



# Part III of IV: Precision Medicine and Pharmacogenomics

How cancer genomics is causing a radical  
shift in cancer research and management

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Author



**Shealynn Buck, M.D.**  
Chief Medical Officer  
Lockton Benefit Group  
214.969.6164  
sbuck@lockton.com

Cancer is a broad term to describe diseases caused by uncontrolled growth of abnormal cells that can invade normal tissues and spread throughout the body.<sup>1</sup> The body is governed by molecular checks and balances, encoded in an individual's DNA blueprint known as the genome, that keep cells in place and properly functioning within tissues. Changes, known as mutations, in one or more of the six billion DNA chemical 'letters' that comprise the genome of a normal cell, can disrupt the body's checks-and-balances system. If unchecked, a mutated cancer cell can produce clones of cells genetically programmed to look and behave abnormally, grow and outlive normal cells, and bypass the body's means of containment.

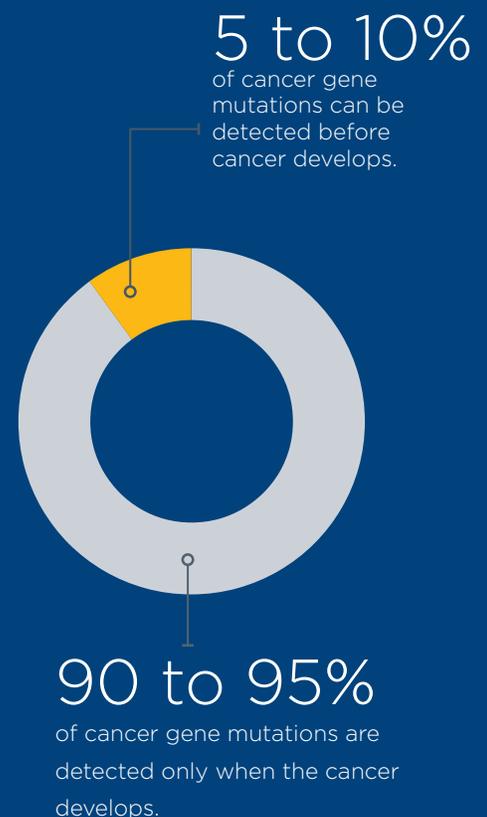
An estimated 5 to 10 percent of cancers result from genetic mutations inherited from an affected individual's father or mother, known as germline mutations, and can be detected within any cell of the individual, even before the cancer manifests.<sup>2</sup> The other 90 to 95 percent of cancers are caused by mutations that occur spontaneously with age and environmental exposure, known as somatic or acquired mutations, and are only present within the cells of the cancer itself.<sup>2</sup> These somatic mutations can only be detected once the cancer develops.

Cancer was once understood, diagnosed and treated based upon relatively broad criteria that categorized cancers by body location and appearance. With the advent of technology enabling detailed analysis of the human genetic code, the extensive variability among cancers is being elucidated. Cancer genomics — the testing, analysis and study of the mutations in the human genetic code associated with cancer — has resulted in a true paradigm shift over the last decade in how cancer is researched and managed.<sup>2</sup> This shift is moving medicine from a cancer 'one-size-fits-all' model to a precision model in which an individual's cancer risk, in the case of inherited cancers, or tumor genetic code, in the case of spontaneous cancers, is profiled for a personalized cancer management strategy.<sup>3</sup>

While transformational and promising, cancer genomics presents challenges related to health plan coverage.<sup>4,5</sup> The rapid progress in cancer genomic research is outpacing the real-world translation to the doctor's office and patient bedside, raising questions about which cancer genomics test is 'investigational and experimental' with unclear applicability to patient care and which is considered medically necessary for cancer diagnosis and treatment.

Cost is another issue. Health plan sponsors and fiduciaries are trying to understand how to balance the relatively high cost of cancer genomic testing with the benefit to the plan's members, especially in light of direct-to-consumer marketing campaigns by genomic testing providers that are driving demand.

## CAUSES OF CANCER



Finally, the rapidly changing genomics landscape along with variability across major insurance carriers' medical policies add to confusion about which tests and testing techniques should be covered. What appears to be consistent in determining plan coverage is demonstration that the specific test is analytically valid (e.g., proven accuracy and reproducibility), has clinical utility so the results improve patient outcomes and has reasonable use that balances the test's benefits with concerns about cost, psychological harm and ethical implications. What follows are reviews for three applications for genomic testing:



## Hereditary cancer risk assessment

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Although the promise of gene profiling a healthy individual to determine future cancer risk is often alluded to in direct-to-consumer genomics marketing, the current reality is that only a small percentage of cancers can be predicted through genomic testing.<sup>6</sup> Predictive cancer genomic testing has clinical utility for individuals with a family history that fits a pattern for hereditary cancer and for whom the results have implications for prevention and treatment.<sup>6</sup>

A majority of cancer mutations are not inherited but instead occur spontaneously; as such, genomic testing of an individual without cancer who has average cancer risk and does not have a family history consistent with inherited cancer is typically deemed medically unnecessary.

Even for those individuals with a family history of cancer, genomic testing in the absence of a cancer diagnosis is only appropriate in conjunction with genetic counseling to understand what the results mean for the individual and his or her family.<sup>6</sup> The presence of a hereditary cancer mutation in an individual without cancer does not mean the individual will absolutely develop cancer at some point.

Some inherited genes are more powerful than others and many factors, such as environmental exposure and lifestyle, can be at play for a hereditary cancer to develop. A relatively small number of known inherited mutations, like the familiar BRCA1 or BRCA2 mutations in hereditary breast cancer and ovarian cancer, are linked to a high lifetime risk of cancer, and a positive genomic test result is associated with defined options for medical management.<sup>7</sup>

For most hereditary cancer mutations, determining what clinical steps to take for an individual without cancer in light of a positive result is less clear and knowledge of the result may cause more worry and psychological harm than benefit. As such, it is strongly recommended that a genetic counselor walks the individual through all the pros and cons of testing prior to testing as part of informed consent process.<sup>6</sup>

In general, criteria for health plan coverage of hereditary cancer genomic testing should include genetic counseling as a prerequisite, prior authorization of testing and justification based on clinical utility — in other words, how the test will improve the medical management of the individual for whom the test is ordered.

## Cancer diagnosis and targeted therapy

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When cancer is suspected or cancer has been treated and is in remission, a sample of tissue, blood or body fluid containing possible cancer cells can be tested for distinct markers, such as genetic mutations, that help to confirm the absence or presence of a specific cancer. Once detected and confirmed, the cancer is often profiled using molecular testing, which can include genetic testing. Molecular testing is used to characterize the cancer and provide revealing information about how the specific cancer is predicted to behave in the body and respond to certain therapies.<sup>8</sup>

Over the past decade, genomics research has provided a wealth of knowledge about better ways to diagnose and subtype cancer for targeted treatment and improved survival, ushering in the era of precision medicine.<sup>3</sup> Cancer genomic testing is now the cornerstone of cancer clinical trials for tailored therapies that hone in on specific cancer subtypes allowing for pinpoint destruction of cancer cells and sparing of healthy cells.<sup>9</sup>

As new genetic markers are discovered and new genomic tests are developed, oncologists, who often straddle the clinical research and clinical practice realms, stand ready to apply these tests to their patients even before clinical applicability has been clearly defined and procedure codes for billing have been developed. Additionally, the rapid production of new genetic tests by molecular laboratories is outpacing the work to standardize genetic test performance and quality across laboratories. It is also outpacing the development of evidence-based guidelines for how the genetic test is used in medical management.<sup>10</sup>



*Criteria for health plan coverage of hereditary cancer genomic testing should include genetic counseling as a prerequisite, prior authorization of testing and justification based on clinical utility.”*

For health plan coverage, the line between cancer genomic testing for research versus clinical application is often fuzzy. The challenge in translating genomic testing to cancer patient care is determining which tests are investigational and experimental and which tests have met the validity and clinical utility criteria to be deemed medically necessary.<sup>11</sup>

Although FDA approval or clearance of a cancer genomic test supports test validity, FDA approval or clearance does not signify clinical utility, which is important for determining medical necessity. In general, diagnostic tests more likely to be considered medically necessary target well-defined cancer genes to distinguish different cancer types for the purpose of improved medical management and are referenced as part of guidelines or standards for cancer diagnosis and management.

#### Factors determining medical necessity of genomic testing:

- Does the test target well-defined cancer genes to distinguish different cancer types?
- Does the test serve the purpose of improved medical management?
- Is the test referenced as part of standards for cancer diagnosis and management?
- Are the test results tied to the indication for the targeted therapy?

In contrast, genomic diagnostic tests developed within a specific laboratory for research purposes (i.e., laboratory-developed tests) or that have yet to be linked to specific cancer guidelines or standards are less likely to be deemed medically necessary. For FDA-approved targeted cancer therapies, medical necessity of genomic testing is also supported by reference to the genomic test in the specific therapy's labeling.<sup>7</sup> In other words, the specific genomic test results are tied to the indication for the targeted therapy. Currently, there are over 90 FDA-approved targeted cancer therapies that require some form of testing to profile the cancer prior to therapy administration; however, for the majority of these therapies, genomic testing is not a specific requirement.<sup>12</sup>

As with hereditary cancer genomic testing, prior authorization is suggested for cancer genomic diagnostic testing for diagnosis and targeted therapy, unless there is clear clinical applicability for the genomic test as defined by well-established cancer management guidelines or as indicated by targeted therapy labeling. Given the rapid rate of new tests being developed, individual case review may be required to determine clinical utility of a new test for a specific member.

## Cancer whole-genome sequencing

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Cancer whole-genome sequencing (WGS), a laboratory process that outlines each of the billions of DNA letters in a specific cancer clone's entire genetic code, is a relatively new area within the field of genomic testing, with the first complete cancer genome sequence reported in 2008.<sup>13</sup> Relatively costly, time-consuming and specialized, WGS has been the purview of the research realm, until recently.

Next-generation sequencing (NGS) technology has propelled genomic testing over the past few years by coupling faster and more cost-effective sequencing technology with big data analytics to translate and help interpret the vast amounts of sequencing information. As such, the improved feasibility and direct applicability of WGS is pushing this testing closer to the bedside. While WGS holds promise for highly specific cancer profiling for individualized survival and treatment determinations, it is not yet considered prime time for the medical management of most cancer patients.<sup>14</sup>

Although Medicare and most private insurers currently do not cover WGS, some insurers are now dipping their toes in the water.<sup>15</sup> In 2016, Pennsylvania-based Independence Blue Cross became the largest insurance company to add WGS to its plan for a defined set of cancer patients.<sup>16</sup>

Based on personal communication between one of the paper's authors and laboratories that perform WGS, testing coverage is still typically determined by insurers on a case-by-case basis with the primary justification being evidence of clinical utility. Given the rapid movement in this area, expect ongoing updates to cancer management standards of practice and revisions to carrier medical policies as they relate to WGS.

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<sup>1</sup><https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45333>

<sup>2</sup><https://cancergenome.nih.gov/cancergenomics/whatisgenomics/whatis>

<sup>3</sup><https://www.cancer.gov/about-cancer/treatment/types/precision-medicine>

<sup>4</sup>Hresko A and SB. Haga. Insurance Coverage Policies for Personalized Medicine. *J. Pers. Med.* 2012, 2, 201-216

<sup>5</sup><https://khn.org/news/insurers-approval-of-genetic-testing-for-some-cancers-raises-questions/>

<sup>6</sup><https://www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-testing-fact-sheet>

<sup>7</sup>Jill Stopfer. March 24, 2015 The Promise and Peril of Panel Genetic Testing for Inherited Cancer Susceptibility FORCE Webinar Series (<http://www.facingourrisk.org/understanding-brca-and-hboc/webinars/2015-03-24-promise-peril-genetic-testing.php>)

<sup>8</sup><https://www.cancer.gov/about-nci/organization/ccg/cancer-genomics-overview>

<sup>9</sup><https://www.cancer.gov/research/areas/genomics>

<sup>10</sup>John L. Marshall, MD; Claudine Isaacs, MD; David Spetzler, PhD, MBA. The Frightening Truth about Cancer Genetics Medscape. June 22, 2015 Medical News from the American Society of Clinical Oncology (ASCO) 2015 Annual Meeting. (<https://www.medscape.com/viewarticle/846596>)

<sup>11</sup><https://www.managedcaremag.com/archives/2016/4/health-insurers-struggle-manage-number-cost-genetic-tests>

<sup>12</sup><https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet>

<sup>13</sup>Ley T., Mardis E., Ding L., Fulton B., McLellan M., Chen K., et al. (2008) DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. *Nature* 456: 66-72

<sup>14</sup>Nakagawa H et al. Cancer whole-genome sequencing: present and future. *Oncogene* (2015) 34, 5943-5950 (03 December 2015)

<sup>15</sup><https://news.ibt.com/independence-blue-cross-becomes-first-major-insurer-to-cover-next-generation-whole-genome-sequencing-for-a-variety-of-cancers/>



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