly identified genes involved in Mendelian conditions are now reported weekly; the information is quickly turned into clinical tests for patients in whom the condition is suspected. A second approach that has become clinically available within the last year or so is relevant when a patient appears to have a genetic presentation that is unrecognizable. The service labs can now do a genomic sequencing and look at the profile of that person's variants. The interpretation uses various approaches to identify a likely responsible mutation. To address the second problem of the high costs of traditional single–gene testing, labs have integrated genomic approaches so as to be able to offer testing for many genes at once, dropping the cost of each. Panels holding the dozens of genes now known to be responsible for presentations such as unexplained deafness or cardiomyopathy allow for efficient, economical diagnostic work up.

Reproduction

Genomics is significantly changing what is available in the reproductive realm. Genomics offers alternatives to the traditional amniocentesis with karyotype analysis for assessment of a fetus' chromosomes. The higher resolution aCGH analysis discussed above can be applied to an amniocentesis sample for higher diagnostic yield. Non-invasive prenatal diagnosis, which uses a maternal blood sample to assess for fetal aneuploidy, offers information without the amniocentesis. Further, prospective

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