Handling Individuals with High Cancer Risk: One Size Doesn't Fit All

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Jewish populations express many founder effects that are sometimes translated into syndromes involving high risk of cancer occurrence. Most commonly known and most relevant are the breast-ovary syndrome and Lynch syndrome (generally involving the colon and the uterus).

With 2% of the Ashkenazi Jewish population carrying mutations in one of the BRCA genes [1] and 0.5% carrying mutations in the mismatch repair (MMR) genes [2,3], 6% carrying the I1307K pre-mutation in APC [4] and 4.5% of North-African Jews carrying mutations in MUTYH [5], clinicians are likely to encounter tens of thousands of carriers seeking medical advice. These include people who have already been diagnosed with cancer and people who are healthy, people who carry mutations that put them at very high risk, as well as people who carry mildly penetrant mutations and are at only mildly elevated risk. It also includes people who are knowledgeable about their risk and the diseases involved, as well as people who are not familiar, oblivious or indifferent about their future disease risk; people who believe in faith, in almighty powers, and more rational people, hypochondriacs as well as abstainers.

The mission of the medical team is to deliver sensible and as accurate as possible advice to these very different carriers, in this era of rapidly increasing knowledge. People at high risk should be referred for risk/genetic assessment; they should be evaluated with accurate diagnostic technologies; and should be correctly advised about their genetic changes or the meaning of lack thereof, about their risk of disease (mutation penetrance), the medical means of handling these risks, and their true promise. Failure can occur if a mutation is missed due to improper testing (technical error, lack of comprehensiveness), improper interpretation (wrong proband choice, phenocopies), and incorrect estimation of penetrance. Providing advice for prevention and early detection or treatment of tumors, which is not based on sufficient evidence, is another common potential failure that can potentially lead to unnecessary and stressful follow-up tests, which in many cases is invasive and risky.

In this issue of IMAJ, Yerushalmi et al. [6] describe a follow-up service dedicated to BRCA mutation carriers. The concept of such a follow-up service is smart and provides carriers with both expert follow-up and a social support framework accommodating the fears involved with the notion of high risk status. The authors developed a service that caters to a large group of individuals at risk. The mechanics of the service are appropriate and necessary. People come to a one-stop shop where they undergo all the requisite tests and evaluations according to a protocol. But, here is where the trouble begins. Protocols. Protocols usually call for the same policy for all BRCA carriers [7-13]. Protocols recommend the same policy for families who express many cancers that are aggressive and have a young-age onset, as for families with few or no cancers on their pedigree chart. Protocols reflect the opinion of the people who wrote them, who are mostly influenced by medical guild interests and by liability-driven policies made in America. It follows that if unsuitable, these protocols provide the wrong advice to carriers. Once protocols are in place they serve not as guidance but as “must-follow” tools, disregarding the ability of experts who have spent dozens of years studying and acquiring experience from their practice in order to tailor an intervention to suit a particular patient.

Protocols for BRCA carriers carry numerous flaws. The first is that they are based on estimates of penetrance that are far from consensus [14]. Without agreement regarding the risk that a carrier faces, it is difficult to arrive at a benefit-to-risk estimate for any suggested intervention. Some protocols recommend annual mammography follow-up to healthy carriers from a very young age. In contrast, the concomitantly recommended annual breast magnetic resonance imaging (MRI) has close to 100% sensitivity [15], mammography is extremely non-sensitive, and 40 years of annual mammograms in young women with dense breast and a mutation of DNA repair deficiency could itself cause disease. While the recommendation of preventative bilateral salpingo-oophorectomy [16] is largely accepted (with some controversial issues such as the “right” age for the procedure, the need for hormone replacement therapy, etc.), protocols in the United States which keenly recommend bilateral mastectomies [17,18] are under increasing scrutiny, considered by some to be unmeasured in face of current knowledge on lower mutation penetrance and high survival probability. Questions can be raised regarding the balance between
the physical and mental suffering involved with this extreme disfiguring procedure and the 90% promise of reduced risk of breast cancer in a BRCA2 carrier who has a 40% chance of developing a breast tumor at age 50, likely detected in stage 1, which carries less than 10% overall probability of death due to the disease. The balance is completely tipped to the other side when dealing with a 30 year old woman with a 5382insC BRCA1 mutation, known to carry > 80% risk of breast cancer, frequently bilateral [19], and who has a significant first-degree family history of deaths from cancer. And we haven't even begun discussing the new fashion of pre-implantation genetic diagnosis (PGD) that is commonly suggested without proper evaluation of benefits and risks. The problem is thus not the need for a follow-up service, but the contents of such a service. The magic word, usually not stated, is tailoring: tailoring of individual recommendations to a specific person, rather than reliance on protocols. One size does not fit all. This is the essence of the rapidly developing personalized/precision medicine approach.

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References

Lens regeneration using endogenous stem cells with gain of visual function
The repair and regeneration of tissues using endogenous stem cells represents an ultimate goal in regenerative medicine. Currently, the only treatment for cataracts, the leading cause of blindness worldwide, is to extract the cataractous lens and implant an artificial intraocular lens. However, this procedure poses notable risks of complications. Lin et al. isolated lens epithelial stem/progenitor cells (LECs) in mammals and showed that Pax6 and Bmi1 are required for LEC renewal. The authors designed a surgical method of cataract removal that preserves endogenous LECs and achieves functional lens regeneration in rabbits and macaques, as well as in human infants with cataracts. This method differs conceptually from current practice, as it preserves endogenous LECs and their natural environment maximally, and regenerates lenses with visual function. This approach demonstrates a novel treatment strategy for cataracts and provides a new paradigm for tissue regeneration using endogenous stem cells.

“Would the boy you were be proud of the man you are?”
Laurence J. Peter (1919-1990), Canadian educator and “hierarchiologist” best known for the formulation of the Peter Principle, whereby “In a hierarchy every employee tends to rise to his level of incompetence.” The Peter Principle became one of the most profound principles of management from the University of Southern California