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Integration of Multiple "Omic" Biomarkers: A Precision Medicine Strategy for Lung Cancer

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Abstract

More than half of all new lung cancer diagnoses are made in patients with locally advanced or metastatic disease, at which point therapeutic options are scarce. It is anticipated, however, that the widespread use of Low-Dose Computed Tomography (LDCT) screening, will lead to a greater proportion of lung cancers being diagnosed at an early, operable, stage. Still, the overall rate of recurrence for surgically treated Stage I lung cancer patients is up to 30% within 5 years of diagnosis. Thus, the identification and clinical application of biomarkers of early stage lung cancer is a pressing medical need. The integrative analysis of "omic," clinical and epidemiological data for single patients is a core principle of precision medicine. Through rigorous bioinformatics and statistical analyses we have identified biomarkers of early-stage lung cancer based on DNA methylation, expression of mRNA and miRNA, inflammatory cytokines, and urinary metabolites. Beyond a more comprehensive understanding of the molecular taxonomy of lung cancer, these biomarkers can have very practical implications in the context of unmet clinical needs of early stage lung cancer patients: First, current guidelines for LDCT screening broadly include individuals based on age and history of heavy smoking. Tumor-derived circulating biomarkers in the blood and urine associated with lung cancer risk could narrow and prioritize individuals for LDCT screening. Second, a high number of nodules are identified by LDCT, of which fewer than 5% are finally diagnosed as lung cancer. Biomarkers may help discriminate malignant nodules from benign or indolent lesions. Third, the expected rise in the numbers of lung cancer patients diagnosed at an early stage will necessitate new treatment options. Circulating, urinary and tissue-based biomarkers that molecularly categorize Stage I patients after tumor resection can help identify high-risk patients who may benefit from adjuvant chemotherapy or innovative immunotherapy regimens.

Keywords

Low-Dose Computed Tomography; cytokine; metabolomics; methylation; gene expression; microRNA

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Recent advances in Lung Cancer detection reveal unmet clinical needs

Lung cancer remains the leading cause of cancer-associated deaths worldwide, despite a slow but continuous decline in incidence and mortality in the US and other Western countries over the past two decades [1, 2]. Global variations in lung cancer incidence largely follow historical patterns of smoking, and incidence and mortality rates are still on the rise in Asia and some countries in Latin America and Africa, where the smoking epidemic began later [2]. Most lung cancer patients are diagnosed with locally advanced or metastatic disease, with few therapeutic options and a dismal survival rate. The introduction of innovative therapies targeted to specific molecular alterations continues to improve outcomes for a subset of patients with advanced stage lung cancer [3]. In addition, recent promising results of T cell-based immunotherapy associated high mutational burden in lung cancer patients suggest that exome-guided neoantigen identification may improve treatment responses [4].

When diagnosed at an early, operable stage, the 5-year survival rate from lung cancer climbs above 50% [1]. Cigarette smoking is the major risk factor for lung cancer and other smoking-related diseases [5]. Even as this risk gradually decreases after smoking cessation, former smokers account for most new lung cancer diagnoses. Thus, lung cancer screening efforts have focused on older individuals with a history of heavy smoking. The results of the landmark National Lung Screening Trial (NLST) published in 2011 [6], demonstrated a statistically significant mortality benefit of low-dose computed tomography (LDCT) over chest radiography (CXR) screening in high-risk individuals (defined by age and history of heavy smoking). This evidence and a systematic review of LDCT screening studies [7], prompted the American Cancer Society and other health care organizations to issue guidelines for clinicians to discuss lung cancer screening by LDCT with older patients with a history of heavy smoking, along with smoking-cessation counseling [8, 9].

In early 2015, the Centers for Medicare and Medicaid Services (CMS) made public a decision to cover the cost of lung cancer screening with LDCT for patients at high-risk according to guidelines similar to NSLT eligibility criteria [10]. As a result, the use of LDCT screening is expanding, creating a need for prioritization of the over 9 million individuals who would be eligible for screening under the current guidelines [11]. Non-invasive circulating or urinary biomarkers associated with lung cancer risk, i.e., tumor-derived metabolites, could help prioritize individuals for LDCT screening among those at large high-risk to increase the efficacy of screening and to reduce the cost and morbidity associated with it (Risk biomarkers, Figure 1). The magnitude of the task is compounded by the fact that LDCT scanning identifies a high number of nodules that prompt further, invasive testing but do not result in a lung cancer diagnosis. In the NLST, 96.4% of initial positive screenings were deemed non-cancer on further testing [6]. A recent retrospective study of the clinical management of patients with Intermediate Pulmonary Nodules (IPNs, 8-20 mm) in community practice, found wide variation in nodule management that led to a high number of unnecessary invasive procedures [12]. Thus, there is a need for non-invasive biomarkers that can help discriminate malignant nodules from benign or indolent lesions (Diagnostic biomarkers, Figure 1). Up to 60% of lung cancers detected by LDCT in the

NLST were Stage I, primarily adenocarcinoma histology [6]. With the projected rise in LDCT screening [13], a shift in the stage at diagnosis, towards early, operable disease is expected. The recommended treatment for patients with Stage I Non-small-cell lung cancer (NSCLC) is surgery, which may be followed by chemotherapy in patients with pathologically high-risk, margin-negative Stage IB tumors [14]. Still, up to 30% surgically-treated Stage I patients will die from recurrent disease [15]. Non-invasive or tissue-based biomarkers that molecularly categorize Stage I patients after tumor resection and identify those at high-risk for recurrence could lead to improved clinical management (Prognostic biomarkers, Figure 1). High-risk patients may benefit from adjuvant chemotherapy or innovative checkpoint immunotherapy, while low-risk patients might safely be spared further treatment and instead be followed by surveillance LDCT. In summary, we will discuss three critical needs in early stage lung cancer: 1. To prioritize high-risk individuals for screening by LDCT (screening); 2. To assess the malignant potential of IPNs to reduce overdiagnosis and unnecessary surgery (diagnosis); 3. To identify Stage I patients at high risk of recurrence (prognosis).

Biomarkers in Precision Medicine

Biomarker discovery and validation are main components of the precision medicine strategy (Figure 2). The precision medicine approach, first outlined in the 2011 report from the National Research Council [16], includes four basic premises. First, a disease Information Commons is populated with comprehensive measurements of various types of molecules from individual patients (collectively referred to as “-omic” data). This multi-layer reservoir of molecular data may include global analysis of the exposome, genome, epigenome, transcriptome, metabolome, proteome and microbiome, as well as clinical and epidemiological information. Second, these data are integrated into a Knowledge Network that examines the interconnectivity across data layers from the Information Commons. Third, this Knowledge Network is used to develop new molecular classifications of disease. The ultimate goal of these new Taxonomic Classifiers is to refine risk assessment, more precisely diagnose patients, and make informed decisions on therapeutic strategies. Finally, this knowledge is used to inform biomedical research, preventive care, and clinical medicine and to fuel relevant mechanistic and observational studies. Progress is based on iterative process of acquiring information in individuals or cohorts of patients, making improvements in taxonomy and utilizing that knowledge to care for patients and design new studies that further feed the Information Commons. This approach has come to the forefront with the recent announcement of the oncology “precision medicine” research initiative by the National Institutes of Health [17]. The just-launched NCI-MATCH (Molecular Analysis for Therapy Choice) trial is an example of a precision oncology clinical trial that aims to evaluate the extent to which treating cancers according to their molecular abnormalities will be able to improve patient outcome [18]. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) [19] applies this concept to the treatment of patients with early-stage non-squamous NSCLC, while feeding back into the Information Commons through comprehensive genomic analysis.

Although the field of biomarker research has for years operated within a similar framework as outlined by the precision medicine approach, the more recent focus on high-dimensional

"-omic" data as a source for disease markers has brought with it a new set of analytical and clinical validation challenges [20]. As the number of features measured greatly exceeds the number of samples, analytical strategies have had to evolve to avoid over-fitting of the models and ensure that biomarkers are widely applicable beyond the sample cohort used to generate them. A set of recommendations has been put forward by the Institute of Medicine to guide the translation of omics-based biomarkers into clinical tests [21]. At the Discovery Phase, biomarkers should be confirmed in a set of samples that is independent from that in which the original discovery was made. The primary data and computational procedures should be fully disclosed and the derived algorithms should be defined precisely. At the Validation Phase, it is recommended that the candidate omics-based test and its intended clinical use be discussed with the US Food and Drug Administration (FDA) and that validations are conducted under Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory standards. Evaluation for clinical utility requires close consultation with FDA and a fully defined, validated and locked-down test [21]. To date, no molecular biomarkers that identify individuals for priority screening or facilitate the assessment of IPNs or prospectively identify lung cancer patients at a high risk of recurrence after surgery have been successfully translated into clinical use, although several are at advanced stages of development [22-33].

A strategy to identify OMICS-based biomarkers with potential clinical utility

A strategy for biomarker discovery and validation is outlined in Figure 3. Briefly, a cohort (nested case-control or case series) of sufficient size and with well-curated epidemiological and clinical data is the starting point for comprehensive profiling studies. Measures of association with presence of disease or disease outcome are utilized to select candidate biomarkers. This rigorous assessment requires evidence for statistically significant risk separation as well as improved predictive value over known risk factors, including age and smoking. A candidate biomarker that passes this threshold is then validated internally in the same patient cohort using a secondary, targeted assay, such as quantitative RT-PCR (qRT-PCR) or pyrosequencing, to avoid platform-specific biases. This step also allows the development of an assay that may be more easily adaptable to a large number of samples, compared to the initial comprehensive profiling platform. When possible, we recommend focusing on assays that can be developed within CLIA standards, with a vision of future clinical deployment. To demonstrate robustness, the biomarker is further evaluated in at least one completely independent cohort. Selection of this cohort also takes into account important factors associated with lung cancer that may affect the broad applicability of the biomarker, such as patient ethnicity and history of smoking. A fully specified assay and associated computational procedures emerges from this validation and is ready for further evaluation in other cohorts, such as publicly-available microarray cohorts, in the case of gene expression-based signatures, or prospectively collected samples, for biomarkers of risk. Ultimately, the clinical utility should be tested in the context of a prospective clinical trial.

Based on the unmet needs for management of early stage lung cancer patients, we have investigated non-invasive, blood- and urine-based biomarkers as well as tissue-based biomarkers (Table 1). These encompass various types of molecular data for single patients.

When combined, they may aid patient stratification into risk categories and for cancer diagnosis and treatment, and generate hypothesis that illuminate biology.

Cytokines

Together with our collaborators, we have investigated whether circulating markers of inflammation, such as pro-inflammatory cytokines and C-reactive protein, are predictors of lung cancer diagnosis and prognosis [34-37]. Discovered in the NCI-MD case-control study and validated in the NCI's Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, increased levels of IL-6, CRP and IL-8 were associated with lung cancer diagnosis. Significantly, IL-8 levels were elevated up to 5 years before lung cancer diagnosis, suggesting their potential use in screening [35]. Moreover, a combined IL-6 and IL-8 prognostic classifier was associated with poor outcome in stage I lung cancer patients. Using the PLCO prospective sample cohort, we investigated the relationship between serum cytokines and risk of mortality. Combining IL-8 and IL-6 was a superior prognostic classifier than IL-8 or IL-6 alone. In addition, this classifier was associated with survival in stage I lung cancer patients, and in those with ≥ 30 pack-years of smoking (the relevant patient demographic targeted by LDCT screening) [36]. Specific inflammatory profiles were also associated with risk of lung cancer in African Americans and in European Americans [37]. This latest study underscores the fact that risk prediction models may need to account for racial and other differences in biomarker profile.

Metabolomics

Global and targeted metabolomics studies using mass spectrometry in > 1,000 urine samples from the NCI-MD case-control study, uncovered a set of urine metabolites associated with lung cancer diagnosis and prognosis [38]. Novel and previously un-annotated creatine riboside (CR), and N-acetylneuraminic acid (NANA), were each significantly elevated in the urine of lung cancer patients and associated with worse prognosis. Results were validated in an independent sample set comprising more recently diagnosed cases and further confirmed by quantitation. Both metabolites were enriched in tumor tissue compared with adjacent nontumor tissue, and positively correlated with levels in urine, thus revealing their direct association with tumor metabolism [38]. Recent evaluation of this panel of urinary metabolite lung cancer biomarkers in the well-characterized prospective Southern Community Cohort Study (SCCS) has confirmed the association of CR and NANA levels with lung cancer risk prior to clinically detectable disease [39].

Tissue-based biomarkers

The identification of tissue-based biomarkers has recently been focused on the prognostic value of biomarkers derived from resected lung adenocarcinoma tissues. Many prognostic signatures based on gene expression have been developed but most of them have failed to validate in larger patient cohorts [40]. We have addressed this limitation by validating our classifiers in independently-collected cohorts from populations of diverse ethnicity and smoking habits. We also clearly defined the aim of the prognostic signature within the clinical context of our study as identifying Stage IA patients at high risk for recurrence who might benefit from adjuvant chemotherapy and/or immunotherapy, and Stage IB patients at low risk for recurrence who could be spared [41]. With this goal, we have conducted

comprehensive profiling of the transcriptome, microRNAome and DNA methylome of tissues collected in three independent NCI-MD, Norway, and Japan cohorts of patients, and identified and validated prognostic biomarkers based on expression of genes and microRNA, as well as DNA promoter methylation [42-46]. Increased miR-21 expression is associated with disease progression and survival in patients with stage I adenocarcinoma [43]. An amplification peak encompassing *MIR21* was also recently described by The Cancer Genome Atlas in lung adenocarcinomas [47]. Focusing on genes with a mechanistic role in lung cancer, we discovered, defined and validated a prognostic classifier based on the expression of 4 genes: BRCA1, HIF1A, DLC1, and XPO1 that could stratify stage I, stage IA and stage IB lung adenocarcinoma patients into high and low-risk groups [44]. This 4-gene classifier has been further validated using gene expression values derived from over 1,000 Stage I lung adenocarcinomas from a variety of publically available microarray datasets [44, 45]. Genome-wide screening of DNA methylation in early stage lung adenocarcinoma samples from the NCI-MD case cohort led to the discovery of the prognostic value of HOXA9 promoter methylation, which was further technically validated by pyrosequencing analysis [46].

Large scale characterization of the lung adenocarcinoma genome, transcriptome and methylome has revealed disease subtypes characterized by idiosyncratic combinations of molecular alterations which underscore the heterogeneity of this disease [48]. This implies that any one molecular biomarker may correctly classify tumors as high-risk based on a particular underlying biology, but misclassify others driven by a different set of genomic or epigenomic changes. Thus, in our recent study, we hypothesized that statistical independence would be required for multiple biomarkers to provide incremental improvement in patient stratification [46]. Upon statistical verification that the 4-gene classifier, miR-21 expression, and HOXA9 promoter methylation were each independently associated with outcome (HR, 2.8; $p = 0.002$; HR, 2.3; $p = 0.01$; and HR, 2.4; $p = 0.005$, respectively), we further demonstrated in that study that these biomarkers could be combined into a simple score that identified high-risk, therapy näive, stage I patients (HR, 10.2; $p = 3 \times 10$) [46]. Such integrative analysis of “omic,” clinical and epidemiological data is a core principle of precision medicine. A practical consideration, however, is whether the benefit of combining several biomarkers supports the logistical burden of running multiple tests. Most recurrences in resected stage I lung cancer patients occur within 3 years of surgery [49]. In our study [46], the combined miR-21/4-gene transcriptomic signature correctly identified as high-risk 68% of the patients who recurred or died within 3 years. The addition of HOXA9 promoter methylation into a combined score resulted in correct identification of 78% of high-risk patients. Thus, the extra effort required to add DNA-based biomarker to an existing RNA-based signature may result in better management of resected patients.

OMICs-based diagnostic and prognostic lung cancer biomarkers in advanced clinical development

Targeted and comprehensive profiling technologies have been employed in numerous studies to identify and measure early detection and prognostic lung cancer biomarkers in a variety of

biospecimens (tumor tissue, blood, urine, sputum, nasal swabs, bronchial brushings). The vast majority of prognostic biomarkers derive from comprehensive molecular analysis of mRNA, miRNA and DNA methylation in resected tissues, whereas, the identification of early detection or diagnostic biomarkers relies on the evaluation of surrogate tissues, such as nasal swabs or bronchial brushings, or, most commonly, biofluids, such as blood or urine.

The following omics-based tests have recently become commercially-available and are being clinically evaluated:

Pervenio Lung RS (14-gene signature)

This 14-gene signature was developed on formalin-fixed and paraffin-embedded (FFPE) non-squamous NSCLC tissue samples, using genes identified as prognostic for early stage lung cancer in prior profiling studies [50]. A subsequent study assessed the analytical validity of the assay by evaluating its precision and reproducibility in 2 large international cohorts [51]. A clinical trial to evaluate benefit of adjuvant therapy in high risk stage I non-squamous NSCLC identified by the signature has been initiated (NCT01817192 at www.clinicaltrials.gov) [24]. The test is marketed by Pinpoint Genomics/Life Technologies Corporation (West Sacramento, CA, USA).

myPlan Lung Cancer (CCP score)

This gene signature summarizes the expression of cell cycle proliferation (CCP) genes, originally identified in microarray profiling cohorts, into a score that utilizes FFPE lung adenocarcinoma tissues to predict lung cancer death in resected patients [52]. Subsequent studies tested the analytical validity of the assay [53], and the clinical utility of a prognostic score that takes into account pathological stage [30]. Two registries intended to measure the effect of using this test on treatment decisions by oncologists and surgeons and assess disease-free patient survival have been opened (ONC006 and ONC003, for Oncologists and Surgeons, respectively, at www.clinicaltrials.gov). The test is marketed by Myriad Genetics, Inc. (Salt Lake City, UT, USA).

Other omics-based tests with evidence of clinical utility include:

Percepta (bronchial genomic classifier)

A classifier based on the combination of expression of 17 cancer genes in airway epithelial cells of current and former smokers undergoing bronchoscopy for suspect lung cancer, as a diagnostic aid to reduce invasive procedures [33, 54].

MSC (microRNA Signature Classifier, plasma microRNA signature)

A classifier based on expression in plasma of a panel of microRNAs that stratifies smokers according to the risk to develop lung cancer (high-intermediate-low risk) and improves the efficacy of lung cancer screening by reducing the number of LDCT false positives [27, 55].

miR-Test (serum microRNA signature)

A diagnostic test for lung cancer based on expression of a panel of microRNAs in serum which can identify patients with cancer among those at high-risk who are candidates for LDCT screening [31, 56].

Proteomic plasma test

A diagnostic test based on a multiprotein plasma classifier that can identify likely benign nodules discovered by lung cancer screening [32, 57].

New directions

Biomarkers of response to Immunotherapy

A recent report indicated that tumor-infiltrating lymphocytes (TILs) have prognostic value for stage I in lung cancer patients [58]. We have discovered that the endogenous p53 isoforms Δ133p53 and p53β are physiological regulators of proliferation and senescence in human T lymphocytes in vivo [59]. In that study, CD8+ T lymphocytes associated with human lung tumors harbored senescent cells characterized by a distinct profile of p53 isoforms and surface markers. In light of the efficacy shown in advance stage lung cancer patients of novel therapeutic strategies that modulate the immune system [60, 61], it is imperative to understand how the immunogenic milieu affects lung cancer prognosis and response to therapy. For example, molecular pathways that affect senescence of TILs could be modulated to oppose tumor-induced T cell exhaustion and increase the effectiveness of checkpoint immunotherapy in lung cancer patients.

Prognostic biomarkers of early-stage lung squamous cell carcinoma

Despite an increase in the detection of early stage tumors, there was no benefit of LDCT screening for patients with lung squamous cell carcinoma (SCC) [62], the second most common histological subtype of NSCLC. Further, data are still lacking on molecular signatures that stratify risk of recurrence in these patients. The relative risk for SCC is increasingly higher with cumulative exposure to cigarette smoke [63]. The disease is heterogeneous, and patient outcome is complicated by comorbities such as Chronic Obstructive Pulmonary Disease and Cardiovascular Disease [64]. At the recent Fourth AACR-IASLC International Joint Conference on Lung Cancer Translational Science from the Bench to the Clinic, which was held in January 4-7, 2016 we unveiled a prognostic classifier based on gene expression that is broadly applicable to diverse patient cohorts as a clinical tool for guiding postoperative management and therapeutic decisions in patients with early-stage lung SCC [65]. Efforts towards analytical validation of this signature are ongoing.

Microbiomic biomarkers of lung cancer

There is strong epidemiological evidence that pulmonary infections are associated with increased risk of lung cancer lung cancer [66, 67]. The Human Microbiome Project revealed that a microbiota of astonishing diversity and abundance resides in healthy human tissues [68]. This has enabled and propelled the characterization of the contributions of microbial

species harbored in humans, collectively referred to as Microbiome, to a variety of diseases, including cancer. Studies of microbial species altered in the respiratory track in individuals with lung cancer are now starting to emerge [69, 70]. Thus, the microbiome may be a suitable source for clinical biomarkers of lung cancer risk, diagnosis and prognosis.

Proteomic biomarkers of lung cancer

Recent advances in mass spectrometry-based proteomics technologies are facilitating the quantitative analysis of lung tumor-derived proteins and peptides in tissues, pleural fluids, and blood [71, 72]. These represent candidate diagnostic, prognostic, and predictive markers for lung cancer. Mass spectrometry analysis of serum collected from patients with advanced NSCLC before and after treatment with tyrosine kinase inhibitors led to a test that predicts treatment response [73], and evidence for its clinical utility is accumulating [74].

Radiomics-based biomarkers of lung cancer risk, diagnosis and prognosis— Images obtained non-invasively in the course of diagnosis and treatment of cancer patients can provide a wealth of data that can be systematically captured, mined and interpreted as another layer of the precision medicine [75, 76]. Recently, advanced computational methodologies were applied to the analysis and interpretation of features extracted from CT scans of lung cancer patients to derive a prognostic signature [77, 78]. Imaging-based biomarkers are now being evaluated for performance in risk stratification of lung cancer patients diagnosed by LDCT [79] as well as ability to predict the malignancy of IPNs [80]. Improvements in the identification of diagnostic and predictive quantitative imaging features extracted from data and images from the NLST, were also described at the Fourth AACR-IASLC International Joint Conference on Lung Cancer Translational Science [81].

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Highlights

- Biomarkers are needed to prioritize high-risk individuals for lung cancer screening.
- Biomarkers derive from integrative analysis of molecular data for single patients.
- Validated biomarker combinations may aid patient diagnosis and risk stratification.

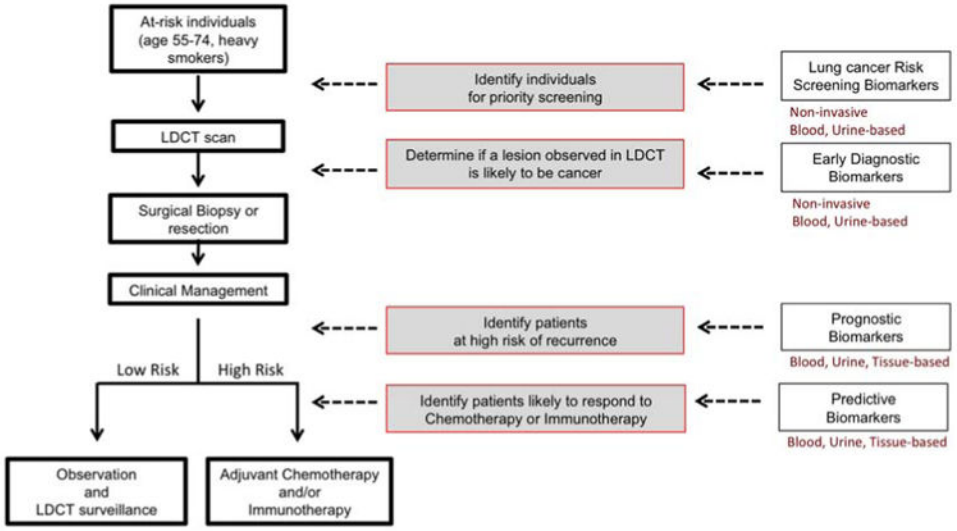

Figure 1.

Early stage lung cancer unmet needs. Screening, diagnostic, prognostic and predictive biomarkers can inform clinical decisions.

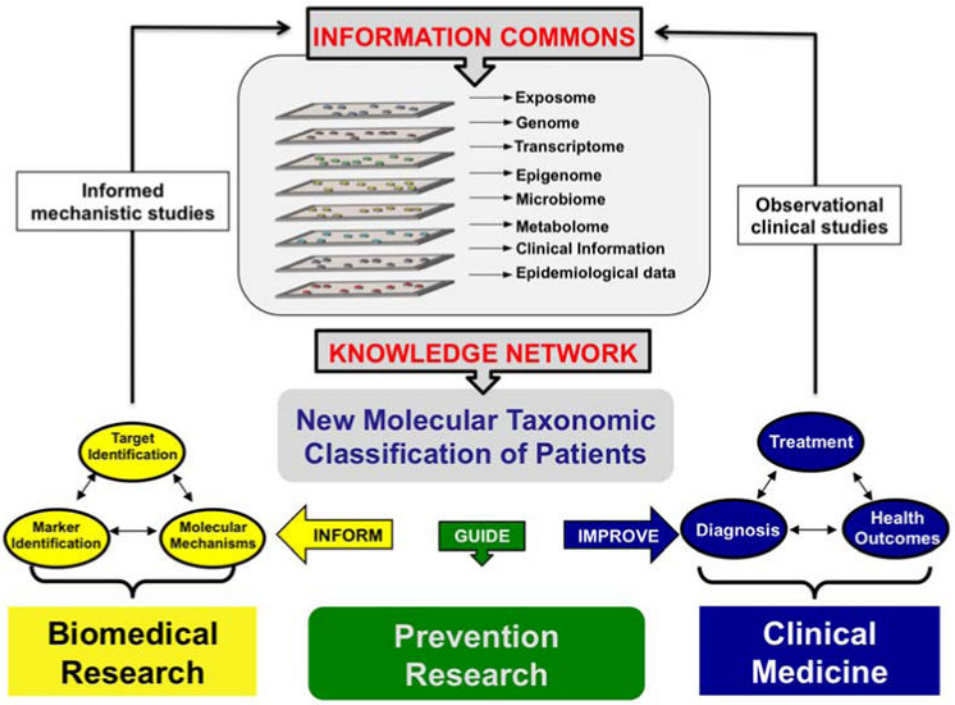

Figure 2.

A Precision Medicine research strategy. Modified from *Toward Precision Medicine*: *Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* [16]. Precision Medicine starts with the creation of an Information Commons that interactively houses multiple "-omics" data types along with historical exposure and lifestyle information from individual patients. Bioinformatic integration of these data will lead to the development of a Knowledge Network that will be used to improve disease taxonomy, the application of clinical medicine and the study of molecular mechanisms of disease. An iterative process of acquiring information on individuals or cohorts of patients, making improvements in taxonomy and utilizing that knowledge to care for patients and design new studies that further feed the Information Commons will refine the molecular taxonomic classifiers and improve clinical medicine.

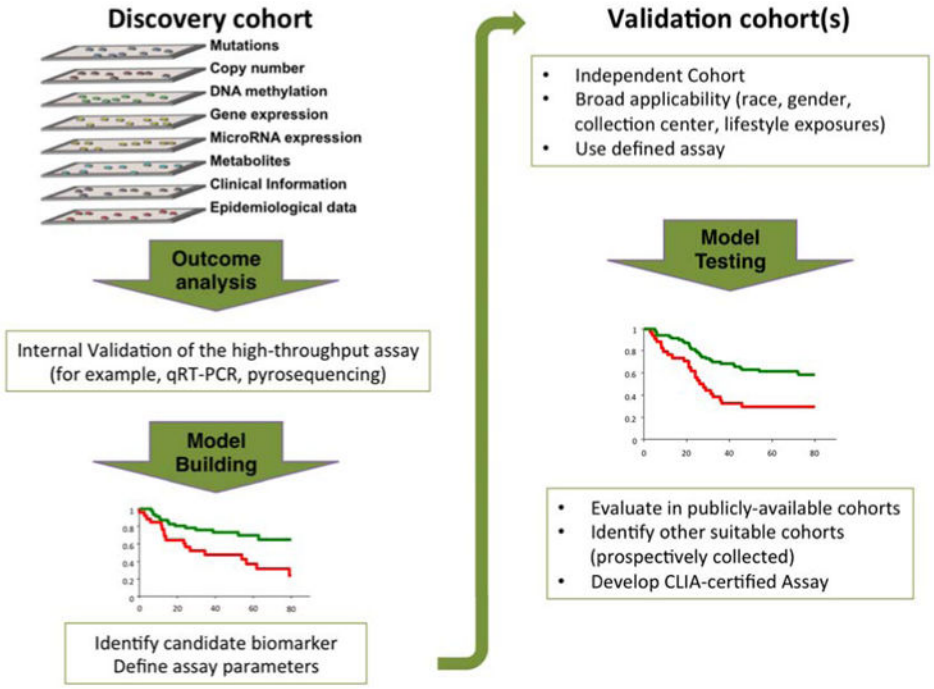

Figure 3.
A strategy to identify biomarkers with clinical utility.

Table 1
Biomarkers of early stage lung cancer risk, diagnosis and prognosis

	Specimen	Training set	Validation set	References
Prognostic (Case Studies)				
mRNA-4gene	RNA (frozen tissue)	Japan (n=149)	NCI-MD/Norway (n=67)	[43, 44]
miRNA	RNA (frozen tissue)	Japan (n=149)	NCI-MD/Norway (n=67)	[42, 43]
Methylation	DNA (frozen tissue)	NCI-MD/Norway (n=99)	Japan (n=113)	[45]
Metabolomic	Urine	NCI-MD (n=469)	Study ongoing	[38]
Cytokine	Serum	NCI-MD (n=67)	PLCO[a] (n=548)	[34, 36]
Diagnostic (Case-Control Studies)				
Metabolomic	Urine	NCI-MD (n=1,005)	SCCS[b] (n=534)	[38, 39]
Cytokine	Serum	NCI-MD (n=566)	PLCO[c] (n=1127)	[35, 37]
Risk (Prospective Studies)				
Metabolomic	Urine	SCCS (n=534)		[39]
Cytokine	Serum	PLCO[c] (n=1127)		[35, 37]

[a] Case series nested within prospective Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

[b] Case-control series nested within prospective Southern Community Cohort Study (SCCS).

[c] Case-control series nested within PLCO Cancer Screening Trial.