European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

# Cystic Fibrosis Research News

## Title:
Real-world association between ivacaftor initiation and lung function variability: A registry study

## Lay Title:
The relationship between ivacaftor and lung function variability

## Authors:
Rhonda D. Szczesniak[ab*], Eleni-Rosalina Andrinopoulou[c], Hancheng Li[ab], Raksha Jain[d], Nicole Mayer-Hamblett[ef], Josh Ostrenga[g], Anushka Palipana[ah], David J. Pasta[i], Margaret Rosenfeld[ef], Jonathan Todd[g], Elizabeth A. Cromwell[g], Wayne J. Morgan[j]

## Affiliations:
[a] Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[b] University of Cincinnati, Cincinnati, OH, USA
[c] Erasmus Medical Center, Rotterdam, The Netherlands
[d] University of Texas Southwestern Medical Center, Dallas, TX, USA
[e] Seattle Children's Hospital, Seattle, WA, USA
[f] University of Washington, Seattle, WA, USA
[g] Cystic Fibrosis Foundation, Bethesda, MD, USA
[h] Duke University School of Nursing, Durham, NC, USA
[i] formerly ICON Clinical Research, San Francisco, CA, USA
[j] The University of Arizona, Tucson, AZ, USA

## What was your research question?
Is starting ivacaftor linked to changes in lung function variability in people with CF?

## Why is this important?
Previous CF research showed that variability in lung function typically preceded decline in lung function. That study introduced five simple measures of lung function variability based on how forced expiratory volume in 1 s of % predicted ($FEV_1$pp) varies over time, but data were collected prior to the use of modulator therapies like ivacaftor. If ivacaftor initiation reduces $FEV_1$pp variability, then measuring this variability may be a useful marker to gauge how effective modulators or other therapies can be in people with CF.

## What did you do?

# Cystic Fibrosis Research News

We analyzed data from children and adults with CF followed in the U.S. Cystic Fibrosis Foundation Patient Registry. We compared change in $FEV_1$pp variability over two time periods: before vs. after starting ivacaftor. The five variability measures, calculated for each period, were i) maximum and ii) median deviations from the best $FEV_1$pp; iii) maximum, iv) median; v) standard deviation about the trendline of the $FEV_1$pp trajectory. We analyzed data separately for subgroups of certain mutations. We also analyzed data from those who were F508del homozygous, since they represented a group of people with CF in the Registry followed over the same time but ineligible for ivacaftor. We compared changes between treated and untreated groups. We looked at relationships between $FEV_1$pp variability and rate of decline before and after treatment.

## What did you find?

$FEV_1$pp variability was reduced for those who started ivacaftor, and reductions were observable for all measures. The typical reduction was 1.85% predicted. Reductions were most pronounced if we used maximum deviation from the best $FEV_1$pp and most consistent (i.e., similar values) if we used trendline measures. Children had different risk factors for high variability than adults. Findings were consistent for subgroups with the G551D or R117H mutation. The F508del homozygous group had virtually no changes in $FEV_1$pp variability over the same time period. Having reduced $FEV_1$pp variability was not strongly related to changes in $FEV_1$pp or rate of decline, but we those who had higher $FEV_1$pp variability before they started ivacaftor tended to have the greatest reductions.

## What does this mean and reasons for caution?

Findings suggest that starting ivacaftor is related to reduced $FEV_1$pp variability and that the measures studied may be able to predict responsiveness to therapies and complement existing markers in CF research. Some limitations are that we excluded those recorded as taking ivacaftor who participated in interventional studies; home spirometry data may yield different conclusions about $FEV_1$pp variability than the clinic spirometry data in this study; reduced variability may relate to unmeasured characteristics (i.e., variables that were not recorded in the Registry); since the F508del homozygous group could never have received ivacaftor, they are technically not a control group.

## What's next?

There is a need to study how these variability markers perform in data from people with CF who have taken other therapies, such as the more recent, widely available modulator, elexacaftor/tezacaftor/ivacaftor.

**Original manuscript citation in PubMed**
https://pubmed.ncbi.nlm.nih.gov/39929763/