

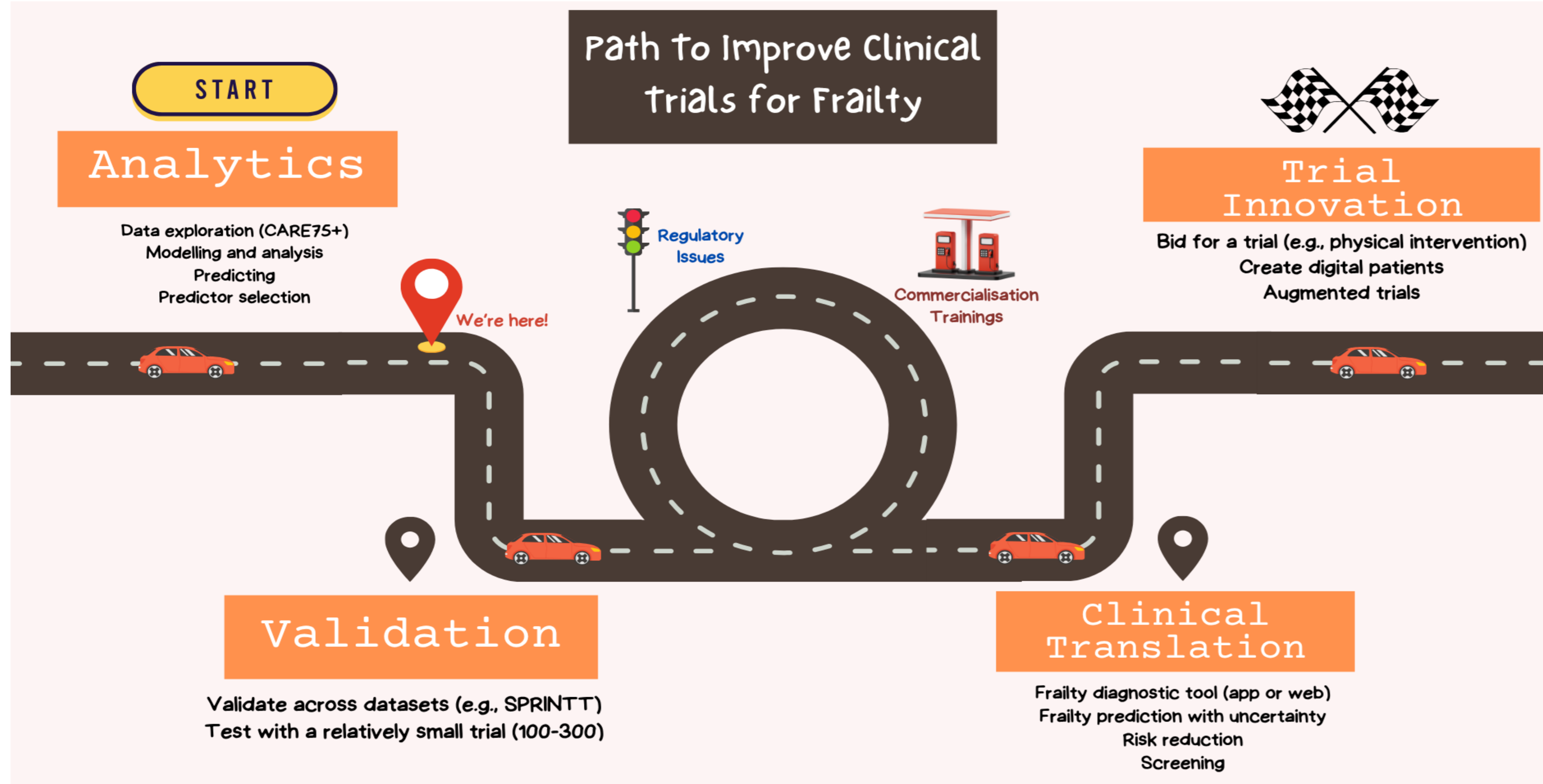
A Statistical Approach for Improving Clinical Trials for Frailty: Present and Future

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1 Path and Milestones

Long-term goal: To develop a robust method to generate synthetic (digital) patients for augmented trials for frailty.



2 Frailty

2.1 Main Characteristics of Frailty

- Frailty is a clinical **condition** without an agreed definition.
- It reflects a **loss** of physiological resilience to adverse events and a **decline** across multiple organs.
- Several assessment tools exist (e.g., eFI, CFS, EFS, Fried Phenotype), capturing different aspects of frailty.
- Frailty is **heterogeneous, multifactorial, age-related** and **degenerative**. There is no agreed effective therapy.

2.2 Why Hard in Clinical Trials (CTs)?

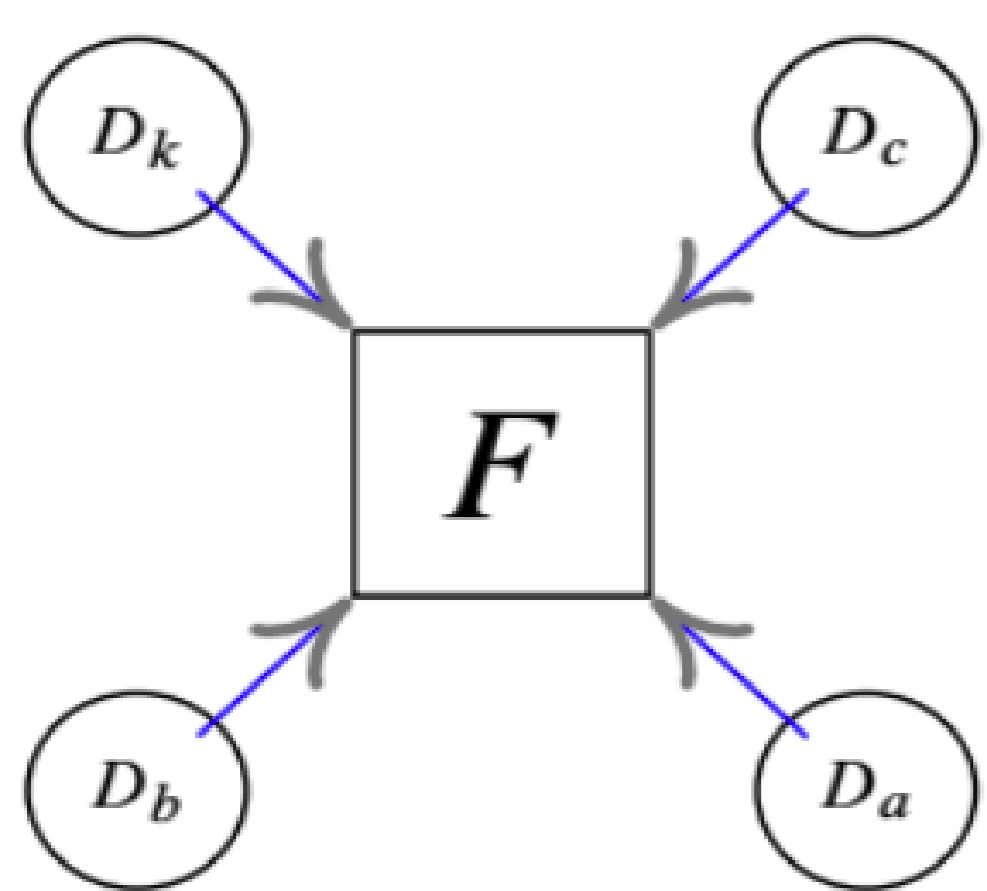
- A large sample size is needed due to heterogeneity.
- It takes long in clinical trials as frailty is age-related and develops slowly.
- Hard to determine whether successful or not, since multiple frailty measures are used.
- Limited number of CTs, and they have **not** had consistent results.

We're trying to use statistical methods to address these issues!

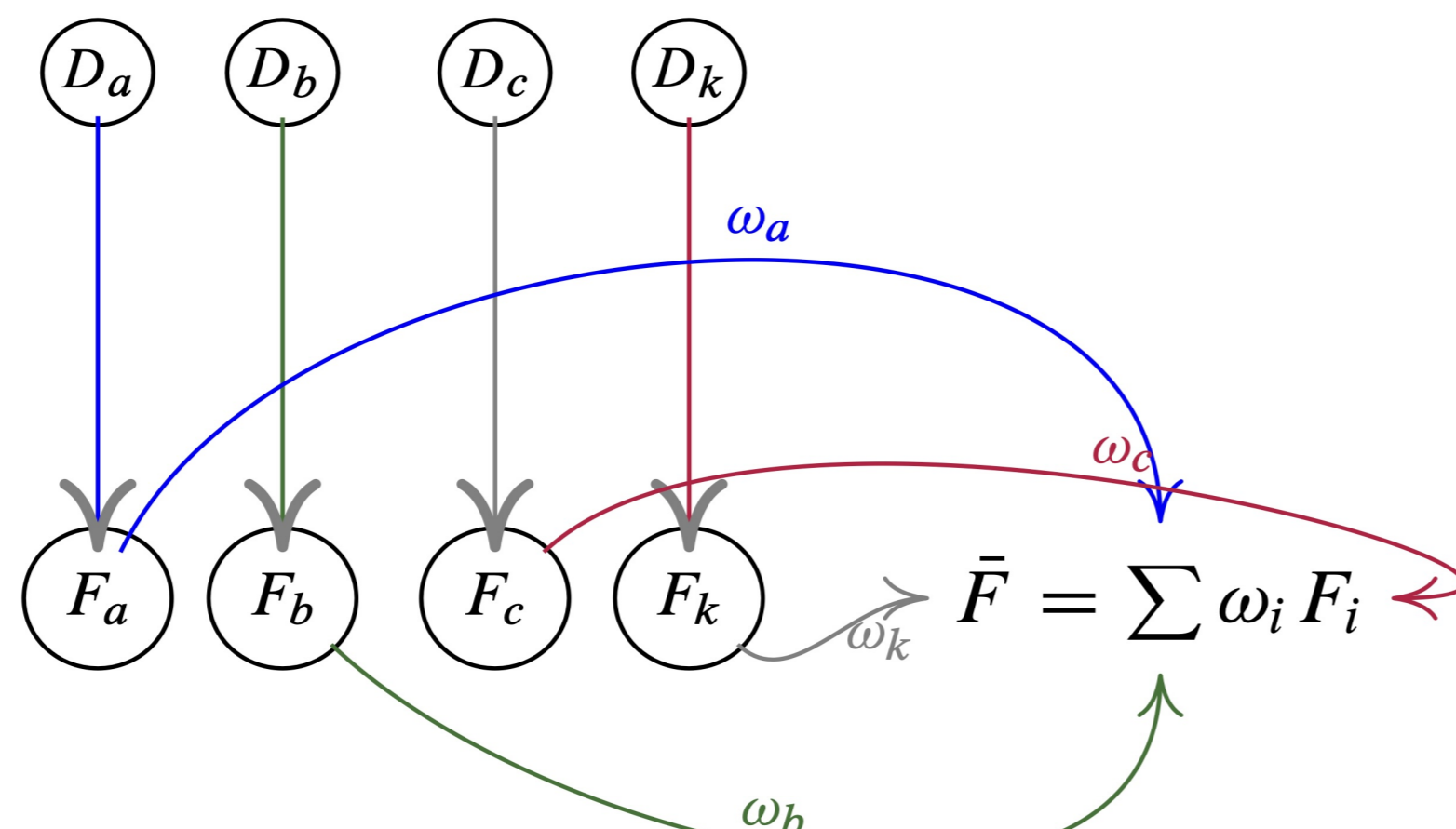
3 The Road So Far

3.1 An Idea: Model Averaging

Standard approach (commonly used)



Our approach (BMA)

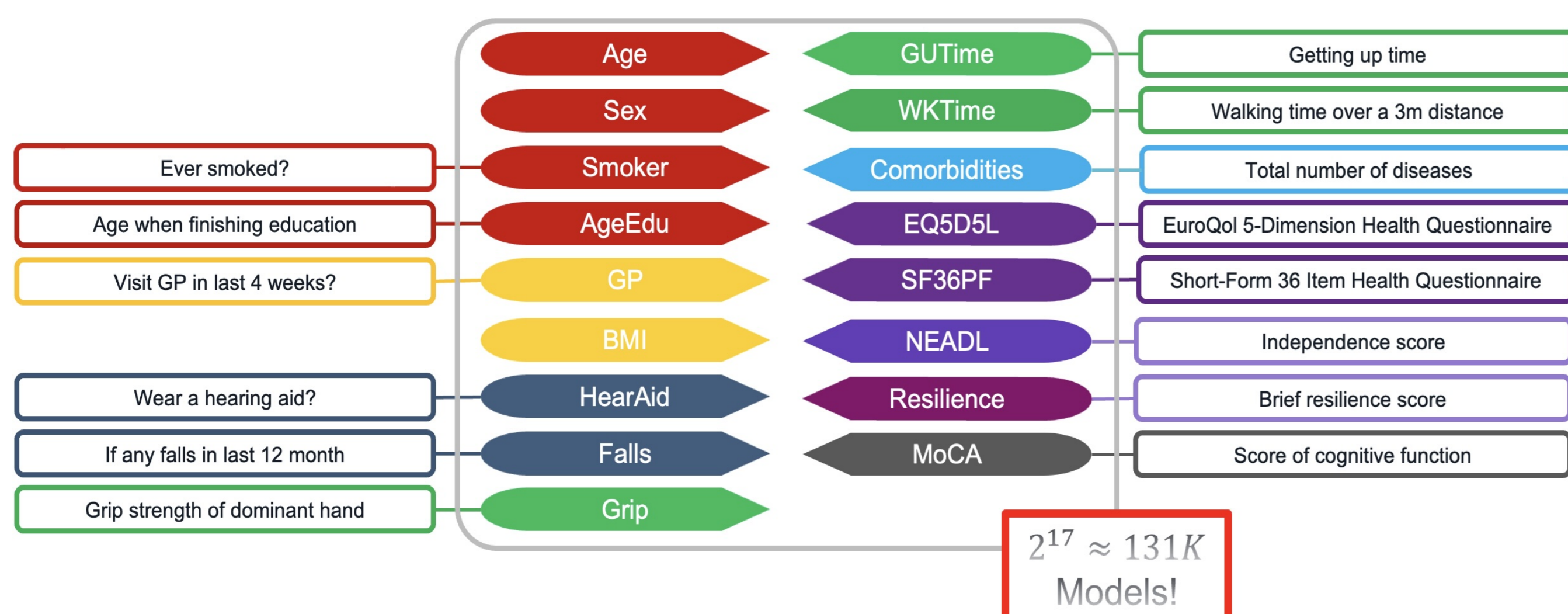


- Chooses the single **best** model.
- Can only model **one** functional relation.
- Ignores model **uncertainty**.
- Considers multiple functional relations.
- Final prediction is a weighted average.
- Informative **weights** reflect predictability.
- Improves **uncertainty** propagation.

Different types of frailty scores are used in practice. Our approach can be used regardless.

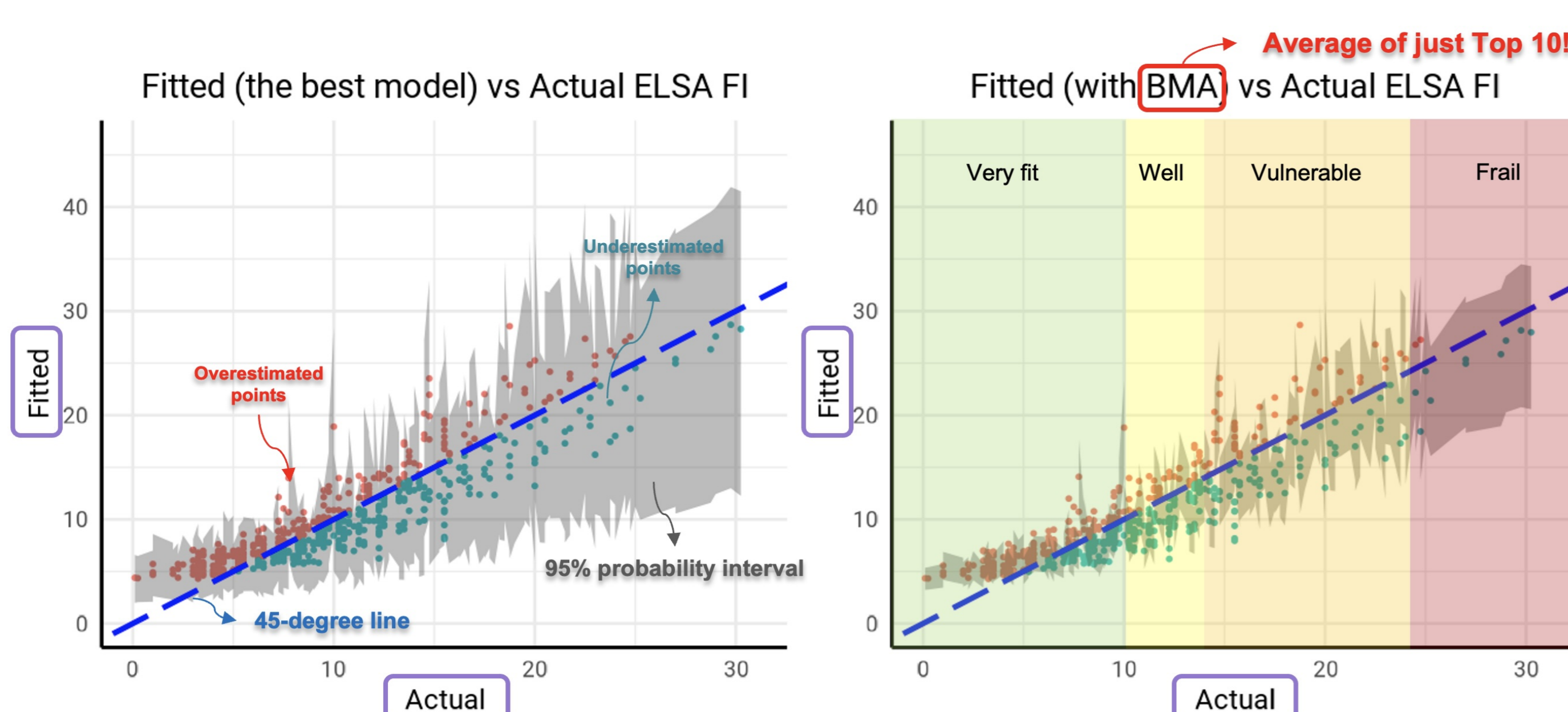
3.2 A Modelling Example: On the ELSA Frailty Index (FI)

Here, the ELSA FI is modelled from the 17 predictors from multiple domains (in different colours below). A total of 131K models has been combined and the predictions from them are averaged.



3.3 Results

3.3.1 Predictions: The Best vs The BMA



Much thinner probability interval on the right, indicating more precise predictions for frailty!

3.3.2 Top 10 out of ≈131K Models

Top models	NO.1	NO.2	NO.3	NO.4	NO.5	NO.6	NO.7	NO.8	NO.9	NO.10
Weights	0.3851	0.1887	0.1583	0.0645	0.0404	0.0357	0.0343	0.0333	0.0321	0.0277
Predictors										
Age										
AgeEdu										
BMI										
Comorbidities	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
EQ5D5L	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Falls	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
GP					✓					
Grip										✓
GUTime										
HearAid										
MoCA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
NEADL	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Resilience	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sex										
SF36PF	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Smoker		✓	✓	✓	✓	✓	✓	✓	✓	✓
WKTime										

The top model contains a combination of predictors including Comorbidity, EQ5D5L, Fall, MoCA, NEADL, Resilience, and SF36PF. The weights assigned to each of the models reflect predictability.

3.3.3 Most Important Predictors (ordered by Variable Inclusion Probabilities (VIPs))

Variable	Probability	Variable	Probability	Variable	Probability
Falls	0.9927	Resilience	0.7309	WKTime	0.0465
SF36PF	0.9927	GP	0.1563	HearAid	0.0424
MoCA	0.9927	BMI	0.0834	Grip	0.0398
Comorbidities	0.9927	AgeEdu	0.0815	Age	0.0384
NEADL	0.9897	Smoker	0.0708	Sex	0.0378
EQ5D5L	0.7643	GUTime	0.0607		

The VIPs can be interpreted as relative importance to frailty, with larger probability suggesting greater importance.

3.4 By-product: A Digital Tool (App/Web)!

In a clinical setting, this is a device (app or web interface) where the clinicians can input ANY characteristics (from a rather long list) and will obtain an **optimised** frailty score with associated **risk** measures. Additionally, it will provide an ordered list of suggested additional measures to minimise the risk of misdiagnosis.

