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Biomarkers, Early Diagnosis, and Clinical Predictors of BPD

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Abstract

Bronchopulmonary Dysplasia (BPD) continues to be an important source of morbidity and mortality in premature neonates. The phenotype of BPD is extremely variable, and diagnosis is a clinical operational definition. A number of clinical and laboratory biomarkers have been proposed for the early identification of infants at higher risk of this disease, to characterize disease activity and severity and for determination of prognosis. Clinical prediction models for BPD have been developed using birth weight, gestational age, indicators of respiratory illness severity, and other clinical variables. Other biomarkers of BPD include those based on imaging of the lungs, lung function measures, and measurements of various analytes in different body fluids (blood, tracheal aspirates, exhaled breath condensates, urine, etc). Novel systems biology 'omic' based approaches including but not limited to genomics, proteomics, metabolomics and microbiomics are required for evaluating the multiple interacting cellular and molecular networks that control lung development and injury in BPD. Here we present a critical evaluation of the biomarker approaches studied in the diagnosis of BPD and highlight the future avenues for research in this field.

Key Words and Phrases

Bronchopulmonary dysplasia; Biomarkers; Prognosis; Early Diagnosis; Infant; Premature; Systems Biology; BPD; Pulmonary Hypertension; Biomarkers of BPD

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a common morbidity in extremely preterm infants. However, BPD defined by oxygen requirement even when more precisely assessed by the physiologic definition of BPD [1] is only an operational definition, which does not indicate the magnitude of lung disease or the underlying pathology. Lung pathology in BPD is

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variable, as certain infants with BPD have pulmonary hypertension as a major component of their pathophysiology,[2] while others have severe tracheobronchomalacia,[3] and many have patchy atelectasis or cystic lesions in their lung parenchyma.[4] It has increasingly become evident that severe BPD may be a different entity from mild or moderate BPD, both in terms of clinical operational definition as well as in terms of genetic predisposition.[5] This genetic predisposition is very different by race/ethnicity, indicating that biologic pathways (and resulting biomarkers) contributing to BPD in different infants are probably dissimilar.[5] Therefore, it is likely that what is now termed "BPD" is not a single entity, nor even a spectrum of disease resulting from a single pathophysiologic process, but a combination of several chronic lung diseases characterized by a common "at-risk population" of infants in the saccular or early alveolar stage of lung development with varying magnitudes of impairment of alveolar septation, lung fibrosis, and abnormal vascular development and remodeling. To modify Leo Tolstoy's quote on happy families from Anna Karenina, all normally developed preterm lungs are alike; each BPD lung is abnormal in its own way. The natural corollary is that the clinical predictors and biomarkers of each of these sub-phenotypes of BPD may be different, depending upon the pathophysiology.

In this manuscript, we first discuss the predictors and biomarkers starting from the clinical arena, and then move on to progressively more sophisticated investigations and research esoterica (which may be at the bedside in the near future).

Why do we need biomarkers or predictors?

Many interventions to reduce the risk of BPD have been tested in randomized clinical trials (RCTs), but only a few have shown significant treatment effects.[6] Hence earlier disease predictors are warranted to initiate preventive strategies in select patients. A biomarker has been defined as "a characteristic that is measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention". [7,8] Biomarkers are any clinical features, radiological findings or laboratory-based test markers that characterize disease activity, which are useful for early diagnosis, prediction of disease severity and, monitoring disease processes and response to therapy. Biomarkers are valuable for earlier diagnosis – it is possible that detection of BPD at an earlier stage may enable initiation of therapies when they may be more effective (a "window of opportunity"). It is also possible that non-detection of risk for BPD may enable the avoidance of therapies and their potential hazards.

Prognosis (risk prediction for development of BPD, or risk prediction for outcome of BPD in infants diagnosed with BPD) can also be evaluated using appropriate biomarkers. Similar to earlier diagnosis, the determination of a very high risk for BPD may enable the use of targeted therapy (e.g. the use of vitamin A supplementation in ELBW infants[9]) and determination of a very low risk for BPD may enable the avoidance of therapies. As mentioned earlier, BPD has much heterogeneity with many sub-phenotypes in clinical presentation. The use of biomarkers may enable targeting specific therapies to specific sub-phenotypes (e.g. use of iNO in infants with biomarkers indicating early elevations in pulmonary arterial pressure).

Biomarkers may also be useful for following the efficacy of therapy as a surrogate measure. For example, the rate of fall of blood b-type natriuretic peptide (BNP) may possibly enable a clinician to determine the efficacy of a therapy for pulmonary hypertension in BPD. The search for reliable biomarkers in BPD is ongoing and remains a challenge. Important issues to be addressed include the accuracy and reliability of biomarkers for the clinical state of interest, evaluation of clinical utility and cost-effectiveness, and real world effectiveness compared to other biomarkers.[10]

Biomarkers

Traditionally, risk prediction was done using clinical variables. Clinical variables can usually be obtained without difficulty. Other biomarkers include those based on imaging, lung function measures, and measurements of various analytes in different body fluids (blood, tracheal aspirates, exhaled breath condensates, urine, etc) that have been determined to be associated with BPD either in a targeted manner (e.g. specific cytokines), or by unbiased “omic” (e.g. genomic/proteomic/metabonomic/microbiomic) profiling (see Figure 1).

(A) Clinical Predictors as Biomarkers of BPD

Many clinical prediction models have been developed to predict the development of BPD.[11–17] However, some of these models were developed many years ago, a few even before the routine use of surfactant therapy or antenatal steroids. These models may not be generalizable to the current era with survival of many infants at the threshold of viability (22–24 weeks gestation). The models have also had a moving target, as the definition of BPD has changed with time, with a transition from the initial definition of oxygen requirement at 28 days to the more recent NIH consensus definition[18] and the physiologic BPD definition.[19] A common problem with most prediction models is that they are often based on statistical analyses that provide odds ratios and risk factors, but not an easy way for a clinician at the bedside to precisely and accurately determine the risk of BPD for an individual infant.

In a recent systematic review, Onland et al. [20] evaluated 26 published prediction models on BPD in premature infants. Onland et al. [20] also did external validation on a relatively recent cohort of infants (the PreVILIG dataset),[21] and reported that most existing clinical prediction models are at best only moderate predictors for BPD, as none had an AUC of ROC of >0.80.[20] We will describe four models that had fair performance (AUC >0.70) for predicting BPD in the analysis by Onland et al.[20]

In the mid 90’s, Ryan et al. [22] developed models to predict chronic lung disease (CLD) in VLBW neonates using clinical and radiological variables.[22] Logistic regression analysis was used to identify independent risk factors for CLD, and the area under the ROC curve (AUC of ROC) was used to determine the discriminatory capacity of the models. The AUC was similar in a model with and without radiographic information (0.926 vs. 0.913), and was 0.937 in a validation cohort.

In 1999, Yoder et al.[12] developed a respiratory failure score (RFS) for infants of <32 weeks' gestation to predict neonatal CLD at 36w PMA and compared it to the Sinkin[11] and Ryan models.[22] Five clinical parameters, reflecting the severity of pulmonary dysfunction, were selected for development of the scoring system and were assessed at 12, 24, 48, 72, and 168 h of age. The RFS method at 72 h demonstrated the greatest area under the ROC curve for prediction of neonatal CLD in the groups as a whole. A limitation of this study is that this model was developed in infants born during 1990–92, and included preterm infants who are at lower risk of BPD during the current era.

A predictive model was created by Kim et al.[23] based on their findings that peak inspiratory pressure over birth weight (PIP/kg) and mean airway pressure over birth weight (MAP/kg) were more significant risk factors for the development of CLD than PIP and MAP *per se*. A scoring method was developed using clinical data and modified respiratory variables to predict CLD on postnatal days 4, 7, and 10.[23] The primary outcome variable for this study was CLD diagnosed at 36 weeks of corrected age, and AUCs obtained (0.92 on day 4 to 0.95 on day 10) were comparable to those obtained by the Yoder et al.[12] model.

As most of these models typically do not include postnatal age and therefore cannot quantify the variable contribution of neonatal exposures over time, investigators at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) recently introduced a web-based BPD estimator to determine a risk estimate for BPD and the competing outcome of death by postnatal day.[24] This study was a secondary analysis of the data from a benchmarking trial on BPD.[25] This online tool can be found at https://neonatal.rti.org/index.cfm?fuseaction=BPDCalculator.start

(B) Imaging biomarkers of BPD

1. Chest radiographs (CXR)—Studies in the 1970's first described an association between the presence of fibrosis/interstitial shadows on CXRs and respiratory morbidity.[26] Mortensson et al.[27] described that focal or general hyperinflation or both were associated with a greater risk of airway obstruction in newborn infants whereas infants with only interstitial abnormalities were at a higher risk to develop general hyperinflation and increased airway obstruction even at 8–10 years of age, as compared to infants with a normal chest examination.[27] In a study of scoring CXRs of premature infants at 1 month of age, radiographs with cystic elements or interstitial changes were scored the highest and a high score was associated with oxygen dependency at 28 days and an abnormal airway resistance at 6 months of age.[28] Greenough et al.[29] formulated an objective scoring system for the assessment of CXRs at 1 month and concluded that scoring only for the presence of fibrosis/interstitial shadows, cystic elements and degree of hyperinflation predicts oxygen dependency at 36 weeks post-menstrual age.[29] The same group later reported that CXR appearance on postnatal day 7 facilitates prediction of outcome of infants born very prematurely.[30] Chest x-rays however have significant limitations in the evaluation of children with BPD as there is a poor correlation between chest x-ray appearance and clinical status.[31]

2. Chest computed tomography (CT) scans—Chest radiography has a drawback of superimposition of structures and there is controversy on the reliability of chest radiography in preterm infants.[32] CT scans can potentially provide more objective and definitive evidence of pulmonary structural damage in preterm infants with BPD.[33,34] Tracheobronchomalacia is commonly seen in children with BPD, and hence advanced CT techniques are often useful. Oppenheim in 1994 systematically described the chest CT findings of BPD.[33] Kubota et al.[34] and Ochiai and coworkers[35] have described CT-based scoring systems. Recently Shin et al.[36] developed a high-resolution computed tomography (HRCT) scoring system for BPD for both evaluation of the disease status and the prediction of clinical severity.[36] In all the above studies, CT scans were performed at late PMA when the disease is well established and hence these models do not aid in predicting development of BPD, but may help in forecasting outcome of established BPD. The utility of CT scans as a predictor of BPD in premature infants remains to be fully defined. Moreover, the risks of irradiation during CT should not be underestimated despite recent efforts at reducing irradiation.

3. Chest magnetic resonance imaging (MRI)—Magnetic resonance imaging (MRI) of the lung is technically challenging due to the low proton density and fast signal decay of the lung parenchyma itself.[37] However, pathological changes resulting in an increase of tissue density such as atelectasis, nodules, infiltrates, mucus, or pleural effusion, are readily identified. Adams et al.[38] used MRI to assess lung water content and tissue injury in infants of 23 to 33 weeks' gestational age. Proton density was significantly higher in dependent regions of the lungs and average proton density, proton density gradient and, severity of lung damage were greater in infants with severe BPD.[38]

Newer MRI technologies can facilitate measurements of perfusion, blood flow, ventilation, gas exchange as well as respiratory motion and mechanics.[39] In addition, hyperpolarized gas MRI is particularly sensitive to early changes in emphysema.[40] The technique of helium-3 MRI has been used to compare alveolar structure in term-born and preterm-born schoolchildren (including survivors of neonatal BPD).[41] Such advanced techniques complemented by the non-ionizing nature of the method could potentially help BPD evaluation in premature infants, although the current duration of procedure and requirement of sedation are limitations.

4. Echocardiogram for the diagnosis of Pulmonary Hypertension (PH) in BPD —Pulmonary hypertension is relatively common, affecting at least 1 in 6 ELBW infants, and persists to discharge in most survivors.[2] There are limited studies on this subject and a large prospective study from a single center by Bhat et al.[2] found that around 18% of ELBW infants were diagnosed with PH before discharge from the NICU and routine screening of ELBW infants with echocardiography at 4 weeks of age identifies only one-third of the infants with PH.[2] In another recent study by Mourani et al.[42], it was found that early PH was a risk factor for increased BPD severity and late PH.

Although echocardiography is widely used in the determination of PH in BPD, estimates of pulmonary artery pressure are not obtained consistently and are not reliable for determining the severity of PH.[43] A major limitation of echocardiographic evaluation of tricuspid

regurgitant jet velocity (TRJV) is that it relies on a TR regurgitant jet, which might not be present in all patients. The TRJV is also rarely of sufficient quality to adequately estimate right ventricular systolic pressure as in a recent study, 58% of children without a measureable TRJV had PH by cardiac catheterization and overall echocardiogram was accurate in determining severity of PH in just 47% of cases.[42] Hill et al.[44] also found a poor correlation between transthoracic echocardiographic estimates of right ventricular systolic pressure based on TRJV and cardiac catheterization. In essence, the lack of a measurable TRJV on echocardiogram should not be interpreted as absence of PH.

(C) Lung function biomarkers

Lung compliance and resistance have been demonstrated to differ between infants with and without BPD[13,45,46] but most of these studies were undertaken prior to the routine use of surfactant. Recent studies suggest that BPD survivors continue to have airway obstruction and lower FEV_1 (forced expiratory volume in 1 sec) even as late as young adult life.[47]

Freezer et al.[46] observed that the dynamic compliance of the respiratory system in intubated premature infants was significantly lower on day 1 and during the first week of life in the infants who went on to develop BPD. Lung compliance on day 1 and birth weight or gestational age were significant independent predictors for the development of BPD.[46] May et al.[48] found that airway resistance, compliance, functional residual capacity (FRC) and end tidal carbon monoxide (ETCO) differed significantly on day 3 between infants who did and did not develop BPD. On day 14, however, only a higher ETCO and none of the pulmonary function parameters were predictive of BPD.[48] Van Lierde et al.[49] found that gestational age and the ventilatory index (ventilator frequency x maximal inspiratory pressure) on day 3 were the best early predictors of poor outcome but pulmonary function tests were not helpful.

(D) Biofluid biomarkers

Various cytokines and growth factors mediate lung development or may be involved in lung injury.[50] Hence various investigators have explored the biomarker potential of various cytokines and growth factors in premature infants.

1. Blood—Limitations of systemic cytokine or growth factor measurement are that they may not accurately reflect the concentrations of the mediator in the lung and it is not possible to identify if pulmonary cells are producing or releasing them. Nevertheless, blood biomarker measurement for BPD has been frequently studied mainly because blood is relatively easily accessible.

a) Inflammatory Markers: Chorioamnioitis, [51] ureaplasma infection[52] and postnatal sepsis [53] have all been associated with the development of BPD, presumably due to the proinflammatory environment resulting from these conditions. In one of the larger studies in this field, investigators of the NICHD NRN developed a multivariate logistic regression model for the outcome of BPD and/or the competing outcome of death at PMA of 36 weeks by using a repository of prospectively collected clinical and cytokine data [54]. Higher serum concentrations of certain cytokines (IL-1β, IL-6, IL-8, IL-10, and IFN-γ) and lower

concentrations of other cytokines (IL-17, RANTES, and TNF-β) were associated with the development of BPD/death in ELBW infants, after adjustment for other clinical variables and concentrations of other cytokines. However, addition of cytokine data did not add much predictive ability to models using only clinical data, which suggests that clinical variables (eg, mechanical ventilation or its duration) may drive changes in cytokine concentrations, rather than *vice versa*.

b) Angiogenic Growth Factors: Abnormal angiogenesis may contribute to the development of BPD.[50,55] Investigators have therefore explored the biomarker potentials of pro-and anti-angiogenic factors. The angiopoietin (ANG)/Tie-2 ligand/receptor system interacts with the vascular endothelial growth factor (VEGF) pathway to determine the fate of blood vessels during angiogenesis. Low concentrations of the proangiogenic ANG-1 and high concentration of the antiangiogenic endostatin in cord blood have been found to be predictive of subsequent BPD.[56,57] VEGF and the proangiogenic factor platelet-derived growth factor BB (PDGF BB) were significantly elevated in blood at 5 days of life in infants who later developed the "new" BPD.[58,59] Tsao et al.[60] found that a higher level of placental growth factor (PlGF) in cord blood was associated with a higher risk of BPD.[60] Similarly the potent antiangiogenic endothelial monocyte activating polypeptide II (EMAP II) which downregulates VEGFR2 phosphorylation has been speculated to play a role in BPD pathogenesis.[50]

c) Epithelial and Fibrotic Markers: Pulmonary epithelial cell markers as well as extracellular matrix molecules may serve as biomarkers of alveolar hypoplasia in preterm infants. Members of the transforming growth factor (TGFβ) family, including TGFβ, activins and bone morphogenetic proteins (BMPs), are crucial factors during normal lung development, as well as in the response to lung injury.[61] Clara cells are epithelial cells which line respiratory and terminal bronchioles and secrete clara cell proteins (CCP). The levels of CCP in cord blood and serum have been reported to be low in infants who developed BPD[62] whereas conflicting results were noted in another study in which serum CCP levels within 2 h of life and on postnatal day 14 were higher in preterm neonates who later developed BPD.[63] Elevated cord blood levels of KL-6 which is a lung injury marker and ratios of matrix metalloproteinase-9 (MMP-9) to tissue inhibitor of metalloproteinase-1 (TIMP-1) have also been found to be predictors of moderate to severe BPD.[64,65]

d) Markers of Pulmonary Hypertension in BPD: Pulmonary hypertension is common in BPD and is associated with increased mortality and morbidity.[66] B-type natriuretic peptide (BNP) or NT-pro-BNP is being increasingly used for evaluation of pulmonary hypertension in BPD.[67] However, BNP could be elevated in the absence of echocardiographic signs of pulmonary hypertension or *vice versa*. It is important to remember that BNP is a marker of cardiac ventricular strain that is not specific to the right ventricle. Infants with systemic hypertension, persistent ductus arteriosus [68] or left ventricular dysfunction for other reasons may also have elevations of BNP.

2. Tracheal Aspirate or Bronchoalveolar Lavage—Tracheal aspirate analysis has historically served as a surrogate to analyze biological processes in the pulmonary

compartment, in the absence of fresh neonatal lung tissue being readily available. One of the major advantages of tracheal aspirate evaluation is the ease of sample collection through the endotracheal tube, although this leads to lack of sampling of initially non-intubated infants who may later develop BPD. In addition, the quantities of analytes in tracheal aspirate may have to be adjusted for dilution using an internal standard such as secretory IgA, urea, or total protein.[69] In presence of severe lung inflammation there is a possibility of influx of protein due to epithelial disruption making total protein a less useful internal standard. Despite its shortcomings, tracheal aspirate evaluation may provide useful information about the status of lung disease.

a) Inflammatory, fibrotic and epithelial markers: Various cytokines and chemokines are synthesized by neutrophils and other inflammatory cells in the airway and interstitium, in addition to a variety of cells of the lung parenchyma (eg, airway and alveolar epithelial cells, endothelium and fibroblasts). The pro-inflammatory cytokines IL1, IL6, IL8 TNFα and IL1β in tracheal aspirates have been shown to predict adverse pulmonary outcomes in preterm infants and increased IL1β concentrations and IL1β/IL6 ratios are associated with increased risk for BPD, especially when infants are colonized with *Ureaplasma urealyticum*.[70–72] Increased IL1, TNFα, IL6 and IL8 correlate with the duration of supplemental oxygen and mechanical ventilation and are increased in infants who develop BPD compared with infants of similar gestational age who do not develop BPD.[71] In addition, tracheal aspirate MCP-1, -2 and -3 were increased in infants developing BPD.[73] Nuclear factor-kappa B which is a critical component of the inflammasome was increased, while parathyroid hormone-related protein levels were decreased in tracheal aspirates of infants at higher risk of BPD.[74] Lower levels of CCP (CC10) have been associated with an increased risk of BPD similar to studies using blood as mentioned earlier.[74] Among fibrotic markers, TGFβ1 is increased in tracheal aspirates of infants who go on to develop BPD.[74] Neutrophil-gelatinase-associated lipocalin (NGAL) included in a large macromolecular complex together with matrix metalloproteinase-9 (MMP-9), is considered a marker of infectious/inflammatory processes and induction of apoptosis. In a study by Capoluongo et al.[75], NGAL was increased both in infants developing BPD and in those with a patent ductus arteriosus (PDA) even after adjustment for possible confounders.

b) Oxidant Injury Markers: Reactive oxygen species (ROS) may cause tissue damage in lungs via multiple mechanisms.[76] Premature infants may be particularly vulnerable to oxidant injury because they have a relative deficiency of these antiproteases and deficient quantities of enzymes responsible for scavenging ROS, including superoxide dismutase and glutathione peroxidase.[77,78] Contreras et al.[79] established the presence of oxyradical constituents in tracheal aspirates such as epithelial lining fluid leukocytes, elastase, myeloperoxidase, xanthine oxidase, catalase, and total sulfhydryls as one aspect of the pulmonary inflammatory response in infants who progressed to develop BPD.[79] Also, increased concentrations of epithelial lining fluid carbonyls, an indicator of protein oxidation, have been linked to increased risk of BPD.[80] Increased levels of 3-chlorotyrosine and malondialdehyde are seen in oxidant injury and correlated with BPD [81].

c) Angiogenic Growth factors: A recent study speculated that that low levels of VEGF in tracheal aspirate fluid, concurrent with elevated soluble VEGFR1 levels on the first day of life, are biological markers for the development of BPD.[82] EMAP II is a mediator of pulmonary vascular and alveolar formation and its expression is inversely related to the periods of vascularization and alveolarization in the developing lung.[50] Its role as a tracheal aspirate biomarker of BPD is being investigated in ongoing studies.

d) Other factors: Polyunsaturated fatty acids (PUFA) and plasmalogens are the two main substrates for lipid peroxidation in the pulmonary surfactant. Rudiger et al.[83] found that higher levels of PUFA and plasmalogens initially are associated with a reduced risk of developing BPD, and are reduced during the first day of ventilation.[83]

3. Urine—Joung et al.[84] compared urinary inflammatory and oxidative stress markers between infants with no/mild BPD group and moderate/severe BPD, and between BPD cases with significant early respiratory distress syndrome (RDS) (‘classic’ BPD) and with minimal early lung disease (‘atypical’ BPD). 8-hydroxydeoxyguanosine (8-OHdG) levels on day 7 of life were an independent risk factor for developing moderate/severe BPD. In classic BPD, the 8-OHdG values on the 3rd day of life were higher than those of atypical BPD. In atypical BPD, leukotriene E4 values on day 7 of life were higher than the values in classic BPD.[84] In other studies, high urinary concentrations of bombesin-like peptide (BLP), which are stimulated by hyperoxic exposure, were associated with an increased BPD.[85] Further studies for the prediction of BPD by analyzing proteomic signatures in the urine or blood are ongoing.

(E) Exhaled breath condensates (EBC) as Biomarkers

Advances in technology have produced small portable “electronic noses” that use a variety of technologies to emulate the human nose, with volatile organic compounds adsorbing onto sensors to produce a change in conductivity, color or oscillation of a crystal, leading to readouts that are analyzed. Similar to how human nose can tell the difference between different scents without needing to know the chemical constituents of the vapor, the electronic nose is able to discriminate between two vapor mixtures without needing to characterize the exact molecules responsible. In a recent study, Rogosch et al.[86] showed that smellprints of volatile organic compounds measured with an electronic nose (Cyranose 320) differ between tracheal aspirates from preterm infants with or without subsequent BPD [86].

BPD is marked by lung inflammation and exhaled breath condensates may be a useful technique for non-invasive assessment of markers of airway inflammation.[87] Exhaled breath condensate collected from ventilated infants can be used for diagnostic purposes using gas chromatography and mass spectrometry. [88] Increased end-tidal carbon monoxide (ETCO)[48] and exhaled nitric oxide (NO)[89] were also found to be higher in infants with BPD on postnatal day 14 and 28, respectively.

(F) Genomic Biomarkers

Advances in molecular genetics have enabled improvement of knowledge in pathogenesis and diagnosis of either monogenic or multifactorial neonatal lung diseases. Recent studies

have indicated a major genetic contribution to BPD susceptibility.[90,91] Genetic variants predisposing to BPD may be single nucleotide polymorphisms (SNPs) that may increase susceptibility to the disease. Identification of infants at higher risk of this disease by genomic analyses may be useful to provide them individualized therapies in the future.[92]

1. Differences in the Genome—In a genome-wide association study, Hadchouel et al.[93] identified SPOCK2 as a new possible candidate susceptibility gene, but this target was not confirmed by Wang et al. [94]. As single marker approaches might not explain more than a small fraction of heritability of BPD, an integrated genomic analysis was conducted recently by the NICHD NRN.[5] Genome-wide association and gene set analysis was performed for BPD or death, severe BPD or death, and severe BPD in survivors. Specific targets were validated via the use of gene expression in BPD lung tissue and in mouse model. Pathway analyses confirmed involvement of known pathways of lung development and repair (CD44, phosphorus oxygen lyase activity) and indicated novel molecules and pathways (adenosine deaminase, targets of miR-219) involved in genetic predisposition to BPD. In addition, this study observed marked differences in pathways by race/ethnicity suggesting that although the clinical phenotype of BPD may be similar, the underlying genetic predisposition may differ significantly. An additional major finding was that the pathways associated with mild/moderate BPD were very different from those associated with severe BPD, suggesting that the pathophysiology and potential therapies of severe BPD may be substantially different from those for mild/moderate BPD.

2. Differences in Gene Expression—Using a biorepository of autopsy tissues, Bhattacharya et al.[95] performed a genome wide transcriptional profiling to comprehensively define gene expression changes from the lung tissue of premature babies who died with a diagnosis of BPD. This study identified both general mast cell (tryptase) and mucosal-type mast cell specific (CPA3) markers increased in BPD tissue. Pietrzyk et al.[96] carried out genome wide transcriptional profiling of RNA extracted from peripheral blood mononuclear cells of BPD subjects and non-BPD controls followed by pathway enrichment analysis. They found that the expression of nearly 10% of the genome was altered in BPD infants, mostly in the cell cycle pathway and T cell signaling pathway.

Recently discovered microRNAs regulating target mRNAs have been seen to be dysregulated in multiple disorders. Because miRNAs have the ability to modify gene expression rapidly and reversibly, they are ideal mediators for sensing and responding to hypoxic or hyperoxic stress and may therefore be associated with alveolar dysplasias. In a recent analysis by Yang et al. [97], four up-regulated miRNAs (miRNA-21, miRNA-34a, miRNA-431, and Let-7f) and one down-regulated miRNA (miRNA-335) were differentially expressed in BPD lung tissues compared with normal lungs. In addition, eight miRNAs (miRNA-146b, miRNA-29a, miRNA-503, miRNA-411, miRNA-214, miRNA-130b, miRNA-382, and miRNA-181a-1) were found to show differential expression in the process of normal lung development and during the progress of BPD. Finally, several meaningful target genes (such as the HPGD and NTRK genes) of common miRNAs (such as miRNA-21 and miRNA-141) were systematically predicted. Also as mentioned previously, in the

integrated genomic analyses conducted by the NICHD NRN, the pathway with lowest false discovery rate (FDR) for BPD/death was the targets of miR-219.

(G) Respiratory Microbiome as a Biomarker of BPD

'Microbiota' can be defined as the microbes associated with a particular context and unlike traditional microbiological approaches that aim to identify individual pathogens, microbiota analysis characterizes all of the bacterial species present, both in terms of their identities and relative abundance.[98] High-throughput sequencing of 16S rRNA gene generated from bacteria-containing samples yields a large number of short sequences that can be subsequently aligned and sorted according to a predefined level of homology and classified according to taxonomic databases. To date, there are few studies that use culture independent methods for detection of airway organisms in preterm infants. Recently in a small study of 25 preterm infants, Lohmann et al.[99] demonstrated that the airways of premature infants are not sterile at birth. They speculated that reduced diversity of the microbiome may be an associated factor in the development of BPD. In a small study of 10 infants, Abman et al.[100] demonstrated by newer techniques that early bacterial colonization with diverse species are present in the airways of intubated preterm infants, and can be characterized by bacterial load and species diversity. None of the above mentioned small studies used a control population for comparison and hence a much larger study in this field is warranted to evaluate the biomarker potential of the respiratory microbiome.

The Future of BPD Diagnostics and Biomarkers

BPD is a disease, which has many different sub-phenotypes with a common operational definition. Hence better phenotyping of the disease and more detailed data collection of clinical variables, in addition to careful determination of 'specific and temporal biomarkers' are warranted. Novel systems biology approaches are required for evaluating the multiple interacting cellular and molecular networks that control lung development and regeneration or remodeling in response to injury and in chronic diseases. These are the newer "omic" strategies that supplement or expand upon genomic, proteomic and microbiomic approaches that were discussed earlier. State of the art prediction tools involving an amalgamation of clinical predictors with systems biology analysis might provide better insight to understanding the pathogenesis of the disease and could facilitate novel biomarker development for early detection and treatment of BPD.

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Synopsis

The pathogenesis of Bronchopulmonary Dysplasia (BPD) is multifactorial and the clinical phenotype of BPD is extremely variable. A number of clinical and laboratory biomarkers have been proposed for the early identification of infants at higher risk of BPD, and for determination of prognosis of infants with a diagnosis of BPD. We review the available literature on prediction tools and biomarkers of BPD, using clinical variables and biomarkers based on imaging, lung function measures, and measurements of various analytes in different body fluids (blood, tracheal aspirates, exhaled breath condensates, urine, etc) that have been determined to be associated with BPD either in a targeted manner (e.g. specific cytokines), or by unbiased “omic” (e.g. genomic/proteomic/metabonomic/microbiomic) profiling.

KEY POINTS

- BPD is a disease with a clinical operational definition and multiple different clinical sub-phenotypes.
- Most clinical prediction models of BPD do not have a high predictive accuracy.
- Various biofluid biomarkers have been studied over the years but none are currently used in routine clinical care.
- Newer “omic” strategies are promising for discovery of novel biomarkers of BPD diagnosis, prognosis, and therapeutic response.

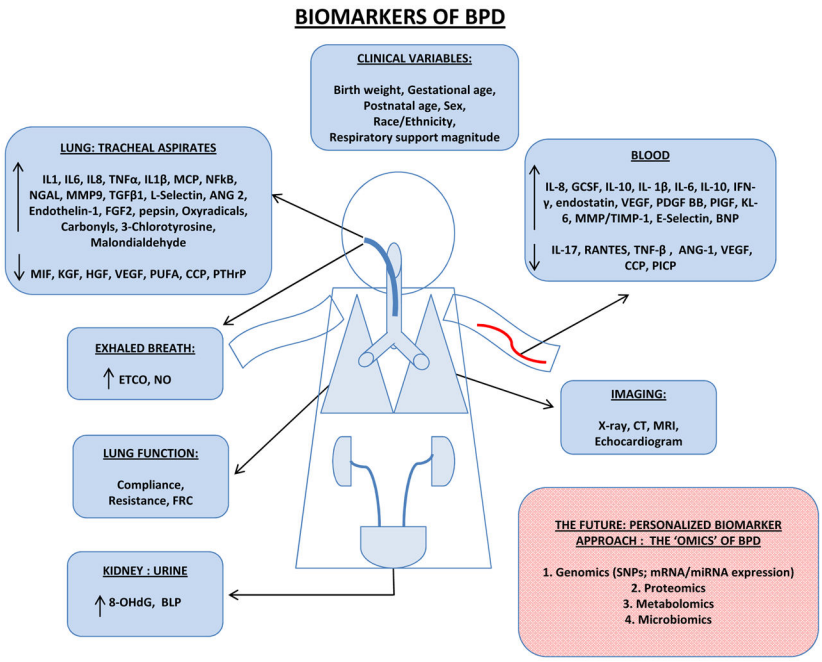

Figure 1.
Biomarkers of BPD