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Genomic approaches to accelerate cancer interception

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Summary

While the last decade has witnessed major advances in the treatment of late stage cancers with targeted and immune-based therapies, there is a critical unmet need to develop new approaches to impact the prevention and early detection of cancer. Recent advances in the field of genomics and computational biology offer unprecedented opportunities to understand the earliest molecular events associated with carcinogenesis, leading to novel strategies to intercept the development of invasive cancers. This review will highlight emerging “big data” genomic approaches that have the potential to accelerate advances in cancer prevention, screening and early detection across a variety of tumor types along with the challenges inherent in developing these tools for use in the clinic. Through coordinated multicenter consortia, these genomic approaches promise to transform the landscape of cancer interception in the coming years.

Introduction

The mainstay of cancer treatment has involved surgical resection of early stage solid tumors and/or treatment with chemotherapy or radiation. Targeted therapies have been approved to inhibit unchecked growth factor signaling in patients harboring specific mutations or gene fusions. More recently, cancer immunotherapies have achieved durable responses in the treatment of late stage solid tumors such as castration-resistant prostate cancer, melanoma, and lung cancer. Despite these advances, the prognosis of patients with certain types of cancer, such as lung cancer, has only modestly improved (18% of all people diagnosed with lung cancer will survive 5 years or more). There is an urgent and unmet need to move these genomic and immunology advances earlier in the disease process and leverage these approaches to “intercept” cancers by developing novel tools for cancer prevention and early detection.

The era of personalized cancer treatment has been evolving since the completion of the human genome sequence in 2003. The Cancer Genome Atlas (TCGA) has recently performed genomic profiling on over 11,000 late-stage tumors across 33 tumor types. Tumors have been characterized with a various genomics assays to assess somatic mutations,

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Conflict of Interest Statement

A.S. is a founder of AllegroDX Corporation and a consultant to Veracyte, Inc. and Janssen Pharmaceuticals.

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copy number variations, DNA rearrangements, DNA methylation, and expression of mRNAs, miRNAs, and proteins. Integrative analyses of TCGA data have identified novel “driver” events and pathways leading to new insights into the molecular mechanisms of carcinogenesis that can be used for diagnosis and targeted treatment. The tumors characterized by the TCGA, however, were largely late-stage making it difficult to infer the events that preceded the development of the tumor thereby potentially diminishing the ability to translate findings into novel strategies for preventing or delaying the development of cancer.

The TCGA has provided a foundation from which we are poised to expand our genomic profiling efforts into high-risk tissues prior to the development of cancer. We have previously outlined our vision for a TCGA-like initiative, called the Pre-Cancer Genome Atlas (PCGA), where we call for cellular and molecular profiling of precancerous tissue and its associated microenvironment sampled over space and time¹. Two major aims include understanding mechanisms of disease progression to identify biomarkers of cancer risk and to develop new cancer interception strategies to prevent or delay disease development or recurrence. This review will focus on how the collection of “big genomic data” from at-risk and precancerous tissue is beginning to provide new opportunities to impact patient care and “intercept” cancer at critical points prior to treatment that include prevention, screening and diagnosis.

In this review, we will highlight how large genomic datasets measuring RNA and DNA analytes are emerging as novel tools to interrupt cancer development and progression alongside the challenges and opportunities inherent in moving this field forward (see Table 1). We will not cover the emerging epigenomic, proteomic, metabolomics, microbiome, and molecular imaging approaches in this space. The term cancer interception refers to the interruption of the carcinogenesis process at any point prior to the development of invasive disease². It is inclusive of approaches in precision cancer prevention to identify and eliminate exposures to cancer-causing agents as well as identify genetic susceptibility to cancer. It also includes efforts in the cancer screening, prevention and early detection space to identify molecular alterations associated with precancerous disease, develop novel prophylactic treatments and find cancer at an early stage in higher-risk individuals (see Figure 1).

Novel Genomic Approaches to Cancer Prevention

The Unmet Need

The long latency period that precedes the development of cancer allows for the implementation of a variety of cost effective preventative measures that include lifestyle changes and limiting environmental and occupational exposures. A 2010 study showed that lifestyle factors, including high body-mass index, low fruit and vegetable intake and physical activity, tobacco use, and alcohol use were responsible for 24% of new cancer cases and 30% of cancer deaths among six type of cancer – lung, liver, breast, cervical, colorectal, and stomach³. Estimates suggest that more than half of cancers could be prevented based on the knowledge of current risk factors⁴. Reducing cancer-related mortality by preventing exposure has been best demonstrated by the fact that an increased rate of smoking cessation

has resulted in decreased lung cancer incidence⁵. Implementation of cancer prevention by eliminating known risk factors, however, is challenging and requires coordinated efforts by government agencies, health care providers, and communities to improve current and create effective policies and programs. Genomic data may augment the aforementioned cancer prevention strategies by providing personalized knowledge of exposure-related mutations and germline variation conferring cancer susceptibility as well as allow for the development of personalized prevention strategies.

Prevention via eliminating exposure

Genomic alterations resulting from exposure to carcinogens can drive cancer growth by activating or deactivating genes in the hallmarks of cancer pathways⁶. Identifying and removing agents that cause these genomic alterations remains an important goal to prevent cancer initiation. However, many different exogenous exposures or endogenous biological processes can contribute to the overall mutational load observed in human tumors^{7,8}. Indeed, many mutational patterns (i.e. mutational signatures) have been characterized across many different human cancer types. Well-known mutational signatures include the patterns of C:G>A:T mutations caused by the carcinogens in cigarette smoke such as benzo[a]pyrene (BaP) or the clusters of C:G>T:A or C:G>G:C mutations caused by aberrant activation of protein cytidine deaminases (i.e. APOBECs)⁷. These signatures can provide a record of environmental exposure and can give clues about the etiology of carcinogenesis⁹. For example, aristolochic acid is a chemical present in aristolochia plants, which grow in wheat fields in Southeastern Europe and was characterized as a renal carcinogen with a specific mutational signature¹⁰. Some lung squamous cell carcinomas had high levels of a mutational signature associated with ultra-violet radiation suggesting that they may have been metastases from the skin¹¹. To date, over 30 mutational signatures have been identified and are curated in the COSMIC database including six related to exposures: cigarette smoke, UV-light, alkylating agents, aristolochic acid, aflatoxin, and oral chewing tobacco (cancer.sanger.ac.uk/cosmic/signatures).

Measurement of these signatures in end-stage tumors, premalignant lesions, or exposed tissue can provide a concrete record of exposures that can be used in cancer prevention and risk assessment; however, several of these signatures still have unknown etiology. The number of environmental chemicals that could be responsible for these mutational patterns is large. The Environmental Protection Agency (EPA) (<https://www.epa.gov/tsca-inventory>) has more than 84,000 chemicals registered, but only a small proportion of these have been tested for carcinogenicity. Studies have begun to apply genomic sequencing technology to experimental systems exposed to carcinogens. For example, *Caenorhabditis elegans* and mouse embryonic fibroblast models exposed to known genotoxic agents were able to largely recapitulate mutational signatures observed in human tumors^{9,12}. In the future, genomic profiling of model systems can be integrated into a multi-tier screening platform to elucidate the mutational signatures observed in human cancers, predict genotoxicity of untested chemicals with greater accuracy, and reveal mechanistic insights into how different chemical structures and can induce different types of genomic alterations. In the end, both continued genomic sequencing of tumors from diverse populations with mutational signature characterization combined with experimental systems designed to directly assay the

mutational impact of carcinogens will provide a comprehensive picture of exposures that lead to cancer.

Prevention via identification of genetic susceptibility

Another major focus of cancer prevention is to identify individual susceptibilities for cancer development. Well-established genetic variants that increase risk of disease include those in *BRCA1* and *BRCA2* for breast cancer, *MLH1* and *MSH2* for Lynch syndrome, *STK11* for Peutz-Jeghers syndrome, and *TP53* or *CHEK2* for Li-Fraumeni syndrome, among others. Individuals can receive genetic testing and undergo intensified surveillance or prophylactic measures in the hopes of reducing the likelihood of cancer occurrence. Large-scale genome wide association studies (GWAS) continue to identify novel common variants associated with breast, lung, colorectal, and prostate cancer^{13–17}. While earlier GWAS studies used microarray technology, next-generation sequencing has accelerated the rate at which susceptibility genes are discovered. Nearly 30 novel susceptibility genes have been identified using various forms of DNA sequencing in the last five years. Some of these novel genes are listed in Table 2^{18–24} while others were summarized in a previous review²⁵. Examples include variants in the *POLE* gene in colorectal cancer²⁶ or variants in the promoter region of *TERT* in familial and sporadic melanoma²⁷. Furthermore, interactions between genes and the environment continued to be studied to understand how an individual's response to exposure may increase cancer risk, thereby combining exposure- and susceptibility-related research²⁸.

Novel genomic approaches for cancer screening

The unmet need

Currently, in the clinic, cancer screening occupies a prominent role as the mainstay in mitigation of cancer-related mortality. Routine screening is widespread for breast, colorectal and lung cancer. In the United States, breast cancer screening for average risk women commences with annual mammography at age 45. Biennial mammography is offered from age 55 until life expectancy is less than 10 years. Colorectal cancer screening for average risk individuals commences at age 50. While 90% of screening in the United States is performed with colonoscopy at 10-year intervals, there are numerous acceptable screening regimens. These incorporate methods that detect cancer, such as tests of fecal occult blood and tumor-associated DNA, as well as tools that detect both cancer and advanced pre-cancerous lesions, such as colonoscopy, flexible sigmoidoscopy and CT colonography. Lung cancer screening with annual computed tomography (CT) is offered to individuals aged 55–74 years who are at higher risk, primarily based on smoking history²⁹. There is strong evidence that screening saves lives. Mammography is estimated to reduce breast cancer mortality by 20%³⁰. Mortality from colorectal cancer fell by 3% per year in the 2000s, attributed to widespread uptake in screening³¹. In the NLST trial, CT screening reduced lung cancer mortality by 20% over a median 6.5 years of follow up³².

Despite reducing cancer mortality, current screening tools are far from perfect. Their overall major shortcomings are failure to detect clinically relevant cancer early enough to intervene, and conversely, the high rate of false positives and detection of clinically insignificant

cancers. These problems are magnified by the necessity to screen large segments of the population, due to the dearth of clinical tools for nuanced individual risk assessment³³. Applying imperfect screening to the vast “average risk” population creates frequent diagnostic and management dilemmas for physicians, while patients face confusion, anxiety, and harm from unnecessary procedures.

Given the multiple challenges encountered in cancer screening today, what is essential for the screening armamentarium of tomorrow? Fundamentally, physicians and patients need a test that can reliably predict the trajectory of cancer before invasive disease is present, and guide tailored preventive measures by identifying the pre-disposing oncogenic pathways. The imaging and procedure-based screening tools that are now applied to wide swaths of the population can then be applied to targeted at-risk populations, thus retaining their usefulness while minimizing their potential for harm. Genomic data are poised to provide personalized biomarkers of risk and improve screening compliance by providing non-invasive tests. Additionally, genomic data will provide mechanistic insights into the process of early carcinogenesis suggesting novel chemoprevention agents as well as biomarkers to monitor response.

Identification of early precancerous genomic alterations

Genomic profiling provides important insights into the mechanisms that lead to cancer that can ultimately facilitate new avenues for interception. Cancer is thought to proceed through a multi-step process where accumulating alterations in driver genes allow cells to clonally expand and invade surrounding tissues³⁴. A limited number of RNA and DNA sequencing studies interrogating a range of precancerous tissues from the breast^{35–39}, colon^{40–44}, lung^{45,46}, head and neck⁴⁷, skin^{48,49}, and esophagus^{50–55} have indicated that the path to cancer development is context-specific and involves diverse processes. These studies suggest that early lesions are polyclonal and driver mutations present in late-stage disease, and that tumor development occurs via large-scale genomic rearrangements and copy number changes. These findings challenge our conventional wisdom of stepwise carcinogenesis, have implications for the appropriate timing of interception, and underscore the need for additional genomic profiling of precancerous lesions across many tissue types. Many of these studies are cross-sectional and investigate precancerous tissue in the presence of tumor tissue. Increasing spatial and temporal sampling in combination with multiomic approaches will be critical to fully understand the relationships between precancer and cancer. Based on recent recommendations from the NCI Blue Ribbon Panel associated with the Moonshot initiative, the NCI is assembling a precancer genome atlas to develop a national and international roadmap for these types of studies in the future.

By way of example, Barrett’s esophagus is a precancerous condition characterized by metaplasia of the esophageal squamous epithelium. Few cases of Barrett’s esophagus (0.33%/year) progress from non-dysplastic Barrett’s esophagus through low-grade dysplasia followed by high-grade dysplasia (HGD) and subsequent esophageal adenocarcinoma (EAC) development⁵⁶. However, exome sequencing of matched Barrett’s esophagus and esophageal adenocarcinoma (EAC) revealed that 80% of mutations were in common⁵¹. A subsequent study⁵⁷ attempted to assign an ordering of mutations in early disease states by profiling

treatment are largely absent. The recently published Erlotinib Prevention of Oral Cancer (EPOC) study⁶⁵ was the first to use a molecular marker for patient selection in the cancer prevention setting. The randomized, placebo-controlled, double-blind chemoprevention trial used a specific loss of heterozygosity (LOH) profile to select high-risk patients with oral premalignant lesions to take the epidermal growth factor receptor (EGFR) inhibitor, erlotinib, for prevention of head and neck squamous cell carcinoma (HNSCC). Although erlotinib did not improve oral cancer-free survival in these high-risk patients, LOH was validated as a marker of oral cancer risk that can be leveraged in future trials. Recently in 2015, the U.S. Preventive Services Task Force recommended low-dose aspirin use for the primary prevention of colorectal cancer in addition to cardiovascular disease. Aspirin is the first agent to be recommended at a population level, however, a large body of work suggests that mechanistic insights into how aspirin prevents cancer will soon lead to personalized biomarkers for aspirin use⁶⁶. Several new aspirin trials such as ASPIRED⁶⁷ are collecting biospecimens to examine the correlation between aspirin use and the modulation of several cancer-related biomarkers. The potential use of genomic biomarkers of efficacy was shown in randomized phase 2b trial of myo-inositol in smokers with bronchial dysplasia, in which proportions of patients with complete response and progressive disease were not significantly different⁶⁸. In the trial, patients who had achieved a complete response as measured by histological criteria, had alterations in gene expression post-treatment in bronchial epithelial cells, indicating a significant decrease in a previously described gene signature associated with PI3-kinase activity. These findings suggest that the potential efficacy of myo-inositol could be increased through the use of an intermediate genomic marker of therapeutic benefit. These examples indicate the possibilities of personalized chemoprevention as we expand our genomic knowledge of premalignant disease.

An increase in the number of therapies available in the prevention setting requires a combination of an improved understanding of the molecular events that occur in the earliest stages of disease and innovative trial designs incorporating both molecular markers for patient selection and surrogate markers of efficacy. Advancements in understanding the molecular changes that precede the development of cancer will allow increased testing of targeted therapies, immunotherapy, and vaccines based on neo-antigens currently approved or in trials to treat late-stage disease in the prevention setting, if safety profiles (potentially at lower dosages and shorter time periods) are acceptable.

Cancer screening with genomic biomarkers

Genomic data are also being used to address screening challenges, including high false-positive rates and low screening compliance, by providing alternative non-invasive biomarkers. A test approved by the US Food and Drug Administration (FDA), Cologuard[®] (Exact Sciences; Madison, WI, USA), is a multi-target, non-invasive, and accurate stool DNA test for screening of colon cancer. Its use at 3-year intervals provides significant clinical net benefits and fewer complications per life-years gained than annual fecal immunochemical testing, annual high sensitivity guaiac based fecal occult blood testing, and screening colonoscopy every 10 years⁶⁹. The Cologuard test assays for aberrantly methylated *BMP3* and *NDRG4* promoter regions and mutant *KRAS* and includes an immunochemical assay for human hemoglobin and measurement of beta-actin to assess

DNA quantity⁷⁰. The Epi proColon[®] 2.0 test (Epigenomics AG) is another test for colon cancer screening that is blood based and detects hypermethylated *septin 9* in circulating DNA⁷¹. Additionally, plasma-based miRNA signatures have been shown to reduce the false-positive rate associated with low-dose CT screening for lung cancer^{72–74}. One signature that measures 24 miRNAs resulted in a five-fold reduction in LDCT screening false positive rates⁷⁵.

Novel genomic approaches to early cancer diagnosis

The unmet need

Diagnosis of cancer generally requires sampling of tumor tissue. Procedures used to obtain biopsies vary widely in risk and cost, depending on the tumor type. These challenges in obtaining diagnostic tissue from the diseased organ can play a significant role in delaying cancer diagnosis and exposing patients with benign disease to unnecessary invasive procedures. Genomic-based tests have the potential to allow diagnosis of solid tumors from less invasive sites and to accelerate the work-up of patients with suspect cancer.

Genomic biomarkers for cancer diagnosis

We have highlighted the identification of molecular alterations that occur in tissue surrounding precancerous lesions. The presence of a tumor similarly imparts alterations on nearby non-malignant tissues, and these can be leveraged to develop genomics-based biomarkers based on sampling from non-invasive and minimally invasive sites. For example, abnormalities such as *EGFR* mutations and loss of heterozygosity are highest adjacent to the tumor but are present at reduced frequency in the surrounding field of injury. Greater understanding and the ability to detect these signatures would substantially expand the diagnostic target, which would remove the necessity to obtain malignant cells from poorly accessible sites⁷⁶. The power of this approach was illustrated by the gene expression-based diagnostic test, Percepta[®] (Veracyte), measured in the histologically normal bronchial epithelium in the field of injury among ever smokers with pulmonary lesions. This gene-expression based biomarker^{77–79} is able to rule out lung cancer (91% negative predictive value) among intermediate-risk patients with a non-diagnostic bronchoscopic examination, thereby avoiding unnecessary invasive procedures in those with benign lung disease⁸⁰. In a 2017 study, a similar lung cancer detection biomarker was developed in the more readily accessible nasal epithelium using 30 genes⁸¹.

Beyond the field of injury, we are increasingly able to detect tumor cells and their genetic material (cell-free DNA, exosomes, and circulating tumor cells) in blood, using high-throughput genomic technologies. The “liquid biopsy” has been demonstrated in patients with late-stage disease to monitor response to therapy, drug resistance, and cancer recurrence^{82–84}. The FDA-approved CellSearch system, for example, is designed to detect circulating tumor cells in the blood for monitoring of metastatic breast, colorectal, and prostate cancer patients⁸⁵. Recent studies indicate detection of circulating tumor DNA in about 50% of stage I non-small cell lung cancer patients⁸⁶, 36% of early stage small cell lung cancer patients⁸⁷, and between 48 and 73% in patients with localized tumors in colorectal cancer, gastroesophageal cancer, pancreatic cancer and breast adenocarcinoma⁸⁸.

Future improvements in sensitivity and specificity may allow many cancers to be diagnosed with a blood draw. A deeper understanding of the genomic alterations responsible for carcinogenesis will continue to expand targets for early detection and diagnosis.

Genomic biomarkers that predict tumor recurrence

High-throughput technologies also provide oncologists with new tools to predict cancer recurrence. In breast cancer there are several multigene classifiers that predict cancer recurrence, primarily in patients with estrogen-receptor-positive, node-negative breast cancer, including Oncotype DX (Genomic Health; Redwood City, CA, USA), MammaPrint (Agendia; Irvine, CA, USA), PAM50/Prosigna (Nanostring Technologies, Inc; Seattle, WA, USA), EndoPredict (Salt Lake City, UT, USA), and the Breast Cancer Index (Biotherasnostics, Inc; San Diego, CA, USA)⁸⁹. These tests measure the expression of estrogen receptors and proliferation-associated genes and have varying efficacy in predicting recurrence beyond 5-years. Liquid biopsies to identify the extent of surgical resection and the presence of disease relapse in many cancer types including breast, oral, lung, and colorectal cancer are the focus of current research^{73,90–93}. In the case of colorectal cancer⁹⁰, for example, the mutation status of 4 genes (*APC*, *KRAS*, *TP53*, and *PIK3CA*) was identified in colon tumors in 18 subjects and circulating mutant DNA was quantified before and after surgery and at follow-up. Circulating tumor DNA was detectable at follow-up in all cases of cancer recurrence. These studies indicate the potential that liquid biopsies offer to monitor and detect cancer recurrence.

Conclusions

Substantial advances in the treatment of late-stage cancers have occurred over the past decade, highlighted by the durable responses seen in various solid tumors in response to immunotherapy. There is, however, a clear and growing need to develop novel approaches to intercept cancers before their advanced phase. Advances in genomic technologies (including single-cell sequencing) and computational biology have provided us with an unprecedented opportunity to understand the earliest molecular events associated with carcinogenesis and have used this insight to interrupt the development of invasive cancer. We have highlighted a number of promising examples of how large genomic datasets have already begun to alter the landscape of cancer interception.

For the full potential of these genomic approaches to be realized, we will need to overcome many crucial barriers to interception. Arguably, one of the main challenges for this field will be the longitudinal collection and annotation of premalignant tissues from at-risk cohorts. National and international consortia will need to be developed where large numbers of these biospecimens are collected and banked in a manner suitable for genomic analyses. Advances in next generation sequencing of single cells from frozen and paraffin tissue samples (as opposed to fresh specimens) and the computational approaches to analyze these complex datasets will be critical for this initiative to succeed. New preclinical models of premalignant disease will be needed to test the functional significance of genomic alterations seen in these human tissue samples. High throughput screening of potential compounds for chemoprevention using these models will facilitate translation of the genomic signatures into

new prevention strategies. The impact of all these approaches will depend on government-academic-industry partnerships to translate these novel genomic approaches into clinical tools for cancer interception.

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Search Strategy and Selection Criteria

We identified references for this Review through searches of PubMed using the following search terms or combinations of these search terms: “cancer prevention”, “precancerous”, “preinvasive”, “premalignant”, “genomics”, “mutational signatures”, “genetic susceptibility”, “cancer screening”, and “biomarker.” Articles were also identified through searches of the authors’ own files. Only papers published in English between Jan 1, 1995, and December 30, 2016, were included for review. The final reference list was generated on the basis of originality and relevance to the scope of this Review.

Figure 1. Opportunities for Genomics to Impact Cancer Interception

Prior to cancer treatment, there are opportunities for cancer interception in the prevention, screening, and diagnostic settings. Genomic profiling can detect exposure-specific mutational signatures and genetic susceptibility loci to identify high-risk individuals. Genomic profiling of precancerous tissue can identify targets for chemoprevention and biomarkers for risk stratification. For advanced cancer, less-invasive genomic biomarkers can aid in diagnosis and disease monitoring.

Table 1

Overview of genomic approaches used to effect cancer interception

Cancer Prevention		
Relevance	Major findings	Refs
<i>Identification and avoidance of mutagen exposure</i>	Identifies over 20 mutational signatures in 30 tumor types	7
	Aristolochic acid causes a distinct mutational pattern in urothelial cell carcinoma	10
	UV-associated mutational signatures are found in some lung squamous cell carcinomas	11
<i>Selection of high-risk individuals for closer monitoring or prophylaxis</i>	Identified variants associated with susceptibility to prostate cancer using genome-wide association studies	16
	Inherited variants of <i>POLE</i> or <i>POLD1</i> are associated with colorectal adenomas and carcinomas	26
	Inherited variants of <i>TERT</i> are associated with melanoma	27

Cancer Screening and Personalized Prophylaxis		
Relevance	Major findings	Refs
<i>Identification of genomic events associated with early carcinogenesis</i>	High mutational burden exists in Barrett's esophagus, even without dysplasia	50
	Key genomic changes of cutaneous squamous-cell carcinoma found in early precancerous lesions	58
<i>Chemoprophylaxis tailored to and guided by genomic biomarkers</i>	Loss of heterozygosity validated as an oral cancer risk factor in study of candidate chemoprophylactic agent erlotinib	65
	Changes to an airway genomic signature associated with PI3-kinase activity were associated with response to a chemoprophylactic compound in smokers with bronchial dysplasia	68
<i>Improving accuracy of existing screening algorithms</i>	Multiplex DNA colorectal cancer screening test diagnosed more colon cancers than faecal immunochemical testing	70
	Assay of aberrantly methylated DNA in blood as an adjunct to traditional colorectal cancer screening methods	71

Cancer Diagnosis		
Relevance	Major findings	Refs
<i>Minimally invasive diagnosis of cancer incidence and recurrence</i>	Bronchial genomic classifier improved the sensitivity of bronchoscopy for lung cancer detection	80
	Circulating tumor DNA allowed detection of early-stage non-small-cell lung cancer and correlated with tumor volume	86
	Circulating tumor DNA assay outperforms carcinoembryonic antigen testing in predicting recurrence of colorectal cancer after surgery	90
	Presence of circulating tumor cells after chemotherapy for breast cancer associated with poor prognosis	91

Table 2

Cancer susceptibility genes discovered by next-generation sequencing.

Cancer Type	Gene	References
Acute myeloid leukemia	<i>CEBPA</i>	18
Breast carcinoma	<i>FANCM, FANCC, BLM</i>	19,20
Hodgkin lymphoma	<i>KDR</i>	21
Multiple spinal meningiomas	<i>SMARCE1</i>	22
Rosette-forming glioneuronal tumor	<i>PTPN11</i>	23
Waldenström macroglobulinemia	<i>LAPTM5; HCLS1</i>	24