

What constitutes a simple, reliable,
message for outcome in a rare disease?

An argument for governments from the ECFRG

1. **Historical Context** podcast
2. **European CF**
3. **EU versus non EU (2003)**

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University of Dundee, Scotland

For full details see: www.lancet.com (header section: audio; march20)

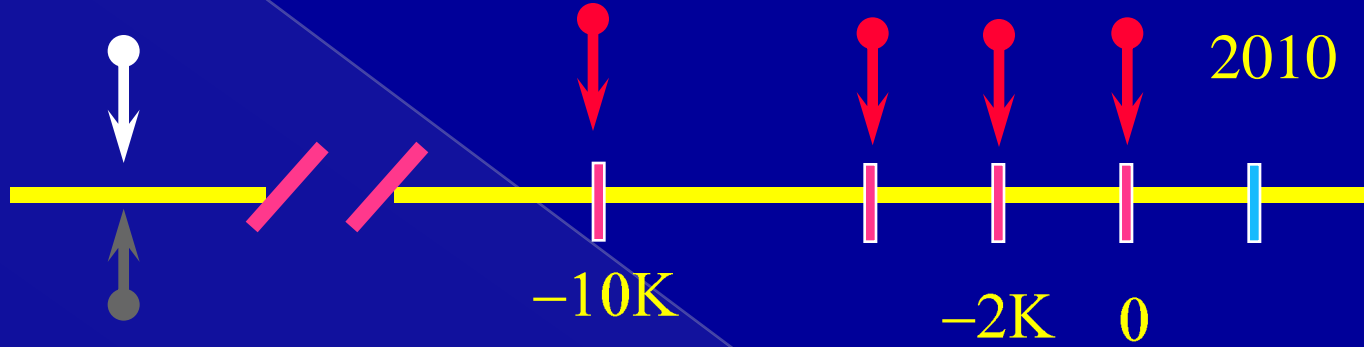
Imagine the first modern human carrier of CF

We are here

$\Delta F508$, F508del
or Phe508del

10K

2010



-10K

-2K

0

50,000 years ago

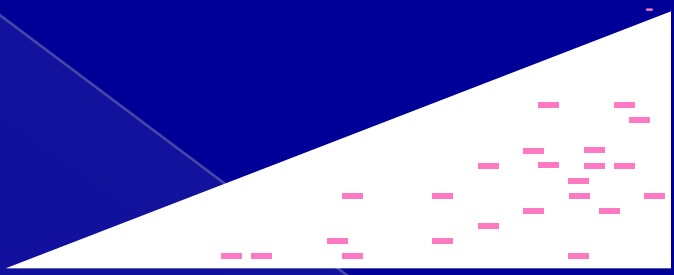
Population

3 base pairs lost on chromosome
7 in a single gene *cftr*

-



Fibrogenicum (- us or - a)



Today's Europeans are the survivors of the 25% amongst which fibrogenicum is a super-survivor

- **F508deleted (recessive) CFTR carriage is common**
- **Randomly, every 50th - 80th European has it in single copy**
 - > this creates an unbiased source population sample
 - > (genetic incidence of carriage is known in Europe)



- **BUT 2 copy carriage is lethal without therapy by 5yrs**
 - > Mortality-reducing Therapy is relatively affordable
 - > set the budget (see paper by Sims et al 2007 in the *Lancet*)

EuroCareCF partnered with
European CF Registry ECFS

2006
FP6



www.eurocarecf.eu

Work Package 2
Data Centre

Dundee

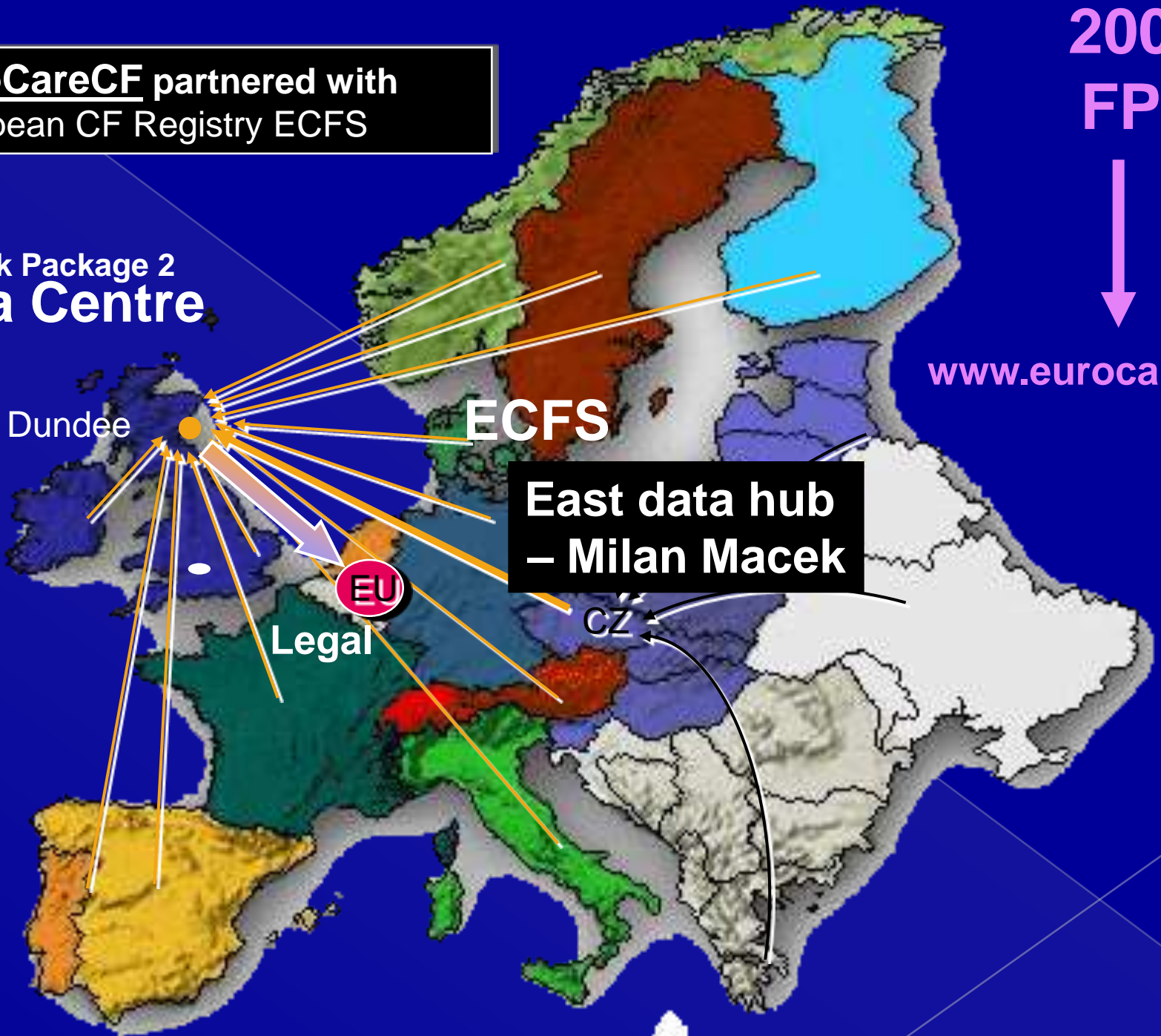
ECFS

**East data hub
– Milan Macek**

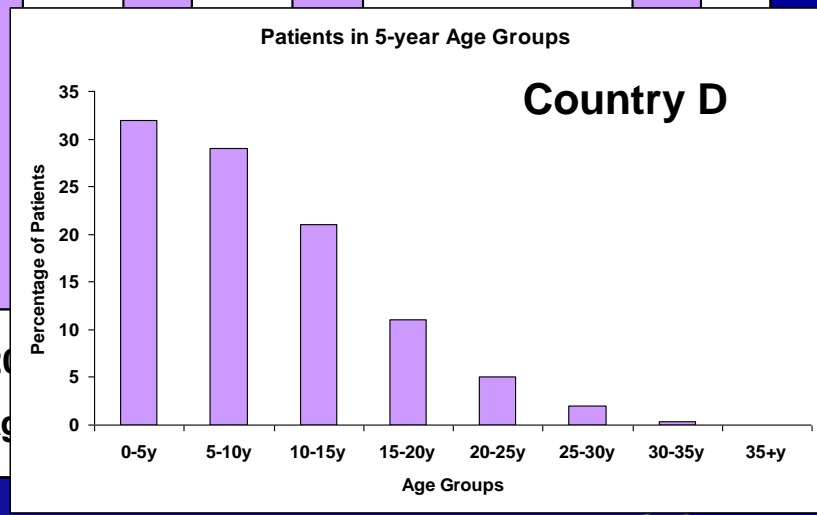
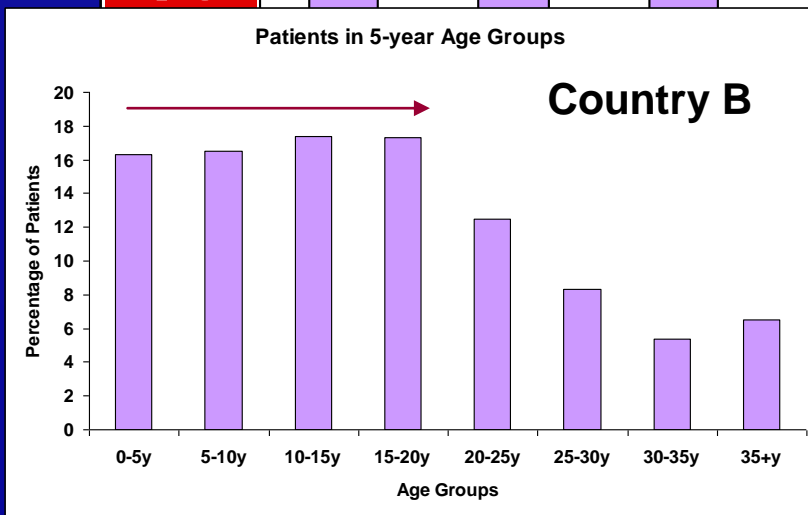
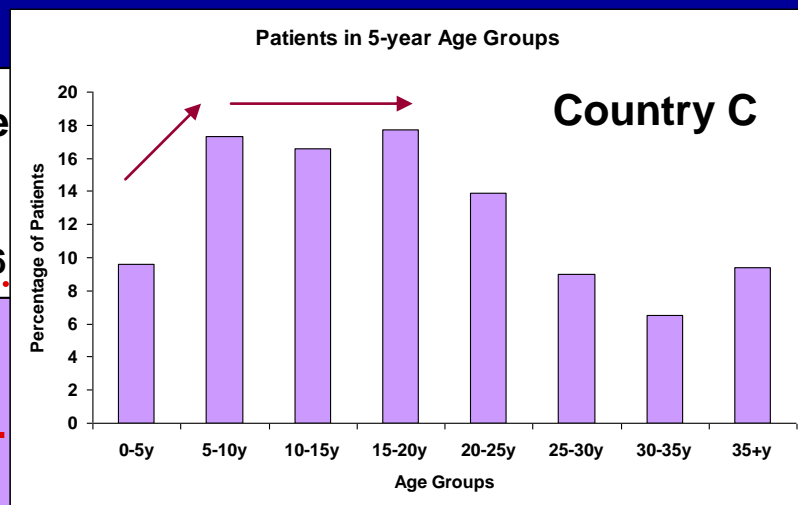
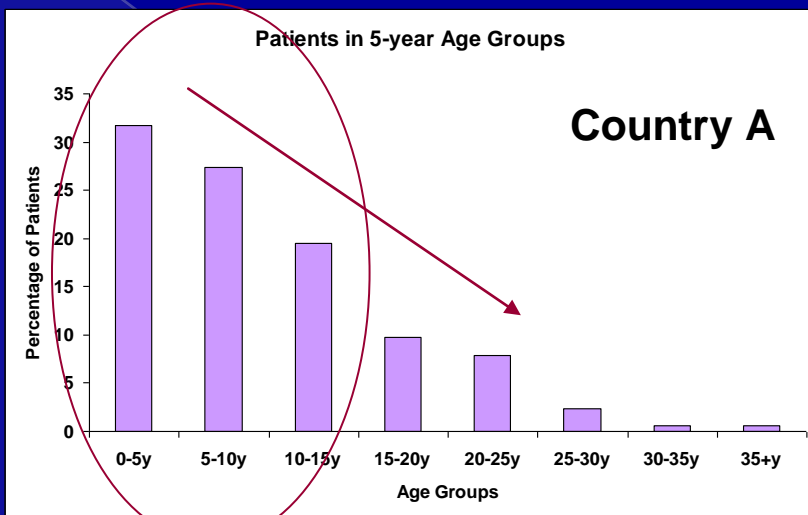


Legal

CZ



Each Bar shows a 5 year age band, except last one



16
5-20
Ag

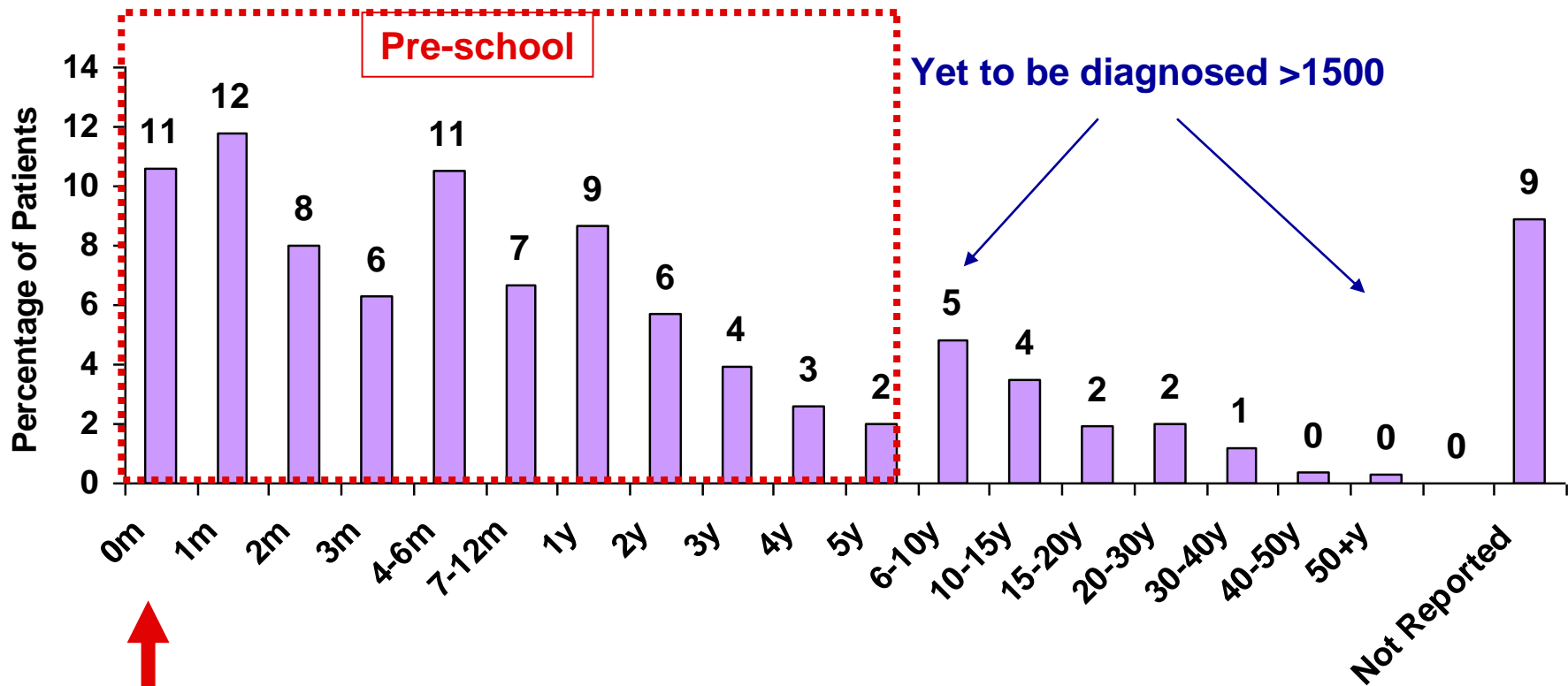
~3550

0-5 yr	5-10 yr	10-15 yr	15-20 yr	20-25 yr	25-30 yr	30-35 yr	>35 yr	Total
3549	4676	4922	4795	3945	2768	1854	2584	29093

Let us expand the age at diagnosis....

What Message does the pattern provide?

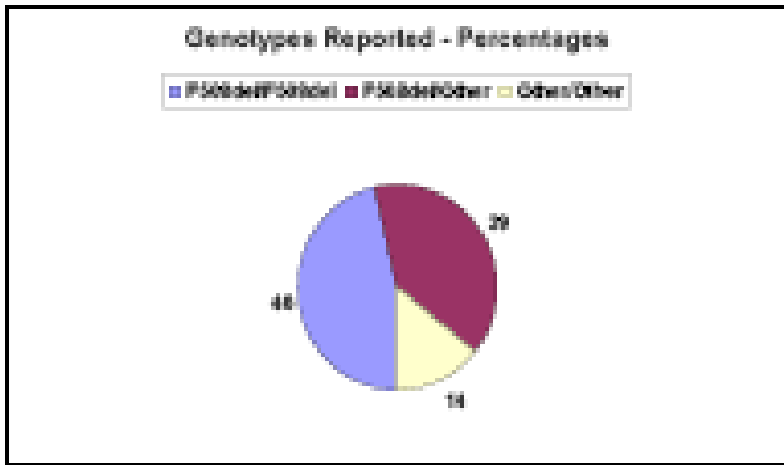
Age at Diagnosis for all Patients



⊙ AM: to find prognostic significance

Expanded age scale from birth

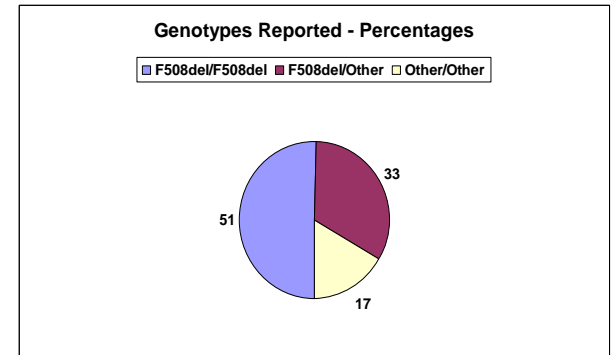
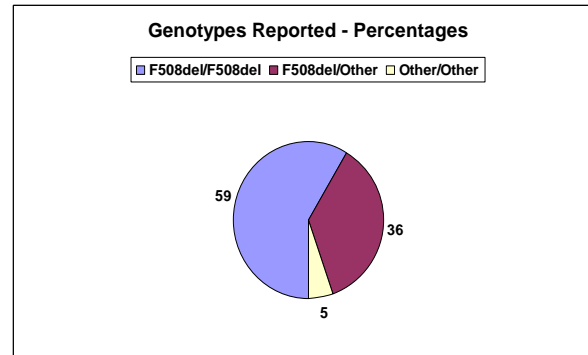
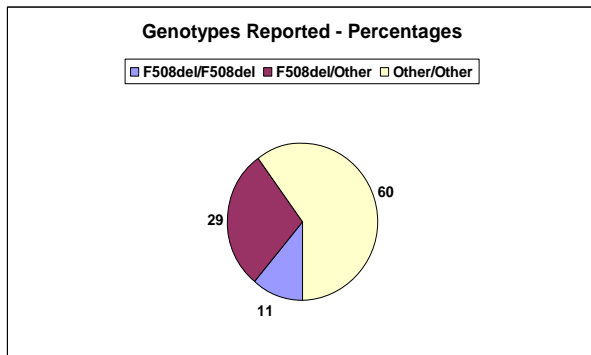
At Birth Diagnosis



F508del/F508del

F508del/Other

Other/Other

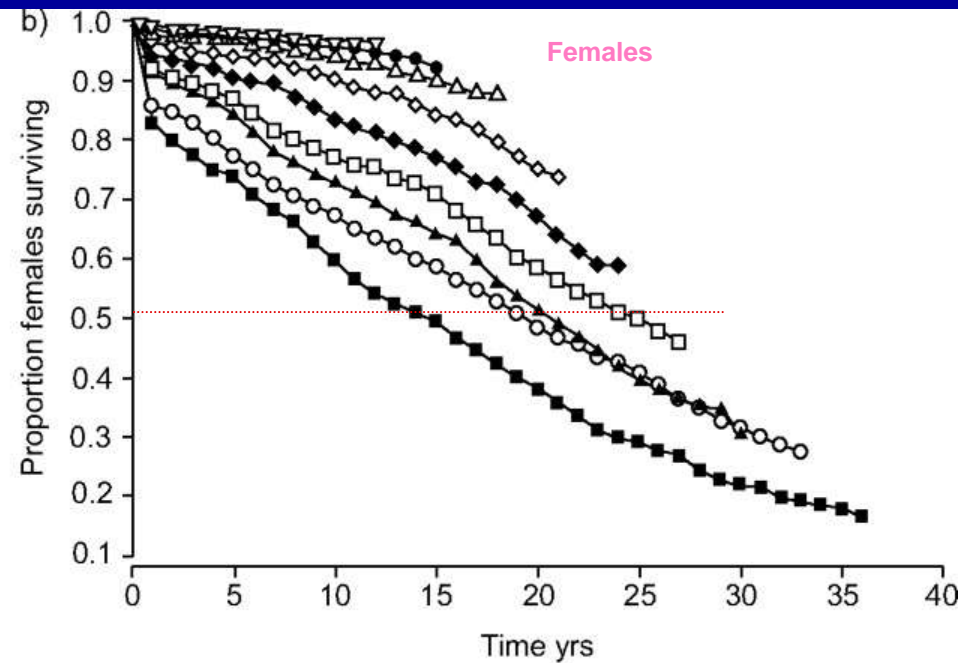
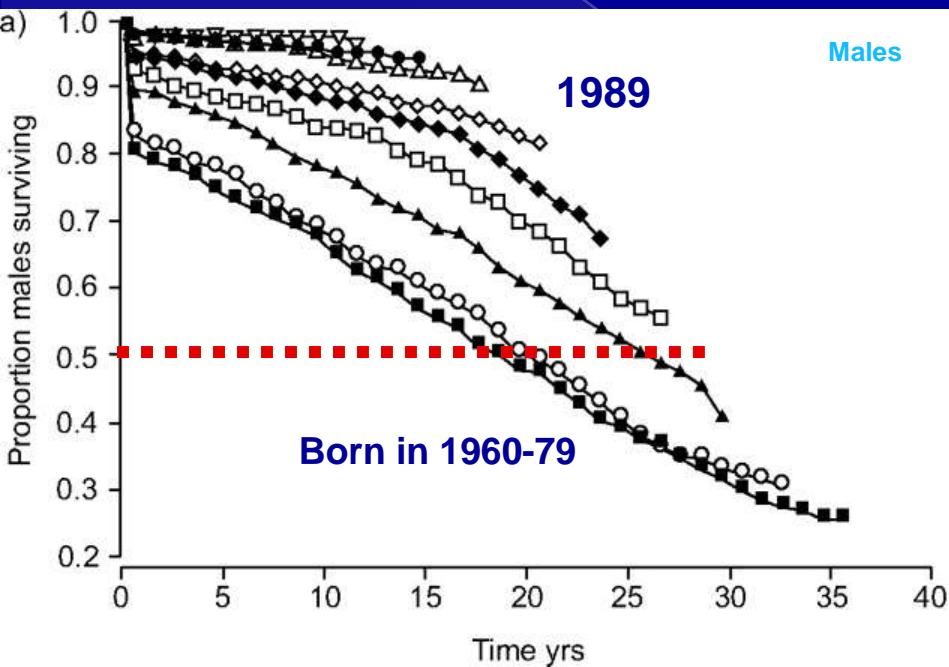


This common form arose once, presents in childhood almost always creating a marker for CF diagnostic ability and eliminates European geographic differences

Setting Up the Hypothesis on Demography

Eur Respir J. 2007 29:522-6Data from the UK

100



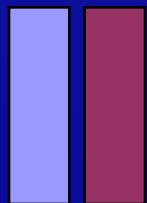
> ...UK Data as an example

How can the EU use this information at a country level to measure outcome?

- **Calculate the number with common CF (eliminate 98% of ascertainment bias)**
 - > Divide that Phe508del number by all CF patients to get a percentage in childhood
- **Assume that <5% should die by 15 years of age (if care is good)**
- Look at the pattern of ages

Country 1 EU \$€€

+++



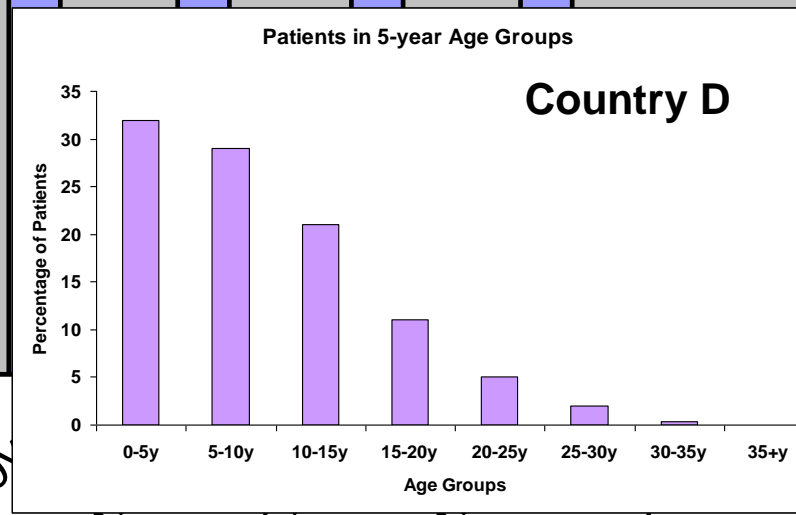
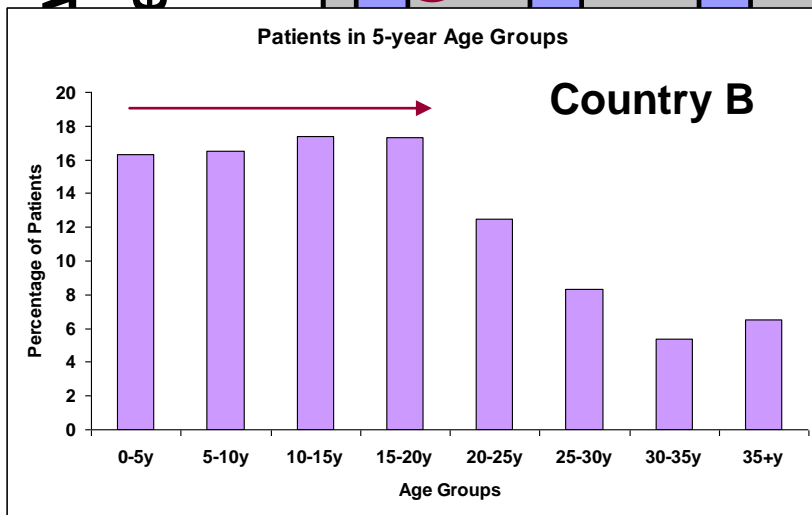
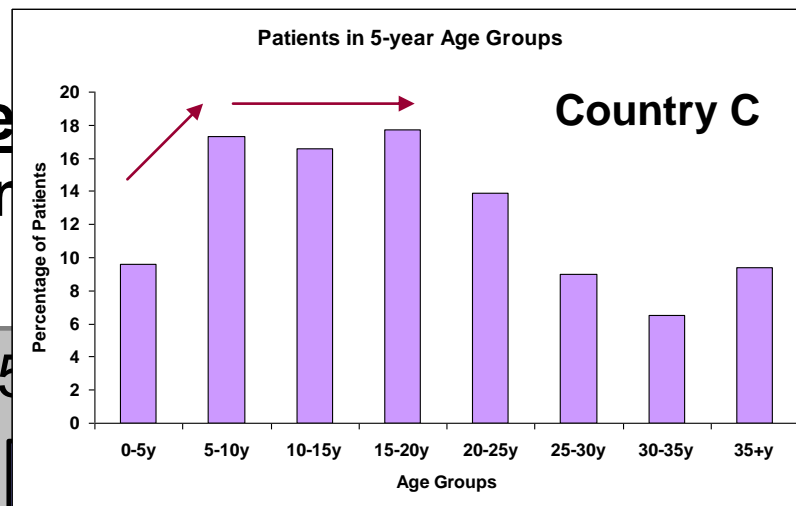
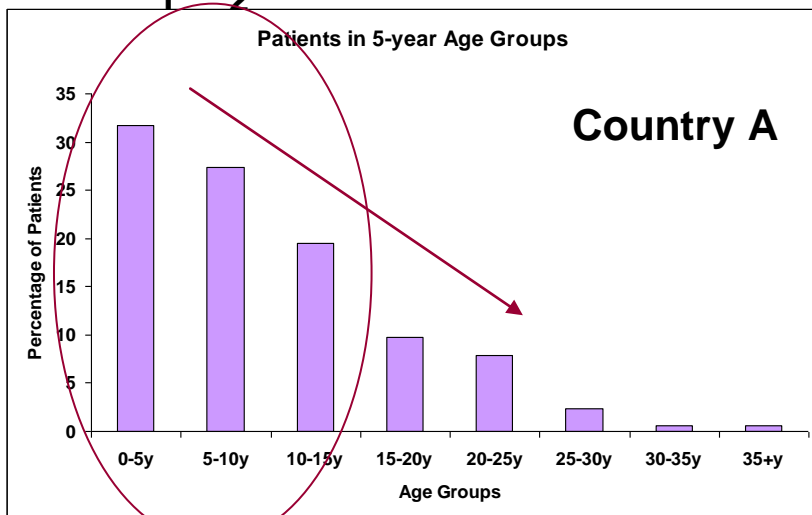
Country 2 NON-EU MONEY

~ +

Severe-common CF to All-CF ratio by age

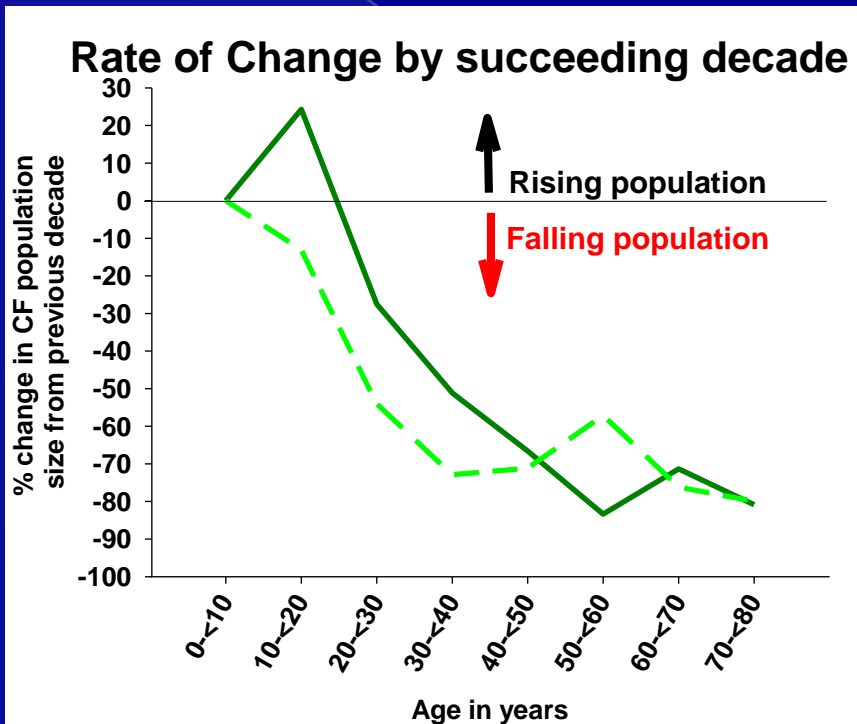
Country

1 2

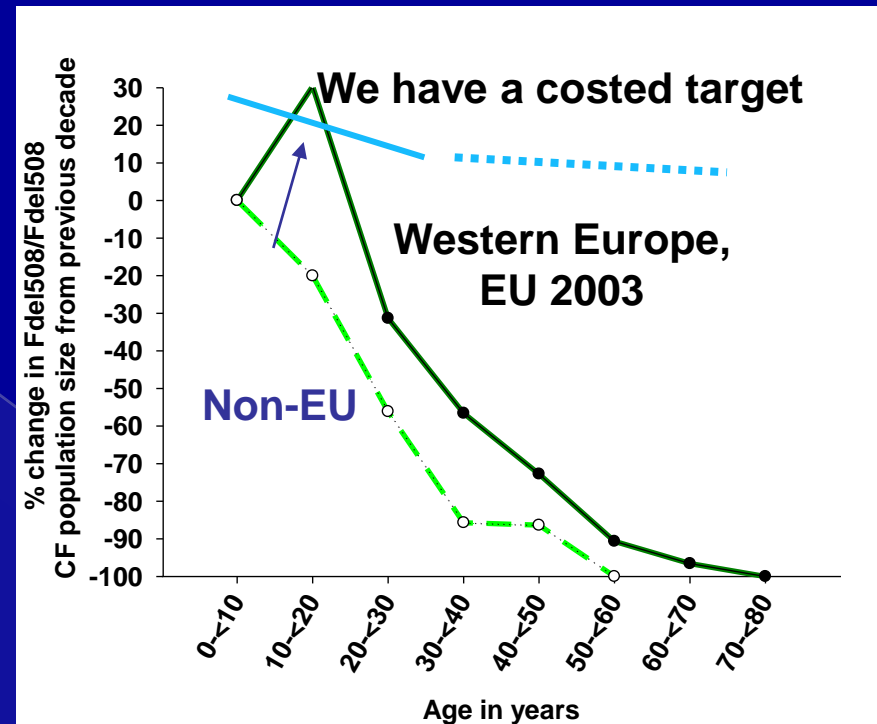


Now we have both a target and the costs

All CF



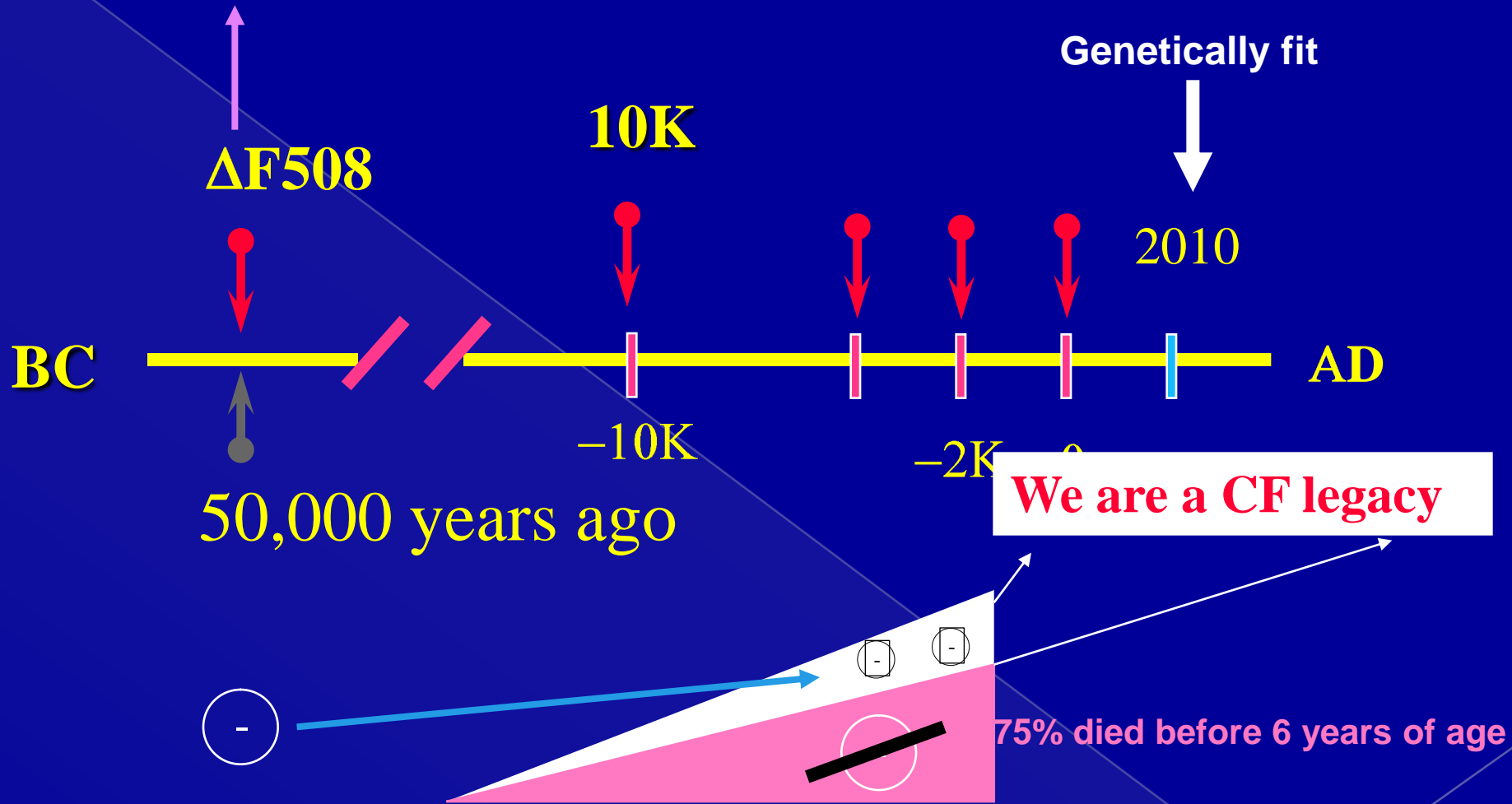
Common Phe508deleted form



1. McCormick et al Lancet 2010:
2. Sims et al Lancet 2007:
3. Jagger et al Lancet 2008:

sets the target
sets the costs
sets the context

We should thank patients with CF for suffering on our behalf



Fibrogenicum super-survived dystentry, typhoid, pneumonia, TB, malaria etc

Treharne et al 2009 Febs Lett CF and smallpox

In Rare Diseases, Demographics are Powerful if...

Look at and use

- > **Direct Genetics**
X%
- > i.e. common severe/severe/total ratio
- > i.e. divided into stable (e.g. CF)

Chromosome 6/Toll

Indirect genetics
(mosaic of DNA inherited
from early man)
Y%

Inflamm bowel
Arthritis
SLE

Z%

Environment

Calculate age at death

- > Compare medians with the most robust re

Conclusion

SKILL MIX IS THE KEY: J McCormick MD

Margaret Fraser.....someone who knows data

Gita Mehta.....someone who knows project management

Milan Macek.....someone who has a network (through genetics)

David Sheppard.....manage the resources

Funding.....EU FP6 EuroCareCF

SKILL MIX → www.eurocarecf.eu → Register

Standards → www.cystic-fibrosis.org.uk → Legal Framework





Overview of Outcomes in rare diseases

