HER2 testing: The patent "genee" is out of the bottle

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Since the first rough draft of the human genome was completed in 2000, the public has waited patiently for the benefits that were promised breathlessly by researchers. Increasingly, these benefits come at a steep price.

According to Jensen and Murray,[1] more than 4000 of the nearly 24 000 known human genes have been patented in the United States. Of these patents, 63% have been assigned to private corporations and 28% have been assigned to institutions such as hospitals and universities or to foundations set up by these institutions to own and exploit their patents.[1] Genes are being patented almost as quickly as they are discovered; it is estimated that private corporations have filed more than 20 000 preliminary patent applications for human genes.[2]

Gene patents cover much more than genetic testing and potential treatments. Many patents cover the genes themselves. The gene may occur naturally in humans, but the person who discovers the gene usually holds the patent. As the list of patented genes increases, there are growing fears about the impact on everything from research to the practice of medicine itself.

The example of human epidermal growth factor receptor-2 (HER2) and trastuzumab (Herceptin) illustrates both the promise and the perils of gene patenting. Trastuzumab is an antibody against the product of a known breast cancer oncogene; it acts on HER2 either to inhibit cancer cell proliferation or to signal the immune system to destroy the cancer cell. Trastuzumab therapy has been shown to increase survival among women with metastatic as well as localized breast cancer.

All innovative drugs are patented, so why shouldn't drugs such as trastuzumab be patented as well? The difference in this case is that the trastuzumab patent holder (Genentech Inc.) also holds multiple patents related to the *HER2* gene and HER2 ligands.[3–5] The implications of this are enormous: any researcher or pharmaceutical company who wants to develop a breast cancer treatment based on the *HER2* gene must obtain permission from Genentech or risk being sued for patent infringement.

Given the above, it is not surprising that the drug is as expensive as it is. The annual cost of trastuzumab therapy in Canada is as high as $50 000.[6] The cost of tamoxifen is much lower. Currently, the cost of trastuzumab is covered according to eligibility criteria set by provincial cancer care agencies or by individual hospitals that provide cancer care.

One can argue that the study by Dendukuri and colleagues[7] in this issue of *CMAJ* (page 1429) is necessary only because patenting issues have made the drug so expensive. For the drug to be effective against breast cancer, the cancer must be HER2 positive (overexpress the *HER2* gene). About 25% of all breast cancers are HER2 positive.[8] Given how expensive trastuzumab is and how many women with breast cancer could benefit from this drug, it is critical that the provinces find the most cost-effective way of determining HER2 status.

There are other cost implications of gene patenting. Myriad Genetics Inc., a US biopharmaceutical company, has obtained patents in the United States and Canada on the breast cancer genes *BRCA1* and *BRCA2* (breast cancer 1 and 2, early onset). *BRCA1* and *BRCA2* mutations have been found in about 10% of breast cancer cases. In 2001, when the provinces started testing for *BRCA1* and *BRCA2* mutations at publicly funded Canadian laboratories, Myriad Genetics alleged patent infringement and demanded that all testing be performed at its laboratories in the United States. Testing at Myriad Genetics costs 2–3 times more than in Canada. In July 2001 Myriad issued a cease and desist notice in Canada. British Columbia stopped all testing at that time but offered to facilitate testing by Myriad Genetics for patients willing to pay. The province later sidestepped this claim by sending samples to Ontario for testing.[9] In Quebec, *BRCA1* and *BRCA2* testing was performed at Myriad Genetics. Other provinces such as Alberta, Ontario and Manitoba continued to offer the testing in Canada.

Critics of gene patenting also say that the practice slows and even halts scientific progress by discouraging scientists from doing research on patented genes. Hereditary hemochromatosis is an autosomal recessive disease affecting mainly people of European descent. Up to 85% of cases of hemochromatosis are caused by 2 mutations in the hemochromatosis gene (*HFE*; H63D and C282Y). Before patents on the *HFE* mutations were awarded, many US laboratories performed testing for the mutations. According to a survey published in 2002,[10] 30% of respondents reported that they stopped developing a genetic test or stopped testing for *HFE* mutations altogether after the gene was patented. According to the authors of the survey,[10] the result has been that validation of genetic testing for hemochromatosis has not proceeded as quickly as it would have had the mutations not been patented.

Currently under Canadian law, a gene can be patented if it meets 3 criteria: it is regarded as a new invention; this "invention" works and is of interest to industry; and the discovery is not so obvious that anyone working in the field could have made it. Patents are not awarded for medical and surgical procedures. These procedures are in the public domain so that all of society can benefit from them. Why should genes be treated differently?

Proponents of gene patenting say that patents are necessary to provide incentives for innovation, to recover the costs of research and development and to attract investment capital. Given that, this practice is not likely to end soon. The

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key, therefore, is to offer patent protection while protecting society's right to benefit from new discoveries. Some have called for the creation of an independent, nonprofit patent clearing house whose aim would be to ensure a fair financial return for patent holders and fair access to genetic discoveries for researchers.[11]

The danger is that patent holders will fail to cooperate in the formation of such an agency. As genetic testing and treatment with gene-based therapies become routine, the prohibitive expense of gene patenting will become clearer. At that point, governments will probably have to take action to make certain that gene discoveries will be available to all and not just to those who can afford them. The stakes are too high to leave this issue to the vagaries of the "market." Already, this government action has begun: in 2004 the European Patent Office revoked the patent it granted to Myriad Genetics for the *BRCA1* breast cancer gene. In Canada, Alberta, Manitoba and Ontario have defied Myriad Genetics and offer *BRCA1* and *BRCA2* testing.

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