



# AGM

29 June 2023

synairgen

# Today's speakers

---



Professor Sir Stephen Holgate, CBE, FMedSci  
**Co-Founder and Non-Executive Director of Synairgen**

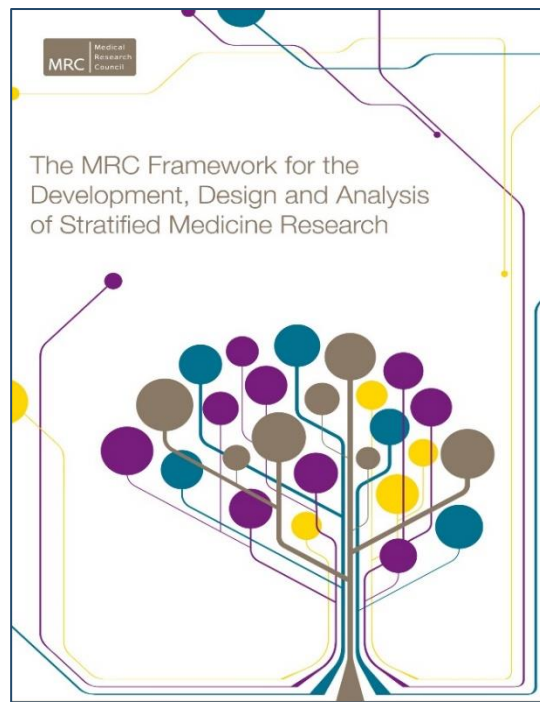
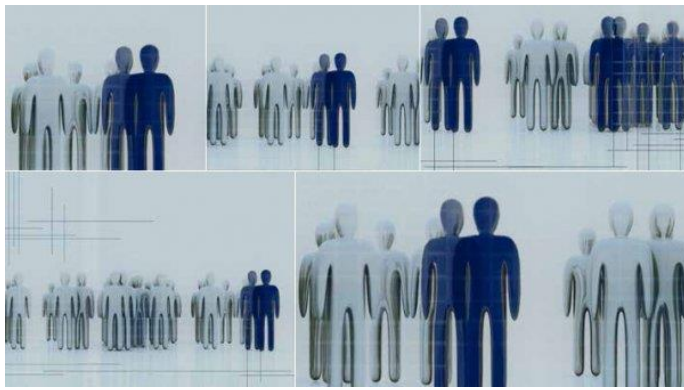
- Co-founder of Synairgen and non-executive director
- Medical Research Council Clinical Professor of Immunopharmacology at the University of Southampton
- Research focused on the cellular and molecular mechanisms of asthma
- Over 1,300 papers published in peer-reviewed literature



Dr Phillip Monk  
**Chief Scientific Officer of Synairgen**

- Joined Synairgen in 2006 as Head of Bioscience Development. Appointed Chief Scientific Officer in 2009
- Previously Director of the Respiratory and Inflammation Biology group at Cambridge Antibody Technology
- Prior to this, worked at Bayer AG within the respiratory disease, focusing on the development of novel therapies for asthma, COPD and cystic fibrosis



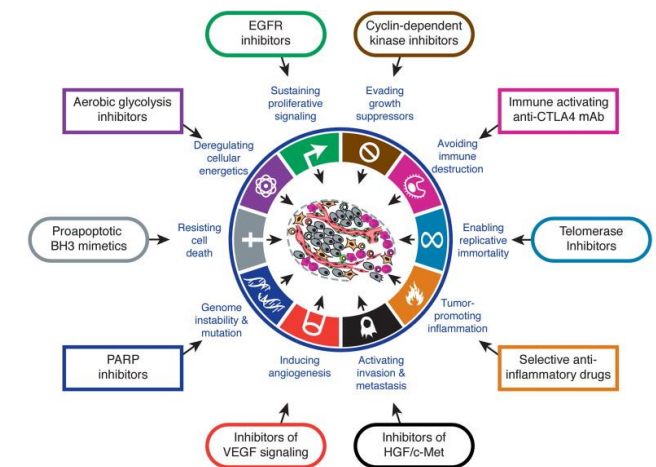
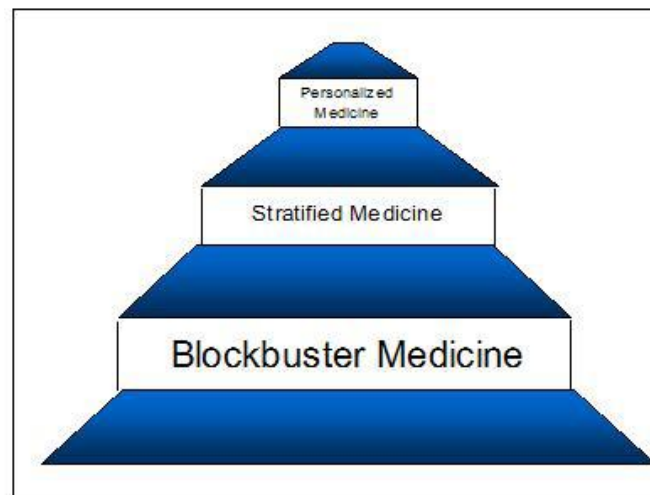
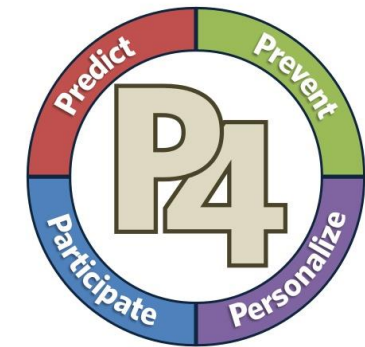


**Stratified Medicine**

## Introducing the Era of Stratified or Precision Medicine

Stephen T Holgate

Personalized Health Care is P4/Systems Medicine

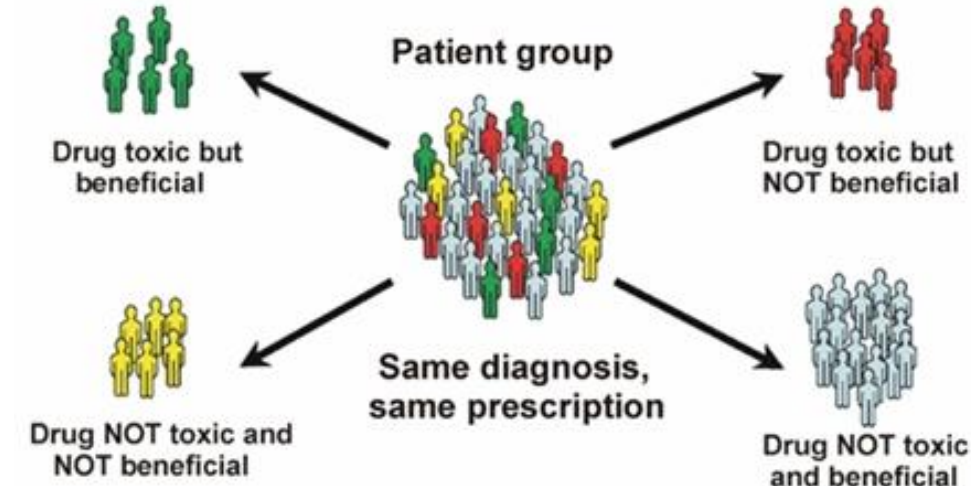


In his 2015 State of the Union address, President Obama announced that he's launching the Precision Medicine Initiative  
A bold new research effort to revolutionize how we improve health and treat disease.



Until now, medical treatments designed for the “average patient.” As a result of this “one-size-fits-all” approach, treatments can be very successful for some patients but not for others. Precision Medicine is an innovative approach that gives medical professionals the resources they need to target the specific treatments of the illnesses we encounter.





A significant proportion of medical research seeks to better understand complex, heterogeneous patient and population groups, and to divide them into subclasses defined by markers.

**Stratified, precision, P4 or personalised medicine** has the ultimate goal to ensure that the **right patient receives the right therapy at the right time**

# Stratification can be used to:



Stratification of complex, heterogeneous patient groups is possible through measurement of traits assessed through any number of modalities

- Improve mechanistic understanding of disease processes and enable the identification of new targets for treatments
- Develop biomarkers for disease risk, diagnosis, prognosis and response to treatment
- Allow treatments to be developed, tested and applied in the most appropriate patient groups

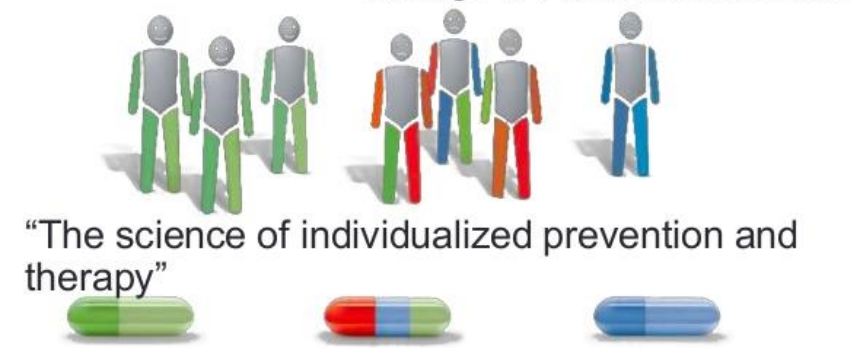
# The Process

- International Expert Steering Group:
  - MRC SM Consortia, industry, diagnostics, statistics, informatics

## Personalized Medicine

“is the tailoring of medical treatment to the individual characteristics of each patient”

The Age of Personalized Medicine



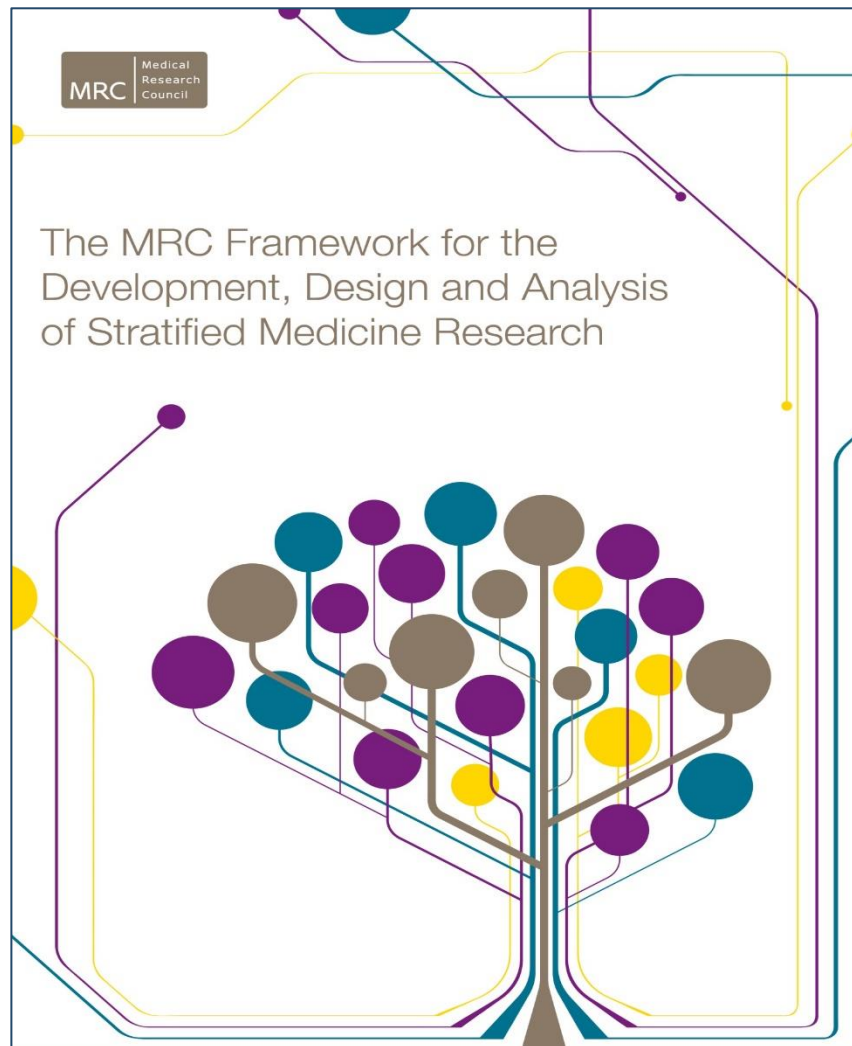
## Workshop, Ascot 9<sup>th</sup>-10<sup>th</sup> July, 2015

- 40 invited participants
- Consortia, clinical, clinical scientists, industry, diagnostics, statistics, informatics, epidemiology, behavioural research, regulators, systems biology
- Plenary presentations, thematically structured discussion



# The need to improve Methodology in Stratified Medicine (M4SM) – June 11<sup>th</sup> 2018

<https://www.ukri.org/publications/the-mrc-framework-for-stratified-medicine-research/>



## Analysis of Stratified Medicine Research

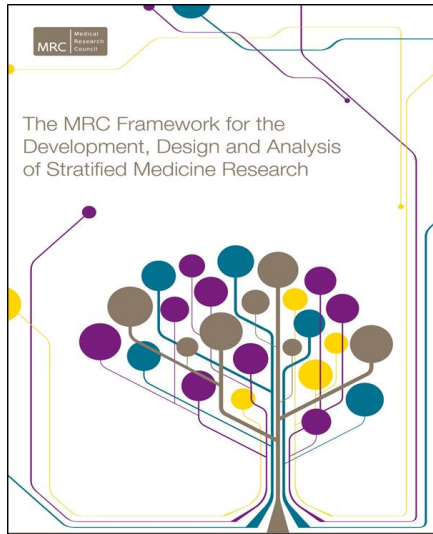
### Enabling Stratified, Precision and Personalised Medicine

**Authors:** *David Crosby<sup>1</sup>, Patrick Bossuyt<sup>2</sup>, Peter Brocklehurst<sup>3</sup>, Chris Chamberlain<sup>4</sup>, Caroline Dive<sup>5</sup>, Chris Holmes<sup>6</sup>, John Isaacs<sup>7</sup>, Richard Kennedy<sup>8</sup>, Fiona Matthews<sup>7,9</sup>, Mahesh Parmar<sup>3,10</sup>, Jonathan Pearce<sup>1</sup>, David Westhead<sup>11</sup>, John Whittaker<sup>12,13</sup>, Stephen Holgate<sup>14</sup>.*

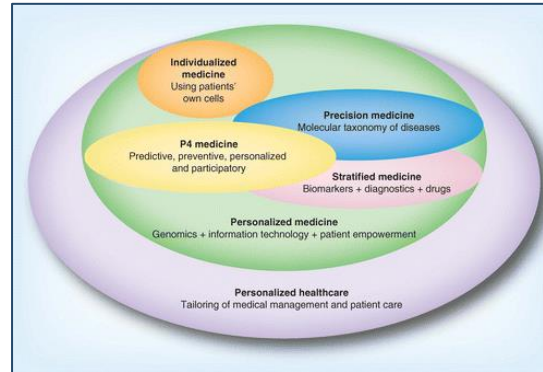
*<sup>1</sup>Medical Research Council Head Office; <sup>2</sup>Academisch Medisch Centrum, Amsterdam; <sup>3</sup>University College London; <sup>4</sup>UCB; <sup>5</sup>University of Manchester; <sup>6</sup>University of Oxford; <sup>7</sup>University of Newcastle; <sup>8</sup>Queens University Belfast; <sup>9</sup>MRC Biostatistics Unit; <sup>10</sup>MRC Clinical Trials Unit; <sup>11</sup>University of Leeds; <sup>12</sup>Glaxosmithkline; <sup>13</sup>The London School of Hygiene and Tropical Medicine, <sup>14</sup>University of Southampton*

This Framework was developed by the authors, informed by the presentations and discussions taking place at the Medical Research Council (MRC) Methodology for Stratified Medicine (M4SM) workshop, 9th-10th July 2015 at Sunninghill, Ascot, UK, which was funded by the MRC. The authors of the Framework are the M4SM Steering Group, chaired by Professor Stephen Holgate.





# The Framework is structured into six themes



- **Theme 1:** Framing the Question/Defining the Population
- **Theme 2:** Designing Stratum Discovery Studies; selecting variables, defining response and powering
- **Theme 3:** Assay Design; managing complexity and variability
- **Theme 4:** Defining Strata; data integration, linkage to existing knowledge, linkage to outcome
- **Theme 5:** Stratum Verification
- **Theme 6:** Progression Towards Clinical Utility

## Framing the Question

- What are you looking for/what is your research question and why?
- What is the clinical context/benefit of being able to stratify?
- What is known about your population of interest and how is it defined?
- What is the mechanistic rationale for the plausibility of the stratum you are investigating?

## Stratum Discovery

### Design

- Understand existing knowledge
- Specify population, variables, outcomes
- Study type and powering
- Assay design

### Conduct

- Patient engagement and consent
- Sample/Data collection/storage
- Biomarker measurement

### Interpret

- Define strata by model building
- Incorporate existing knowledge
- Assess mechanistic plausibility

### Analyse

- Re-frame the question
- Data preparation and integration
- Statistical confidence in association

## Stratum Verification

### Design

- Assess confidence in the association
- Re-frame the question
- Attempt to break the association

### Conduct

- Independent data set – existing or new?
- Document the analysis plan
- Consider representativeness to ultimate clinical context

### Interpret

- Re-evaluate marker identity and strata model in light of existing knowledge
- Does the verification population represent the clinical population?

### Analyse

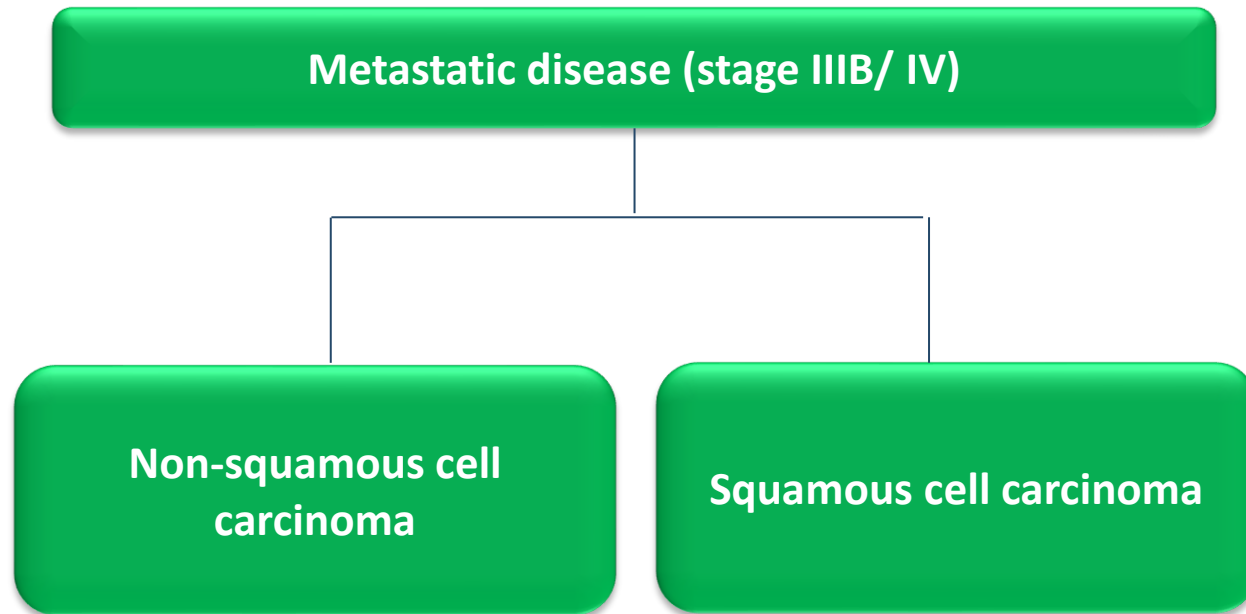
- Assess confidence in the association
- Consider meta-analysis of associations

## Progression Towards Clinical Utility

- Report in enough detail to support reproducibility
- Plan to move towards clinical assay development and validation
- What is the required level of evidence to move to a stratified clinical trial?
- Will stratification by the marker(s) affect patient outcomes in wider clinical, organisational and health economic context?

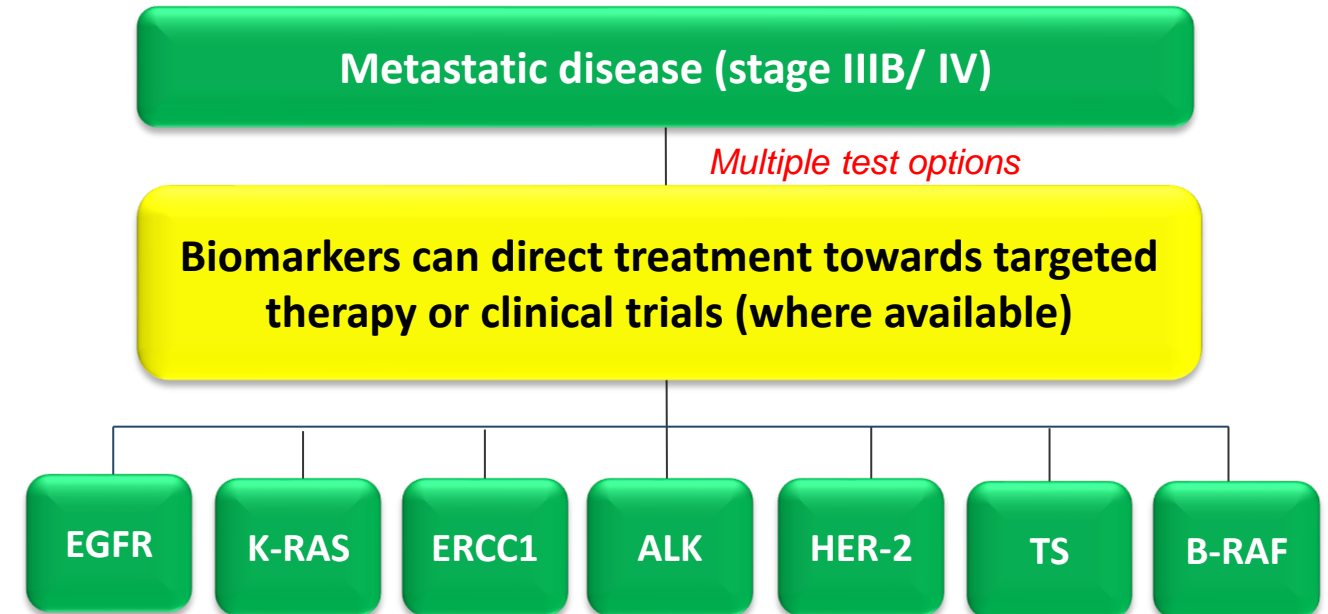
# Diagnostic challenges: cancer is leading the way

## Traditional Paradigm



- Oncologist sole treatment decision maker
- Treatment decisions depend on histology

## Evolving Personalized Paradigm

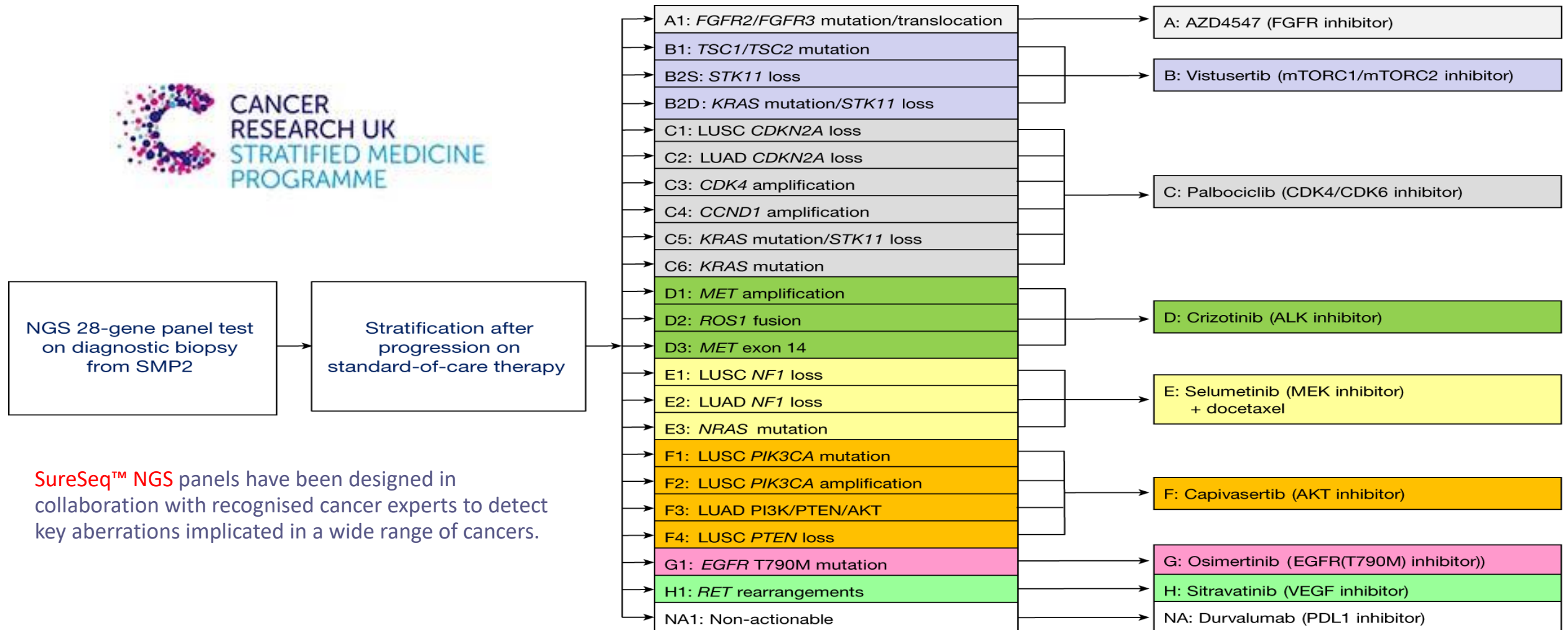


- More complex decisions involving more stakeholders beyond oncologist (surgeon, pathologist)
- Education required to integrate molecular diagnostics into treatment decisions
- Not a “simple” issue of a single drug-diagnostic combination



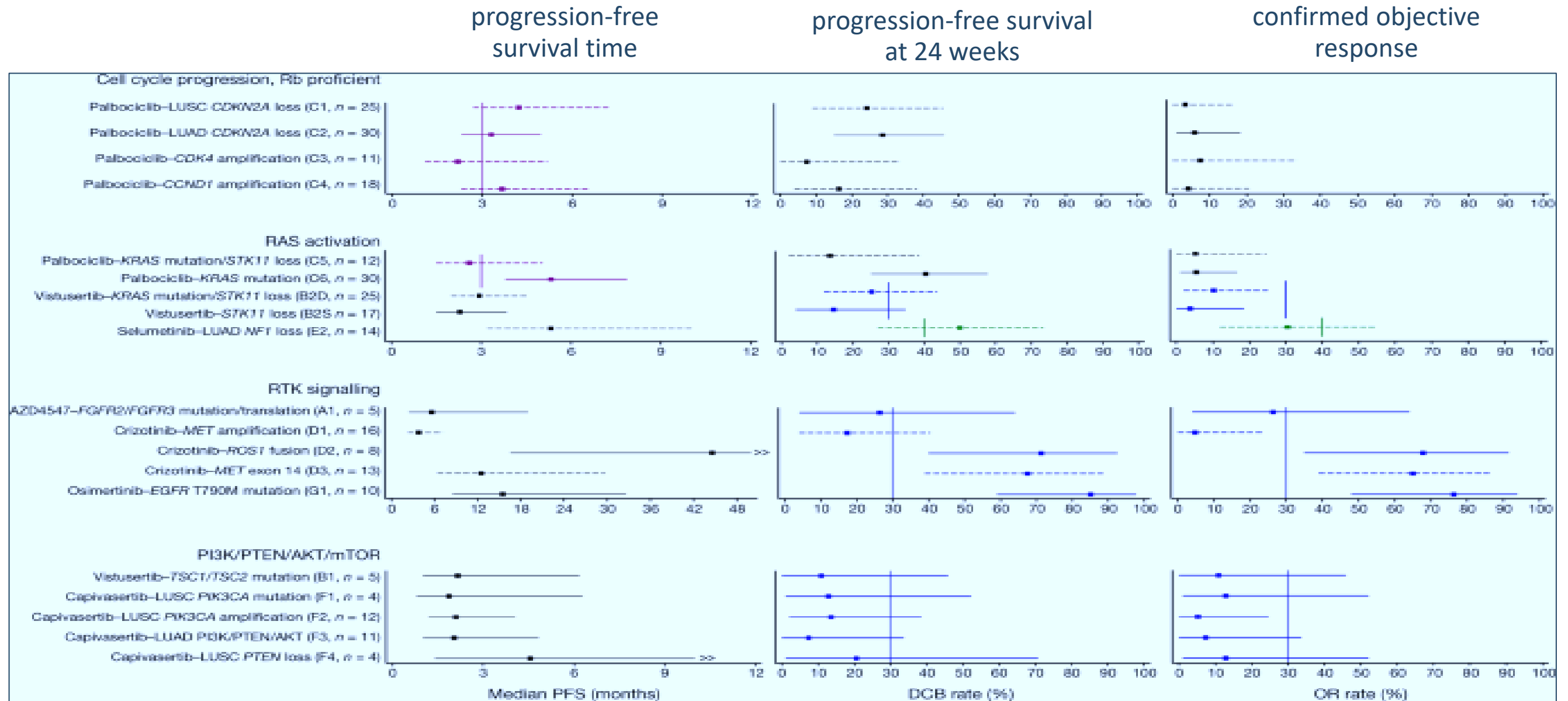
# The National Lung Matrix Trial of personalized therapy in non small cell lung cancer.

Middleton, G., Fletcher, P., Popat, S. et al. Nature. 2020; 583: 807-12



# Estimates of primary outcome measures for 19 drug-biomarker cohorts in National Lung Matrix Trial grouped according to 4 modules of genomic aberrations.

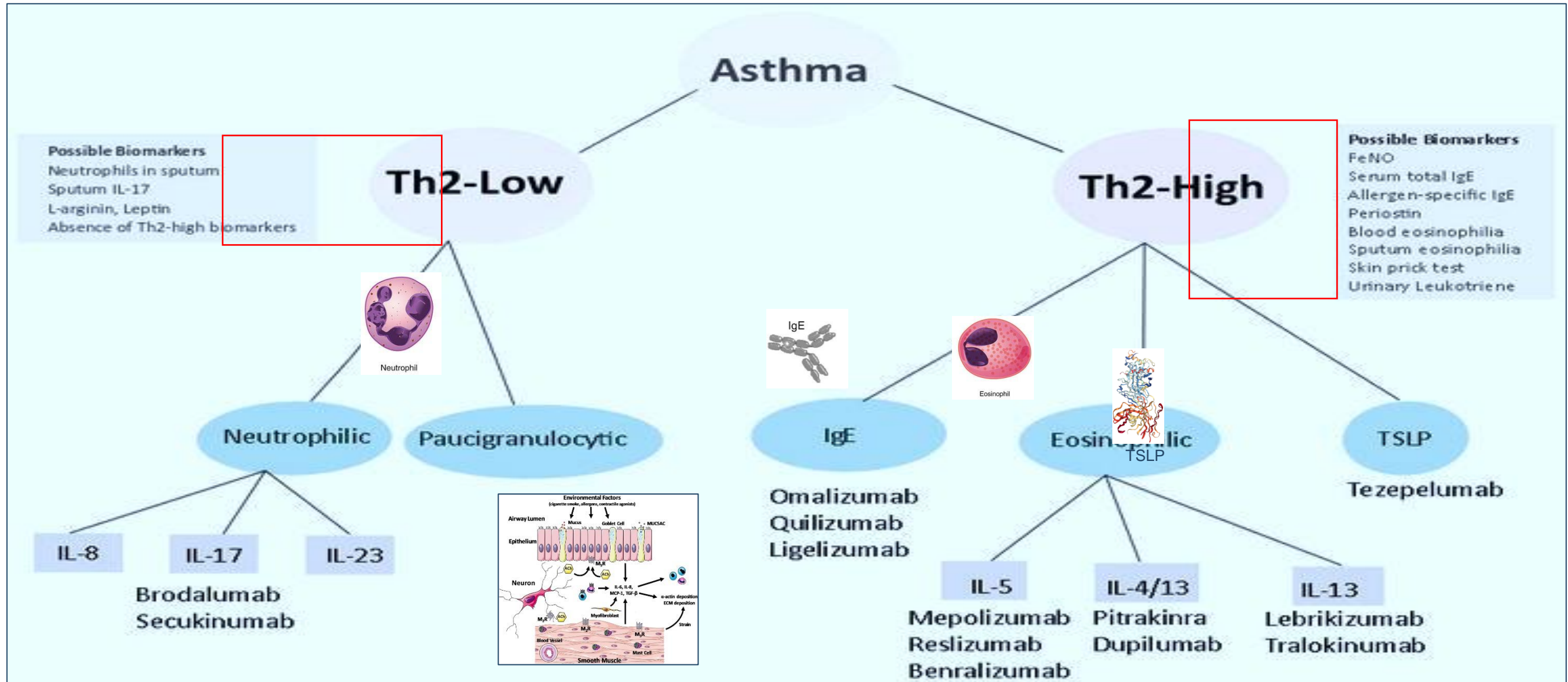
Next-generation sequencing to match patients to appropriate targeted therapies on the basis of their tumour genotype.



# Asthma phenotypes and current targets for biological treatment

Stratified by whether T helper lymphocyte Type 2 cells are increased (Th2 high) or not (Th2 low)

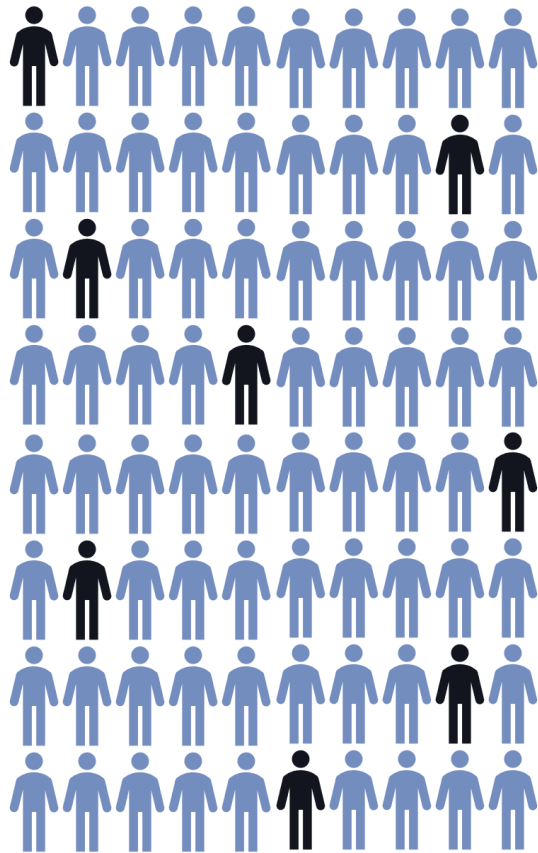
Th2, T-helper type 2 cell; IL, interleukin; IgE, immunoglobulin E; TSLP, thymic stromal lymphopoietin



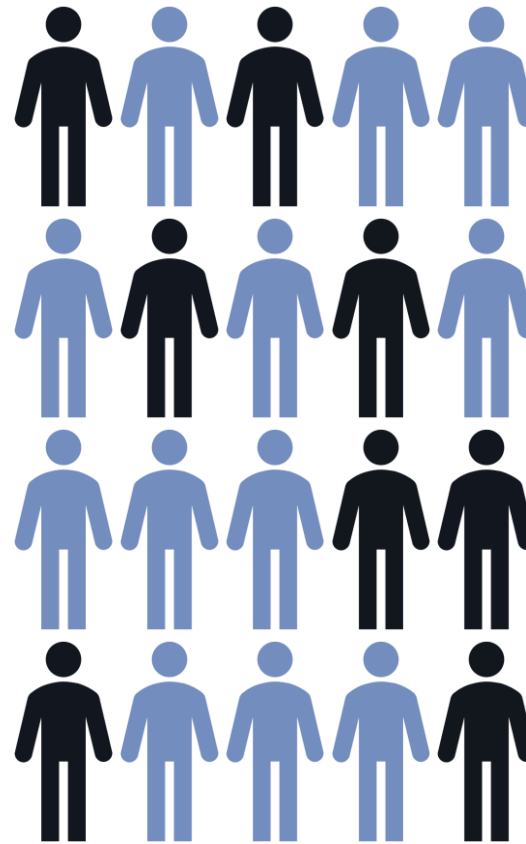


# Selecting the patients most likely to develop severe viral lung disease and respond to treatment with SNG001

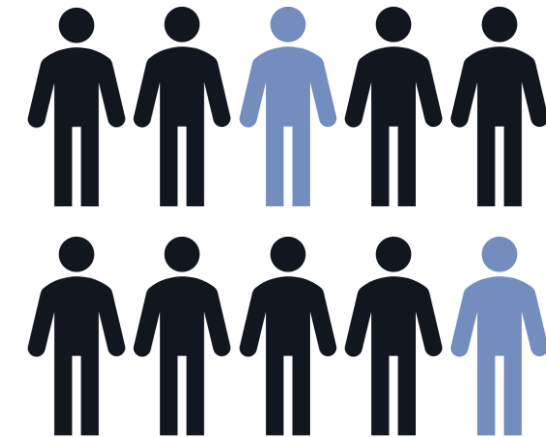
General population



At risk groups:  
e.g. elderly, immunocompromised



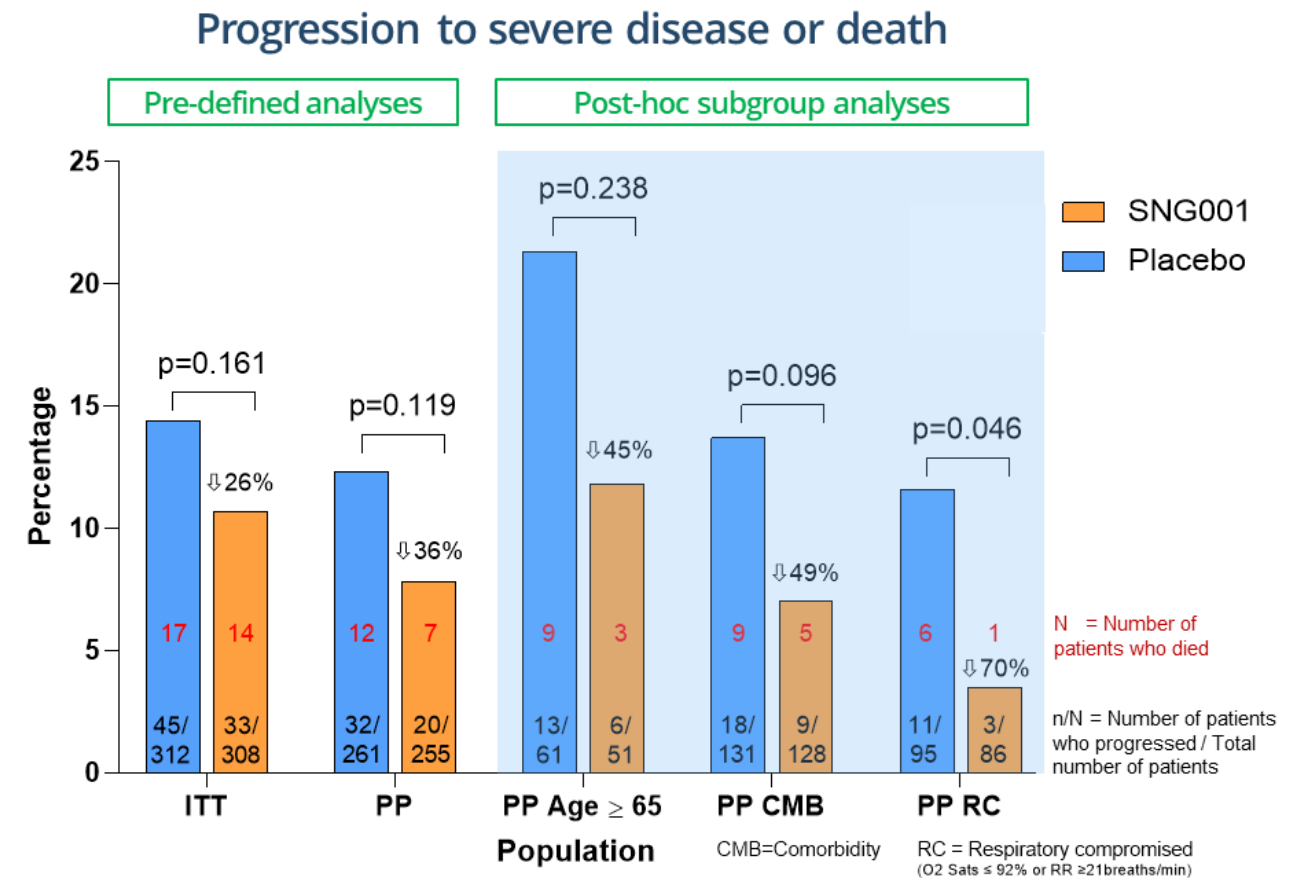
Further enrichment



- Poor innate immune (IFN) response
- Autoantibodies (IFN- $\alpha$  and IFN- $\omega$ )
- High virus load
- Other factors

# Patient populations at greater risk of developing severe viral lung infections

- Stronger treatment effects seen in the elderly and those with comorbidities in the Phase 3 SPRINTER trial in patients hospitalised with COVID-19
- Scientific advisory board and individual meetings held with experts in the impact of respiratory viruses on immunocompromised patients



Monk et al. (2023) Nebulised interferon- $\beta$ 1a (SNG001) in hospitalised COVID-19: SPRINTER phase III study. ERJ Open Res. 2023;9(2):00605-2022

# Selecting patients with higher viral load

---

Collaboration will look at the relationship between viral load on admission and clinical outcome in patients admitted to Southampton General Hospital with respiratory viral infections





# Benefits of participation UNIVERSAL study

Assessment of impact of risk factors for a poor outcome

- Autoantibodies against other type I IFNs ( $\alpha$  and  $\omega$ )
  - Presence of naturally occurring antibodies against other type I IFNs associated with a poorer clinical outcome in patients with SARS-CoV-2 and more recently flu infections
- Poor innate immune response
  - Comparison of baseline immune (IFN) response versus viral load and outcome



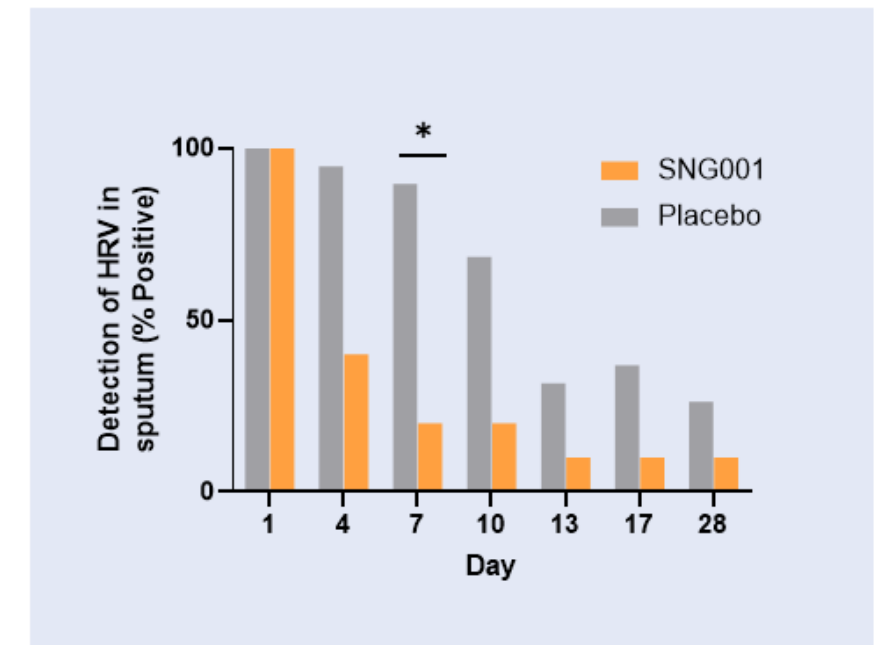
Understanding Infection, Viral  
Exacerbation and Respiratory  
Symptoms at Admission-  
Longitudinal (UNIVERSAL) Study



# Assessing lower respiratory tract viral load

- Previously shown accelerated viral clearance from the lungs (sputum) in our Phase 2 COPD trial
- Sputum samples are not readily obtainable from many target patient populations
- Breath sampling offers a potential alternative to assess lower respiratory tract viral load
- Clinical trial to be conducted in COPD and immunocompromised patients to compare viral load in nasal & throat swabs, sputum and breath samples

## Viral clearance from the lungs (sputum)



Monk *et al.* (2023) Nebulized interferon beta-1a (SNG001) in the treatment of viral exacerbations of COPD. Submitted for publication

# Summary

---

- Stratified medicine is being used to target drugs at patients most likely to benefit most from treatments and to inform the design of clinical trials to increase the likelihood of a successful outcome
- Activity to enhance patient selection, trial design, trial delivery and chance of success is underway and will continue through the summer and autumn this year
- Preparing to commence trials with SNG001 this coming winter

