Completion of The Human Genome Project in 2003 marked the dawn of the Age of Genomics. Many optimistic predictions regarding future medical use of the exploding volume of genetic knowledge were made. There would be “personalized health care” in the future where selection of medications directed at treating common conditions such as hypertension would be guided by a person’s genome, enabling efficient establishment of the most effective therapeutic regimens. There would be gene therapy for both monogenetic and polygenetic diseases. Better understanding of genetics would enable improvement in survival of organ transplantation and would foster the development of “regenerative medicine.” However, the human genome has proven more complex than was initially appreciated and we are still waiting for the realization of many of the hoped for advances.

One area where there has been substantial progress is in tumor genetics. Molecular analysis of cancerous tissue has led to the development of targeted therapies that enhance treatment effectiveness and, in some instances, significantly improve survival. When resistance to initial therapy occurs evaluation of tumor tissue is required to best select subsequent therapy. However, obtaining tumor tissue for DNA analysis requires a biopsy which has multiple negative aspects: cost, risk of complications, discomfort and inconvenience. In an effort to avoid these negative aspects new techniques have been developed which are less invasive and provide the same genetic information as tissue biopsy specimens. It has been found that evaluation of circulating tumor DNA (ctDNA) present in the blood is less invasive and provides the same genetic information as tissue biopsy specimens. The procedure of evaluating blood for the presence of a cancer’s genetic material was first given the term “liquid biopsy” in 2010. Since then the types of bodily fluids evaluated by this technique have expanded to include not only blood but saliva, urine and stool as well. The direct to consumer genetic testing by “23andMe” also uses the saliva collection technique but 23andMe assesses a person’s DNA, not that of a cancer. In April of 2017 the FDA approved limited genetic health risk testing by 23andMe. Genetic screening for ten rare diseases, none of them cancer, is offered. The accuracy and utility of this test has been criticized in current medical literature.1 This discussion will consider only liquid biopsy of blood.

Normally, when cells in the body die or are injured some of their DNA leaks out into the blood stream, so-called “cell free DNA” (cfDNA). The same phenomenon occurs when tumor cells die or are injured and circulating tumor DNA (ctDNA) is released. The liquid biopsy technique identifies circulating DNA (both cfDNA and ctDNA) found in the plasma (the liquid component of the blood without the hematologic cells and platelets). The
amount of ctDNA found in the plasma tends to correlate with the burden of tumor present. However, on average, ctDNA represents less than 1% of the total circulating cfDNA and may amount to only 0.1% of all DNA in the plasma. Identification of ctDNA and differentiating it from normal cfDNA is aided by the fact that ctDNA is defined by mutations. Evaluation of ctDNA obtained via liquid biopsy has been found useful in monitoring tumor burden (similar to monitoring viral load in HIV). Liquid biopsy may detect minimal residual disease or recurrence of a cancer long before it can be identified through imaging techniques or by the monitoring of tumor biomarkers. Liquid biopsies are also effective in monitoring for the development of tumor resistance during the course of treatment. The amount of ctDNA relative to normal cfDNA can be infinitesimal even when substantial tumor mass may be present and this currently limits the sensitivity of this technique and makes it impractical for use as a screening tool. More sensitive next-generation sequencing (NGS) techniques are being developed that may improve the ability to identify small amounts of circulating DNA in the future.²

Most of the scientific work on liquid biopsy techniques has focused on individuals with previously diagnosed cancer. Clinical use of liquid biopsy is very limited. This is supported by the fact that when one searches for this term in a very excellent and current online medical textbook, UpToDate, one obtains only one hit. Use of liquid biopsy so far centers on evaluating the status of known cancers to help guide treatment and other aspects of patient management. For example, the technique is used to assess progress and help select adjuvant therapy in individuals with advanced non-small cell lung cancer. Detection of ctDNA is associated with more advanced non-small lung cancer.³ There are two types of liquid biopsy that are approved by the FDA for this purpose. Their sensitivity is between 60 and 80 percent. More sensitive assays using NGS are available but take several weeks for results.

The idea that liquid biopsy techniques might become sufficiently refined to enable detection of occult, preclinical cancer is a natural extension of current activity in this field. Articles presenting research findings directed at studying this potential are to be found in recent scientific medical literature and this is now being reported in the mainstream lay press as well.⁴ The main problem is that early preclinical (asymptomatic) cancers almost always have low tumor burden which is associated with less (maybe none) ctDNA. This implies that these techniques if used as screening procedures to identify early stage subclinical cancers would be even less sensitive than when used in individuals already diagnosed with cancer. This suggests that use of liquid biopsy as a screening test for subclinical occult cancers is not currently practicable. Dr. Pedram Razavi, a researcher at the 2017 American Society of Clinical Oncology in Chicago, noted that liquid biopsy techniques used “to screen for cancer were ‘a very long way’ from development,...”⁵ Another researcher at the same conference, Peter Gibbs, said “he could envision that within five years, people would receive tests that search for about 20 cancer gene mutations.”⁶ This method of screening for occult, preclinical cancer may well come to pass but it is wise to remember that after completion of the Human Genome Project many of the clinical applications for genomic medicine which were proposed at that time still remain unfulfilled fourteen years later.

The possibility that occult cancer could be screened for using a liquid biopsy technique as part of an underwriting evaluation has sparked some interest in the insurance industry as this might result in the avoidance of early claims resulting from such cancers as pancreatic or lung cancer where no effective screening test currently exists. However, current genetic testing laws in both the United States and Canada would preclude obtaining such tests as part of an underwriting evaluation. Genetic test results found in medical records being evaluated during the underwriting process could be used in the United States but not in Canada.

Screening life insurance applicants for cancer using a blood test has been attempted before. A prominent west coast insurer began testing applicant whole blood in 1990 for a Tumor Associated Antigen (TAA) developed by Osborn Laboratories. If TAA was found to be positive, then additional blood testing by a backup panel of nine known tumor markers was performed. If any of the backup panel tumor markers was found to be positive, decisions on applicants were postponed, pending evaluation for occult cancer by their personal physician. The specificity of this testing was suboptimal, resulting in the subjection of inappropriately large numbers of applicants to medical evaluations, which ultimately demonstrated no cancer to be present. The TAA test was not accepted by the medical community and was never approved by regulatory authorities. The result was much negative coverage in the local press in California.⁷ It is well to remember this experience when consideration is given to adopting a blood screening test for subclinical cancer that might be used as part of underwriting evaluation. Such a test must be widely accepted by the medical community and must have sufficient sensitivity (it detects disease when disease is present) and specificity (it is negative when disease is absent – i.e., low false positive rate) to avoid disaffecting applicants and agents.
Key Points

| Genetic testing laws in the United States and Canada preclude insurance companies from obtaining any genetic tests in the course of underwriting. Use of genetic test results that appear in medical records is permitted in the U.S. but not in Canada |
| Tests that screen for cancer must be generally accepted as valid by the medical community at large and must have sufficient sensitivity to detect cancer when present and specificity to avoid unacceptable numbers of false positives when cancer is not present |
| If liquid biopsy ever becomes refined enough to be used as a method to screen for occult, preclinical cancer or if there will ever be an FDA approved direct to consumer genetic screening test for occult, preclinical cancer there will be potential for anti-selection among insurance applicants |

References

6. Ibid