European Cystic Fibrosis Society

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Cystic Fibrosis Research News

Title:

Elexacaftor/tezacaftor/ivacaftor (*ETI*) for *CFTR* variants giving rise to diagnostic uncertainty: personalised medicine or over-medicalisation?

Lay Title:

A serious consideration about the wise use of the new, highly efficient, very expensive, treatment for cystic fibrosis (Trikafta©/Kaftrio©)

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What was your research question?

Is it justified to treat subjects with mutations of the cystic fibrosis gene that respond to *ETI* when tested in a lab, but giving rise to uncertain diagnoses of cystic fibrosis? Is it a step towards personalized medicine or an excess of medicalization with potential harmful consequences?

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Why is this important?

We question the relevance of use of costly treatments (i.e. the new drug Trikafta©/Kaftrio©*)* on the sole basis of efficacy evaluated in lab on 178 mutations of the cystic fibrosis gene, as actually approved for subjects with cystic fibrosis 6 years and older by the US Food and Drug Administration. We hypothesize that several of the 178 approved mutations are not able to cause cystic fibrosis with certainty.

The annual retail cost of Trikafta©/Kaftrio© exceeds $300,000 per patient, which is much more expensive than the cost of other chronic treatments for cystic fibrosis.

What did you do?

We examined the 178 mutations using three different mutation databases with the aim of classifying the mutations as:

- Causing cystic fibrosis (pathogenic),
- Mutations of varying clinical consequence,
- Mutations uncertainly interpreted as being pathogenic,
- Mutations of unknown significance,
- Non-causing cystic fibrosis

Subsequently, in order to assess a real-world frequency of the three categories that may give rise to diagnostic uncertainty (mutations uncertainly interpreted as being pathogenic, mutations of unknown significance, and non-causing cystic fibrosis mutations), we queried the Italian Registry of subjects with cystic fibrosis.

What did you find?

Examining the 178 approved mutations, we found that only about half were considered causing cystic fibrosis, one third resulted in an uncertain diagnosis of cystic fibrosis, and the remaining (near 20%) could or could not be associated to signs and symptoms of cystic fibrosis.

Querying the Italian Registry, we found 113 subjects (about 2% of the total), whose cystic fibrosis is dubious. In fact, their mutations are included in the three categories that may give rise to diagnostic uncertainty. Nevertheless, these subjects could theoretically be treated with Trikafta©/Kaftrio©, according to the criteria of the Food and Drug Administration.

What does this mean and reasons for caution?

We wonder whether lab data alone are sufficient to justify the use of a very expensive treatment, especially in the case of patients with a dubious diagnosis of cystic fibrosis. On the other side there is a need to test the potential efficacy of new drugs for the treatment of

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subjects with rare genotypes causing cystic fibrosis. In fact, these subjects are not usually included in clinical trials.

What's next?

The wise use of economic resources is an important consideration when attempting to improve the access to treatment of those patients with rare diseases who could really benefit from new, very effective and very expensive drugs. Patients, caregivers, researchers and clinicians should collaborate for this purpose.

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