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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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parents can now purchase genomic panels that are designed to diagnose carriers of Mendelian diseases. These panels are designed to identify if a couple has increased chances of giving birth to a baby affected by a recessive condition.

Cancer: a somatic genomic disease

It is believed that a series of mutations at the somatic level transforms a cell into a cancer cell. The specific path to tumourogenesis can vary significantly between cancers with similar histological diagnoses. What has therefore emerged in cancer management is the recognition that histologically defined tumours that were previously binned together in fact often represent a heterogeneous group of diseases, each with a different genomic profile. This recognition has informed an approach to personalizing prognostication and treatment. For example, "*HER2* status" of a breast cancer is routinely assessed with a test which determines whether there is an up-regulation of the *HER2* gene within the cancer cells. This is done to guide treatment decisions. The concept has been expanded into a multigene expression test now commercially available that has clinical evidence validating its ability to predict the likelihood of chemotherapy benefit as well as recurrence in early-stage breast cancer.[2]

OBTAINING PROBABILISTIC ASSESSMENTS

The "multifactorial" model has been applied to clinical problems ranging from spina bifida to cardiovascular disease. These have rested largely as clinical diagnoses, and empiric data has been used in their management and counselling. Genomics research is starting to identify associations at the population level between variants and multifactorial conditions. The hope is that this is revealing susceptibility alleles, even if of low risk, and that effectively interpreting the pattern of variants across an individual's genome could inform rational anticipatory care. This is an area in which many are investing. Determining evidence-based practice regarding integration into the clinic of variants shown in population studies to be associated with disease requires further development.

Direct-to-consumer (DTC) companies have started marketing analyses to the public using this approach. The marketing sometimes leaves a lack of clarity as to whether the testing is "recreational" or health related. Often there are disclaimers related to potential medical applications. Nevertheless, reports get brought into the health care system by their owners seeking follow-up. The DTC products vary in their approaches and analyses, and in their abilities to be independently validated and replicated. Real care is required to determine what kinds of genetic markers are being assessed, and the bases for the interpretations.

PHARMACOGENOMICS

Pharmacogenomics refers to the use of genome wide arrays or variant profiles to identify genetic differences associated with between-individual differences in responses to drugs. This includes efficacy and side effects. This is a promising area in development, and requires development of the knowledge translation aspects.

ETHICAL CONSIDERATIONS

Many of the ethical issues related to integrating genomics into clinical practice are routinely dealt with, at least in some iteration, within other areas of medicine already. With genomics, however, the vast scope and ready access of the information are unprecedented. These may be the two factors contributing most to the excitement and anxiety associated with genomics as it evolves beside and within the health system. The World Health Organization offers thoughtful discussion on issues such as confidentiality, informed consent, discrimination, stigmatization, and interests of third parties such as family members, governments, insurance companies, law enforcement or scientific researchers as they relate to genomics.[3]

How genomics will influence who has access to what in the public health system going forward deserves proactive exploration by Canadian physicians. Will those who purchase DTC services disproportionately use the public system? Some have questioned whether seeking interpretation of or confirmation of privately purchased risk assessments, or related follow-up surveillance within the public system is just. On the other hand, as anticipatory health care applications of genomics become proven, how will the promise for better preventative health through genomics be realized for the broader population? Any proactive approach takes an upfront investment. There will be a cost associated with the finding of each actionable variant, and any preventative strategies would require resources too. Our public system is not currently set up for either on a large-scale basis, and will need some reorienting if this is to be a reality for the population at large.

CONCLUSION

Genomics will contribute to the more "personalized" approach to treatment, prevention, and patient safety that the population is increasingly wanting and expecting. More and more evidence-based applications will become available, and will move this science beyond the niche areas it is currently revolutionizing. The medical community should be careful to recognize "recreational" or partial risk assessments for what they are, as we await the soon-anticipated more sophisticated broad risk assessment products.

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