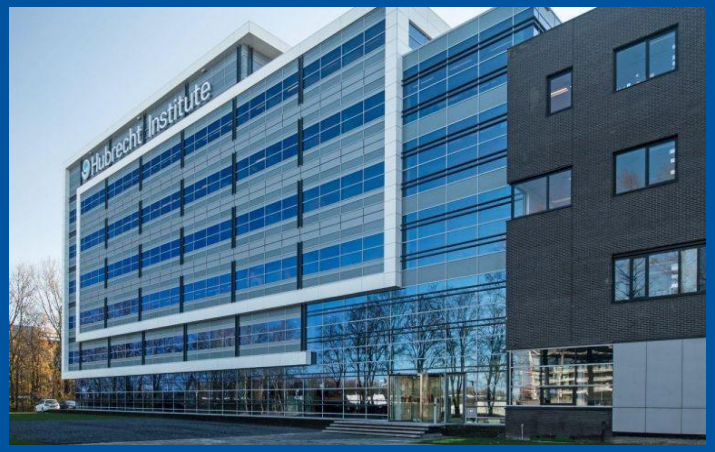
UMC Utrecht

The future starts today:

an update on the role of innovative diagnostic and therapeutic approaches.

November, 2018

Ljubljana, Slovenia



H.G.M. Arets, Pediatric Pulmonologist, MD, PhD, Associate professor Medical education, UMC Utrecht, Utrecht, The Netherlands

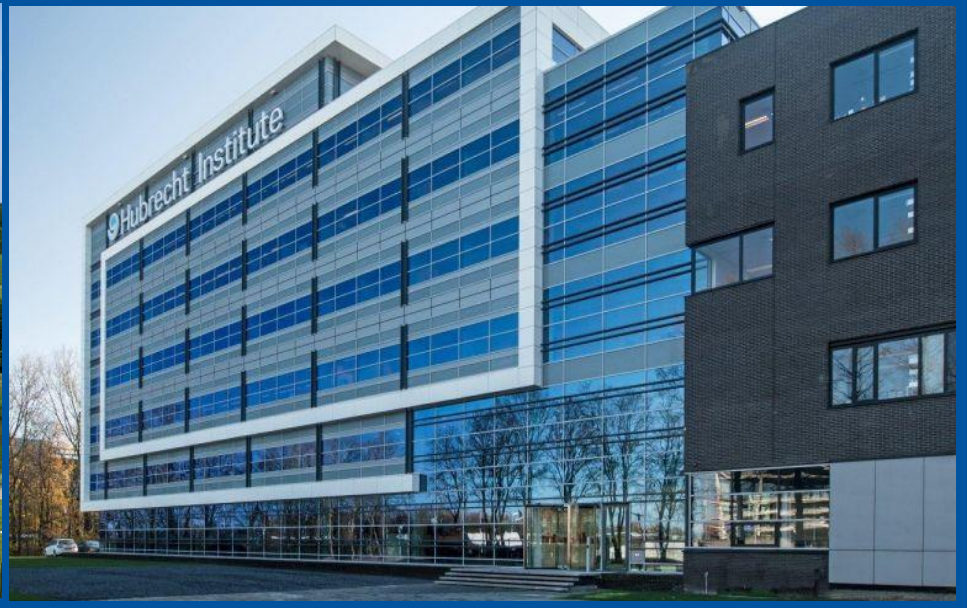
CF center for children UMC Utrecht

University Medical Center Utrecht

CF center for children UMC Utrecht

University Medical Center Utrecht

Clinics and research…

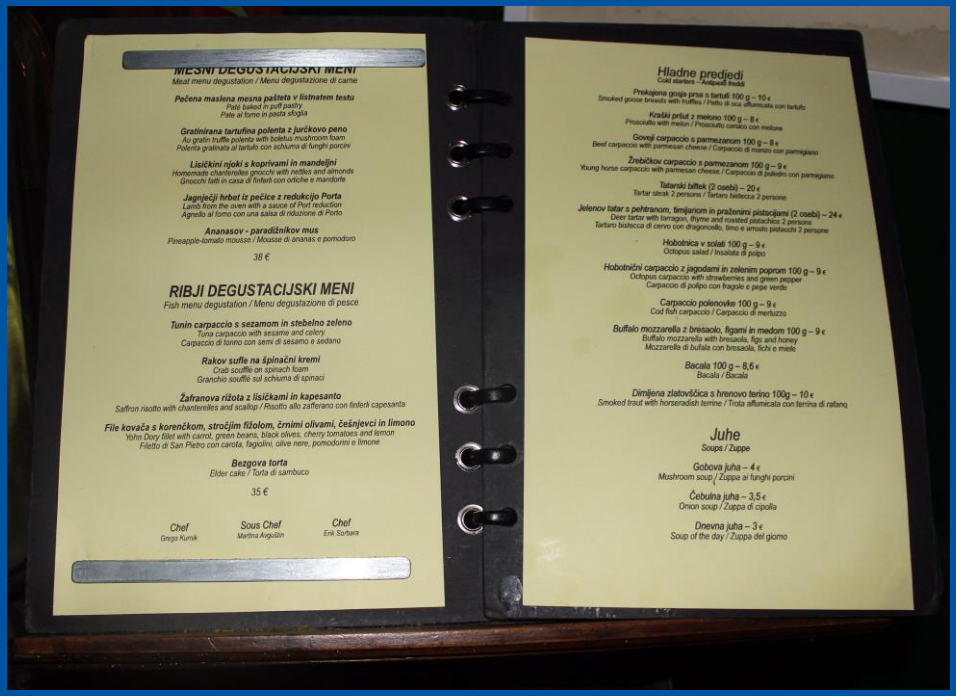


Care and cure…….

Today's Slovenian CF menu……

University Medical Center Utrecht

- Entree: The basics
  - *CF and CFTR*
  - *mutations*
- Main dishes:
  - *Organoids in CF*
  - *New treatments anno 2018*
- Dessert: Looking into the future



Worldwide……..?

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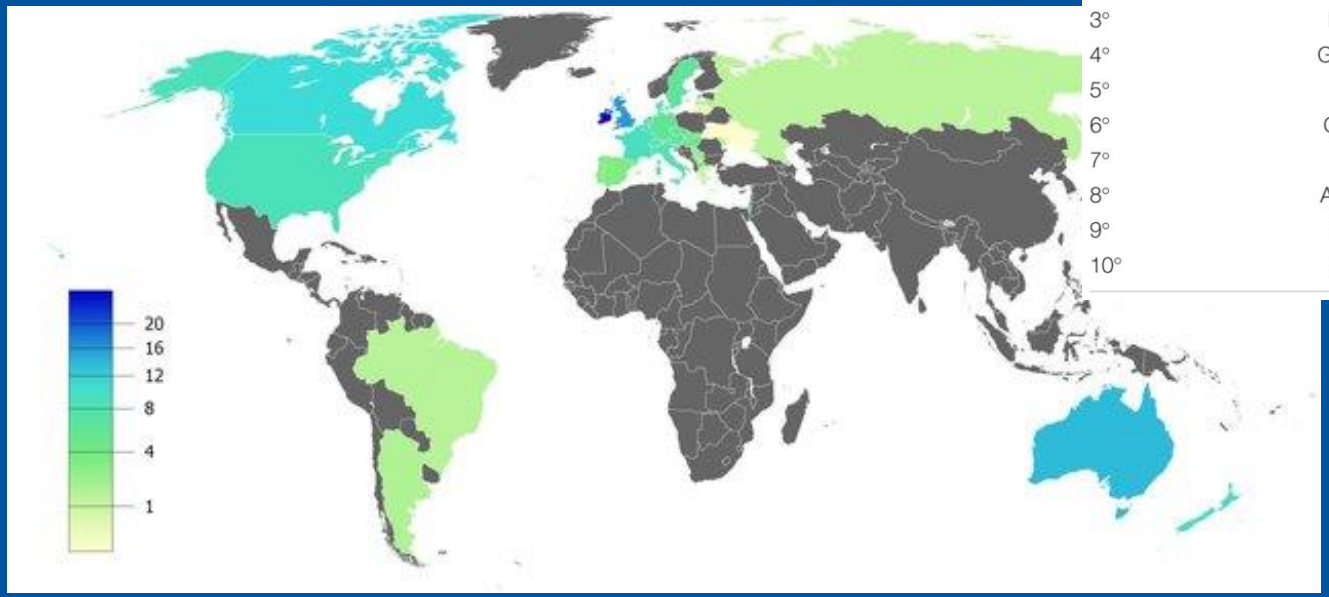


	Registered patients	Per 100,000 habitants
1°	United States	Ireland
2°	United Kingdom	United Kingdom
3°	France	Australia
4°	Germany	Canada
5°	Italy	Belgium
6°	Canada	New Zealand
7°	Brazil	France
8°	Australia	United States
9°	Russia	Switzerland
10°	Spain	Denmark

Estimated prevalence of cystic fibrosis per 100,000 habitants

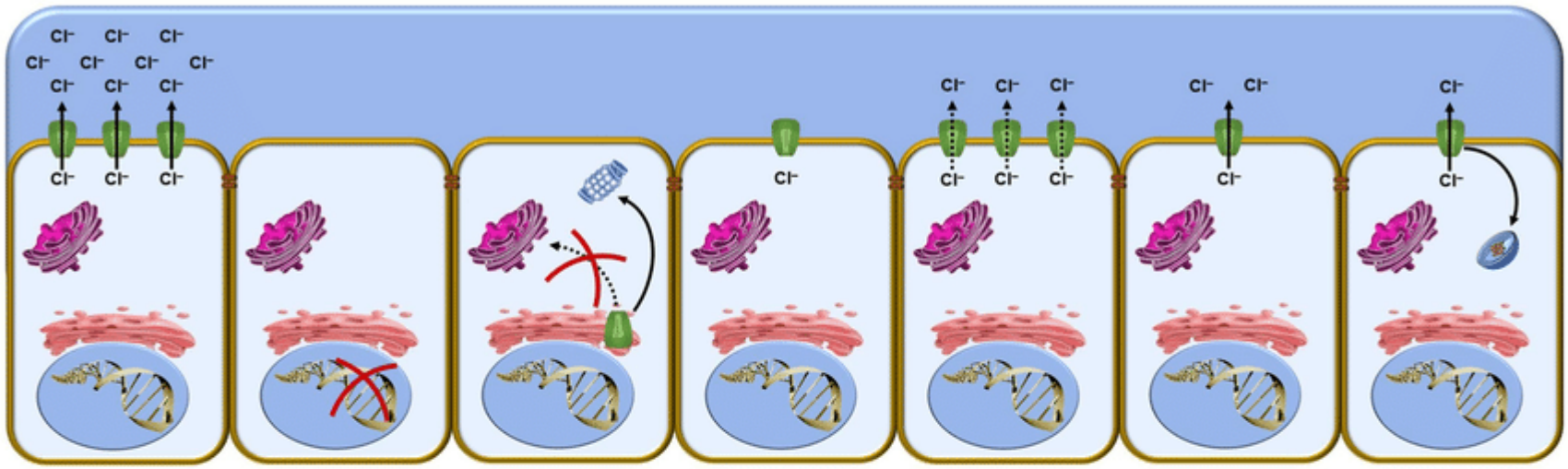
…… few data for South Eastern Europe

What every European country is worst at….

University Medical Center Utrecht

Different genotypes: “Classes”

University Medical Center Utrecht



	wt-CFTR	I	II	III	IV	V	VI
Defect types		**No protein**	**No traffic**	**No function**	**Less function**	**Less protein**	**Less stable**
Mutation examples		G542X R553X W1282X	G85E ~~ΔI507~~ **ΔF508** ~~N1303K~~	V520F S549R G551D	R117H R334W S1235R	A455E 1680-886A>G 2657+5G>A	**rΔF508** Q1412X
Required approaches		Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation / Correct misplicing	Promote protein stability

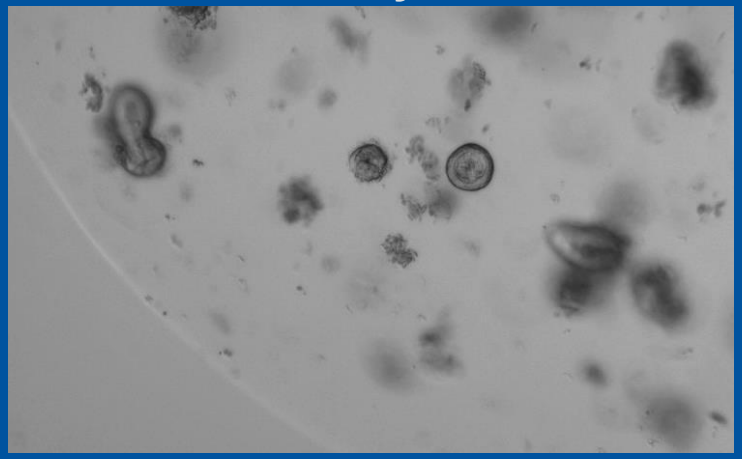
Today's menu of cystic fibrosis

University Medical Center Utrecht

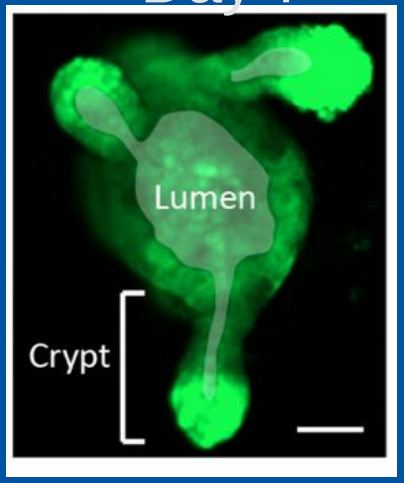
- Entree: The basics
  - *CF and CFTR*
  - *mutations*
- Main dishes:
  - *Organoids in CF*
  - *New treatments anno 2018*
- Dessert: Looking into the future

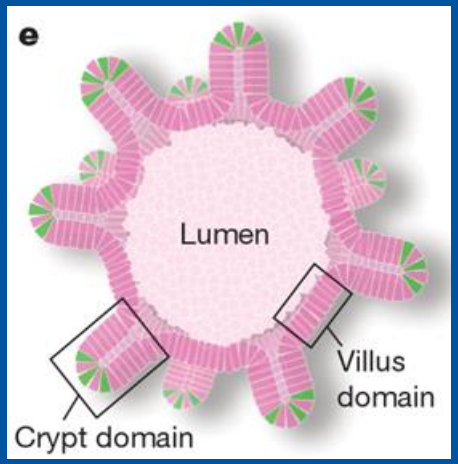
Organoid model

Day 1

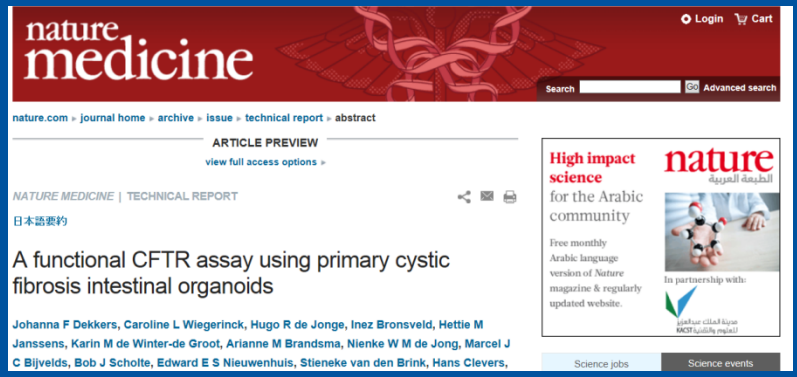


Day 7





- Intestinal stemcel culturemodel: single sample



Crypt isolation and organoid culture

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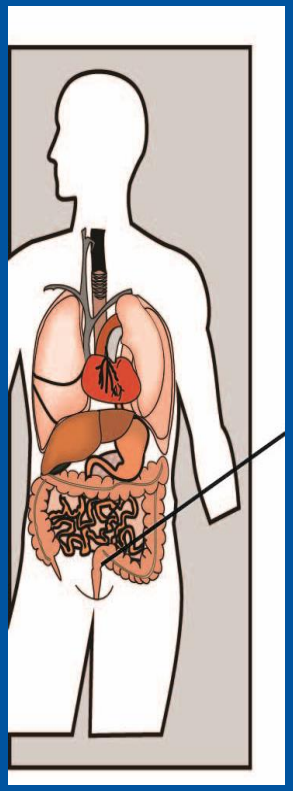
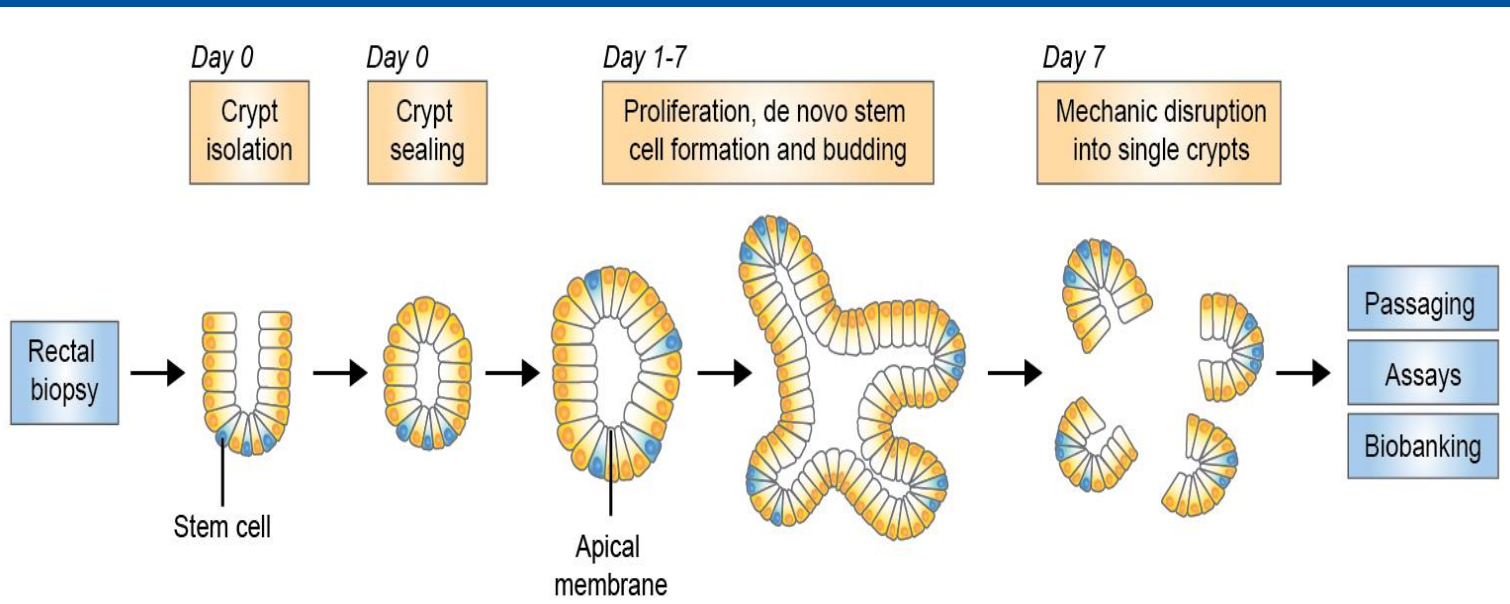
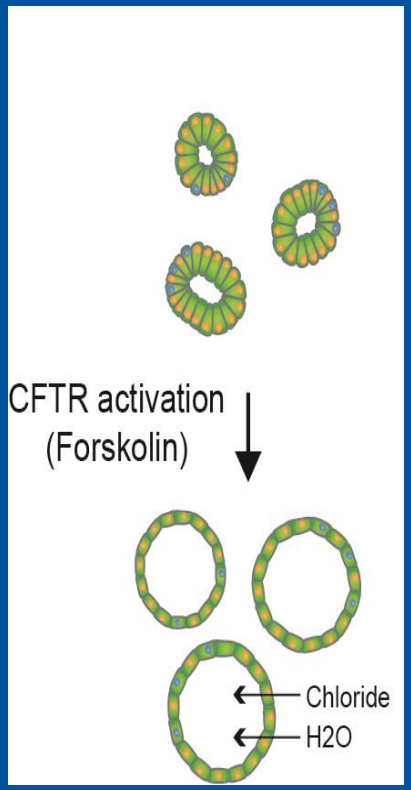


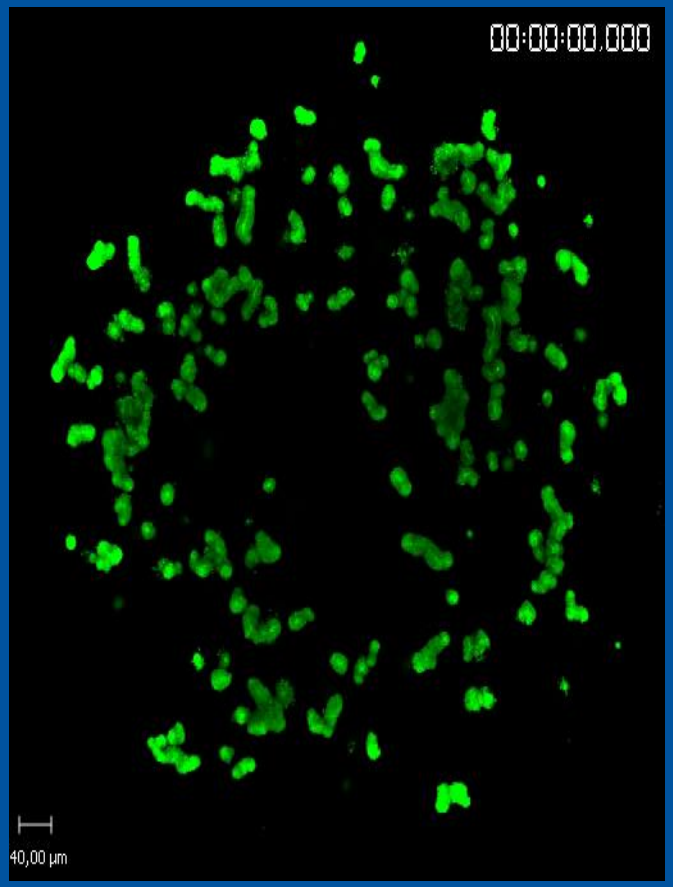


Forskolin-induced swelling (FIS) measures the CFTR activity

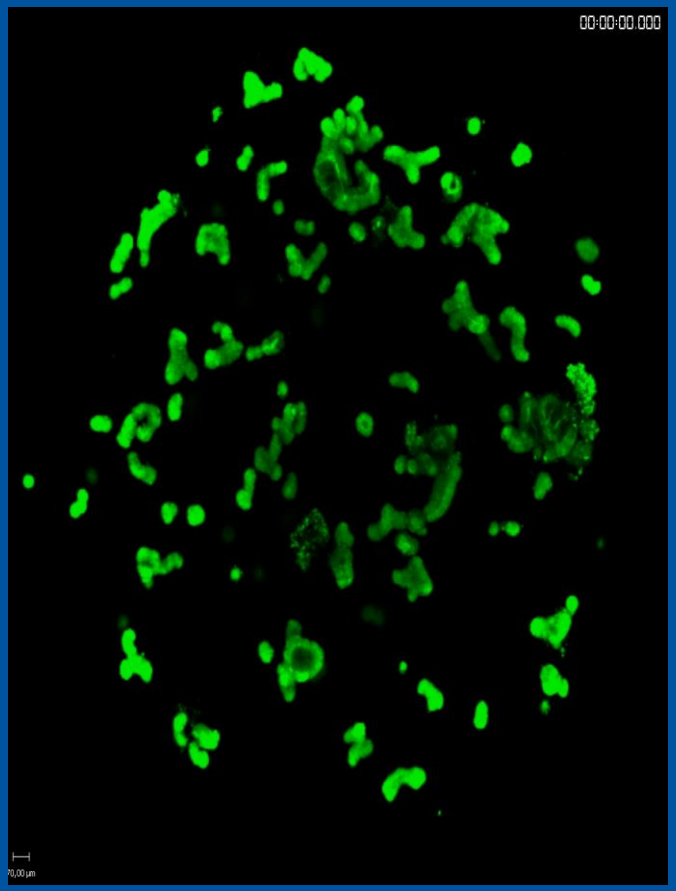
University Medical Center Utrecht



F508del / F508del (severe)



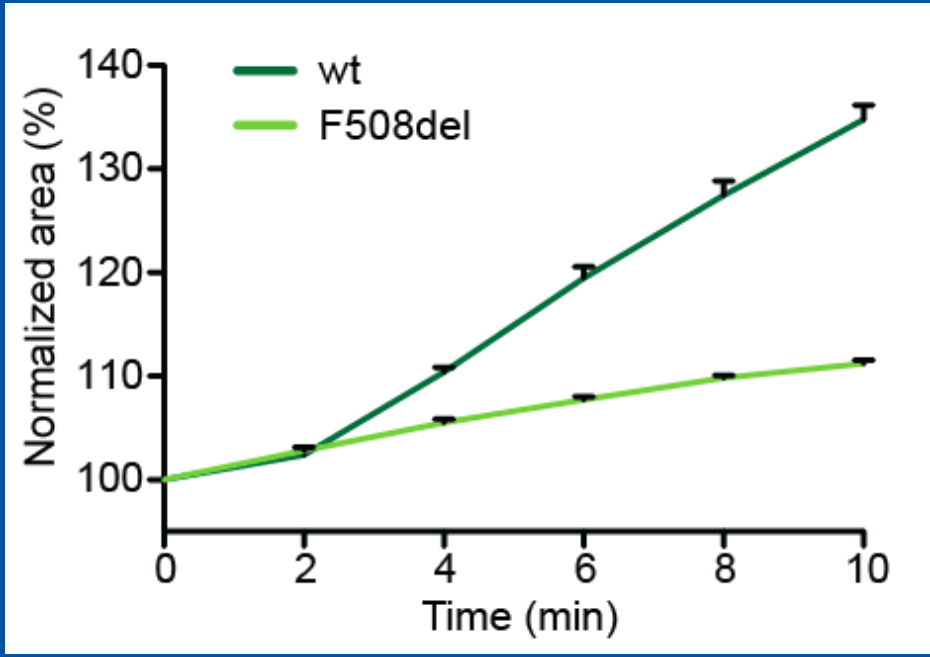
F508del / A455E (mild)

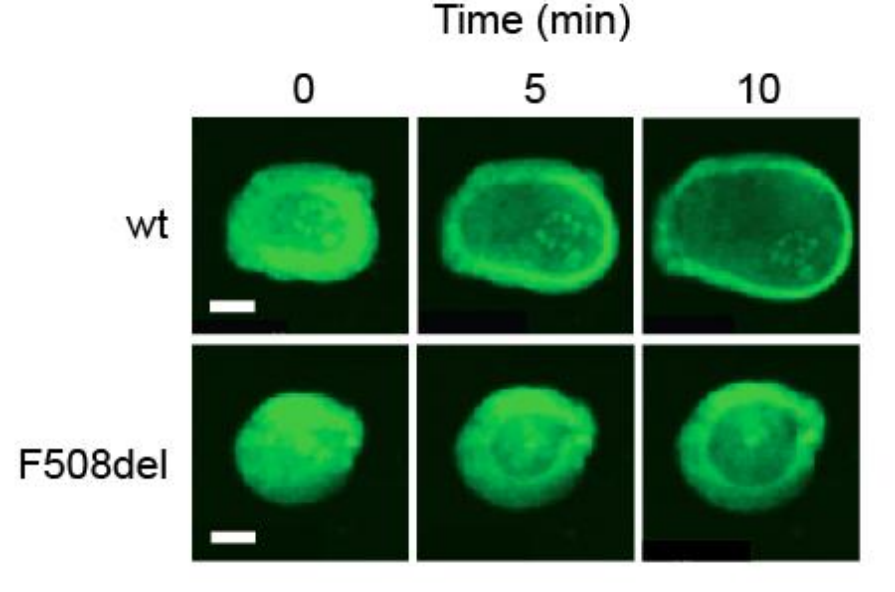


Dekkers *et al.*, Nature Medicine (2013)
Dekkers *et al*. Rare Diseases (2013)

Organoid model discriminates between health and disease

University Medical Center Utrecht





Genotype and CFTR function

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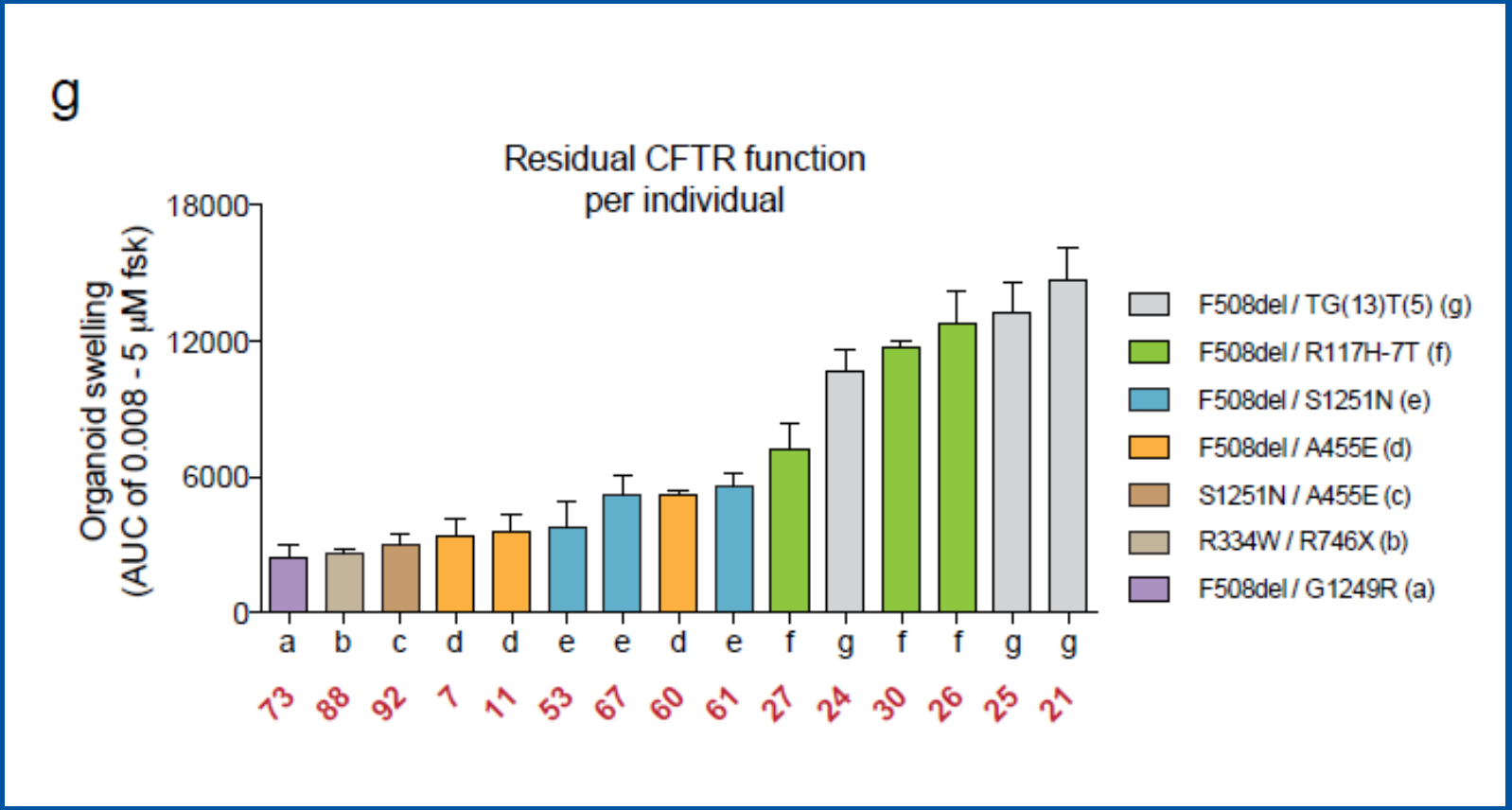
- Correlation genotype and CFTR function
- But variation between patients withn the same genotype:

"there is more than genotype"



Today's menu

University Medical Center Utrecht

- Entree: The basics
  - *CF and CFTR*
  - *mutations*
- Main dishes:
  - *Organoids in CF*
  - *New treatments anno 2018: mutation based and personalised*
- Dessert: Looking into the future

Therapeutic developments and survival

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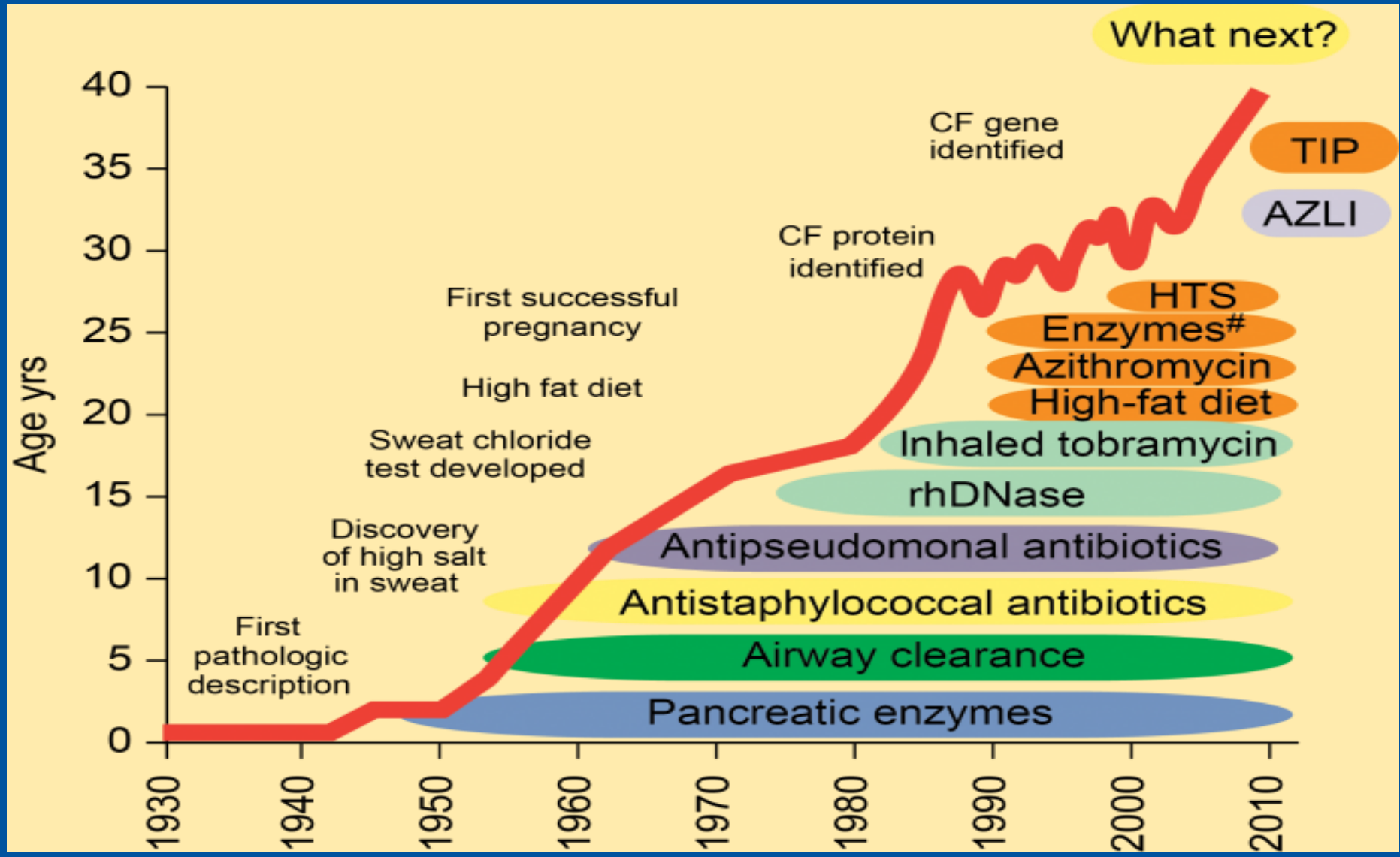

Etiologic (mutation based) treatment

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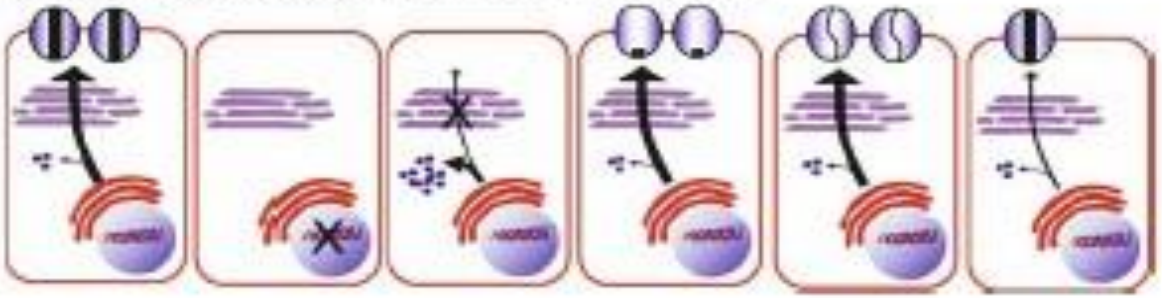
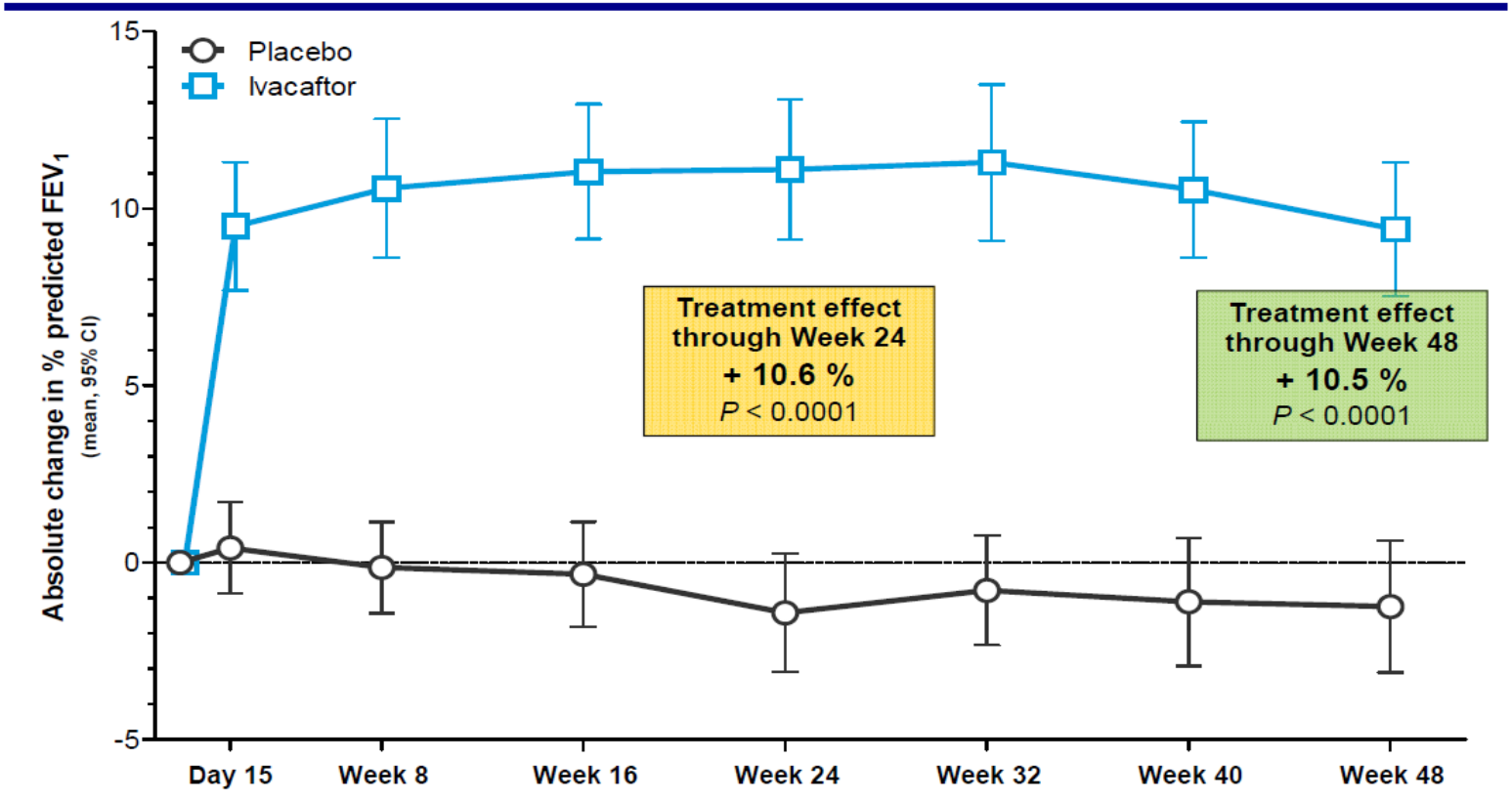
Table 1 CFTR mutant classes and their molecular consequence



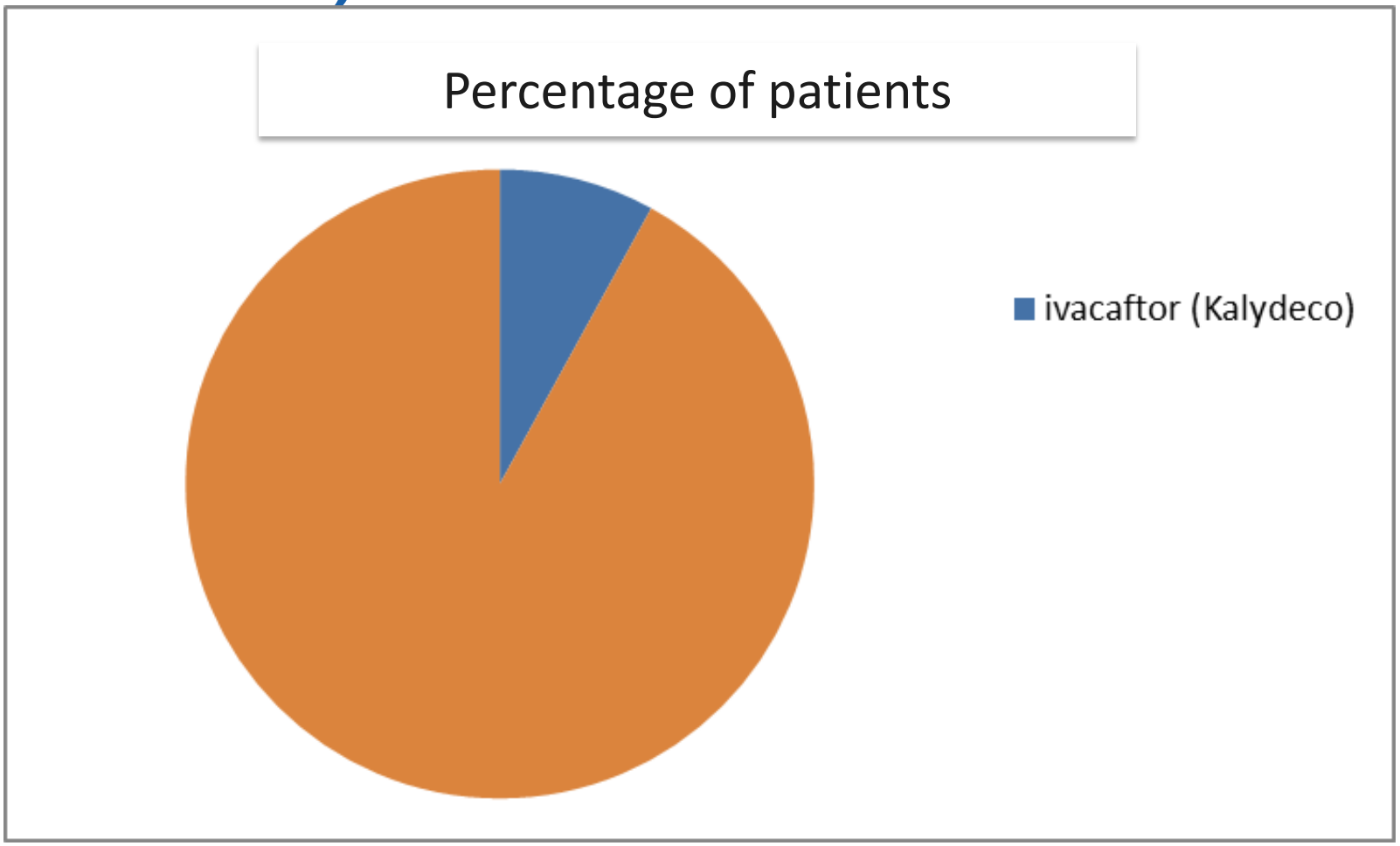
Class	Wt	I	II	III	IV	V
Molecular defect		No synthesis	Reduced processing	Reduced gating	Altered conductance	Reduced synthesis
Prevalence (%)		9	55	4	2	2
Type of mutations		Nonsense frameshift	Missense amino acid deletion	Missense amino acid change	Missense amino acid change	Missense amino acid change, alternative spicing
Common genotypes		G542X W1282X	ΔF508 N1303K	G551D	R117H	A445E 2789+5G→A
Desease severity		Severe	Severe	Severe	Moderate–mild	Moderate–mild
Potential therapy		PTC-124	Corrector potentiator	Potentiator	Potentiator	Potentiator

Ivacaftor (potentiator) in G551D



Ramsey et al., N Engl J Med. 2011 Nov 3;365(18):1663-72

Ivacaftor for G551D (and other gating mutations)……



Lumacaftor/ivacaftor in 2xdF508

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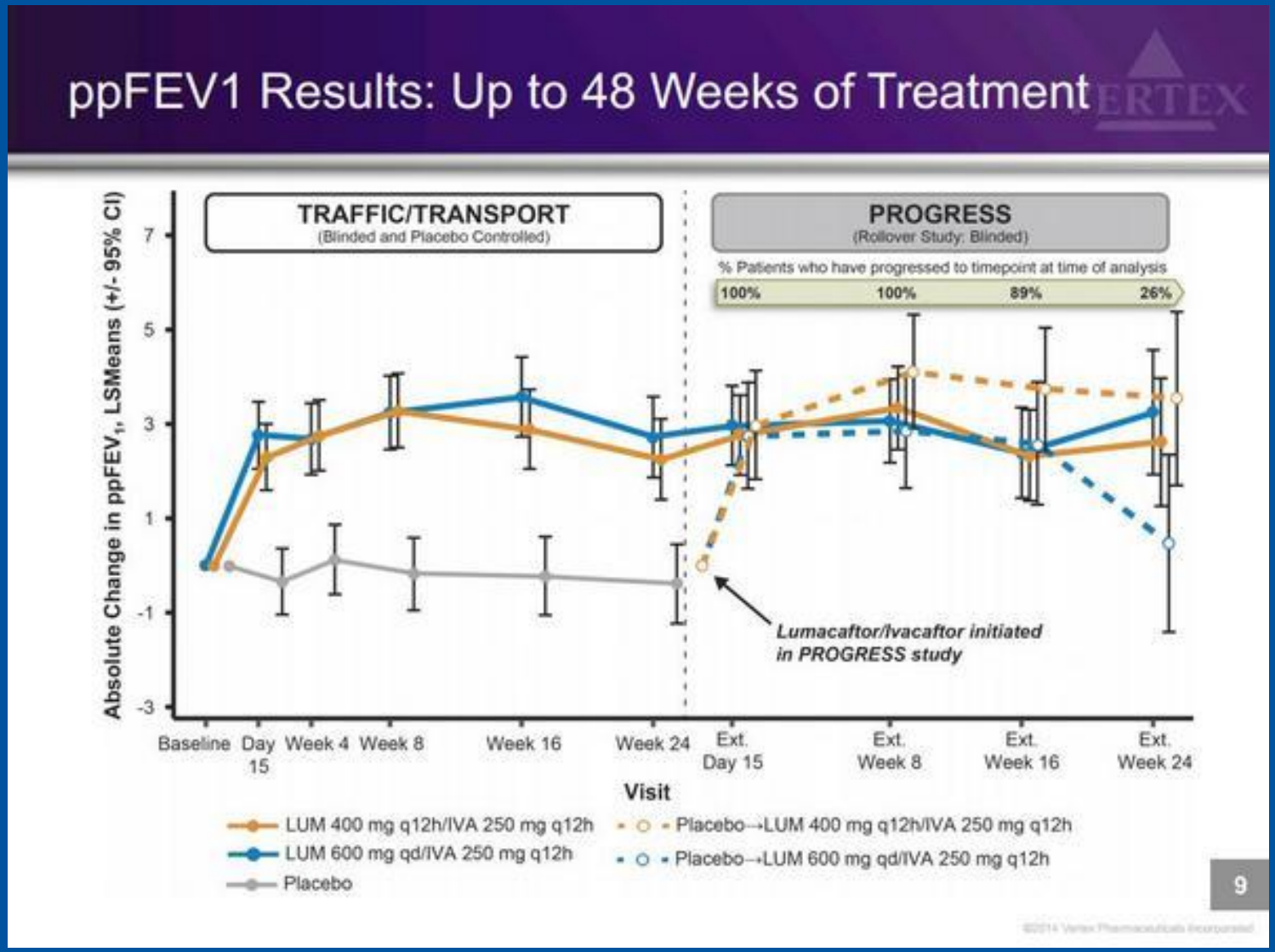
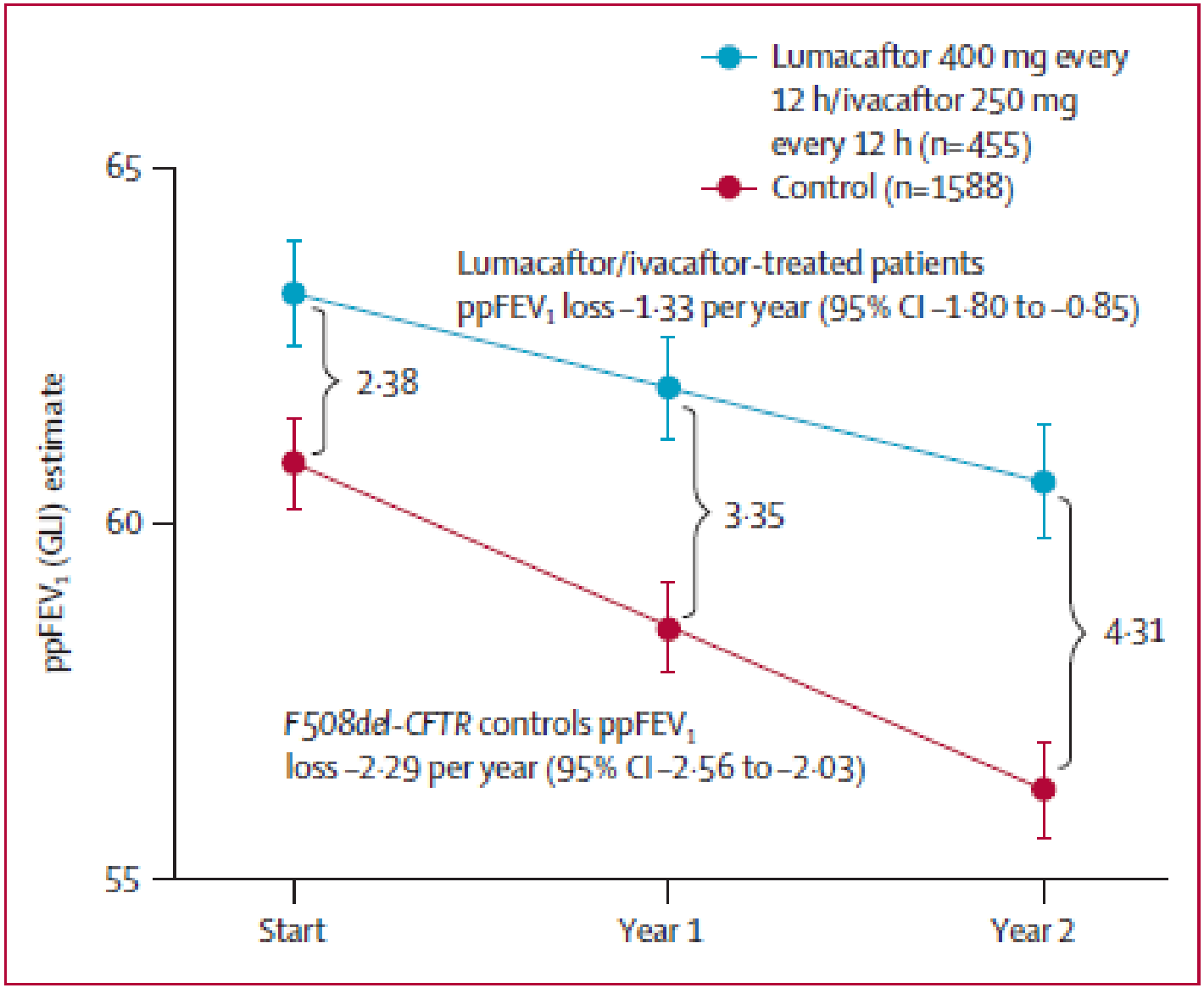
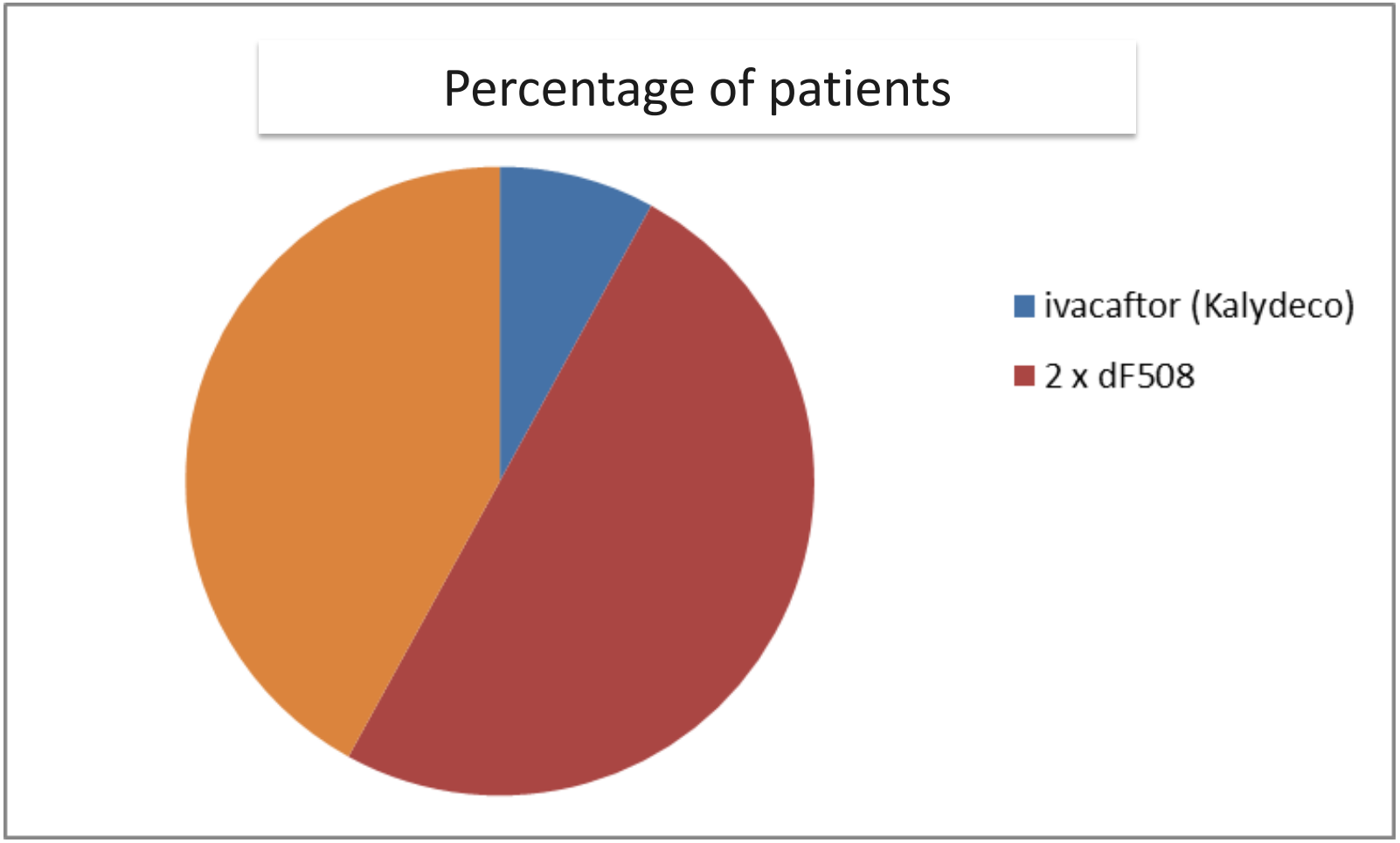
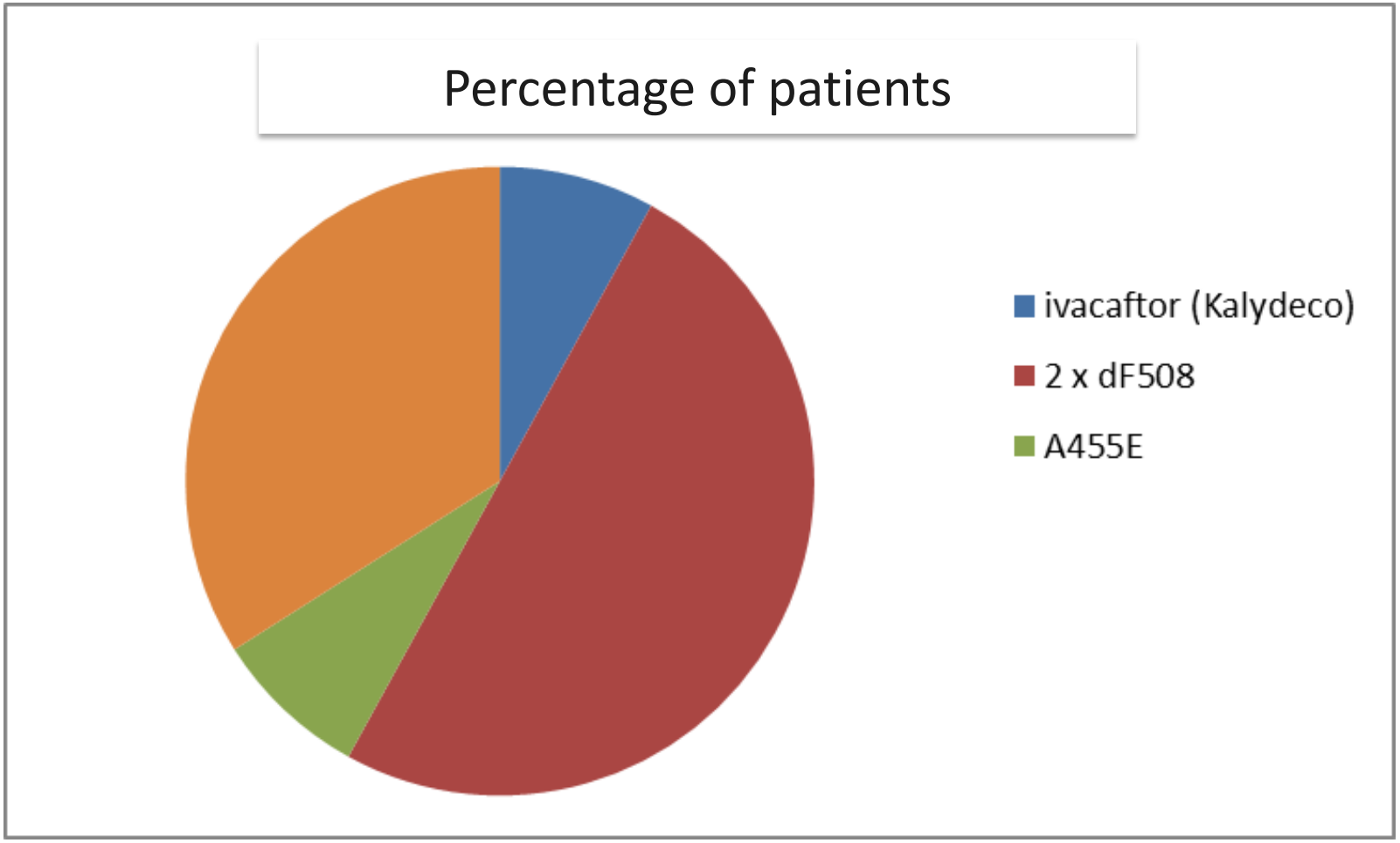



Lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h (n=455)
Control (n=1588)
Lumacaftor/ivacaftor-treated patients
ppFEV1 loss –1·33 per year (95% CI –1·80 to –0·85)
2·38
3·35
4·31
F508del-CFTR controls ppFEV1 loss –2·29 per year (95% CI –2·56 to –2·03)
ppFEV1 (GLI) estimate
65
60
55
Start
Year 1
Year 2

Orkambi for homozygous dF508



Orkambi for A455E



Personalised treatment effect?

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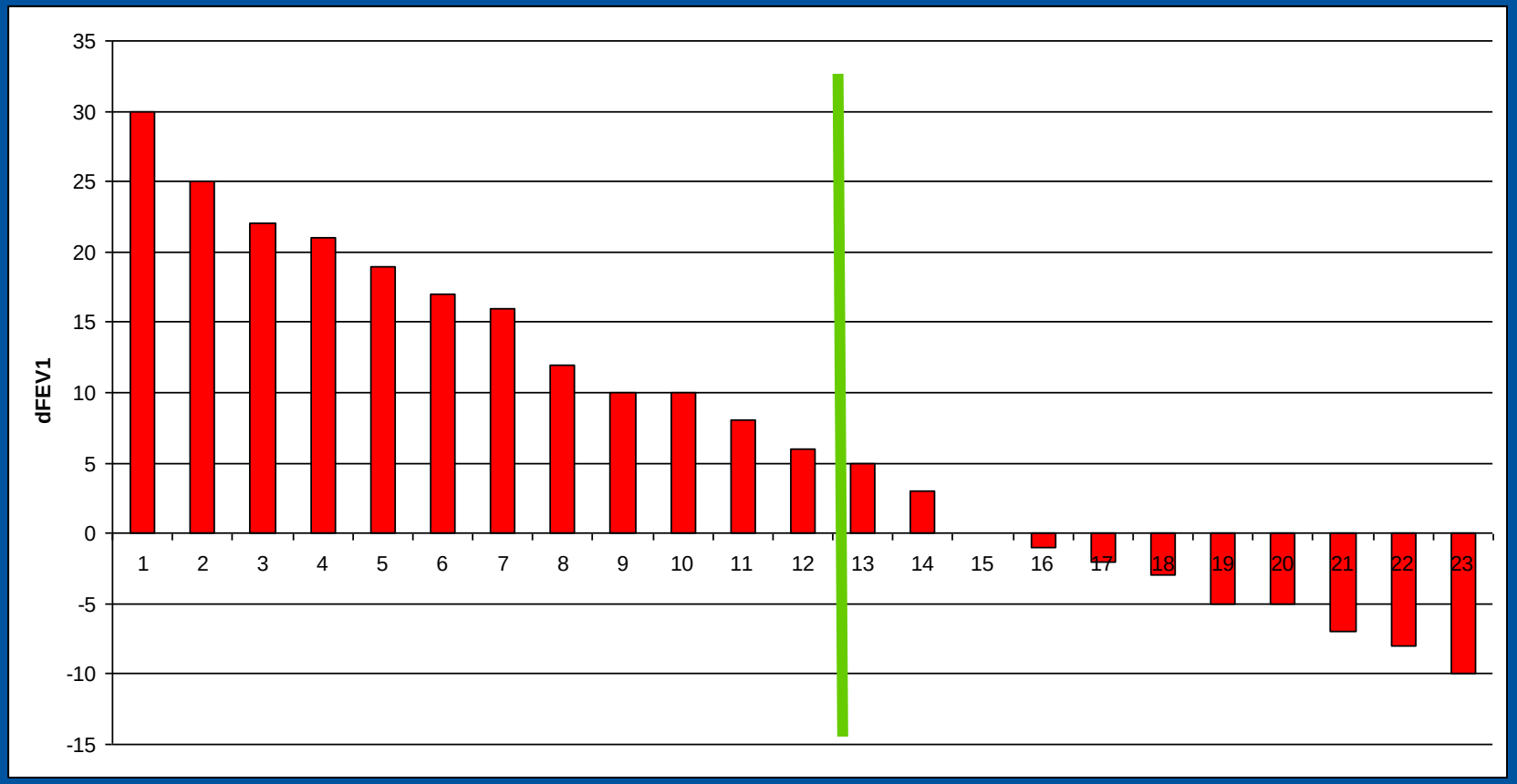

- VX770/VX809 (ivacaftor/lumacaftor; Orkambi®) for dF508 homozygous patient

Genotype does not “perfectly” predict therapy response

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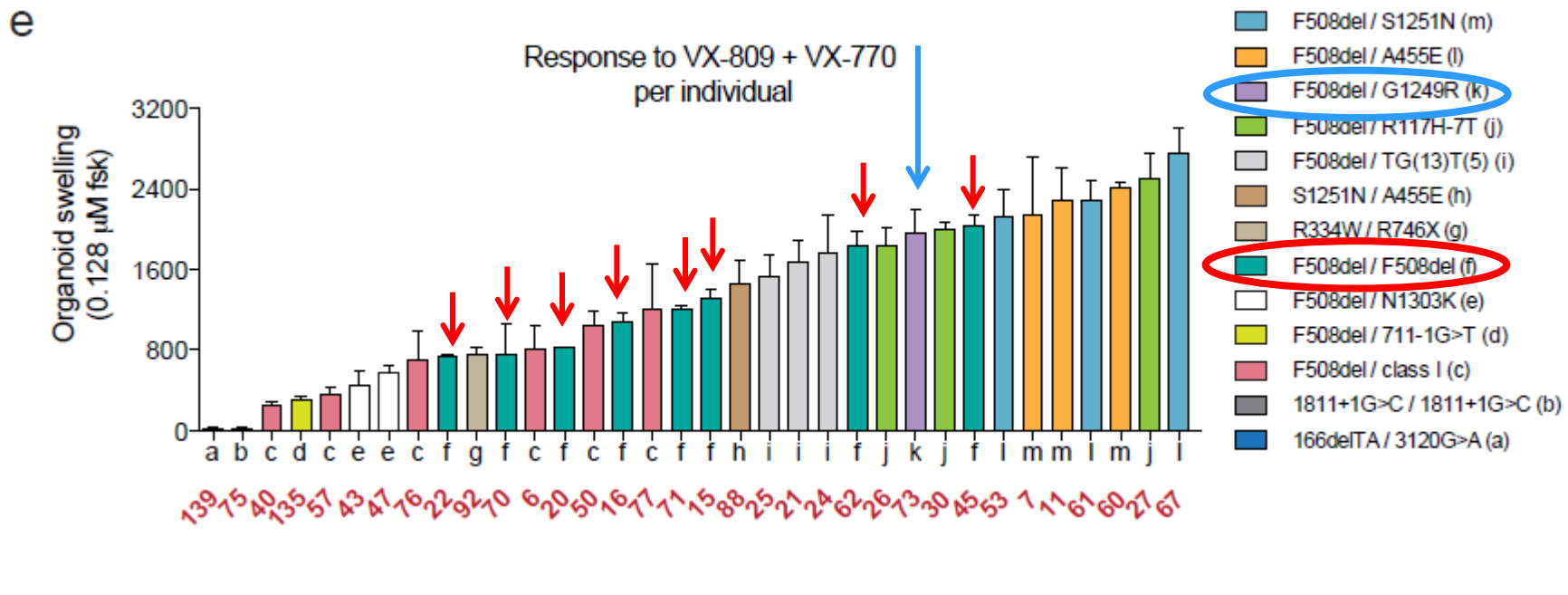

.....and rare mutations can be “compared to known mutation

- *Typing of CFTR restfunction*
- *Typing of possible treatment effects?*

Today's menu

University Medical Center Utrecht

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- Dessert: Looking into the future

What's next?

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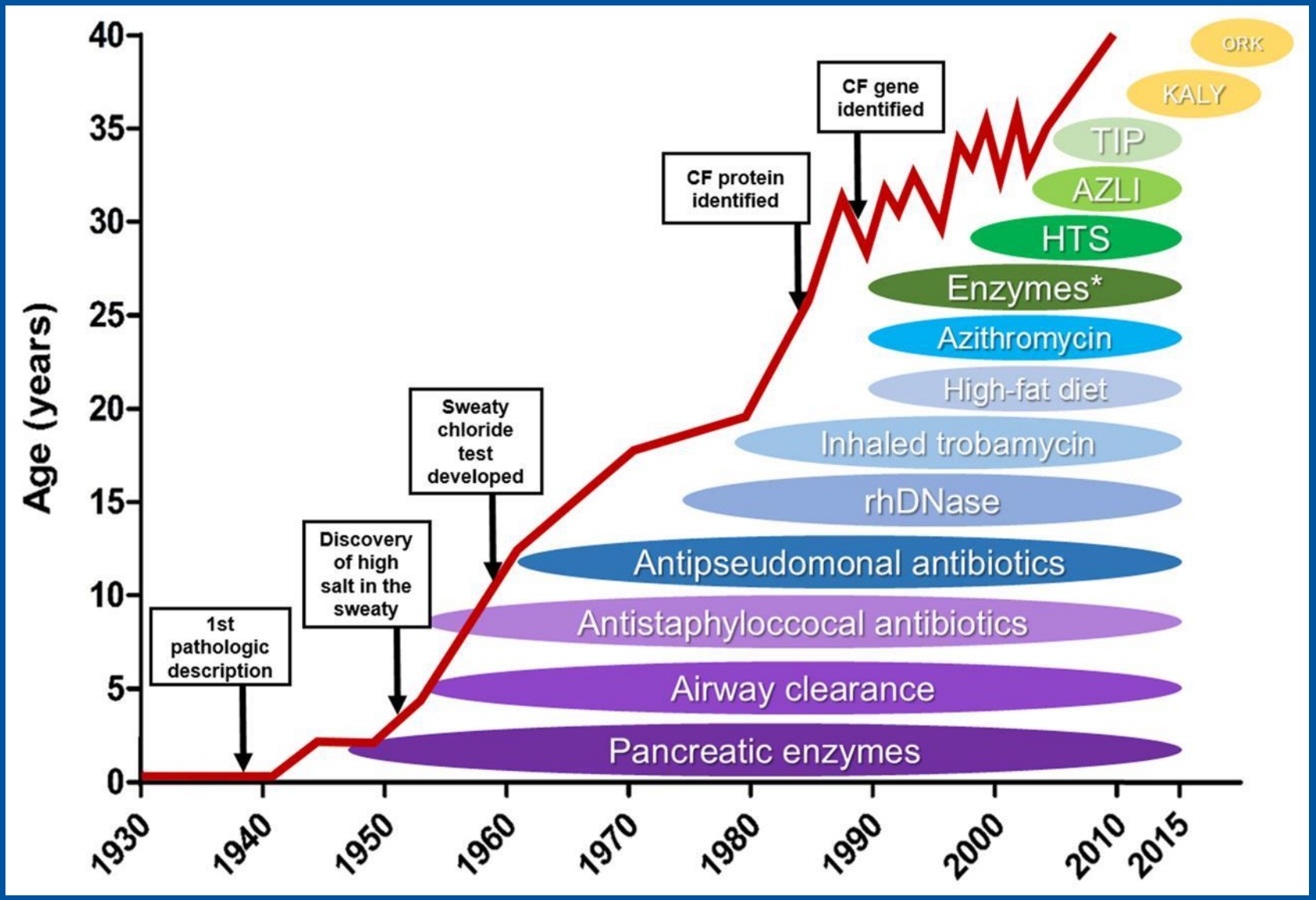

The future…… in 2018!

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1. Can we do better for responders??
   - *Improvement of existing drugs for 2xdF508*
     - Tez/iva for lum/iva: somehat better effect
     - Triple combinations:

2. Can we do better for non-responders
   - *New drugs for new indications/mutations?*
   - *The patient with rare mutations > no studies (possible)*
     - Rainbow/HIT CF

1. Better for responders?

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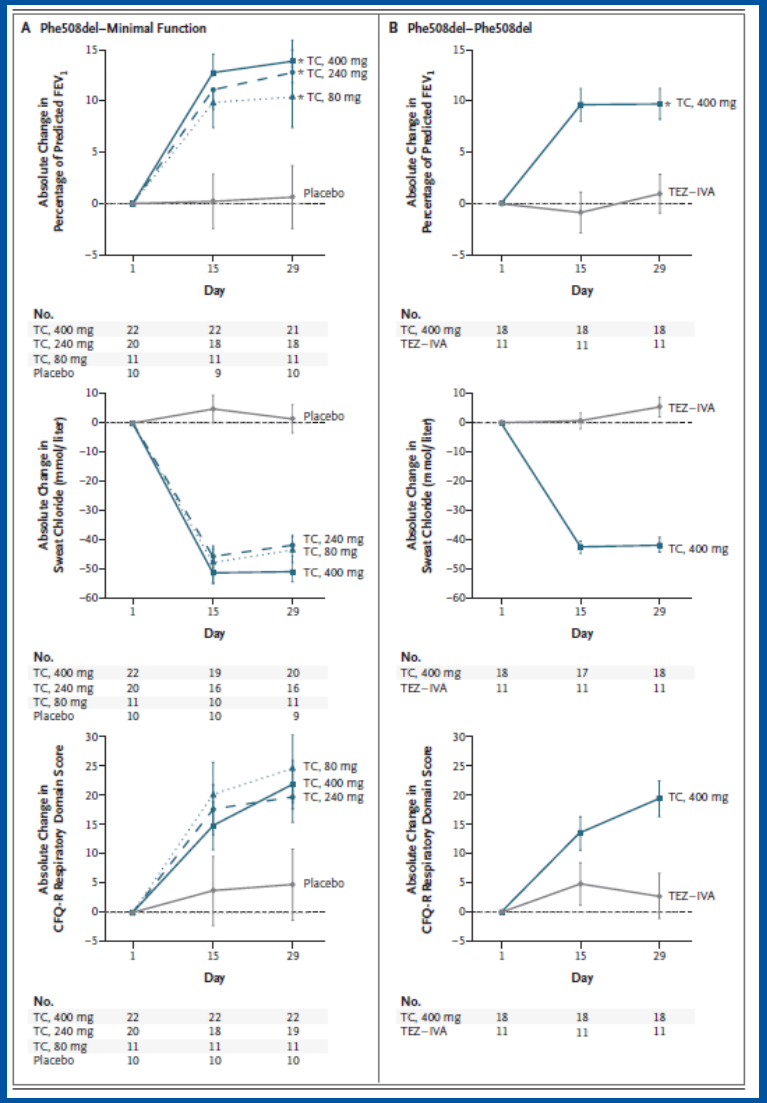
ORIGINAL ARTICLE

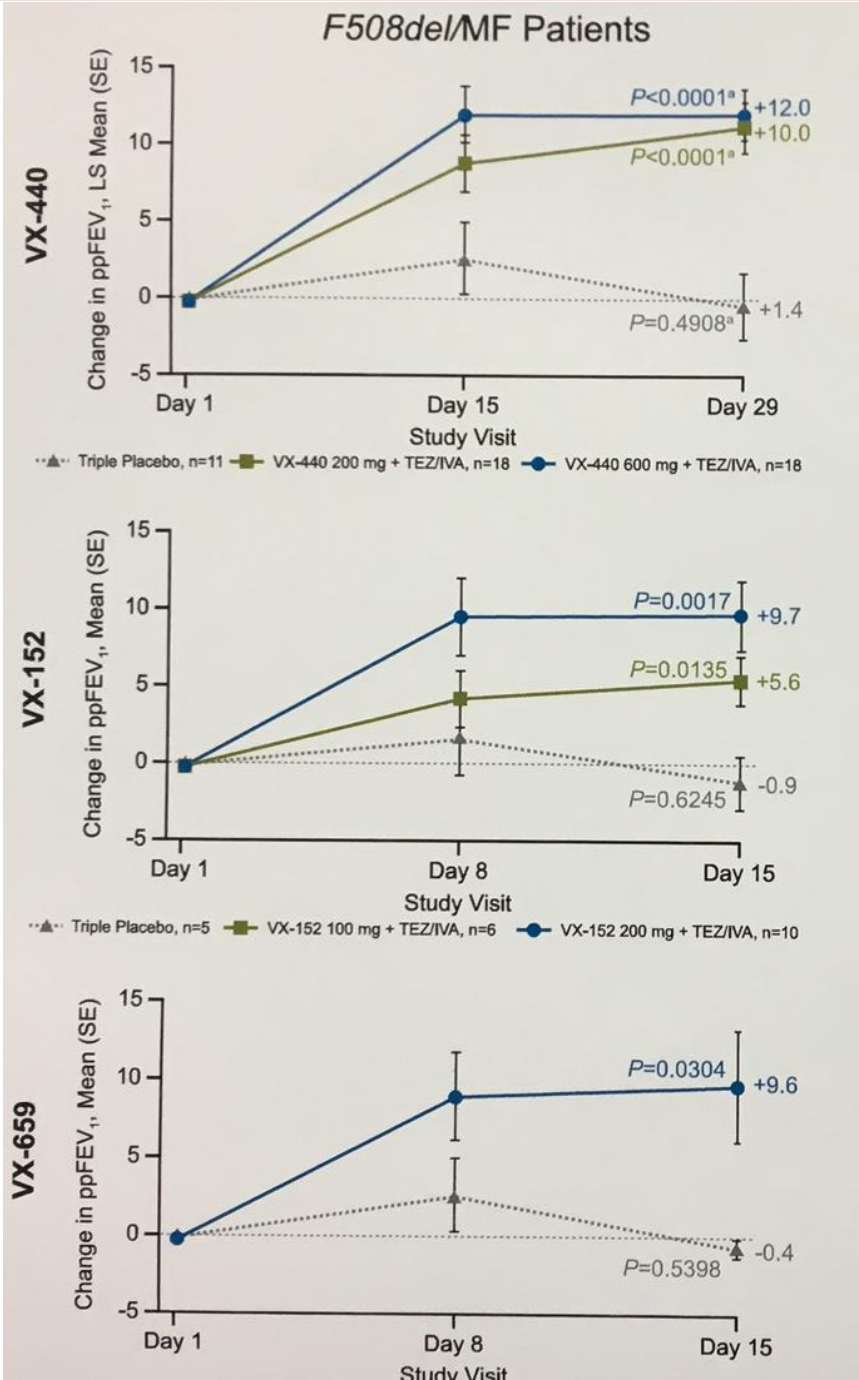
VX-659–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles

J.C. Davies, S.M. Moskowitz, C. Brown, A. Horsley, M.A. Mall, E.F. McKone, B.J. Plant, D. Prais, B.W. Ramsey, J.L. Taylor-Cousar, E. Tullis, A. Uluer, C.M. McKee, S. Robertson, R.A. Shilling, C. Simard, F. Van Goor, D. Waltz, F. Xuan, T. Young, and S.M. Rowe, for the VX16-659-101 Study Group*

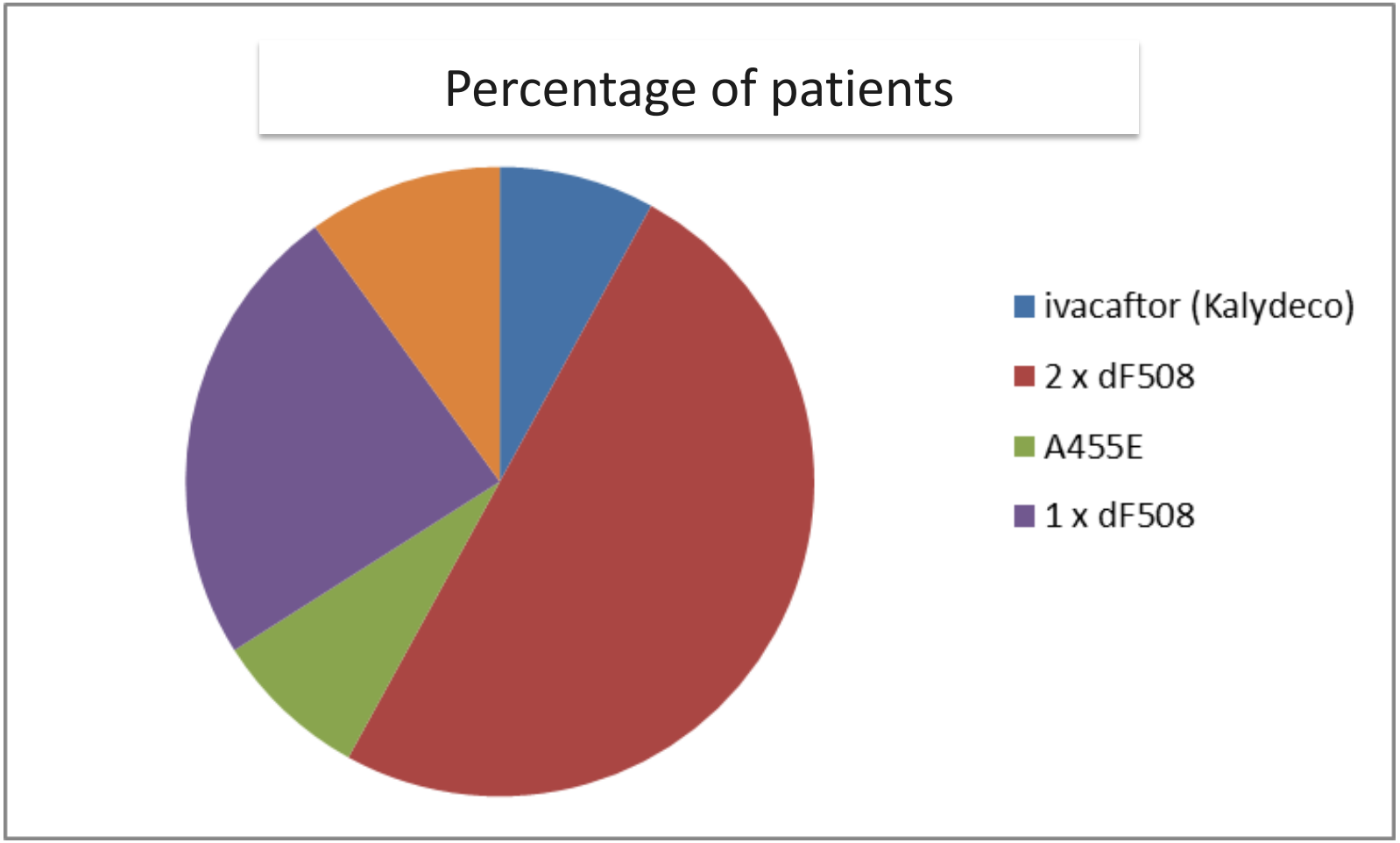


Triples?

Next generation?

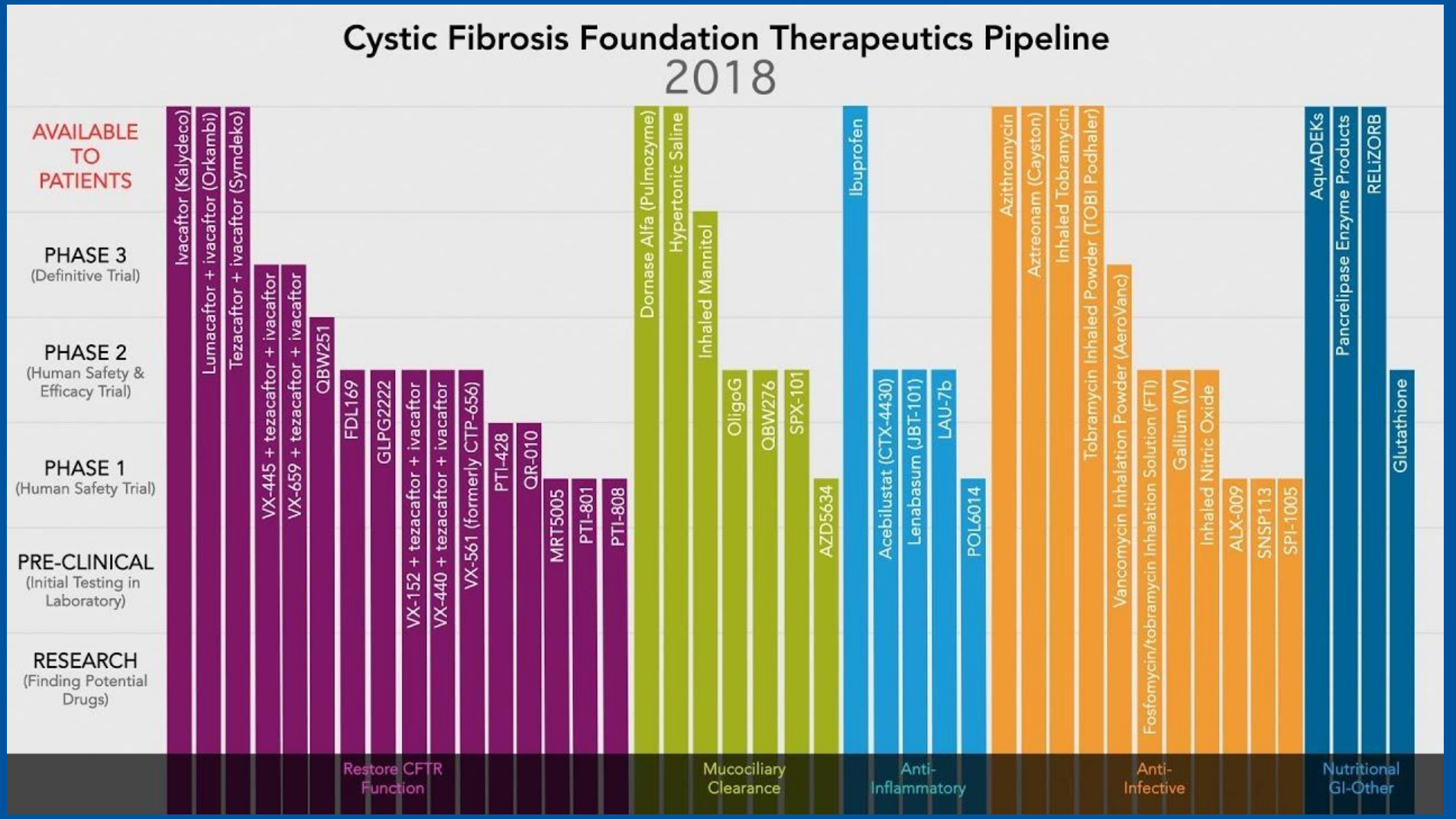


NextGen for one dF508



3. New drugs: where are we in 2018?

University Medical Center Utrecht



CFTR modulators….. not only Vertex

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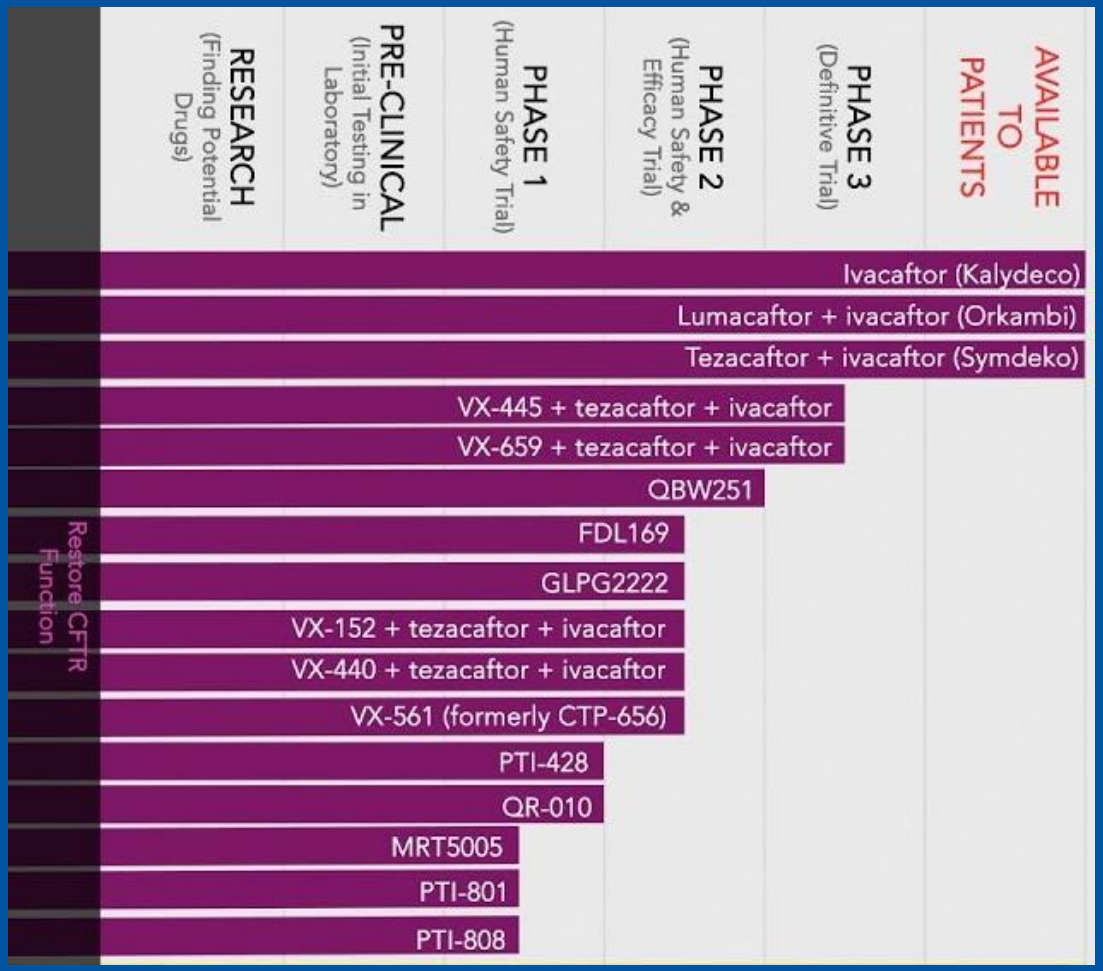
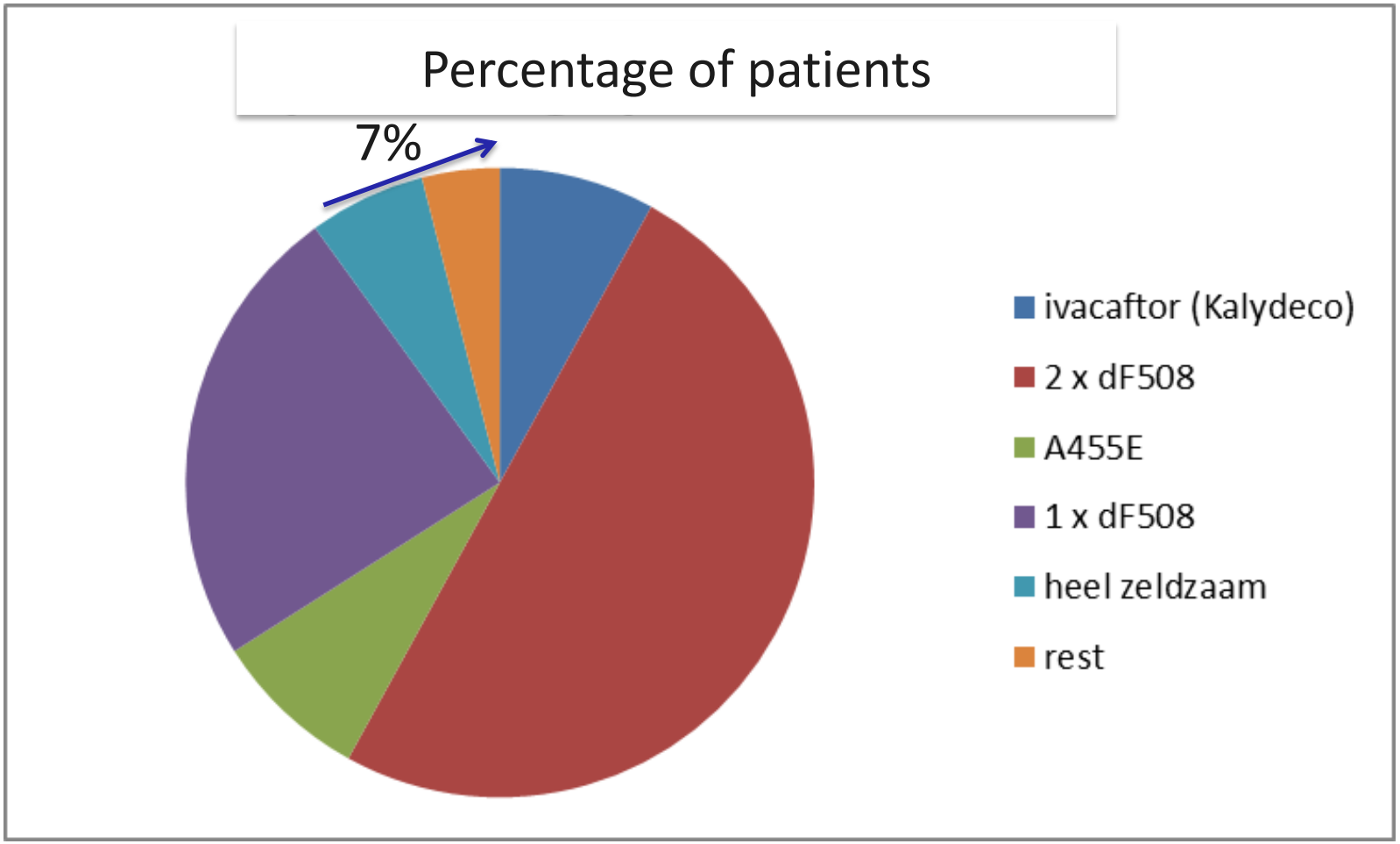


Vertex

others

93% can be treated in 2020s…..
(only) stop mutations and very rare mutations are still very difficult…….



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How to reach the last 7 -10 percent of patients?

2. Rare mutations: Rainbow project

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- Study of all rare mutations (prevalence <0.5%)
  - *In NL around 100 patients*
- Typing of organoid function
- > extended drug screen

January 2018 EU funded initiative on cure for the rare

University Medical Center Utrecht

Goals of the Project

iversity Medical Center
Utrecht

- Access to CFTR-modulating drugs for patients with rare CFTR-mutations
- Personalized CF treatment using organoids
- Generate easily accessible Biobank for future CF-research

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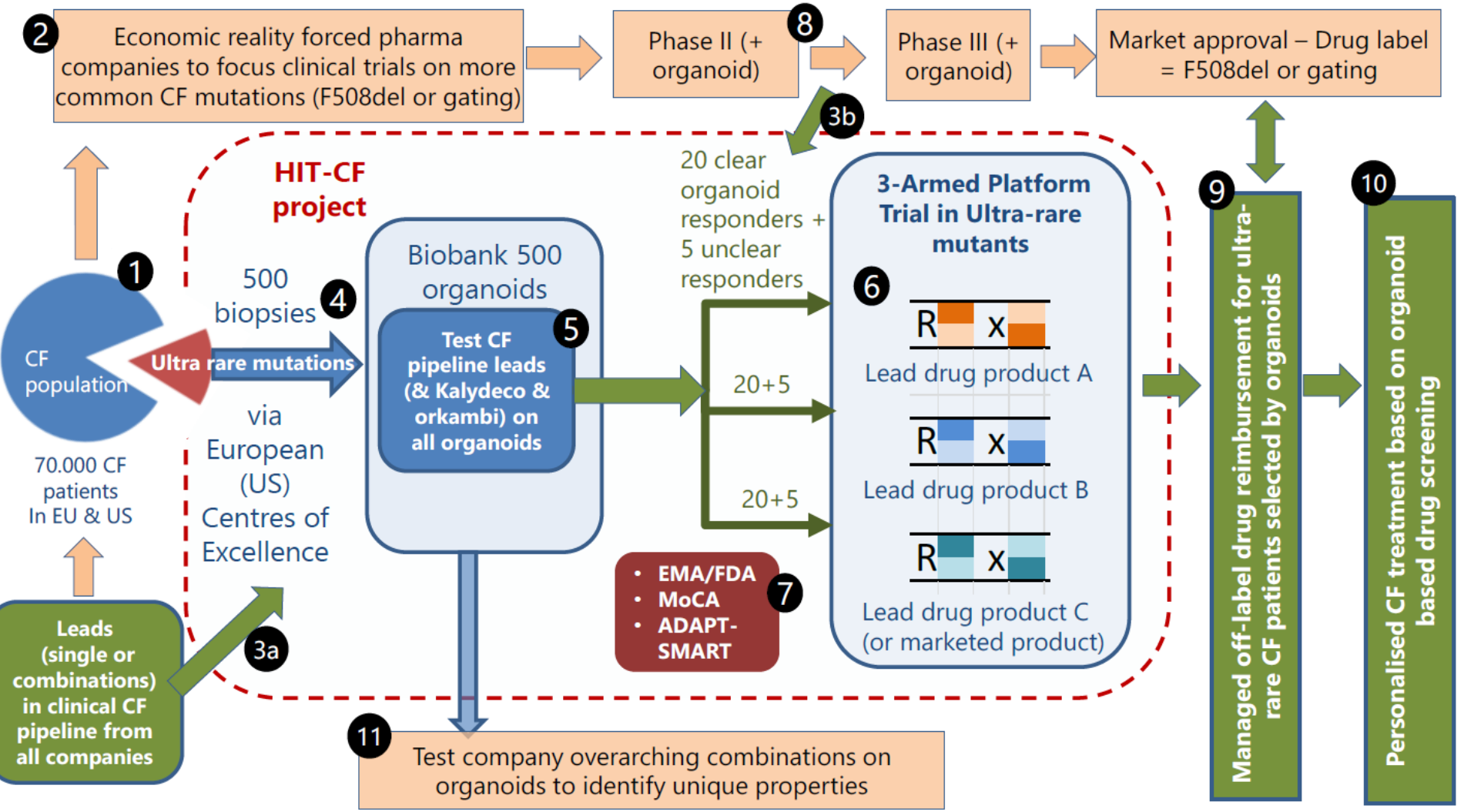
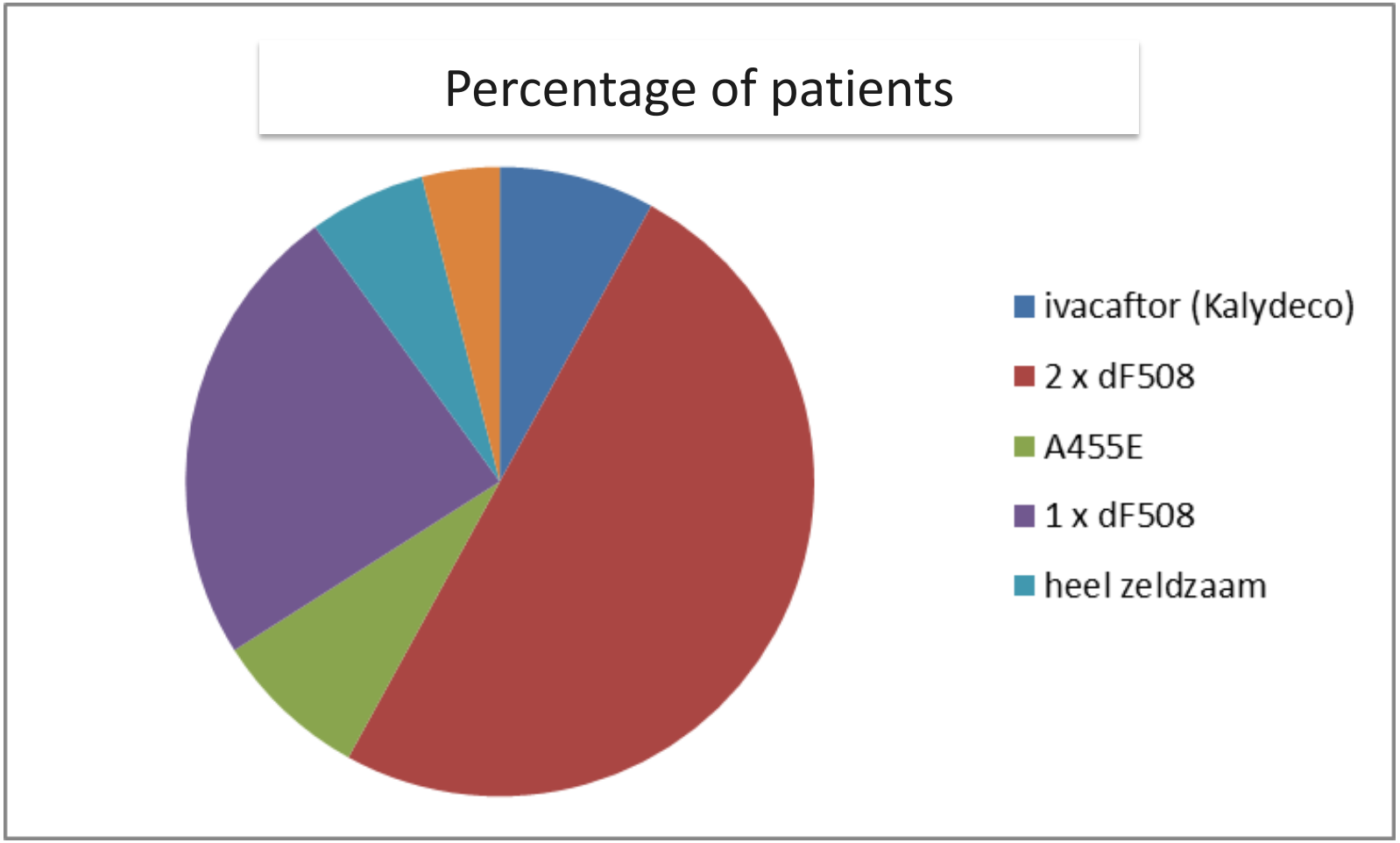


Very rare mutations



In conclusion…….

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- Life expectancy now almost 50 years
- Quality of life improvement
- In 2020 effective medication for 93% of all patients?
- Organoids and new treatment options “collaborate” to reach personalised treatment

Thanks for your attention and happy to answer your questions……

University Medical Center Utrecht

Greetings from Utrecht
the Netherlands