Cancerous tumors shed whole cells or tiny bits of DNA and other genetic material into the bloodstream and other bodily fluids. This allows clinicians to potentially analyze blood samples to detect a tumor's unique mutations and o□er a personalized treatment regimen, all without an invasive tissue biopsy.

Science fiction is swiftly becoming reality according to Dr. Daniel Zimmerman, Senior Vice President and Chief Medical Director, Global Support Team for RGA. With a background in molecular biology and medical microbiology, Dr. Zimmerman is board-certified in internal medicine and pediatrics and has more than a decade of experience in insurance medicine. He makes the case in the interview below that liquid biopsies have the potential to transform clinical and insurance medicine by enhancing risk selection and potentially improving mortality and morbidity.

## First, define "liquid biopsy"

Liquid biopsies are noninvasive tests to detect and classify cancers by identifying the small amounts of genetic material that tumors shed into the bloodstream or other bodily fluids.

Start with a traditional biopsy. As underwriters or claims adjudicators know, the traditional diagnosis of cancer relies on a histopathological specimen. How is that obtained? First, a doctor has to physically perform a biopsy of a suspected tumor, either via needle or an open procedure. The specimen is then sent to a laboratory. Technicians thehd1R T-10Tc -0Tw 0.14Td[s)2(p)-13(il)12(l)-3(s)7( t)-1(hese)7( c)7(o)-15(n)-2(t)8(en)-2(t)-4(s)-7(.)]TJ0 0 0 scnGS1gs/T1_1Tf-0Tc 0Tw 3[W

Tumors also change over time, and so liquid biopsies allow physicians to monitor that evolution. Currently, for example, a cancer patient undergoes surveillance after treatment to look for recurrence; this may take the form of scans or other tests. If you could detect the DNA or other genetic products earlier from a recurrence or changes in a cancer as part of regular liquid biopsy tests, physicians could change or initiate treatment faster.

Liquid biopsies also address the problem of intra-tumor heterogeneity and assessing metastatic lesions. Basically, a tumor is a mass of cells, but all those cells are not the same; different cells can have quite different genetic variations. A single tissue sample collected for a traditional biopsy could miss important mutations with very different prognostic implications just millimeters away. By contrast, a liquid biopsy should reflect all the variation present. Similarly, metastatic lesions also have genetic differences and these can also be detected, theoretically, by liquid biopsies.

## No wonder so many people are enthralled by the promise of liquid biopsies. What is hype and what is reality?

It's important to keep a sense of balance. To evaluate any of these new tests, large groups of individuals will need to be evaluated through clinical studies. That's going to take some time.

Having said that, we already have something similar to liquid biopsies in wide use. Underwriters are very familiar with the PSA, CEA, and the AFP (alpha fetal protein) tests performed on blood samples. These are tests for biomarkers of tumors. They don't actually identify tumors directly, but they do detect certain biochemical changes that signal a tumor could be present. We know from experience that these tests are quite imperfect.

We must also recognize something called lead time bias. For example, say a screening test picks up breast cancer months or even years before the patient might actually feel a lump. This "lead time" allows doctors to identify and treat the cancer earlier, but this extra time may or may not confer an actual survival advantage. I don't want to imply that earlier detection of cancer is not of value. Often times it is very beneficial, but we need to be careful to make sure that we don't identify tumors that may have no impact on life expectancy and "over treat" the patient.

Finally, clinicians must differentiate between "driver" versus "passenger" genetic variations detected by liquid biopsies. A driver mutation is the root cause or explains why a tumor is growing. A passenger genetic variation may have nothing to do with tumor growth. This adds an extra layer of complexity when it comes to interpreting liquid biopsies.

Insurers should rely on three criteria to assess the use of liquid biopsies in insurance medicine: analytical validity, clinical validity, and clinical utility.

This all seems very complex and qualified. How should insurers evaluate these tests?

Like any test, insurers should rely on three criteria to assess the use of liquid biopsies in insurance medicine: analytical validity, clinical validity, and clinical utility. When we look at any test result, we need to determine if the test is reproducible and reliable. That's analytical validity: If I send a sample to three different laboratories, will I get the same result back? Then, there's clinical validity: Does the result have value in determining whether someone will or will not develop an impairment or does it provide prognostic value

Then, there is clinical utility: Is the test result actionable? Can test results be applied to improve patient outcomes, inform behavior or influence treatment decisions?

Last, insurers need to consider local regulation regarding use of genomic information in insurance. Most, but not all, liquid biopsies would likely be considered genetic tests and thus may be subject to regulation.

## Put liquid biopsies in an insurance context. How will these potentially impact our industry?

Historically, medical advances which have led to improvements in morbidity and mortality have generally benefited the insurance industry as well as the general population. Having said that, certain advances can be very challenging. Anti-selection is always a risk. Also existing critical illness product definitions can pose problems.

For example, when the clinical definition of myocardial infarction changed, interpreting certain critical illness definitions of myocardial infarction became quite di□cult and changed what we had calculated as the expected incidence rates. Liquid biopsies might likewise change the basis of cancer diagnosis and incidence rates, and