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Beyond SNPs—genetics, genomics and other 'omic approaches to ARDS

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Abstract

This article summarizes the contributions of high throughput genomic, proteomic, metabolomic, and gene expression investigations to our understanding of inherited or acquired risk for acute respiratory distress syndrome (ARDS). While not yet widely applied to a complex trait like ARDS, these techniques are now routinely employed to study a variety of disease states. Omic applications hold great promise for identifying novel factors that may contribute to ARDS pathophysiology or may be appropriate for further development as biomarkers or surrogates in clinical studies. Opportunities and challenges of different techniques are discussed, and examples of successful applications in non-ARDS fields are used to illustrate the potential utility of each technique.

Keywords

Acute respiratory distress syndrome; Genomic; Proteomic; Metabolomic; Gene expression; Complex trait

Acute respiratory distress syndrome (ARDS) inflicts considerable morbidity and mortality among critically ill patients and lacks any specific pharmacologic therapy.[1,2] Because clinical factors alone fail to explain which patients with ARDS risk factors will develop the syndrome, or to accurately predict which patients will die as a result of ARDS, there is great interest to understand whether one could leverage new biologic techniques to better characterize risk and prognosis. With major advances in the fields of genomics, mass spectroscopy, and bioinformatics, there are numerous approaches that can now be applied to a complex trait like ARDS, yet the benefit of these is uncertain (Table 1). The goal of this paper is to review the state of knowledge of genetic contributions to ARDS risk and mortality, to briefly review broader applications of genomics to ARDS pathogenesis, and to consider examples from non-ARDS fields whereby genomic approaches have yielded major advances. Applying similar approaches to ARDS may deepen our understanding and offer new therapeutic paradigms for patients with ARDS.

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Shifting the Paradigm: What can genomics teach us about a trait like ARDS?

Many investigators associate the word genomic with inherited conditions that obviously cluster among families. Because there are no reported families in whom ARDS has affected multiple members, one might conclude that genomics would offer little to our understanding of ARDS. However, an alternative perspective is to consider ARDS as a pattern of response to injury, be it pneumonia, sepsis, or trauma. As a trait, the response to injury has significant heritability.[3–7] In fact, death from infection was the most heritable condition when studied in a large Danish registry of adoptees, with a much stronger heritability than vascular disease or cancer.[8] Rather than acting as monogenetic, or Mendelian, traits, whereby a single genetic variation explains the bulk of the observed phenotype, ARDS risk and severity are likely influenced by multiple genetic variants that each contribute to a modest degree. Small effect sizes of each contributing gene variant mandate large study populations for detection. In addition, ARDS is ripe for the utilization of intermediate traits and the identification of endotypes, or subtypes, which may demonstrate a more homogeneous genetic background.

Surveying the Landscape of ARDS Genomics

Numerous candidate gene association studies have been reported in ARDS, and several reproducible associations have emerged. While a complete review of the genetic associations with ARDS risk or ARDS mortality is beyond the scope of the present review, comprehensive reviews recently have been published.[9–11] The best replicated genetic variants for ARDS risk represent our present understanding of ARDS pathophysiology; pro- and anti-inflammatory cytokine gene polymorphisms are well represented (*IL6, IL10, IL1RN, MBL2*),[12–18] as are vascular injury markers (*VEGFA, ANGPT2, ACE, MYLK*),[19–24] innate immunity pathway members (*IRAK3, TLR1, NFKB1, NFKBIA, FAS, PI3*),[5,25–28] and markers of respiratory epithelial injury (*SFTPB*).[29,30] While each of these associations has been associated with ARDS risk or outcome in at least 2 populations, none influences ARDS risk or severity to a degree that warrants genetic testing of at-risk populations. Instead, the main contribution of ARDS genetic associations to date has been to focus attention on molecular pathways at play in causing or perpetuating the syndrome.

Further, it is tempting to speculate that genetic associations may highlight potential therapeutic targets to either prevent ARDS or to improve outcomes once it has developed. For example, the association of variants in the angiopoietin-2 gene (*ANGPT2*) with ARDS risk in mixed ICU population and trauma populations,[22,23] coupled with strong animal evidence that antagonizing angiopoietin-2 protein (ANG2) or augmenting its counterpart, angiopoietin-1 (ANG1), results in decreased mortality[31–34] suggests that it may be helpful to block this protein in humans at risk for ARDS. Given numerous failed trials to prevent or treat ARDS, however, it may be that investigators should seek a molecular marker, such high ANG2 plasma protein level or carriage of an *ANGPT2* genetic variant, to enrich a clinical trial population for subjects likely to respond. A similar case could be made for the use of human neutrophil elastase (hNE) inhibitors, already used in Japan to treat ARDS albeit with scant evidence of efficacy,[35–37] since the gene pre-elafin (*PI3*) has evidence for 1)

dysregulation among patients who fail to resolve ARDS,[38] 2) functional promoter variants that associate with ARDS,[27,28] and since 3) plasma levels of its gene product elafin are reduced in ARDS patients.[39] Perhaps patients with low elafin levels or high hNE activity would be more likely to respond to hNE inhibitors. The angiotensin converting enzyme (ACE) gene also may suggest a therapeutic strategy, as *ACE* gene variants that increase ACE1 levels have been associated with ARDS mortality,[24,40–43] and the counterregulatory ACE2 enzyme seems to decrease lung injury.[44,45]

ARDS enters the Genomic Age

The earliest contributions of genomics to our understanding of ARDS successfully leveraged animal models, quantitative traits, and bioinformatics. Grigoryev and colleagues used bioinformatic approaches to find overlap in the gene expression, or messenger RNA (mRNA) levels from human cells or animal lung tissue subjected to repeated mechanical stress or models of ventilator-induced injury. Orthologues, or genes with common structure and function across different species, that behaved in a reproducible manner across numerous models of injury were subsequently investigated through mouse knockout models or gene silencing. In this manner, Ye and colleagues identified pre-B cell colony enhancing factor (PBEF), also known by the gene name *NAMPT*, as a regulator of inflammatory cytokines which in turn cause epithelial and endothelial permeability.[46–48] In addition, independent groups have now replicated the association between promoter variants in *NAMPT* and the development of ARDS.[49] New candidate genes can also arise from screening multiple rodent species for differential susceptibility to lung injury, as Leikauf and colleagues performed using inhalational injury models.[50–52] When translating animal and *in vitro* work to human populations, however, the choice of experimental model is highly relevant. Dos Santos and colleagues demonstrated that the gene expression response to ventilator-induced lung injury is distinct from endotoxin models of sepsis,[53] which is consonant with findings in human populations that gene variants associated with ARDS may be specific to ARDS risk factor.[54]

In the first published human genome-wide association study (GWAS) for ARDS susceptibility, Christie and colleagues identified a novel locus, *PPFIA1* or liprin alpha, as a replicable risk factor for ARDS following trauma.[55] While little was known about how liprin alpha would contribute to lung injury at the time of discovery, subsequent work has implicated liprin alpha as a binding partner and downregulator of Mammalian homolog of Diaphanous (mDia), a Rho effector that mediates stress fiber formation.[56] Just as nonmuscle myosin light chain kinase is a critical regulator of the endothelial cytoskeleton with implications for ARDS,[57,58] liprin alpha may also prove to have relevance for barrier enhancement.

As future GWAS are published, new candidates will undoubtedly emerge and meta-analysis will be possible to harness the power of multiple populations. At the same time, however, GWAS may prove more fruitful if the heterogeneity of ARDS is acknowledged *a priori*, and analyses are conducted within more homogenous subtypes. For instance, Tejera and Christiani demonstrated that the genetic risk factors for extrapulmonary ARDS and pulmonary ARDS were distinct,[54] a finding echoed by most reviews.[9,41] In addition to

ARDS precipitant, factors such as ancestry,[12] gender,[59] age or comorbidity[17] may be important. Furthermore, given the notable heterogeneity of ARDS, there are almost certainly additional subtypes that may become apparent with additional data, as elegantly proven by Calfee and colleagues applying latent class analysis to 2 populations from the NHLBI ARDS network.[60] Since the unbiased model suggested 2 classes of patients with ARDS, one characterized by higher inflammatory cytokine plasma levels, lower plasma bicarbonate, and a tendency for shock, and as the 2 subclasses had dramatically different outcomes and response to a high positive end-expiratory pressure, it may be that leveraging GWAS within each subclass would yield important insights about processes driving each type of ARDS.

Advances from Gene Expression

In addition to the animal studies mentioned above, several human investigations have explored the utility of gene expression to identify novel candidate genes in ARDS. Gene expression analysis can be very advantageous, since the output of the analysis is a quantitative trait which offers strong statistical power relative to a dichotomous trait like the presence or absence of ARDS. In addition, because mRNA reflects the mature transcript that will be translated into protein, changes in transcript abundance are likely to be functional and thus offer strong evidence for involvement in a trait. Finally, multidimensional analysis of global gene expression changes are possible using microarray technology, whereby a small amount of starting mRNA can be assessed for roughly 20,000 transcripts simultaneously. This technique is not only a very efficient way to assess gene expression level, but also allows multidimensional analytic strategies to define patterns of expression. Two general types of analyses can be performed: a supervised, or hierarchical analysis, in which samples are assigned to their class by the investigator, or an unbiased or machine learning analysis, whereby the analysis seeks to detect unobserved patterns from unlabeled data. An early example of the hierarchical analysis involved the demonstration that gene expression changes between acute myelogenous leukemia (AML) bone marrow mononuclear cells were distinct from acute lymphogenous leukemia (ALL) cells.[61] A subsequent group performed a similar genome wide expression analysis of ALL blast cells in an unsupervised manner, identifying 6 major molecular subtypes that reflected different biological mechanisms and suggested differential response to treatment.[62] Expression patterns of specific factors in tumor tissue are now routinely assayed in both hematolgic and solid organ malignancies in an effort to personalize therapy.[63,64]

Research in ARDS transcriptomics is hampered by the lack of available lung tissue upon which to perform microarray analysis, since only the minority of patients – less than 10% – progress to lung biopsy.[65] Without lung tissue, most investigations have relied upon gene expression of either specific blood cell populations or white blood cells collected from whole blood. While whole blood is a relatively convenient way to sample RNA, this collection method may introduce variability and will never reflect the expression pattern of lung endothelium or epithelium, since gene expression is cell-specific (Figure 1).[66] In one of the first descriptions of applying microarray technology to human ARDS, Howrylak and colleagues reported the global whole blood gene expression of 13 patients with sepsis and ARDS compared to 20 with sepsis alone, and reported that differential expression of 8

transcripts distinguished patients with ARDS.[67] The most dysregulated transcript encoded for the heavy subunit of ferritin, which is interesting given the role of iron in catalyzing reactive oxygen species (ROS) and the potential contribution of ROS towards lung injury.[68–71] A novel approach was applied by Wang and colleagues to compare the whole blood gene expression profile of patients during acute ARDS and convalescence, which allowed for each patient to be her own control and to filter much of the background variability between expression across individuals. Using this approach, the investigators identified the peptidase inhibitor 3 gene *PI3*, encoding elafin, as downregulated in ARDS.[38] Functional promoter variants in *PI3* associate with lower cytokine-induced transcriptional activity and greater sepsis-associated ARDS, potentially acting through more durable binding of pre-elafin to extracellular matrix proteins.[27]

To date, there has been no large systematic application of gene expression in human samples with ARDS. Furthermore, it remains unclear whether the signature obtained from whole blood or from circulating leukocytes will provide relevant answers for a condition of alveolar epithelial and endothelial dysfunction. While questions remain about the suitability of studying whole blood to gain insights into a lung-centric condition, advances have been made by applying this approach in sepsis, generally considered a systemic vascular disorder. Wong and colleagues performed unbiased clustering analysis to whole blood gene expression of approximately 100 septic children and identified 3 subclasses that correlated with differential mortality.[72] The highest mortality subclass was characterized by significant downregulation of genes annotated to glucocorticoid signaling, the adaptive immune system, and zinc-related biology. The investigators were able to extend their findings by analyzing the secreted protein products of some of the most dysregulated genes in the high-mortality group, resulting a 5-biomarker decision tool that reliably identifies a higher risk group for death when applied to both children and adults with septic shock.[73,74] Thus, despite limitations of whole blood or even leukocyte gene expression to inform about lung tissue expression, large scale peripheral blood gene expression may yield advances in ARDS.

Untapped potential: transcriptomics of the future

While the field of transcriptomics to date has been dominated by microarray studies quantifying mRNA, the transcriptome encompasses all forms of RNA, including transfer RNA, ribosomal RNA, and many forms of noncoding RNA. The science of noncoding RNA molecules has exploded in the past 10 years, with the identification of multiple new classes of non-protein coding entities[75] and emerging understanding of their complex roles in regulating gene expression.[76] Advances in next generation sequencing capabilities, coupled with improved bioinformatic support and efficiencies of scale have fueled high throughput sequencing of RNA in both targeted and genome-wide approaches.[77] Because the technology of RNA sequencing is so nascent, there are few published reports applying these methods to a complex trait like ARDS. However, applications of RNA-seq to cancer and cardiovascular traits may exemplify useful approaches for the future. MicroRNA, or miRNA, only described in 1993,[78] are now understood to be small, roughly 22-nucleotide RNA sequences that typically bind the 3’ untranslated region of target mRNA and inhibit translation or promote mRNA degradation.[79,80] Candidate genes influencing ARDS, including *MYLK* and *PBEF/NAMPT*, are regulated by miRNA[81,82] which raises the

possibility that engineered miRNA or their antagonists may be a therapeutic strategy in the future. In cancer, circulating miRNA profiles in plasma are being investigated as biomarkers with diagnostic or prognostic utility,[83] approaches that may prove fruitful in ARDS.

Another as yet underexplored aspect of genomic regulation of ARDS is whether epigenetic modifications influence disease susceptibility or outcome. Epigenetic changes are classically construed as heritable changes in gene expression, function, or activity that occur without a change in DNA sequence, such as might occur due to changes in DNA methylation, histone modification, gene silencing, or imprinting.[84,85] Epigenetic mechanisms are attractive explanations for severe gene by environment interactions, and thus may be relevant to a complex trait like ARDS which only manifests in the setting of a severe environmental insult like mechanical ventilation, systemic infection, or severe trauma. Much of our understanding surrounding DNA methylation and histone modification comes from cancer biology. Tumor-suppressor gene hypermethylation leads to transcriptional silencing, promoting tumorigenesis.[86,87] Histones are dynamically regulated by processes including acetylation, methylation, phosphorylation, and ubiquitinylation, resulting in dynamic effects on gene expression and chromatin structure.[87,88] Differential epigenetic regulation can be assessed in either targeted or unbiased, genome-wide approaches by leveraging bisulfite sequencing (for methylation) and/or mass spectrometry to detect post-translational histone modification.[87] Given evidence from the Encyclopedia of DNA Elements (ENCODE) project highlighting vast complexity of genome regulation,[76,89,90] future studies should explore the role of epigenomic variation in the context of ARDS and potentially for distinct ARDS precipitants.

Proteomics and Metabolomics: Searching for the key players

While it was once assumed that gene expression would adequately describe the state of expressed proteins in a body site or cellular compartment, the correlation between mRNA and protein profiles is surprisingly poor.[91–93] Understanding the differential regulation of proteins relative to gene expression has enabled a better understanding of alternative splicing and post-translational regulation, while focusing on the expressed proteins has aided the identification of biomarkers for diagnosis, prognosis, and potentially, mechanistic importance. Proteomic approaches are generally conceived as large-scale analyses, going beyond individual or even multiplex protein quantification by enzyme-linked immunosorbent assay (ELISA) or bead-based immunoassays. Parallel to the explosion in next generation sequencing technology to analyze the genome have been advances in matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry to analyze high dimensional protein populations, including the identification of unknown proteins. Over 10 years ago, Bowler and colleagues performed 2 dimensional electrophoresis (2DE) followed by mass spectrometry upon edema fluid from 16 subjects with ARDS compared to 12 healthy controls.[94] Compared to healthy subjects, alveolar fluid albumin, transferrin, IgG, and clusterin were increased, and surfactant protein A and alpha-1-antitrypsin were decreased in ARDS patients.[94] In addition, several proteins detectable in the alveolar fluid of ARDS subjects demonstrated significant posttranslational modifications.[94] Schnapp and a group from the University of Washington applied liquid chromatography-tandem mass spectrometry (LC-MS/MS) proteomics to 3 bronchoalveolar lavage (BAL) samples from ARDS subjects, and analyzed almost 900 resulting unique

proteins.[95] Focusing on secreted proteins, the authors identified increased insulin-like growth factor-binding protein-3 (IGFBP-3) and its ligand insulin growth factor 1 (IGF-1) early in ARDS and suggested that IGF-1 contributes to fibroblast survival in ARDS.[95] Several investigators have since reported the identification of increased BAL apolipoproteins,[96] S100 calcium-binding proteins,[96–98] and inflammatory proteins including acute phase proteins and cytokines (TNF-α, interleukin-1β).[95,98] Investigating the plasma compartment, Chen and colleagues identified 16 proteins as differentially expressed in ARDS patients compared to healthy controls, with ARDS subjects showing significantly downregulated plasma apolipoproteins (apo A-I, A-IV, B-100, C-II, and CIII) and complement factor H, with upregulated complement C9, serum amyloid A, and Creactive protein.[99] Consonant with the individual protein findings, the most dysregulated pathways were annotated as acute phase signaling, complement system, interleukin-12 signaling, and production of nitric oxide and reactive oxygen species.[99]

A complementary approach to proteomics is to examine the small molecule metabolite profile of either the blood or lung compartment, in order to gain more information about the physiologic processes occurring in that compartment. Metabolites, the intermediate products of metabolism, can be endogenous or exogenous, and can be peptides but also lipids, carbohydrates, amino acids, nucleotides, hormones, vitamins, or foreign chemical substrates as from a drug, diet, or other exposure. Metabolites are first separated with gas and/or liquid chromatography and then quantified with mass spectrometry or isotope-labeled nuclear magnetic resonance spectroscopy (^{1}H-NMR or ^{13}C-NMR).[100,101] Stringer and colleagues at the University of Michigan first reported on ^{1}H-NMR-identified metabolites in the plasma of 13 sepsis-associated ARDS subjects compared to 6 healthy controls.[102] Forty metabolites were identified, and ARDS plasma was characterized by higher adenosine, glutathione, sphingomyelin, and phoshatidylserine, and pathway annotation analysis suggested that each metabolite participated in a unique metabolic network.[102] Because sepsis-associated ARDS samples were compared to healthy control subjects' plasma, it remained unclear whether the analytes identified were specific to ARDS or whether they might reflect alterations from sepsis. To study ARDS-specific metabolites would require a study with non-ARDS septic subjects as controls.

Metabolomic profiling of plasma has been applied more commonly to sepsis. Seymour identified numerous differences in the initial emergency department plasma sample of sepsis survivors versus non-survivors after matching subjects on clinical characteristics and procalcitonin level.[103] Metabolism of bile acids, sterols, amino acids, nucleotides, and energy were among the most dysregulated pathways in non-survivors.[103] Langley and colleagues performed multiple analyses, comparing sepsis survivors to noninfected subjects presenting with non-infectious systemic inflammatory response syndrome (SIRS), and also sepsis survivors to non-survivors.[104] There was a progressive decline in glycerophosphocholine and glycerophosphoethanolamine esters among septic subjects that was more pronounced among non-survivors, as well as increased lactate and increased carnitine esters, products of fatty acid metabolism, in nonsurvivors.[104] One of the limitations of metabolomic investigations is the lack of consensus for analytic strategy using multiple layers of large data. This fact is highlighted by a second metabolomic investigation in the same populations as the Langley study, but done in reverse order and with a different

analytic strategy. Rogers and colleagues first identified and then validated individual metabolites associated with death during critical illness, and then developed an iterative Bayesian network to risk stratify for mortality.[105] Compared to Langley study which identified 4 critical metabolites, 2 clinical variables (age, hematocrit), and lactate in a predictive model, the Rogers model identified no clinical data but 7 metabolites, all of them distinct from those chosen by the Langley model.[104,105] In a pediatric septic population, Mickiewicz applied ^{1}H-NMR spectroscopy to serum samples and demonstrated with principal components analysis that the metabolic profile of septic shock differed from that in healthy children or those with SIRS, and septic shock was characterized by increased levels of metabolites associated with muscle turnover, amino acid oxidation, and decreased energy supply.[106] The field of metabolomics seems ripe for the development of consensus recommendations governing analytic approach, need for independent replication, and to prompt both meta-analysis and application of unsupervised learning methodologies for class prediction.

Bronchoalveolar lavage fluid has posed a challenge for metabolomics due to the fluid's high protein and salt content, and relatively low concentration of most metabolites.[107] However, Evans and colleagues recently overcame these limitations by testing BAL fluid on multiple high-performance liquid chromatography platforms, and determining that the optimal performance was with reversed phase and hydrophilic interaction chromatography prior to mass spectrometry.[102] Consonant with proteomic studies of ARDS BAL fluid that demonstrated reduced surfactant proteins, Evans reported measuring reduced phosphatidylcholine, the major phospholipid of pulmonary surfactant, in BAL fluid among ARDS subjects.[108] Alveolar fluid from ARDS subjects also demonstrated higher levels of products associated with energy metabolism – lactate, citrate, creatine, and creatinine – all of which were similarly increased in the plasma of ARDS patients.[102,108] As novel findings, several guanosine network metabolites were increased in ARDS BAL fluid, prompting re-examination of xanthine oxidase activity in lung injury models.[108]

Introducing the Interactome: a systems biology approach

The common thread through this review of various 'omic approaches have been the exponential growth in complex data fueled by major technological advances. The explosion of data has created new challenges for computing power and analysis, but similarly new opportunities to describe how multiple aspects of human data fit together. Groundbreaking examples of integrative thinking paired whole genome genotyping to tissue-specific gene expression and identified not only the genetic determinants of specific traits, but used annotation and enrichment analysis to determine which transcription factors were critical to obesity[109] or coronary artery disease (CAD).[110] This approach, sometimes termed network biology, is particularly successful when it helps to prioritize further mechanistic study, translating observations in human populations back to the laboratory for testing of causality. In one notable example, Rader and colleagues built on the demonstration that one genetic variant strongly associated with CAD, low density lipoprotein (LDL) cholesterol levels, and hepatic expression of the sortilin gene *SORT1*.[110] The investigators then performed fine mapping of the SNP's linkage disequilibrium block to identify the functional variant, replicated the genetic association in populations of different ancestral background, and used

overexpression and knockdown experiments in mice to prove that *SORT1* expression modifies plasma LDL and a novel pathway of LDL regulation was identified.[111,112] Thus the network analysis integrating multiple threads of data not only suggested putative candidates for mechanistic follow up, but helped to prioritize the functional candidate and suggested the causal pathway through which it acted. Network science is most effective with multiple platforms of systematic data acquisition, thus it has been leveraged successfully with several cancer networks[113] and common traits like CAD.[114] As investigators begin gathering ARDS-specific systematic data, a network based approach may prove feasible in the future.

Further complexity may be added to the system by considering not only the human interactome, but also the interaction between the human host and resident microbial flora. While not yet widely applied to lung injury models, careful examination of gut microbiota in animal models of metabolic syndrome has demonstrated the critical interaction between inflammasome signaling and gut microflora.[115] Not only have microbes shaped genetic architecture of global populations through natural selection,[116] but they may be dynamic partners in the evolution of a complex phenotype like ARDS.[117] Next generation sequencing technology makes it possible to characterize the lung microbiome,[118] which may yield important insights in the future.

Summary

Acute respiratory distress syndrome is a complex trait poised to benefit from the application of high throughput technologies to assay DNA, mRNA, proteins, metabolites, microbiomes, and systems. Though hindered by infrequent access to lung tissue, researchers have made important advances in the early application of multiple ‘omic applications. As we apply lessons from non-ARDS phenotypes highlighting the potential for these techniques to expand our pathophysiologic understanding, new discoveries in ARDS await.

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Key points

1. Numerous candidate gene association studies and protein investigations have been employed in ARDS to moderate success, but large scale genomic, proteomic, or metabolomic studies have not yet been undertaken. There exists significant opportunity to apply ‘omic platforms to advance our understanding of ARDS pathophysiology.
2. While small proteomic and metabolomics investigations in ARDS have proven feasibility, to date there have been limited mechanistic follow up of compelling candidates and questions remain regarding the optimal target tissue and the best analytic strategy for ARDS.
3. Future studies could leverage ‘omic experience gained evaluating other non-ARDS complex traits, and could explore unbiased analytic strategies for class distinction or network analysis.
4. The success of high throughput discovery ‘omic investigations derives from tracing observations in human populations back to their mechanistic underpinnings.

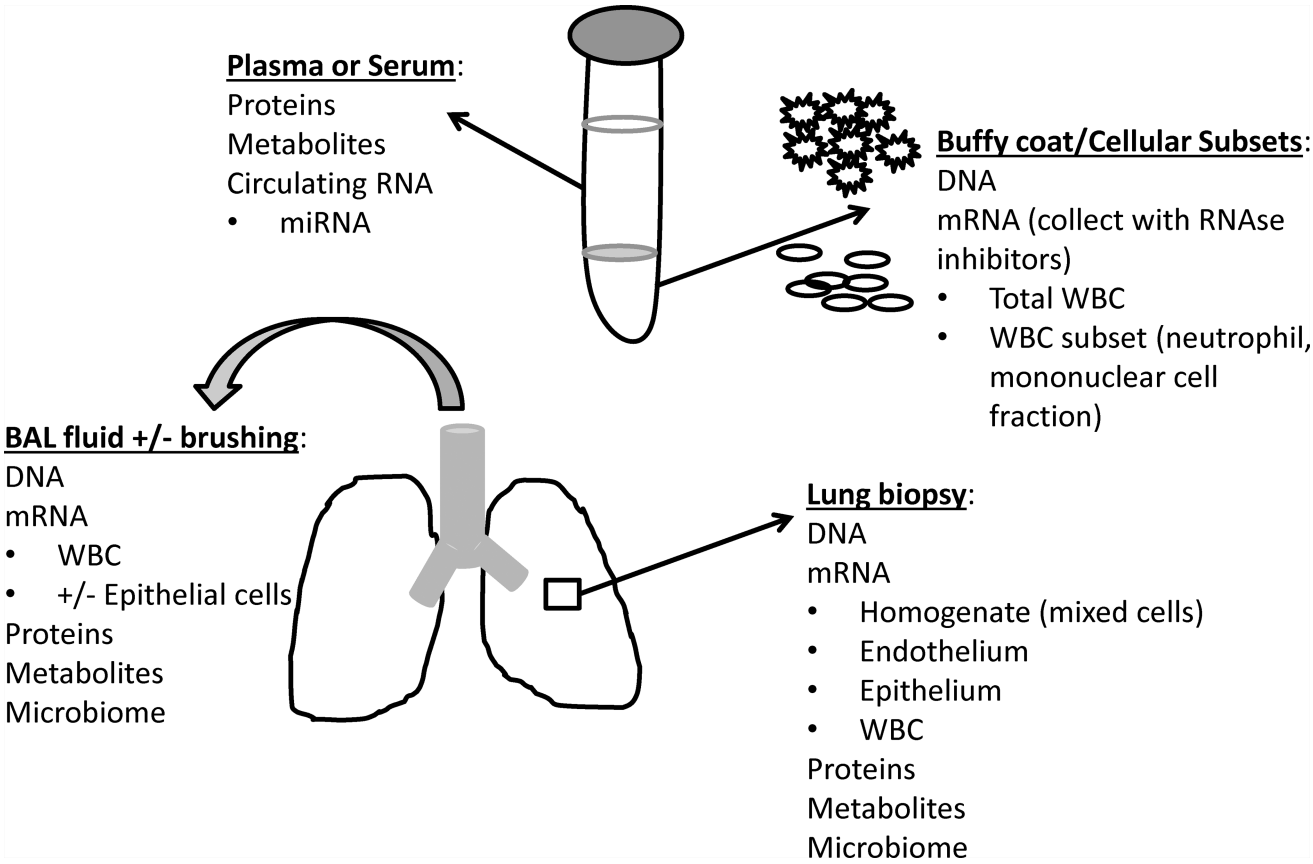

Figure.
Biospecimens available for ‘omic applications in ARDS

Table 1

Potential applications of different ‘omic technologies to a complex trait like ARDS

For each application, the tested analyte is named and the most likely potential applications are highlighted with an X.

Analyte ***Field***	**Infer Mechanism**	**Candidate Marker Validation**	**Candidate Marker Discovery**	**Identify Subclasses**	**Risk Stratify**	**Improve Diagnosis**	**Identify Therapeutic Targets**
DNA *Genomics*	x	x	x		x		x
DNA methylation or acetylation *Epigenomics*	x	x			x		x
mRNA - miRNA - ncRNA *Transcriptomics*	x	x	x	x	x		x
Proteins *Proteomics*	x	x	x	x	x	x	x
Metabolites *Metabolomics*	x	x	x	x	x	x	x
Systems *Interactome*	x			x	x		x
Microbiota *Microbiome*	x	x	x	x	x	x	x

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