

University of Groningen

Transcriptome-based Signatures

van den Berge, Maarten; Faiz, Alen

Published in:
 American Journal of Respiratory and Critical Care Medicine

DOI:
[10.1164/rccm.202110-2353ED](https://doi.org/10.1164/rccm.202110-2353ED)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
 Publisher's PDF, also known as Version of record

Publication date:
 2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
 van den Berge, M., & Faiz, A. (2022). Transcriptome-based Signatures: The Future Biomarkers in Obstructive Pulmonary Diseases Such as Asthma and Chronic Obstructive Pulmonary Disease? *American Journal of Respiratory and Critical Care Medicine*, 205(2), 139-140. <https://doi.org/10.1164/rccm.202110-2353ED>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Transcriptome-based Signatures: The Future Biomarkers in Obstructive Pulmonary Diseases Such as Asthma and Chronic Obstructive Pulmonary Disease?

In recent years, an increasing number of studies have applied whole-transcriptome profiling to identify causal biological pathways and clinically relevant biomarkers. It has recently been shown that gene expression profiles from bronchial brushings can predict lung function decline. Becker and colleagues examined 134 ever-smokers with and without chronic obstructive pulmonary disease (COPD) who had been followed up with longitudinal lung function measurements for a mean period of 6.38 years. They identified a gene expression signature associated with lung function decline. Genes elevated in individuals with more rapid decline were enriched for genes modulated by the transcription factor XBP1 (X-box-binding protein 1) (1). Although the era of “big data” holds promise to advance the application of precision medicine in pulmonary diseases, the challenge that remains is how best to leverage these massive amounts of data for this purpose and obtain samples that can be collected in day-to-day clinical practice. In this issue of the *Journal*, Moll and colleagues (pp. 161–170) take advantage of the large sample size of the COPDGene (Genetic Epidemiology of COPD) study to develop a blood transcriptional risk score associated with susceptibility to develop COPD and with lung function decline (2). The predictive value of the blood transcriptional risk score for future lung function decline was independent of clinical predictors such as age, sex, smoking habits, and baseline level of FEV₁. The effect was quite substantial as for every SD increase in the transcriptional risk score, FEV₁ decreased by 8–17 ml, adding up to a clinically relevant loss of 40–170 ml over a 5- to 10-year period. The blood transcriptional risk score was developed in a mixed population varying from (ex-)smokers with normal lung function to those with quite severe COPD.

Although not formally investigated, the fact that the risk score predicts FEV₁ decline independent of baseline level of lung function suggests that it may also be able to detect early COPD before the development of established disease. The latter is important, as most patients in whom COPD is diagnosed have airflow obstruction that is already quite severe, whereas SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) has shown that many patients already experience the first symptoms before the development of airflow obstruction (3, 4). Identification of those subjects particularly at risk in an early phase may open avenues for intervention via the identification of so-called treatable traits (5).

Ⓐ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please e-mail Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202110-2353ED on November 18, 2021

Examples of treatable traits could be, among others, continued smoking or other exposures. In addition, elevated eosinophil levels in blood or sputum or increased expression of T-helper cell type 2 (Th2)-related genes may identify those subjects in whom accelerated FEV₁ decline could be prevented by (inhaled) corticosteroid treatment. In addition, future studies may identify other gene signatures reflecting biologically relevant pathways amenable for therapeutic intervention with currently available drugs, such as IL-33, IL1RL1 (IL-1 receptor-like 1), IL-17, IL-13, IL-4, and IL-13. It has previously been shown that patients with COPD exhibit an increased expression level of genes associated with Th2 inflammation in the lower airways (bronchial biopsies) compared with control subjects without COPD matched for age and smoking (6). Interestingly, higher activity of a Th2 gene expression signature was found to be associated with eosinophilic inflammation and predicted favorable response to inhaled corticosteroids. In contrast, a higher level of IL-17-associated genes in the lower airways of patients with COPD was associated with neutrophilic inflammation and blunted corticosteroid responsiveness (7).

Several studies have previously identified gene expression signatures associated with COPD, treatment response, and lung function decline (1, 8–10). These studies used bronchial epithelial brushes, biopsies, or lung tissue, whereas the study by Moll and colleagues used peripheral blood, which is easily accessible and relatively noninvasive. The latter is of crucial importance for effective use in daily clinical practice. Apart from peripheral blood, there are other promising sites for noninvasive biomarker development in airways diseases. One example is nasal epithelium, which can be easily sampled using a soft cytobrush. The nasal epithelial gene expression profile has been shown to distinguish effectively between patients with COPD and control subjects without COPD, with COPD-associated gene expression changes in the nose reflecting those occurring in the lower airways (11). Faiz and colleagues recently showed a nasal epithelial gene expression profile to be associated with hyperinflation as reflected by residual volume/TLC% predicted and found this signature to be increased in COPD, in epithelium derived from the upper airways and of the lower large and small airways, indicating a common signature associated with hyperinflation throughout the respiratory tract (12, 13). Future studies are now needed to evaluate if, and to what extent, the nasal epithelium gene expression profile could serve as a biomarker for COPD and COPD-associated traits and whether it could add information complementary to the blood transcriptional risk score. Furthermore, Ditz and colleagues identified a gene expression signature in induced sputum, also readily accessible, that could more effectively predict the risk of having an exacerbation upon steroid withdrawal in COPD compared with sputum eosinophils (14). Future studies investigating molecular gene signatures in relation to clinically relevant traits associated with COPD may lead to the identification of new biomarkers.

Next to a possible biomarker function, another advantage of gene expression signatures in blood, sputum, nasal brushes, or samples from lower airways or lung parenchyma is that they also provide insights in pathobiological mechanisms associated with COPD and COPD-associated traits, which could potentially lead to discovery of novel treatment targets. In the case of the study by Moll and colleagues, blood transcriptional risk score genes were enriched for pathways related to PPAR- α (peroxisome proliferator-activated receptor α) signaling and B-cell activation, which are possibly involved in COPD susceptibility and lung function decline.

In conclusion, gene expression profiling is a promising tool for the development of clinically relevant biomarkers in lung diseases like COPD and can reveal novel treatment targets leading to improved personalized treatment of the disease. The data published by Moll and colleagues in this issue of the *Journal* provide an excellent example of a clinically relevant biomarker that can be easily and noninvasively assessed. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Maarten van den Berge, M.D., Ph.D.
University Medical Center Groningen
University of Groningen
Groningen, the Netherlands

Alen Faiz, Ph.D.
Faculty of Science
University of Technology Sydney
Sydney, New South Wales, Australia

ORCID ID: 0000-0002-9336-7340 (M.v.d.B.).

References

1. Becker EJ, Faiz A, van den Berge M, Timens W, Hiemstra PS, Clark K, *et al*. Bronchial gene expression signature associated with rate of subsequent FEV₁ decline in individuals with and at risk of COPD. *Thorax* [online ahead of print] 10 May 2021; DOI: 10.1136/thoraxjnl-2019-214476.
2. Moll M, Boueiz A, Ghosh AJ, Saferali A, Lee S, Xu Z, *et al*. Development of a blood-based transcriptional risk score for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2022;205:161–170.
3. Fazleen A, Wilkinson T. Early COPD: current evidence for diagnosis and management. *Thorax* 2020;75:1753–1758.
4. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, *et al*. SPIROMICS Research Group. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med* 2016;374:1811–1821.
5. McDonald VM, Fingleton J, Agusti A, Hiles SA, Clark VL, Holland AE, *et al*.; participants of the Treatable Traits Down Under International Workshop; Treatable Traits Down Under International Workshop participants. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. *Eur Respir J* 2019;53:1802058.
6. Christenson SA, Steiling K, van den Berge M, Hijazi K, Hiemstra PS, Postma DS, *et al*. Asthma-COPD overlap. Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015;191:758–766.
7. Christenson SA, van den Berge M, Faiz A, Inkamp K, Bhakta N, Bonser LR, *et al*. An airway epithelial IL-17A response signature identifies a steroid-unresponsive COPD patient subgroup. *J Clin Invest* 2019;129:169–181.
8. Steiling K, van den Berge M, Hijazi K, Florido R, Campbell J, Liu G, *et al*. A dynamic bronchial airway gene expression signature of chronic obstructive pulmonary disease and lung function impairment. *Am J Respir Crit Care Med* 2013;187:933–942.
9. van den Berge M, Steiling K, Timens W, Hiemstra PS, Sterk PJ, Heijink IH, *et al*. Airway gene expression in COPD is dynamic with inhaled corticosteroid treatment and reflects biological pathways associated with disease activity. *Thorax* 2014;69:14–23.
10. Brandsma CA, van den Berge M, Postma DS, Jonker MR, Brouwer S, Paré PD, *et al*. A large lung gene expression study identifying fibulin-5 as a novel player in tissue repair in COPD. *Thorax* 2015;70:21–32.
11. Boudewijn IM, Faiz A, Steiling K, van der Wiel E, Telenga ED, Hoonhorst SJM, *et al*. Nasal gene expression differentiates COPD from controls and overlaps bronchial gene expression. *Respir Res* 2017;18:213.
12. Faiz A, Imkamp K, van der Wiel E, Boudewijn IM, Koppelman GH, Brandsma CA, *et al*. Identifying a nasal gene expression signature associated with hyperinflation and treatment response in severe COPD. *Sci Rep* 2020;10:17415.
13. Imkamp K, Berg M, Vermeulen CJ, Heijink IH, Guryev V, Kerstjens HAM, *et al*. Nasal epithelium as a proxy for bronchial epithelium for smoking-induced gene expression and expression quantitative trait loci. *J Allergy Clin Immunol* 2018;142:314–317.e15.
14. Ditz B, Sarma A, Kerstjens HAM, Liesker JJW, Bathoorn E, Vonk JM, *et al*. The sputum transcriptome better predicts COPD exacerbations after the withdrawal of inhaled corticosteroids than sputum eosinophils. *ERJ Open Res* 2021;7:00097-2021.

Copyright © 2022 by the American Thoracic Society



Repurposing Propofol as a Prognostic Probe for Return of Consciousness

There is a growing realization that behavioral and neurophysiologic responses to general anesthesia can provide useful information

Ⓓ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please e-mail Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202111-2504ED on November 24, 2021

regarding underlying brain health. For example, in response to concentrations of propofol or ether-derived inhaled anesthetic agents (e.g., sevoflurane and isoflurane) associated with loss of consciousness, people with healthy brains often have prominent anterior electroencephalographic α and θ spindles, which exhibit phase–amplitude coupling with slow δ waves (1). In contrast, surgical patients with preexisting cognitive impairment often fail to develop these typical, prominent anterior electroencephalographic spindles in response to propofol or inhaled general anesthetics (2). Furthermore,