Loss of CFTR activity is the underlying cause of cystic fibrosis (CF)\textsuperscript{1}

**Spectrum of Phenotypes Associated With Total CFTR Activity\textsuperscript{1,2}**

<table>
<thead>
<tr>
<th>Total CFTR Activity</th>
<th>No CF Disease</th>
<th>CFTR-related Disorders</th>
<th>Cystic Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Normal</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- **People with 2 CFTR mutations resulting in loss of CFTR activity generally have a CF phenotype, which may include\textsuperscript{1-3,6}**
  - Elevated sweat chloride (>60 mmol/L)
  - Pancreatic insufficiency
  - CBAVD\textsuperscript{a}
  - Lung function decline over time
  - *Pseudomonas aeruginosa* colonization

\textsuperscript{a}CBAVD, congenital bilateral absence of the vas deferens.

**References:**
Levels of CFTR activity affect survival in CF

Survival Curves by CFTR Activity During a 10-Year Follow-Up (1993-2002) of Patients From the US CFF Registry

- Life expectancy in Western countries (general population born in 2000) is ~79 years.
- Between 1993 and 2002, median survival for US patients with genotypes associated with little to no CFTR activity was 36.3 years (95% CI, 35.5 to 37.6 years), while median survival for those having genotypes associated with residual CFTR activity was 50 years (95% CI, 47.1 to 55.9 years).
  - In this study, patients with the N1303K mutation (Class II) were part of the severely reduced CFTR activity group.
- More recent US data (2000-2010) suggest median survival across genotypes continues to improve.

*Data are from a retrospective study of patients enrolled in the Cystic Fibrosis Foundation patient registry measuring risk of death over a 10-year observation period from 1993 to 2002. Patients were grouped as having a high-risk or low-risk genotype based on the functional effects of their class of CFTR mutation on phenotype and mortality. Patients having a Class I, II, or III mutation on both alleles were considered high-risk, while patients having at least 1 Class IV or V mutation were categorized as low-risk. A total of 15,651 patients had a CFTR genotype of a known functional class; 14,525 (93%) had a high-risk CFTR genotype and 1126 (7%) had a low-risk CFTR genotype.*

The **N1303K** mutation is the fourth most common **CFTR** mutation in the world\(^1\)

**Prevalence of the N1303K Mutation in Patients With Cystic Fibrosis (% of Patients With at Least 1 Allele)**

- In the CFTR2 global database, ~2% of patients with CF have at least 1 copy of the **N1303K** mutation\(^1\)

**Additional sources report frequency of the N1303K mutation on CF alleles**

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria(^9)</td>
<td>20%</td>
</tr>
<tr>
<td>Lebanon(^9)</td>
<td>10%</td>
</tr>
<tr>
<td>Tunisia(^9)</td>
<td>6%</td>
</tr>
<tr>
<td>Bulgaria(^9)</td>
<td>6%</td>
</tr>
<tr>
<td>Latvia(^9)</td>
<td>6%</td>
</tr>
<tr>
<td>Italy(^10)</td>
<td>5%</td>
</tr>
<tr>
<td>Greece(^9)</td>
<td>3%</td>
</tr>
</tbody>
</table>

**References:**
The *N1303K* mutation results in defective processing and trafficking of the CFTR protein\(^1-3\)

- *N1303K* is a missense mutation resulting in a severe defect in CFTR processing and trafficking, typical of a Class II mutation\(^1,4\).
- Due to degradation of immature CFTR proteins in the endoplasmic reticulum, CFTR proteins fail to reach the apical cell surface\(^3,4\).

The **N1303K** allele results in little to no total CFTR activity\(^1\-3\)

Total CFTR activity can be defined as total ion transport mediated by CFTR protein channels at the cell surface, depending on CFTR protein **quantity** and **function**.\(^3\)

1. **Defective Processing and Trafficking (Class II)**
   - **N1303K** allele results in few to no CFTR channels at apical surface

2. **CFTR Function**
   - Channel-open Probability: N/A
   - Conductance: N/A

3. **Total CFTR Activity**
   - Little to No N1303K-CFTR Activity

N/A, not applicable.

**References:**

1. Significantly reduced N1303K-CFTR protein quantity…
2. …regardless of **function** since few to no CFTR proteins reach the surface…
3. …results in little to no total CFTR activity
Both *CFTR* alleles play a role in determining phenotype or disease severity\(^1\)\(^-\)\(^7\)

- An *N1303K* allele results in little to no CFTR activity. The phenotype of a particular patient is also influenced by the mutation on the other allele\(^1\)\(^-\)\(^7\).
- *N1303K* typically results in the indicated phenotypes.

### References
**N1303K** in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype\(^1\text{-}5\)

**CFTR Genotype**

- **Modifier Genes**
- **Environmental Factors**

<table>
<thead>
<tr>
<th>Allele #1: N1303K</th>
<th>Allele #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little to No CFTR Protein Activity</td>
<td>Little to No CFTR Protein Activity</td>
</tr>
</tbody>
</table>

**CF Phenotype**

In patients registered in the CFTR2 database with an **N1303K** mutation on 1 allele and a pancreatic insufficient mutation on the second allele\(^1\)

- Elevated sweat chloride (average): 104 mmol/L
- Lung function decline over time\(^2\)
- Pseudomonas colonization: 54% of patients
- Pancreatic insufficiency: 98% of patients

**References:**
Summary

• Loss of CFTR activity is the underlying cause of CF
• Levels of CFTR activity affect survival in CF
• The *N1303K* mutation is the fourth most common *CFTR* mutation in the world
• The *N1303K* mutation results in defective processing and trafficking of the CFTR protein
• The *N1303K* allele results in little to no total CFTR activity
• Both *CFTR* alleles play a role in determining phenotype or disease severity
• *N1303K* in combination with another allele that produces little to no CFTR activity usually results in a CF phenotype