

# Can we learn from advances in personalised care in cystic fibrosis?

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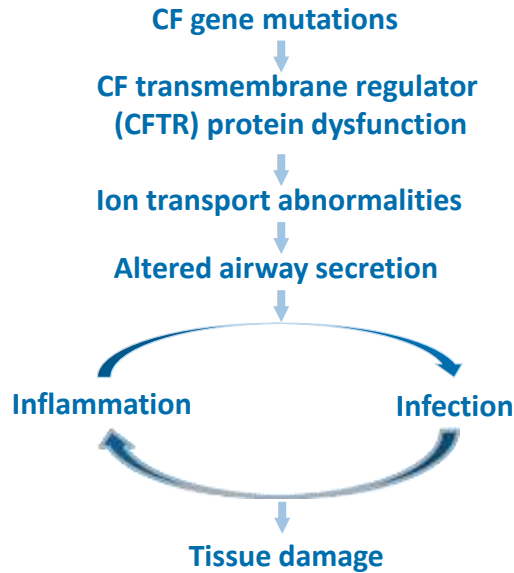
47<sup>th</sup> ESCP Symposium on Clinical  
Pharmacy  
25<sup>th</sup> October 2018



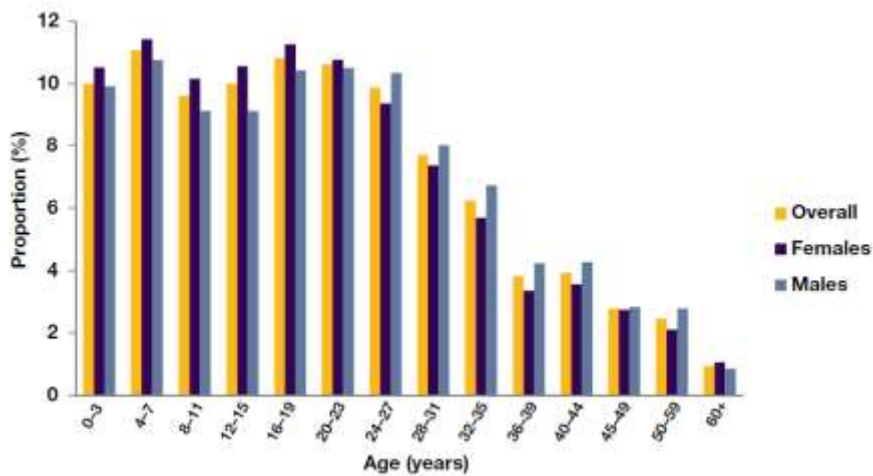
## Outline

- Cystic Fibrosis (CF)
- Personalized care: stratification of therapy based on
  - Genetic make-up of the patient
  - Composition of airway microbiota/microbiome

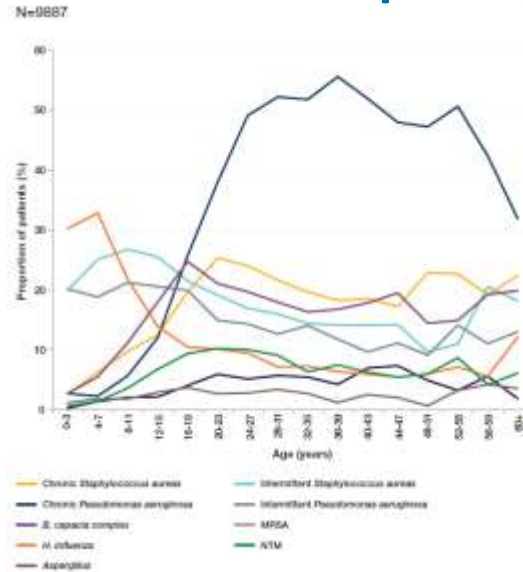
# What is Cystic Fibrosis?



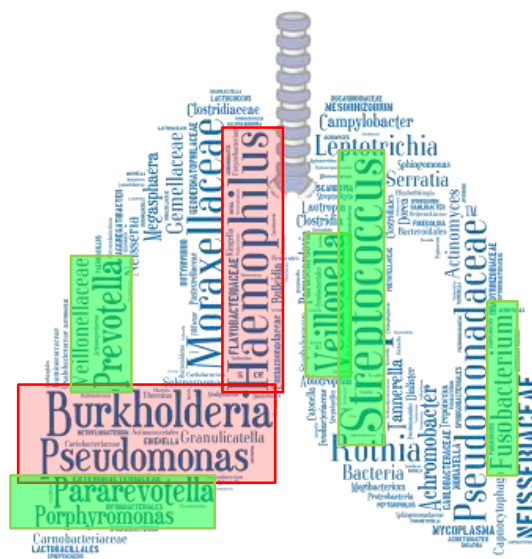
## UK CF registry data



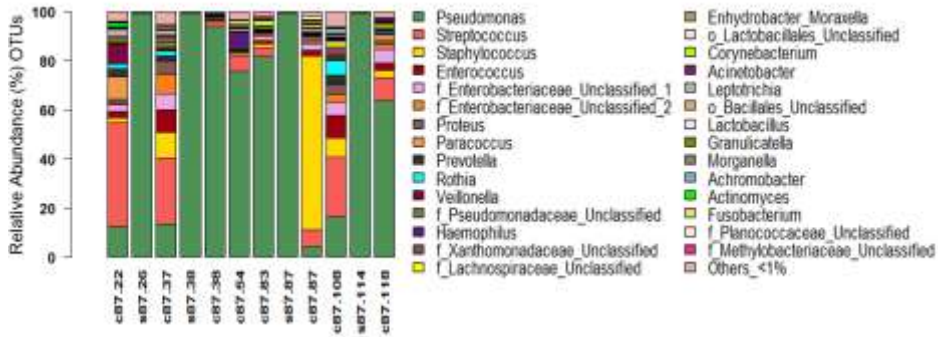
## Routine microbiological culture: CF pathogens



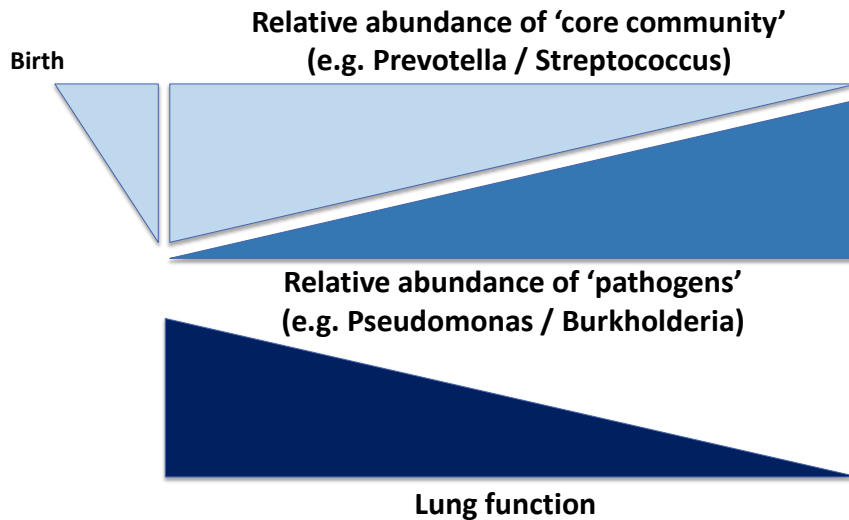
## Enhanced culture & molecular methods: Polymicrobial CF airway microbiota



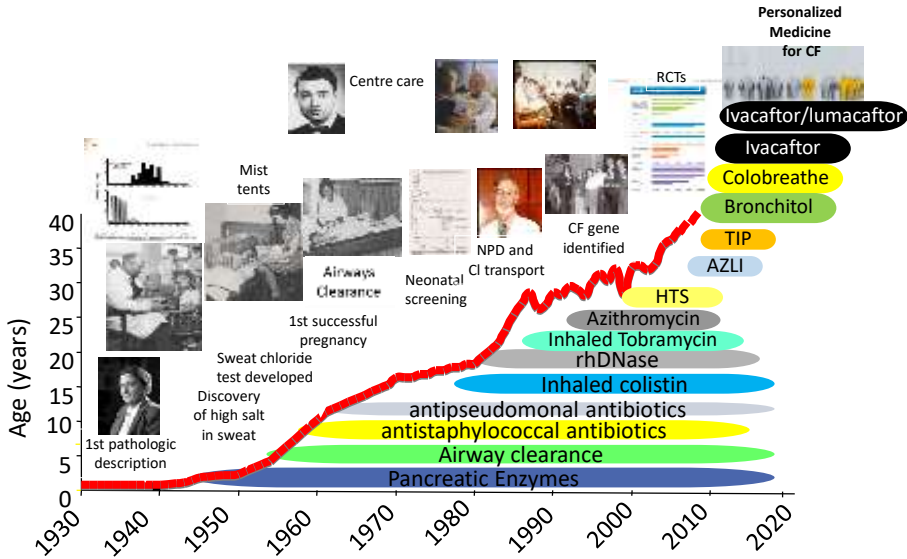
## Enhanced culture & molecular methods: Polymicrobial CF airway microbiota



## Changing communities in CF: Why is this clinically relevant?



## Improved survival: Treatment innovation



## Personalized care in CF

### Change

Provide patients with

- Right therapy
- Right dose
- Right time and context

### Benefits

- Improved outcomes
- Fewer complications
- Better use of finite resources

### Driven by

- Better understanding of pathology
- Ability to measure multiple markers faster and cheaper
- Development of more selective therapies

## Living with CF: One day's treatment

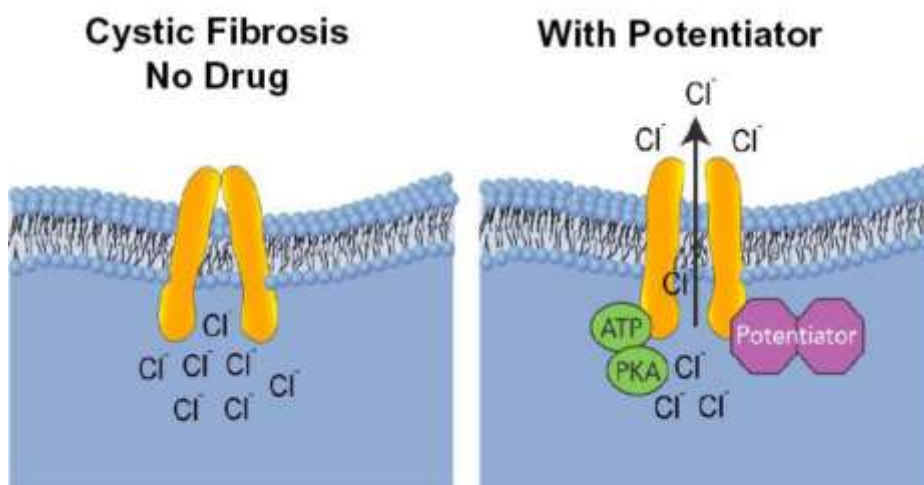


## Personalized care in CF: Mutation targeted treatment



I	II	III	IV	V	VI
Defective synthesis	Defective processing	Defective regulation	Defective conductance	Reduced synthesis	Increased turnover
G542X	<b>F508del</b>	<b>G551D</b>	R117H	A455E	
394delIT	N1303K	S1251N	R334W	3272-26A>G	
1717-1G>A	G85E				

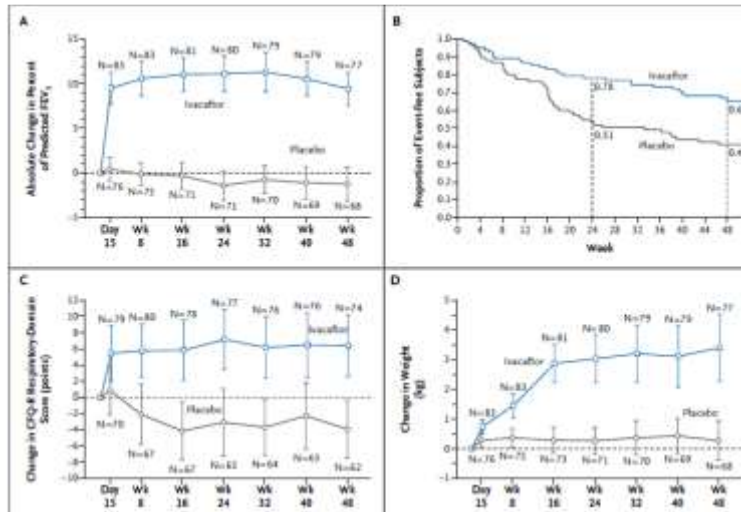
## *Ivacaftor:* CFTR potentiator



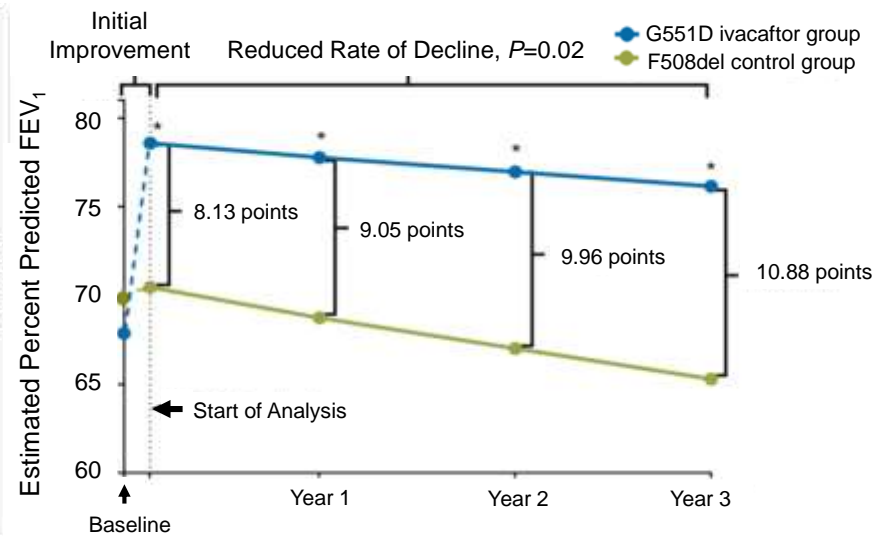
## *Ivacaftor:* Key clinical trial

- Ramsey et al 2011
  - N Engl J Med 2011;365:1663-72
- Phase III trial
  - placebo-controlled
  - At least one G551D mutation
- Subjects randomly assigned to receive either
  - 150 mg of ivacaftor every 12 hours (84 subjects), OR
  - placebo (83 subjects) for 48 weeks

## Ivacaftor: Clinical trial results



## Ivacaftor: Decreases rate of decline in FEV<sub>1</sub>

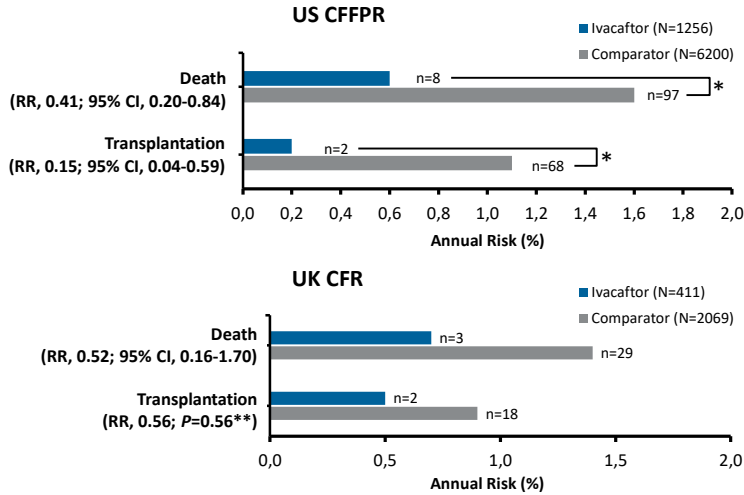


Sawicki G AJRCCM 2015.



## Ivacaftor:

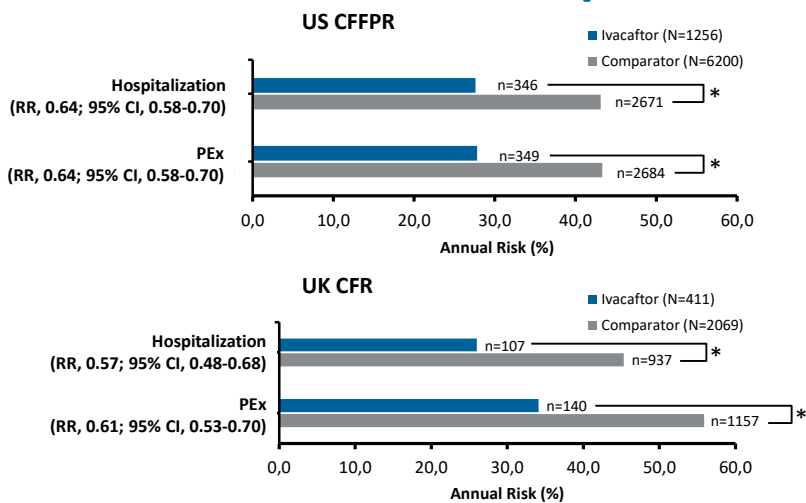
# Deaths and transplantations



Bessonova et al 2018

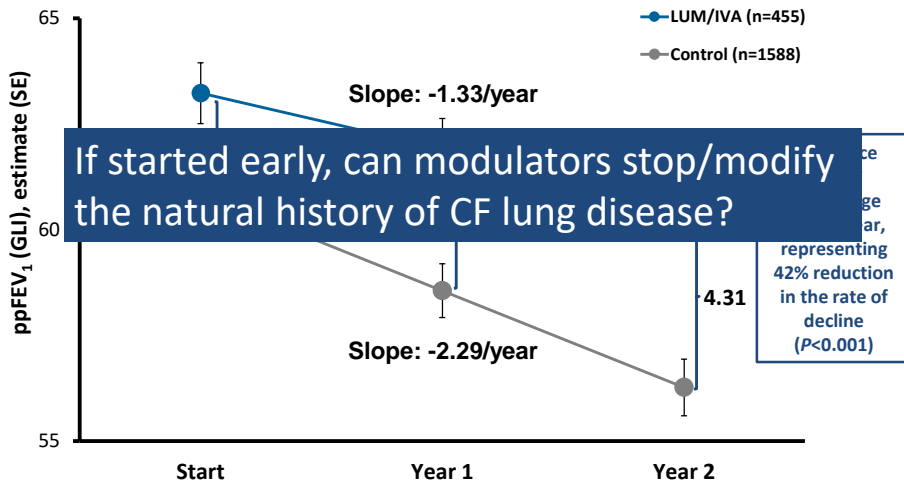
## Ivacaftor:

# Exacerbations and hospitalizations



Bessonova et al 2018

## *Lumacaftor/Ivacaftor:* Slower annual rate of lung function decline

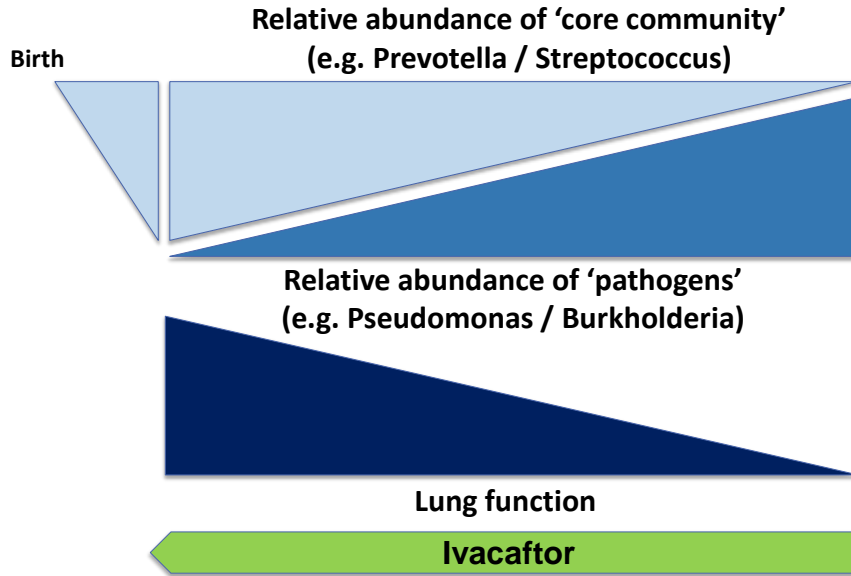


## *Ivacaftor:* Manipulating the microbiota?

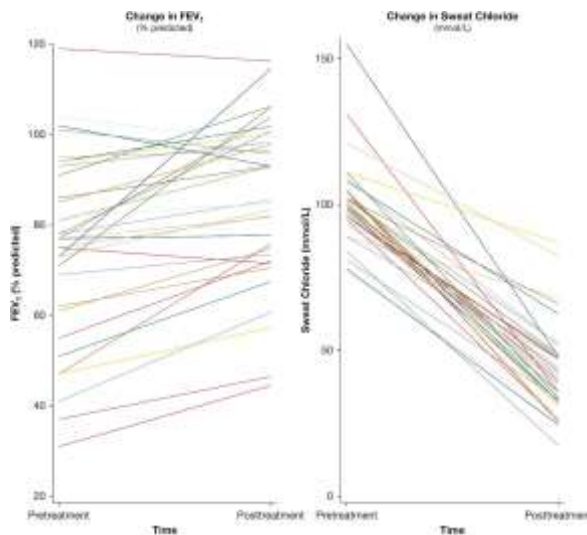
### CORK Study in Cystic Fibrosis

*Ronan et al. CHEST*  
DOI: (10.1016/j.chest.2017.10.005)

## Ivacaftor: Shift towards a 'healthy' microbiota?

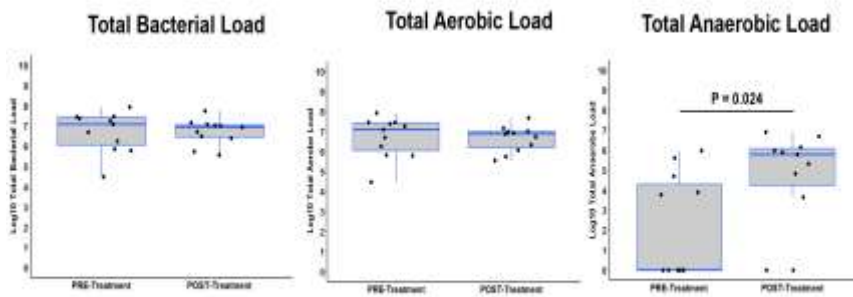


## Ivacaftor: Improved clinical outcomes

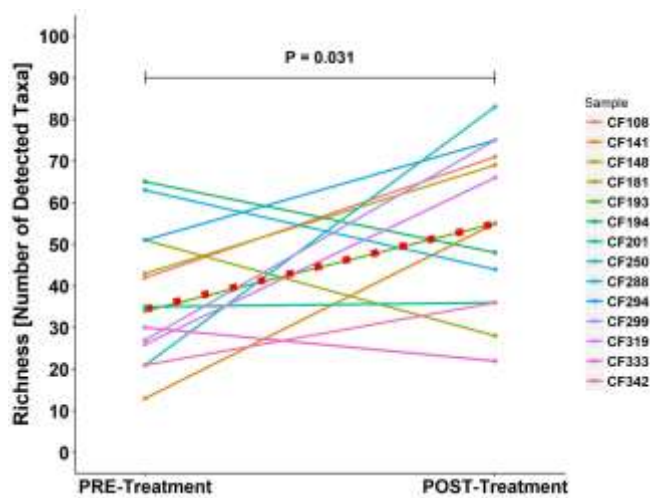


Ronan et al. CHEST DOI: (10.1016/j.chest.2017.10.005)

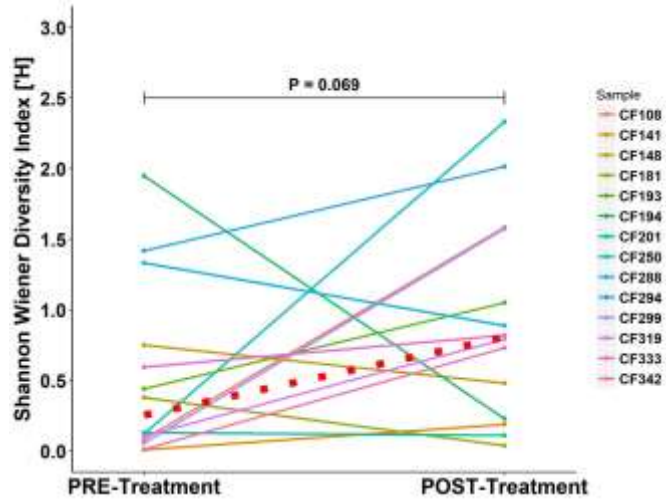
## *Ivacaftor:* Shift towards a 'healthy' microbiota?



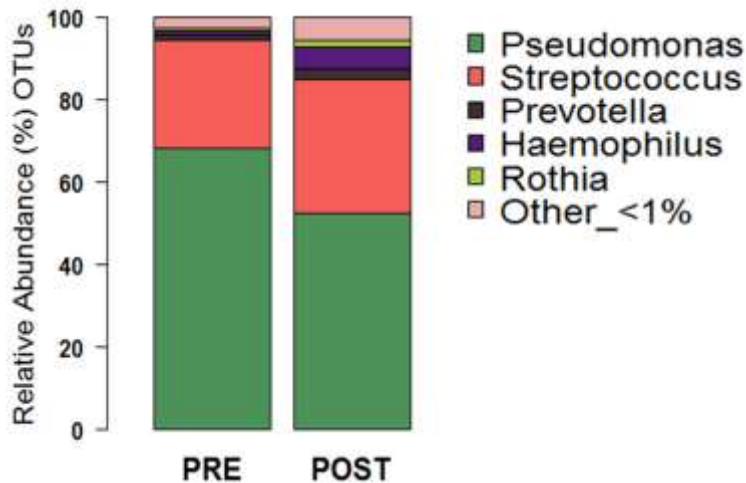
## *Ivacaftor:* Increased microbiota richness



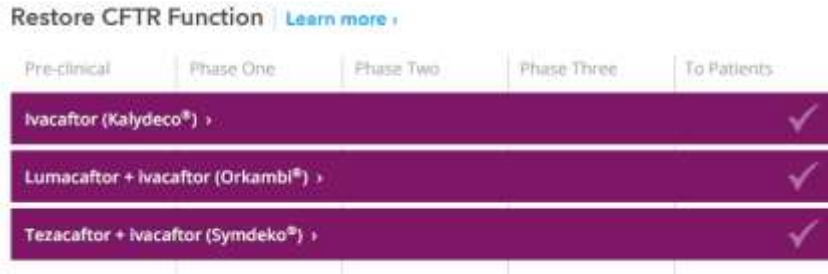
## *Ivacaftor:* Increased microbiota diversity



## *Ivacaftor:* Manipulating the microbiota?



## Mutation targeted treatment: What is currently available?



## Mutation targeted treatment: What is in the pipeline?



# Microbiome directed antibiotic treatment



Cystic  
Fibrosis  
Microbiome derived  
Antimicrobial  
Therapy  
Trial in  
Exacerbations  
Results  
Stratified

## The concept behind CFMATTERS



**Could we use CF microbiota analysis to inform treatment of respiratory infection in clinical practice?**



2011

2014

2018

CFMATTERS is funded by the European Union's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n°603038

## CFMATTERS: Project outline



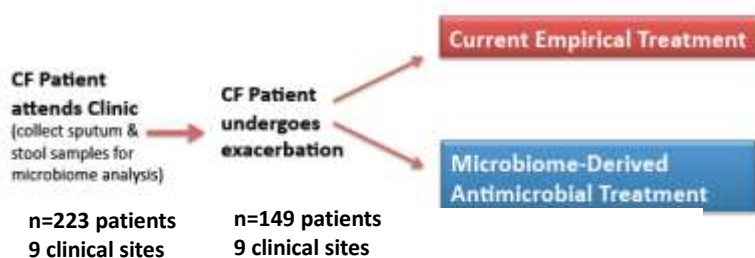
### Inclusion Criteria

- Age 16 years or older at enrolment
- Persistent pulmonary *P. aeruginosa*
- Screening FEV<sub>1</sub> predicted of >25%
- ≥1 course of intravenous antibiotics in the preceding 12 months

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## CFMATTERS: Treatment recommendation

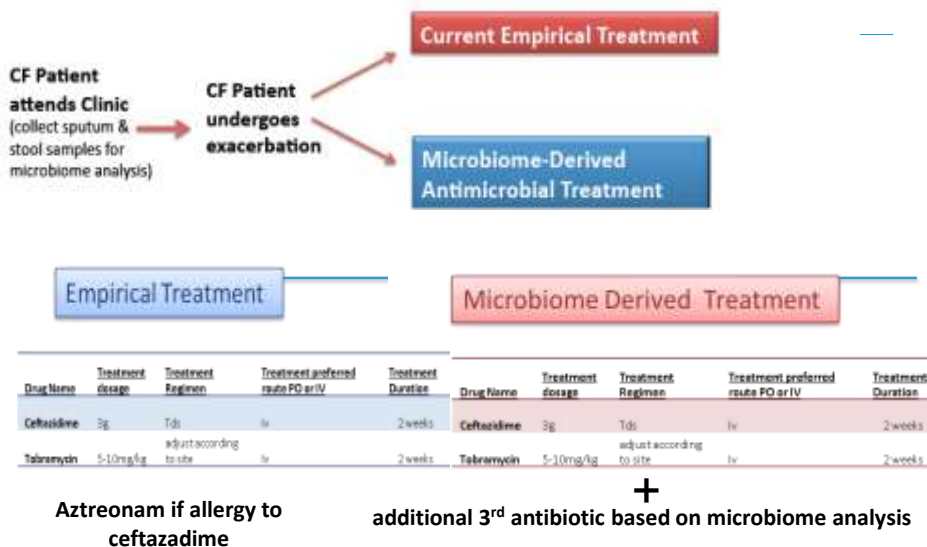


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## CFMATTERS: Treatment recommendation



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## CFMATTERS: Additional 3<sup>rd</sup> antibiotic



### How it was determined....

#### Consensus of PIs

Developed "Guiding principles for Microbiome Based Therapy Post Consensus Review"

#### Monthly treatment panel meeting

Treatment **recommendations** were based on a consensus by **minimum of three clinicians** around the "**Top 4**" taxa observed in samples.

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### Guiding principles for Microbiome Based Therapy Post Consensus review

	1 <sup>st</sup> Line Antibiotic	2 <sup>nd</sup> Line Antibiotic	Rationale
<i>Staphylococcus</i>	Doxycycline	Linezolid	
<i>Haemophilus influenzae</i>	Moxifloxacin	Doxycycline	Specificity
<i>Pseudomonas aeruginosa</i>	Ceftazidime /Aztreonam and Tobramycin.		This resist... has a fo... therefore... of the
<i>Streptococcus species</i>	Moxifloxacin		
<i>Stenotrophomonas maltophilia</i>	Co-trimoxazole	Dox...	
<i>Achromobacter xylosoxidans</i>	Tetracycline		This organism is often pan-resistant and there is limited data on the best antibiotic for treatment. The most active agents are tetracycline, carbapenems, chloramphenicol and co-trimoxazole.
<i>Burkholderia cepacia complex</i>		Amoxicillin and Piperacillin/Tazobactam	This organism is also usually pan-resistant.
<i>Prevotella</i> <i>Veillonella</i>		Meropenem, Co-Amoxiclav or Piperacillin/Tazobactam.	Primary data from QLB laboratory demonstrates both species in CF are generally sensitive to metronidazole.
	Amoxicillin,	Doxycycline, Co-Amoxiclav	There is limited data available regarding the antimicrobial susceptibility of <i>Rothia</i> species. In general, they are susceptible to penicillin

Version 1.0<sup>1</sup> March 2015

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## CFMATTERS: Consensus panel meeting



### Belfast - Analyses sample (BAS101 / F20V101)

Allergy :	Yes	
If yes, specify:	Ceftazidime, Piperacillin/Tazobactam (Tazocin)	
Sample number	888014	Date received 22/03/2017
Sample collection centre	8	Date processed 28/03/2017
Sample type	Sputum	
FEV1	2.29 Litres	
FEV1 predicted	4.41 Litres	
% FEV1 predicted	51.92 %	
<b>Results for the top 5 taxa/organisms detected</b>		
Ranks	Detected Taxa	Relative abundance (%)
1 <sup>st</sup> Ranked Taxa	<i>Pseudomonas</i>	91.26
2 <sup>nd</sup> Ranked Taxa	<i>Streptococcus</i>	5.51
3 <sup>rd</sup> Ranked Taxa	f_Pseudomonadaceae_Unclassified	0.87
4 <sup>th</sup> Ranked Taxa	<i>Veillonella</i>	0.49
5 <sup>th</sup> Ranked Taxa	f_Gemellaceae_Unclassified	0.40
Additional comments Few green plugs, a lot of saliva like material.		

**Treatment: Tobramycin + Aztreonam**

**Microbiome Directed: Moxifloxacin**

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## CFMATTERS: Project outcomes



### Primary Outcome

- Percentage change in recovery (post-exacerbation) FEV<sub>1</sub> relative to the previous pre-exacerbation FEV<sub>1</sub>

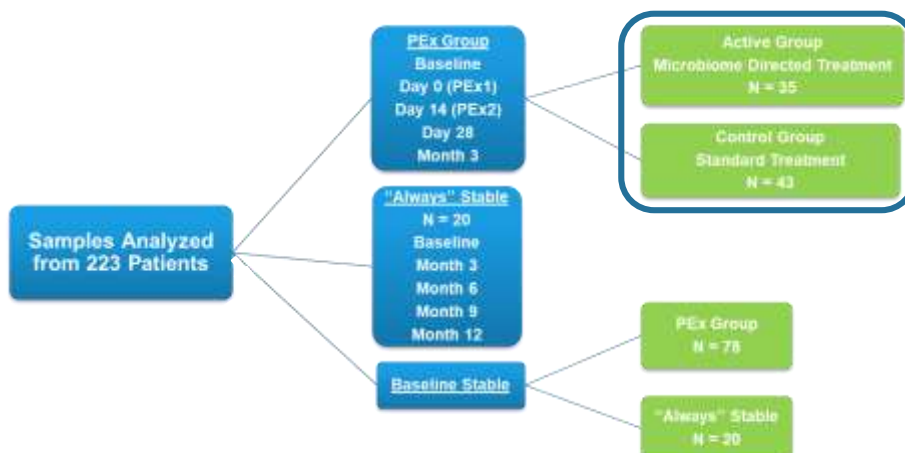
### Secondary Outcomes

- Time to next pulmonary exacerbation
- Improvement in symptom burden by day 7
- Total number of IV antibiotic days from time of randomisation in the trial
- Total number of exacerbations post trial treatment

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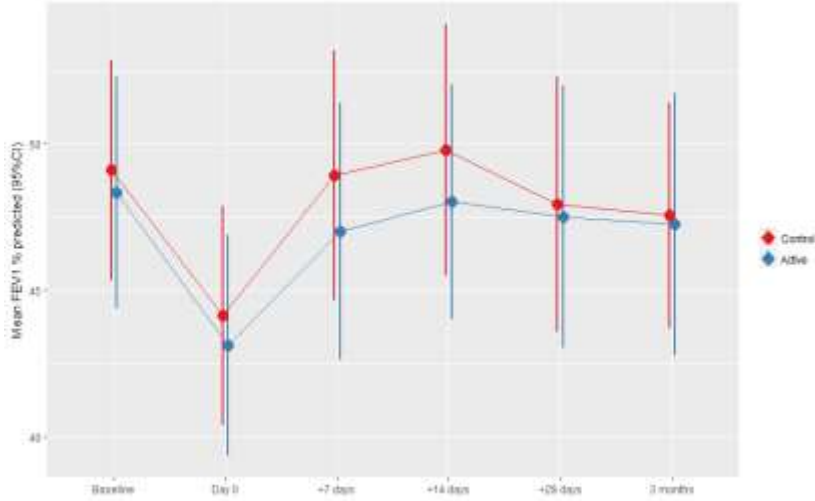


## Microbiome: Sample analysis



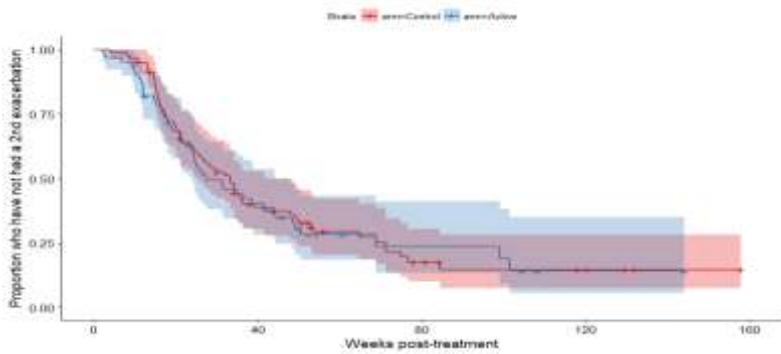
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## Primary outcome: Change in FEV<sub>1</sub>



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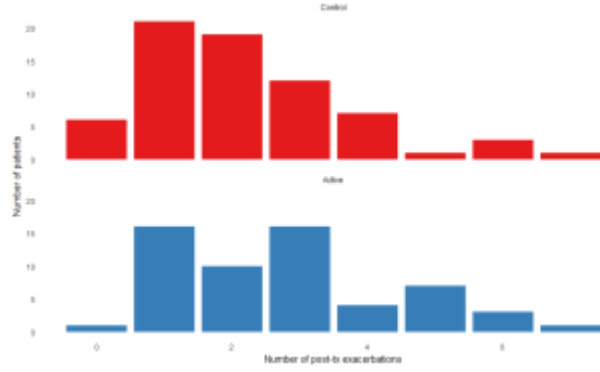
## Secondary outcome: Time to next exacerbation



Arm	N	Exacerbations	Median Time in		
			Weeks	0.95LCL	0.95UCL
Control	80	60	33.15	25.43	47.86
Active	61	44	27.58	24	44.29

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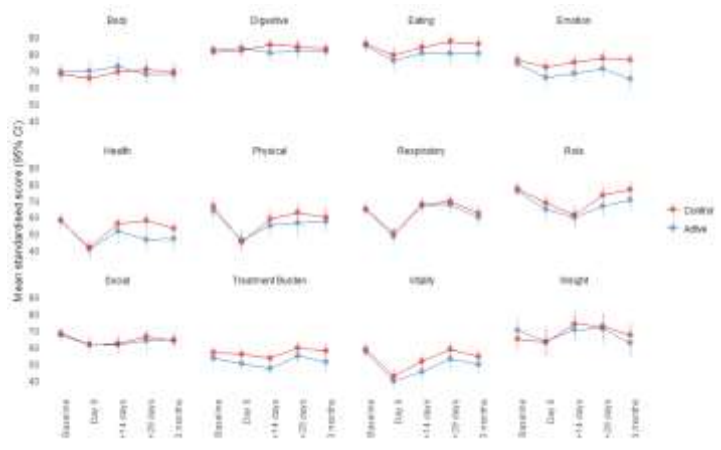
## Secondary outcome: Exacerbations in 1<sup>st</sup> year



arm	n	median	mean
Control	70	2	2.186
Active	60	3	2.759

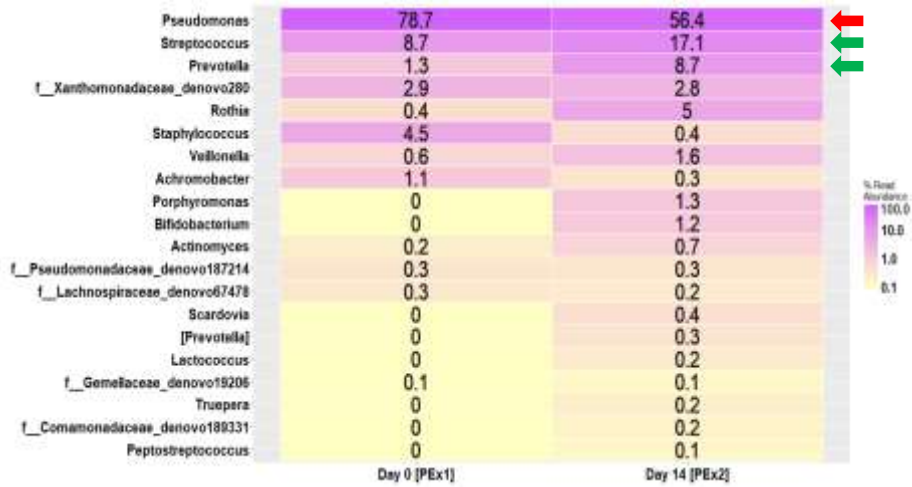
CFMATTERS is funded by the European Union's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n°603038

## Secondary outcome: Health-related QOL



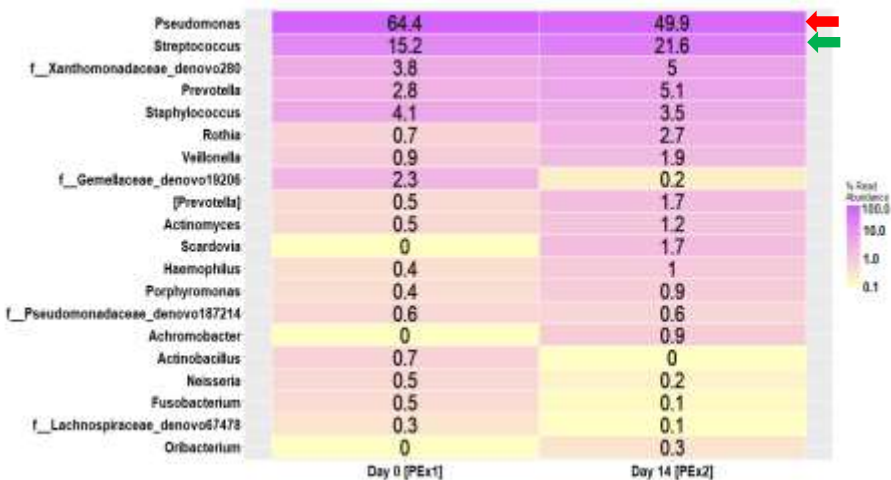
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## Active group: Mean relative abundance



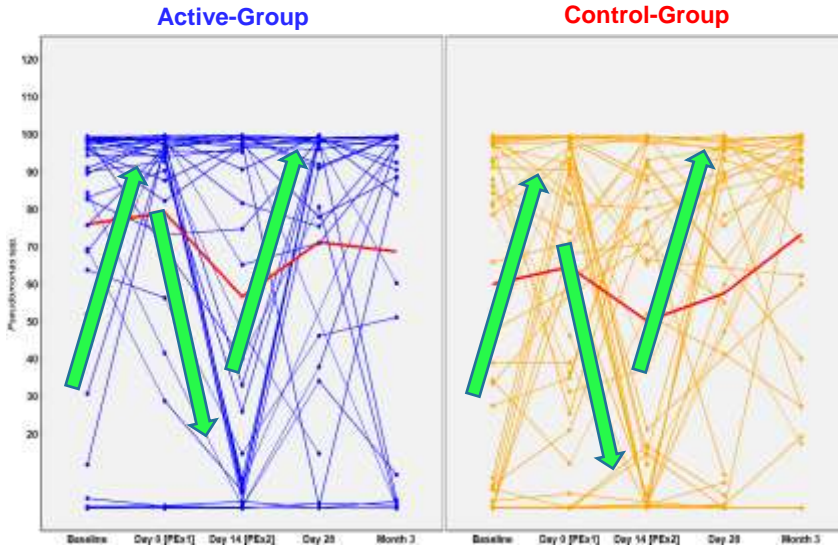
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## Control group: Mean relative abundance



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## Change in *Pseudomonas* spp. relative abundance



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## CFMATTERS: Summary



Are we there yet ? **YES**

### Key findings

Are we willing to use it ? **YES**

- IV Antibiotics work
- Communities resilient over time
- Addition of 3<sup>rd</sup> personalized antibiotic no benefit but doesn't appear to have a detrimental effect

Are people interested ? **YES**

Does it work ? **YES??**



### Limitations

Is it better?

**NOT as an add on to standard therapy**

- Both arms received IV Ceft/Tob
- Not a same day diagnostic microbiome approach

www.cfmatters.eu  
CFMATTERS striving to promote individualised microbiome derived treatment and ensuring access to high quality individualised specialist care

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## Summary/Future work

- **Restoration of CFTR function**
  - **90-95% of mutations covered by 2020**
- **Can we prevent or reverse microbiota evolution?**
- **Telehealth**
  - **Online platform**
  - **Automatic upload of health data from self-assessment equipment**

## Acknowledgements

**QUB** Gisli Einarsson  
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 Deirdre Gilpin  
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