Counseling molecular diagnostics

'We are on the precipice of a new age when genetic counseling will certainly be a challenge.'

Bert Gold, National Cancer Institute at Frederick, MD, USA

Several conflicting tendencies in the current medical services arena make it difficult to deliver high-quality genetic counseling advice. First among these is that, although a patient expects and deserves excellent medical advice from their family practitioner or internist, good genetic counseling is currently in the realm of specialists. Second, strict guardianship of medical information by the primary healthcare provider often prevents genetic counselors' awareness of relevant *a priori* risks. Third, the economies of scale required for accurate molecular testing invariably cause the analytical laboratory to be in a location that is different from the primary care provider. Distance often hinders communication between the primary service provider and the analytic laboratory.

Up until now we have been in an era of testing for relatively simple, mendelian single-gene disorders. We are on the precipice of a new age when genetic testing is expected to include more complex and more common disease susceptibilities. In addition, as pharmaceutical research reveals individual differences in drug metabolism, medicine choice or dosage could be adjusted for the patient's genotype [1]. In this new era, genetic counseling will certainly be a challenge. Proper counseling requires knowledge of the genetic risk and the ability to effectively communicate this to patients. In the future, limiting the practice of genetic counseling to certified nurses, physicians and counselors could become impractical. Whether these clinical skills can be 'mainstreamed' into routine medical practice will be tested over the next few years [2]. The possibility of training pharmacists in genetic counseling, so that they can inform patients simultaneous with discussions of drug interactions, might need to be considered.

The clinical encounter

Patients who present themselves at a physician's office are seeking relevant knowledge. The pregnant teenager, the physician's wife with a palpable lump, or the executive with chest pains, are each deserving of their physician's best response. Each anxious patient possesses a unique landscape of life circumstances and genetic endowment. Every patient carries to such a visit to the physician a developmental microenvironment that stretches at least two generations back in time* and ethnic roots that can be traced through their genetic ancestry at least one hundred millennia [3]. Medical advice must be delivered in this context. Political and economic trends in healthcare delivery have recently focused on diminishing the frequency of adverse events simultaneous with reducing excess medical costs [4]. Given this trend, it is reasonable to predict that future physicians will find themselves required to provide easy to follow and easy to interpret evidence-based advice, in short-order, to an increasing patient load [5].

Until now, genetic counseling has been the task of specialists – mainly following up on and treating relatively rare mendelian diseases that are characterized by simple inheritance patterns (see http://videocast.nih.gov/ram/ctgas022602a.ram). Ethnic clustering of these diseases often provides the practitioner with an index of suspicion high enough to warrant appropriate genetic testing. Test results then permit accurate genetic diagnosis. Ethnic predisposition toward some genetic diseases, that arise through founder effects mediated by geographic or cultural isolation, or inbreeding, form a basis for mutant gene discovery. These discoveries have enabled researchers to rapidly identify a panoply of offending gene variants. Panels of genetic tests designed to screen for specific mutations in specific spots have enabled testing laboratories to provide rapid answers to a growing clientele of clinics [6]. Clinical errors have been made during this complex process, although a variety of safeguards have been put into place to prevent future mistakes (see http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.htm).

Traditional genetic counseling has been provided to families known to be at risk of hereditary disease because of the birth of affected offspring. Mandated neonatal genetic screening has permitted the identification and treatment of rare genetic diseases in affected newborns [7]. In these instances, family history was, and is unlikely to be,

informative for the 'at risk' conditions because of the infrequent nature of predisposing autosomal recessive alleles.

The benefits of genetic counseling

The greatest triumph of genetic counseling has probably been the identification of neonates affected with phenylketonuria. Simple nutritional intervention has alleviated a substantial burden of mental retardation among this cohort. In the past 20 years, a series of robust studies demonstrated that among certain European populations, preconception folic acid deprivation markedly increased the risk for neural tube birth defects [8]. As a result, in the USA the FDA recommended, and industry has agreed to, universal fortification of cereal with folic acid.

Calls for neonatal genetic screening for more common adult-onset conditions have been appropriately resisted by the professional genetics community. Identification of such disorders, those that do not have accepted long-term interventions, would serve only third-party payers (insurance companies) and perhaps governmental agencies responsible for long-term care. However, demand for pre-symptomatic testing for life threatening conditions of adult onset, such as Adult Polycystic Kidney Disease, Huntington's Disease and some familial Alzheimer Disease, have increased as the knowledge of the molecular basis of these disorders has become available.

The area of greatest genetic counseling growth over the past 10 years has been among those specialists engaged in counseling cancer patients and their families. Although most cancer is not hereditary, the hope has been that early detection of cancer would ameliorate treatment outcomes and options. Recent studies have placed this hope into question because efforts at the early detection of breast cancer and neuroblastoma have shown limited success in improving outcomes [9]. The area of pre-symptomatic testing for familial cancers has recently witnessed explosive growth with tests for hereditary breast cancer and colon cancer reaching higher volumes each year. Other tests that confirm cancer diagnosis and provide minimal residual disease assessment for hematopoietic cancer are also growing in volume. Technical diagnostic assessments for these diseases are made by pathologists, only some of whom possess the necessary expertise for molecular diagnosis interpretation. As a consequence, both the American Board of Medical Genetics and the College of American Pathologists have recently created a new specialty certification in molecular pathology.

Phenotype and genotype correlations in mendelian and complex disease

We are now entering a new era, one that will witness common disease diagnosis on the basis of its genetic cause. Researchers are using the comparatively well-understood mendelian diseases, such as the hemoglobinopathies and β-thalassemias, along with cystic fibrosis and hemochromatosis, to provide models for more common and complex gene discovery [10]. Advances in molecular technology will drive future opportunities for clinical laboratories to provide diagnostics for common maladies, such as obesity, hypertension and asthma. Because these advances are technology driven, rather than market driven, and because of the nature of the technology, diagnostics will emerge far in advance of effective interventions.

In the new paradigm, common diseases will either derive from common genetic variants in the population (see http://videocast.nih.gov/ram/wals022702.ram) [11] (that are neither necessary nor sufficient for their causation) or from variants that are rare [12]. These rare variants, which individually contribute a small fraction of the cause of common diseases, will be difficult to routinely detect using current technology. Future technology will require whole-genome scanning, simultaneous examination of multiple gene lesions, more accurate sequencing techniques and more proficient methods for the precise characterization of base insertions and deletions.

The future

Surely, future improvements in healthcare delivery will rely upon rapid and reliable communication of medical records, which can provide detailed health history, family history and ethnographic characterization of the presenting patient. These data are pre-requisites to informing the patient of his or her genetic risks. The consolidation of Bayesian risk statistics into counseling advice provided to patients has long been the standard of care in clinical medical genetics. There is a real question as to how the medical community will respond to its future obligation to provide this kind of molecular diagnostic counseling. Although training programs for clinical genetics professionals are in place, genetic counseling services are inadequately valued and are frequently added on to the cost of molecular diagnostics or obstetrics–gynecology care in hidden ways. Third-party payers and government agencies find it difficult to assess the use of genetic counseling. The dividends of genetic counseling are often not visible over the short term. At the same time, the demand to keep medical costs down has never been greater, and the pace of technical advance in molecular diagnosis has never been faster. As a result, genetic counseling is in danger of being misunderstood by the healthcare community as a specialty that can easily be provided by generalists. Unfortunately, nothing could be further from the truth.

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*As Judith Hall has indicated (personal communication), the oocytes from which we develop are first produced while our mother is in the womb of our grandmother. Therefore, we are each immediate, cytologic products of the two preceding generations. The implication is that the uterine microenvironment, including the nutritional and chemical exposures of our grandmothers, has implications that impact on the genetics of our present physiology.