



**PRECISION MEDICINE OF AIRWAY DISEASES: MOVING TO
CLINICAL PRACTICE**
**Summary and proposals of an ERS Research Seminar held in
Barcelona on Feb 21 2017**

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*Summary and proposals of an ERS Research Seminar
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43 **Key words:** Asthma, Biomarkers, COPD, Endotypes, Phenotypes, Treatable traits

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Take-home message: This paper discusses how to implement precision medicine in patients with chronic airway diseases

Plain language summary: Chronic airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD), are highly heterogeneous and require individualized assessment and treatment, so-called precision medicine. This paper summarizes the discussions of an ERS Research Seminar held in Barcelona on February 21, 2017 on how to best apply precision medicine to asthma and COPD.

ABSTRACT

On February 21, 2017, an ERS Research Seminar held in Barcelona discussed how to best apply precision medicine to chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD). It is now clear that both are complex and heterogeneous diseases, that often overlap and that both require individualized assessment and treatment. This paper summarizes the presentations and discussion of the Seminar. Specifically, we discussed the need of a new taxonomy of human diseases, the role of different players in this scenario (Exposome, Genes, Endotypes, Phenotypes, Biomarkers and Treatable Traits) and a number of unanswered key questions in the field. We also addressed how to deploy airway precision medicine in clinical practice today, both in primary and specialized care. Finally, we debated the type of research needed to move the field forward. Full presentations can be downloaded from <http://www.ers-education.org/events/research-seminars/precision-medicine-in-airway-diseases.aspx>.

Abstract word count: 140 words (<200)

Kola & Bell. *Nat. Rev. Drug Discov.* 2011; 10: 641

Asthma and chronic obstructive pulmonary disease (COPD) are the two most prevalent human airway diseases [1]. Surprisingly, well into the 21st century, they are still diagnosed following 19th century approaches, which are fundamentally based on their clinical presentation and associated lung function abnormalities [2, 3], which are both non-specific. As a result, asthma and COPD are often treated similarly and, potentially, sub-optimally [1, 4]. Further, it can be questioned whether they are clearly separate entities or, alternatively, they may represent a heterogeneous spectrum of airway diseases that are linked to an array of biological deviations from what is considered a healthy state well adapted to its environment [1].

Recently, the term “*precision medicine*” has been proposed to define “*treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations*. Inherent in this definition is the “*goal of improving clinical outcomes for individual patients and minimizing unnecessary side effects for those less likely to have a response to a particular treatment*” [5]. In essence,

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3 100 therefore, the concept of precision medicine relates to the likelihood of responding (or
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5 101 not) to a given therapeutic intervention and/or suffering (or not) undesired side effects
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7 102 (Figure 1). In the context of chronic airways diseases, precision medicine can therefore
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9 103 be a promising strategy to their improve management [6]. Needless to say, that
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11 104 physicians always try to be as precise as possible in relation to the needs of individual
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13 105 patients. The present step-change, however, is based on the integrated assessment of the
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15 106 complex clinical and biological status of individual patients, which until recently was
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17 107 beyond reach [7].
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25 109 On February 21, 2017, the European Respiratory Society convened a research seminar
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27 110 in Barcelona ([http://www.ers-education.org/events/research-seminars/precision-](http://www.ers-education.org/events/research-seminars/precision-medicine-in-airway-diseases.aspx)
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29 111 [medicine-in-airway-diseases.aspx](http://www.ers-education.org/events/research-seminars/precision-medicine-in-airway-diseases.aspx)) aimed at discussing how to best apply precision
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31 112 medicine to airway diseases, specifically to asthma and COPD. The text that follows
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33 113 summarizes the discussions and presents the conclusions and proposals of the seminar.
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35 114 Full presentations can be downloaded from the above URL address.
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42 116 **SETTING THE STAGE, OR WHERE ARE WE COMING FROM**

43 117 **We need a new taxonomy (classification) of human diseases**

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48 118 Human diseases are still classified on the basis of the principal organ system in which
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50 119 symptoms and signs manifest, and in which gross anatomic pathology and
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52 120 histopathology are correlated [8]. This so-called Oslerian paradigm, to honour Sir
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54 121 William Osler by whom it was first proposed, has been useful for clinical practice
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56 122 because it establishes a limited number of syndromic patterns to consider in daily
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123 practice; of note, a *syndrome* is a set of medical signs and symptoms that commonly
124 occur together and may be related to each other without necessarily tying them to a
125 single identifiable pathogenesis [9]. Yet, this Oslerian paradigm over generalizes
126 pathological states (COPD and asthma, for instance are terms that most likely include
127 common as well as unique features), does not include susceptibility states or preclinical
128 disease manifestations, and is of limited value to individualize precise diagnosis and
129 therapy [10, 11]. As appropriately pointed out in the introductory quote from Kola and
130 Bell above, the taxonomy of human diseases is outdated and requires a profound
131 reconsideration that leverages from the most up-to-date and integrated biological
132 knowledge that we currently have [8, 10, 12, 13].

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134 The traditional, physiology-based, classification system of airway disease that we still
135 use today does not represent the state of the art and is out-dated. We now know that
136 there is a heterogeneous mix of distinct cellular and molecular mechanisms that go
137 beyond the traditional physiology mechanisms of pulmonary disease, and that extra-
138 pulmonary co-morbidities, psycho-social, behavioural and environmental factors
139 significantly impact the health status and risk of morbidity and mortality of these
140 patients. Therefore, there is an urgent need to rethink and disseminate the way we
141 classify and manage airway diseases.

142

143 **The players: Exposome, Genes, Endotypes, Phenotypes, Biomarkers and Treatable**
144 **Traits**

Figure 2 illustrates the current multi-level understanding of the different biological players in this scenario. The interaction between our genetic background (*genome*) and the cumulative environmental exposures an individual encounters through life (*exposome*) [14, 15]), via a complex set of *biological networks* [16], determines the emergence of a number of cellular and molecular mechanisms that eventually contribute to the *phenotype* that we phenomenologically observe [16], this being a given disease or, more often, a specific clinical manifestation of a complex disease [17]. In this setting, though, several aspects need detailed discussion: (1) the traditional concept of a phenotype (an observable characteristic of an organism [16]) has been modified to provide a meaningful clinical framework. Hence, a *clinical phenotype* is “a single or combination of disease attributes that describe differences between individuals as they relate to clinically meaningful outcomes” [18]. It is their relationship with meaningful outcomes (e.g., symptoms, health status, death, exacerbations, other) that confer clinical utility to the concept; otherwise, it would remain a useless observational exercise. Importantly, phenotypes can coexist; this is, the presence of one phenotype does not necessarily exclude the presence of other phenotypes [19]. This is pictorially depicted in Figure 3 and forms the basis of the *Treatable Traits* (TT) concept that will be discussed in depth below [6]; (2) the term *endotype* -a contraction of endophenotype- has been defined as “*subtype of a disease defined functionally and pathologically by a molecular mechanism or by treatment response*” [20]. This approach is radically different from the traditional Oslerian paradigm discussed above, which was (and still is) based mostly on the phenotypic presentation. Further, the beauty of the endotype concept is that, according to the definition of precision medicine presented above [5], it is a first step towards its implementation in clinical practice. Yet, to date, it is still, by and large, a theoretical construct since we still do not understand the vast majority of biological

170 mechanisms (i.e., endotypes) underlying different clinical presentations (i.e.,
171 phenotypes); (3) given the key role played by biological networks in health and disease
172 [21], novel analytical techniques (such as network analysis [22]) capable of integrating
173 this multi-level (exposome, genome, endotypes and phenotypes) complexity are needed
174 to unravel and understand the patho-biology of most human diseases, including chronic
175 airway diseases. Such improved understanding should allow the identification and
176 adequate validation of *biomarkers (i.e., a biological, functional, imaging and/or clinical*
177 *characteristic that is objectively measured and evaluated as an indicator of normal*
178 *biologic processes, pathogenic processes, or biological responses to a therapeutic*
179 *intervention* [23]). This is an absolute requirement to move towards precision medicine
180 of airway diseases [24].

182 **Key questions in the management of airway diseases**

183 During the seminar, it was agreed that the following questions need to be answered (by
184 appropriate research and/or consensus) to move precision medicine of airway diseases
185 forward:

187 *Should we continue using the traditional diagnostic labels “asthma”, “COPD”,*
188 *“bronchi(oli)tis” and/or ACO (asthma-COPD overlap)? Which assumptions go with*
189 *them? What are the advantages/disadvantages of using them?*

190 Diagnostic labels have many advantages: they are useful to discriminate grossly defined
191 groups of patients, they are the basis of teaching students, they are easy to explain to
192 patients, they are easy (but right?) to use in interventional studies (i.e., randomized

193 controlled trials – RCTs) and they can be used to convince authorities to fund
194 medications. In clinical practice, they are also useful to identify a syndrome (see
195 definition above) [9] but this will likely lead to empirical (imprecise) management. The
196 implicit assumption that goes with these traditional diagnostic labels is that these
197 diseases are homogeneous in terms of their patho-biology and that, therefore, they need
198 the same treatment in all patients. This is wrong, and if the labels are to remain, it needs
199 to be clear that assumptions of pathophysiology should not be made. Thus, the labels
200 represent the start of the assessment process, not the end. It was agreed that we need
201 validated biomarkers (Figure 2) that allow the clinician to build up a clearer picture of
202 the main drivers of morbidity, allowing provision of the right treatment, at the right time
203 to the right person (Figure 1).

204

205 *Would it be more helpful to deconstruct airway disease into components that can be*
206 *measured and potentially modified (Treatable Traits)?*

207 As discussed above the terms “asthma” and “COPD” actually correspond to syndromes
208 that comprise overlapping disorders/clinical phenotypes [25]. Participants in the
209 seminar agreed that a treatable traits-based strategy was a first, appropriate step towards
210 the deconstruction of these terms into their individual treatable components and, as a
211 result, towards precision medicine of chronic airway diseases. A *Treatable Trait* (TT) is
212 “a therapeutic target identified by “phenotype” or “endotype” recognition through
213 validated biomarker(s)” [6]. Table 1 list a number of potential pulmonary, extra-
214 pulmonary and behavioural/life style TT to consider in patients with chronic airway
215 diseases, and their specific therapeutic recommendations as per current international
216 guidelines [2, 3]. Again, several aspects of this proposal require discussion: (1) TT are

independent of the traditional, syndromic diagnostic “labels” used to date (*i.e.*, they can occur both in patients with “asthma” or “COPD”); (2) TTs can coexist in the same patient and can change within patients over time. These concepts are not captured adequately by the traditional phenotype concept (Figure 3), and are therefore important for the clinician to understand; and, finally, (3) this TT approach requires prospective validation, as discussed in detail below. Identifying (currently) non-treatable traits (e.g. emphysema, airway remodelling) would also be of relevance since it can foster specific research to fill the gap.

Can available biomarkers identify different phenotypes or endotypes of airway disease?

The serum level of alpha-1 antitrypsin deficiency is a well established biomarker of a trait that may be treatable [26]. Other, less well-validated biomarkers that have been proposed in the context of chronic airway diseases include: (i) Circulating eosinophils (Eos). A level of Eos >3-4% or >300 cells/μl appears to identify a subpopulation of patients with asthma or COPD, both when clinically stable as well as during an exacerbation of their disease, that are at higher risk of exacerbations and respond better to corticosteroid treatment [27-31]. Furthermore, COPD patients with persistently elevated Eos (about 10% of the total COPD population [32]) have accelerated FEV1 decline, and a recent reanalysis of the ISOLDE study suggests that this is prevented by inhaled corticosteroid (ICS) treatment [33]. Finally, it is of note that there are different subtypes of Eos [34] which merit further research in patients with chronic airway diseases; (ii) Fractional exhaled concentration of nitric oxide (FeNO) is associated with eosinophilic airway inflammation and raised airway concentrations of type-2 cytokines (so called type-2 inflammation), particularly IL-13 [35]. It also appears to identify

241 accelerated lung function decline in asthmatics [36], as bronchial CD8, CD4 and CD3
242 cell infiltrates do [37]; (iii) High IgE is often viewed as a TT, although it is a
243 disappointing biomarker of response to type-2 targeted treatments, including
244 Omalizumab [38-41]; (iv) Airway bacterial colonization and, eventually, changes in the
245 airway microbiome, also have the potential to be biomarkers of a TT although we are
246 currently lacking good objective biomarkers and well validated treatments for this trait
247 [42]; and, finally, (v) Persistent systemic inflammation occurs in a subset of patients
248 with COPD [43] and asthma [44], and these patients have worse outcomes (mortality
249 and exacerbations) [43]. A pilot study in patients with stable COPD that targeted
250 systemic inflammation showed positive clinical benefits [45].
251
252 This is only the tip of the iceberg. We need more validated biomarkers to predict
253 (Figure 1) response to treatment (including adverse effects), monitor treatment effects,
254 and/or predict clinically relevant outcomes (mortality, exacerbations, lung function
255 decline) [46-49]. Participants in the seminar agreed that by addressing the above
256 discussed questions, airway disease management will move into a new, more precise,
257 better and safer era. To do so, however, it was also acknowledged that, besides a deeper
258 knowledge of the biological basis of airway diseases, large, prospective, long-term,
259 interventional studies across the whole spectrum of airway diseases are needed,
260 probably leveraging on new experimental designs (“*master protocols*”), as discussed
261 below [50].

262

263 **DEPLOYMENT OF AIRWAY PRECISION MEDICINE IN CLINICAL**

264 **PRACTICE, OR WHERE ARE WE NOW**

265 **The problem**

266 Current clinical management of patients with chronic airway diseases is guided by
267 national and international guidelines which, in turn, are based on group mean data from
268 RCTs and do little to recognise individual heterogeneity, although they are slowly
269 evolving in this direction [2, 3]. Despite this, it is fair to recognize that this guideline-
270 based approach has progressively improved outcomes up until the last 15 years or so.
271 Yet, in many developed countries improvements in outcome have stalled [51]. There
272 have been no further decreases in hospitalisations or mortality despite steadily
273 increasing pharmacy costs and increasing use of combination inhalers [52]. Real-life
274 surveys repeatedly reveal that sub-optimal control is common, and frequently show that
275 potentially preventable factors occur in many deaths, hospitalisations and in most
276 quality of life impairment [53]. This emphasizes the need of both, better treatments and
277 more effective (precise) management strategies.

278

279 **Are we ready today?**

280 The challenge is to develop simple algorithms that enable the identification of potential
281 TT which may be contributing to poor respiratory health in a patient with airway
282 disease (Table 1). And, yes, despite the uncertainties discussed above about endotypes,
283 phenotypes and biomarkers, there are a few, relatively simple things, that we can do
284 *today to likely* improve the management of patients with chronic airway diseases. As
285 shown in Figure 4, the first proposed step would be to determine if the patient “really”
286 has airway disease [6]. To answer this question a simple strategy that combines standard

clinical history, assessment of potential risk factors of airway diseases (smoking, allergies, occupation, family history, and early life events) and measurement of spirometry, FeNO and blood Eos can be conceived, both in primary and specialized care. The results of this assessment may determine the probability (High/Low) of airway disease being present. If there is a high probability of airway disease, therapy should be based upon the TT present in that individual patient (Table 1) which, importantly, are not mutually exclusive [6]. By contrast, if the clinical history is atypical, no risk factors of airway disease can be identified and the results of these tests are normal, alternative diagnoses should be considered [6]. Needless to say that, once the patient has been diagnosed and treated for airway disease according to this TT strategy, follow up needs to consider (as already recommended by current guidelines [2, 3]) adherence with treatment, inhalation technique, response to therapy [54] and risk of future events [55]. The concept of “control” has been basically applied to asthma, but some recent alternatives have been also proposed for COPD [56]. Although there is evidence to support the investigation and management of the individual components of this strategy, this prototype schema (and future modified versions) will need to be assessed by RCTs to provide scientific evidence of their effectiveness and safety in clinical practice. Likewise, alternative systems by which precision medicine might be delivered in clinical practice should also be investigated as a priority. Eventually, complex bio-clinical traits will need to be approached by machine learning and artificial intelligence, which provides very powerful computational models for potentially predicting clinical course and treatment responses [57, 58].

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309 **Primary vs. specialized care?**

310 The majority of new diagnoses and the routine management of mild and moderate
311 chronic airway diseases occur in primary care. Although the impetus to precision
312 medicine has come from difficult to control airway diseases, typically seen in tertiary
313 care centres, the concepts of complexity and heterogeneity are equally relevant in
314 patients with milder disease treated in the community because individual patients are
315 different and the reasons for poor control are heterogeneous. The era of precision
316 medicine of airway diseases is dawning, and primary care should be involved.
317 Individualised therapy based on assessment of the two dominant treatable traits –
318 eosinophilic airway inflammation and airflow limitation – would be well within the
319 scope of non-specialist clinicians and would be an important step in this direction.

320

321 **HOW TO MOVE THE FIELD FORWARD THROUGH RESEARCH**

322 **Earlier experiences**

323 *Single biomarker studies*

324 Early trials of targeted management of chronic airway diseases focused on single
325 inflammatory biomarkers. RCTs conducted using sputum eosinophil counts as a
326 biomarker to guide treatment decisions showed reduced exacerbations vs. guideline-
327 based therapy both in asthma [59] and COPD [60]. Other trials used FeNO to guide
328 treatment decisions and a meta-analysis of these studies indicated superior outcomes
329 over an approach focused on asthma symptoms [61]. Finally, the use of bronchial
330 hyper-reactivity (BHR) as a biomarker also showed efficacy and lead to a more
331 effective control of asthma while alleviating chronic airways inflammation, indicating

332 that the concept goes beyond inflammatory markers [62]. All in all, these studies
333 support the paradigm of precision medicine when treatment is targeted to a specific
334 pathway. Importantly, they show the benefit of a precision medicine approach across the
335 asthma severity spectrum. This means that precision medicine of airway disease need
336 not be restricted to severe or refractory disease (as it has been in current guidelines), but
337 can benefit people with mild disease as well [63].

338

339 *Multiple biomarker studies*

340 Precision medicine however extends beyond a single biomarker/TT, since an individual
341 patient can have multiple potentially TT. Only a few studies have so far attempted to
342 apply a multidimensional assessment (MDA) followed by individualised management
343 in patients with chronic airway diseases. McDonald *et al* tested this strategy in a proof
344 of concept study in a COPD population, where the MDA involved the evaluation of
345 airways, co-morbidities, risk factors and behavioural traits, as well as the measurement
346 of several systemic inflammatory markers (“*inflammometry*”) [45]. Results showed that
347 this precision medicine approach led to a highly clinically significant improvement in
348 health status [45]. These observations have been reproduced very recently in patients
349 with severe asthma [64]. Whilst the results of these trials are promising, we
350 acknowledge that this is a complex approach to trial design and execution that raises
351 questions in terms of whether the observed effects are related to any one intervention in
352 particular or are the result of a ‘stacked approach’, that is additive effects of multiple
353 interventions [50]. Thus, in the future different study designs need to be considered, as
354 discussed below [50]. Likewise, it is conceivable that precision medicine will more and

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355 more rely on the fast and on-site (“*point of care*”) assessment of multiple biomarkers
356 derived from high-throughput “omic” platforms [65-67].

357

358 **A Treatable Traits Study proposal**

359 There was consensus that the TT strategy [6] was a potentially feasible approach to
360 deploy precision medicine of airway disease in clinical practice. However, there was
361 also consensus in that it required formal, prospective and controlled validation, most
362 likely in an international multi-center, multi-component interventional study [50]. It was
363 also realized, however, that such a study will be complex, so the following issues were
364 specifically discussed:

365

366 *Trial design*

367 Traditional RCTs are designed to test a single treatment in a homogeneous population.
368 As a result, only a small proportion of patients with asthma or COPD are included in the
369 major RCTs for asthma or COPD which, importantly, form the basis of current
370 guideline recommendations despite it reduced generalisability [53, 68]. Furthermore,
371 this approach is not adequate to test multi-component interventions in heterogeneous
372 populations. Likewise, it is not an effective way to test a biomarker driven treatment
373 algorithm in airway disease [69].

374

375 The so-called “*master protocols*” leverage from novel experimental designs and are
376 better suited for these purposes [50]. A master protocol has one overarching protocol

designed to answer multiple questions, which may involve one or more interventions in multiple diseases or a single disease, as defined by current disease classification, with multiple interventions, each targeting a particular biomarker-defined population or disease subtype [50]. There are several types of master protocols, including the so-called “platform”, “basket” and “umbrella” trials [50, 70, 71]. “Umbrella” trials study multiple targeted therapies in the context of a single disease, “Basket” trials study a single targeted therapy in the context of multiple diseases or disease subtypes, and “Platform” trials (Figure 5) study multiple targeted therapies in the context of a single disease, with therapies allowed to enter or leave the platform on the basis of an agreed decision algorithm [50]. At the seminar, it was agreed that, in order to test the efficacy and safety of a TT strategy for the management of airway disease in practice, *a platform trial design* (Figure 5) *would be probably adequate* because it is precisely designed to identify the optimal “set of treatments” in conditions where management involves multiple therapies delivered concurrently, and has the potential to have independent or interacting effects on outcome. Table 2 contrasts the main characteristics of a platform trial vs. traditional RCTs. Yet, it was also acknowledged that its design and statistical methods involved are complex, and that they would require appropriate knowledge and expertise. Finally, it was agreed that such a trial will create the opportunity to generate a multi-centre bio-bank [72] to store biological samples for future studies.

Intervention(s)

A crucial component of the study will be the standardization of both the MDA and a tailored TT plan. This should be greatly facilitated by a care coordinator, as the proposed intervention is a TT strategy, rather than an individual single component

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401 intervention that targets a specific trait. As such it is likely to require multiple health
402 behaviour changes from the patients’ perspective and significant coordination from a
403 health care perspective. The care coordinator or case manager will ensure that the
404 overall treatment plan is implemented. Early trials with a similar design support this
405 approach [45, 64].
406
407 Complex interventions in health care comprise a number of separate elements which
408 seem essential for the proper functioning of the intervention, although “the” active(s)
409 ingredient(s) of the intervention is (are) often difficult to identify [50]. It is possible that
410 the ‘stacked’ approach, that is multiple traits being treated simultaneously with a
411 measurable and additive benefit to each intervention, leads to a larger than expected
412 improvement [73]. In addition, the impact of treating multiple traits may have effects
413 not only on the intended outcome(s) but may also benefit multiple other domains. For
414 example, treating obesity in COPD not only improves body composition, but also
415 improves exercise tolerance, cardiovascular outcomes and depression [73]. This,
416 combined with pharmacotherapy or pulmonary rehabilitation, may in fact increase the
417 final effect size. A large trial should therefore be able to have enough power to perform
418 regression/mediation analysis of subgroups receiving particular interventions to
419 determine what it is that is having the greatest impact. A final consideration that
420 emerged during the discussion of this particular topic was that “no intervention is, in
421 fact, an intervention” and this should be actually considered when designing the
422 appropriate studies and sub-group analyses. For instance, it may be of interest to
423 identify individuals in whom the active TT strategy resulted in a particular treatment
424 decision that would have been different with ‘usual care’, and where possible compare

425 outcomes with similar individuals from the control group rather treated by diagnosis-
426 driven guidelines.

427

428 *Outcomes*

429 The choice of outcome measure(s) in a TT trial is also of paramount importance. The
430 primary outcome in such a study should be valid and responsive to each of the
431 treatments used. Established outcomes, such as *severe exacerbations*, *hospital*
432 *admissions or death* are likely to be the preferred primary “hard” outcomes, particularly
433 in high risk groups. Yet, because the interventions will target different pathways, it is
434 also necessary to have trait specific outcomes that demonstrate efficacy of the
435 intervention on each pathway. For example, a T2 anti-inflammatory intervention needs
436 to show benefit in reducing T2 inflammation, such as eosinophils or FENO. However,
437 this may not be suitable as the primary study outcome, since it would not be responsive
438 to nonT2 traits, such as treatment for depression. In this situation, a more global
439 outcome measure is needed, and *health status* should not be dismissed albeit it is
440 usually considered a ‘soft’ outcome. Health status is the single outcome that best
441 encompasses the overall impact of disease on an individual’s life, and so is of high
442 importance from the patient perspective. Particularly in light of previous data that
443 indicates that for each additional trait there is a clinically significant decrement to
444 quality of life [74]. Perhaps a *composite outcome* may be ideal incorporating health
445 status with one or more objective outcomes. Also, it cannot be excluded that in addition
446 to such measures of individual well-being, particular biomarkers or biomarker profiles
447 can provide complementary information on therapeutic outcome of a TT strategy.

448

449 Finally, provided the results of the trial are positive, other outcomes that will facilitate
450 its eventual deployment in clinical practice relate to the inclusion of: (1) health
451 economists to design and execute a robust *health economic analysis* (cost –
452 effectiveness analysis) in the context of value-based health care ; (2) *consumers* in the
453 development of the study, since it is likely to be complex and this advice may lead to
454 better patient adherence; and, (3) some sort of *qualitative evaluation* to determine
455 patient and clinician experiences and attitudes about the TT approach (i.e. acceptability,
456 adoption, appropriateness and sustainability), that can help developing a better
457 understanding of the intervention characteristics.

459 **CONCLUSIONS**

460 There was unanimous agreement in the seminar that to improve the current management
461 of complex airway diseases like asthma and COPD a precision medicine approach was
462 required and that, to achieve this in practice, the best available alternative was the one
463 based on the TT strategy. However, this consensus needs prospective, formal validation.
464 Several key aspects of such trial (design (platform trial), interventions (MDA and
465 tailored TT intervention) and outcomes (hard and soft)) were discussed. We now hope
466 that the independent umbrella organisation of the ERS Research Agency takes on the
467 challenge of promoting and facilitating the prospective testing of whether the adoption
468 of a TT strategy as a first step toward precision medicine of airway diseases improves
469 the outcomes and safety of these patients. All participants in the seminar (listed in
470 Appendix I) certainly look forward to doing so.

471

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476

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683

Table 1. List of potential pulmonary, extra-pulmonary and behavioural/life style treatable traits to consider in patients with chronic airway diseases.

	TRAIT	TREATMENT
Pulmonary treatable traits		
	Airway smooth muscle contraction	Bronchodilators
	Eosinophilic airway inflammation	Corticosteroids / Type 2 biologics
	Chronic sputum production	Smoking cessation, Macrolides, PDE4 inhibitors
	Bacterial colonization	Macrolides, Tetracyclines
	Bronchiectasis	Macrolides, Tetracyclines, Nebulised antibiotics/Aminoglycosides
	Cough reflex hypersensitivity	Gabapentin , P2X3, speech pathology intervention
	Chronic respiratory failure	Oxygen / NIV / Lung Tx
	Pulmonary hypertension	Oxygen / NIV / Lung Tx
	Emphysema	Lung volume reduction /Tx
Extra-pulmonary treatable traits		
	Rhinosinusitis	Topical steroids / Surgery
	Deconditioning	Rehabilitation
	Cachexia	Diet / physical activity
	Obesity	Diet / physical activity / bariatric surgery
	Cardiovascular disease	ACE inhibitors / diuretics / β blockers
	Vocal cord dysfunction	Speech pathology therapy
	Depression	Cognitive & Behavioural therapy
	Anxiety	Anxiolytics
	Systemic inflammation	Statins ?
Treatable behaviour / life style factors		

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	Poor inhalation technique	Education
	Non-adherence to treatment	Reassurance / Education / Periodic check-up
	Smoking	Cessation support
	Exposure to sensitizing agents	Avoidance / desensitization
	Side effects of treatments	Treatment optimization
	Polypharmacy	Medication review
	Poor family and social support	Family therapy education / self management support

686

687 Abbreviations: NIV: non-invasive ventilation; Tx: transplant

688

Table 2. Comparison of the main features of traditional vs. platform randomized clinical trials (RCT). Reproduced with permission from ref. [75].

	Traditional RCT	Platform RCT
Intervention	Single public health or therapeutic intervention	Various interventions or combinations of interventions. New treatments might be added during the trial
Population	Homogeneous (high risk)	Homogeneous or heterogeneous. Subgroups defined by clinical phenotypes or biomarkers; might be changed over time
Allocation	Fixed randomisation	Response-adaptive randomisation
Duration	Finite with option of extending duration of follow-up	Potentially long term, extended if novel treatments need assessment
Stopping rules	Trial might be stopped early for success, failure, or futility	Individual treatments might be stopped, but trial might be continued with new interventions
Statistics	Standard in-house methods	Complex, Bayesian, continuous analysis, often needing specialised statistical team
Funding	Government or pharmaceutical company sponsorship	Scope for sponsorship from both government and pharmaceutical companies
Collaboration	Single centre or multiple centres, similar populations	Multicentre, international, from diverse populations

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692 **FIGURE LEGENDS**

693 **Figure 1.** Principles of precision medicine that illustrates the heterogeneity of any
694 human disease and the potential impact of stratifying the population appropriately
695 (courtesy of Prof. C. Vogelmeier).

696
697 **Figure 2.** Schematic representation of the relationships between the exposome and the
698 genome (via complex biological networks), the emergence of endotypes and
699 phenotypes, and the possibility of identifying them through validated biomarkers of
700 treatable traits. Numbers in boxes correspond to quoted references. For further
701 explanations, see text.

702
703 **Figure 3.** Left panel: Pictorial representation of chronic obstructive pulmonary disease
704 (COPD) heterogeneity. Each node represents one patient, and each colour represent
705 different clinical characteristics. Right upper panel: approach to COPD complexity
706 based on similar clinical presentations (colours), so-called phenotypes. Right bottom
707 panel: Given that phenotypes can coexist in the same patient, an approach based on
708 treatable traits has been proposed more recently [6]. Reproduced with permission from
709 reference [19].

710
711 **Figure 4.** Proposed diagnostic strategy for an adult with symptoms, signs or events
712 suggestive of airway disease (without any further “traditional diagnostic labelling”).
713 FeNO: exhaled nitric oxide fraction. #: smoking, allergies, sputum production,

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3 714 occupation, lung development and growth. For further explanations, see text.
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5 715 Reproduced with permission from reference [6].
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11 717 **Figure 5.** Evolution of a platform trial over time. In this example, three interventions
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13 718 (A, B, and C) and their combinations (AB, BC, and AC) are assessed in a population of
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15 719 patients that includes three subtypes of the disease (“blue,” “red,” and “yellow”) (Panel
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17 720 i). When the study is started, randomization is balanced between all possible treatments
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19 721 and all patient subtypes are treated similarly. After a period of time it appears that BC is
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21 722 having a greater effect than the other treatments and, to a lesser extent, so are B, C, and
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23 723 AC. Thus, subsequent randomization enriches the number of patients assigned to the
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25 724 receive BC, shown by the larger font, and B, C, and AC (Panel ii). After the trial
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27 725 continues further, analysis reveals that treatment A and its combinations are not
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29 726 effective in any subgroup and subgroup “yellow” is not effectively treated in any arm,
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31 727 so patients are no longer randomized to receive any combination including treatment A
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33 728 and the “yellow” subgroup is discontinued from further enrollment (Panel iii). At the
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35 729 end of the trial, not shown in the figure, the combination treatment BC may graduate
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37 730 from the trial based on evidence of benefit in the “blue” subtype of disease, to be
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39 731 recommended for clinical use, or for further evaluation in a separate phase III trial.
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41 732 Reproduced with permission from reference [70].
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734 **APENDIX I**

735 List of registered participants in the Seminar (alphabetical order).

Prof. Dr Amany Abd Al-Aziz
Ms Natia Adamia
Mr Abdelilah Benslimane
Dr Irina Bobolea
Dr Ioannis Bonovolias
Dr Carlos Celis
Dr Aleksandra Chwist-Nowak
Prof. Dr Renata Da Palma
Dr Denitsa Dimitrova
Dr Nino Jessielito Doydora
Dr Gunnar Einvik
Prof. Dr Ramcés Falfán-Valencia
Dr Laura Fregonese
Dr Judith Garcia-Aymerich
Dr. Gareth Hynes
Dr Truls Ingebrigtsen
Dr. Neves Joao
Dr Alejandra López Giraldo
Prof. Dr Flavia Mafra De Lima
Prof. Dr Anke-Hilse Maitland-Van Der Zee
Dr Stoilka Mandadzhieva
Prof. Dr Dora Marinova
Dr Alexander Mathioudakis
Prof. Dr Eduard Monsó
Prof. Dr Oxana Munteanu
Dr Marta Oliveira
Prof. Dr Gloria Pérez-Rubio
Prof. Dr Martin Petrek
Prof. Dr Emilio Pizzichini
Dr. David Ramos Barbon
Prof. Roberto Rodriguez-Roisin
Prof. Dr Alizaman Sadigov
Dr Sabina Schmitt-Grohé
Dr. Ulla Seppala
Prof. Dr Rahul Shrimanker
Dr Eman Sobh
Dr Kseniia Sytnyk
Dr Susanne Vijverberg

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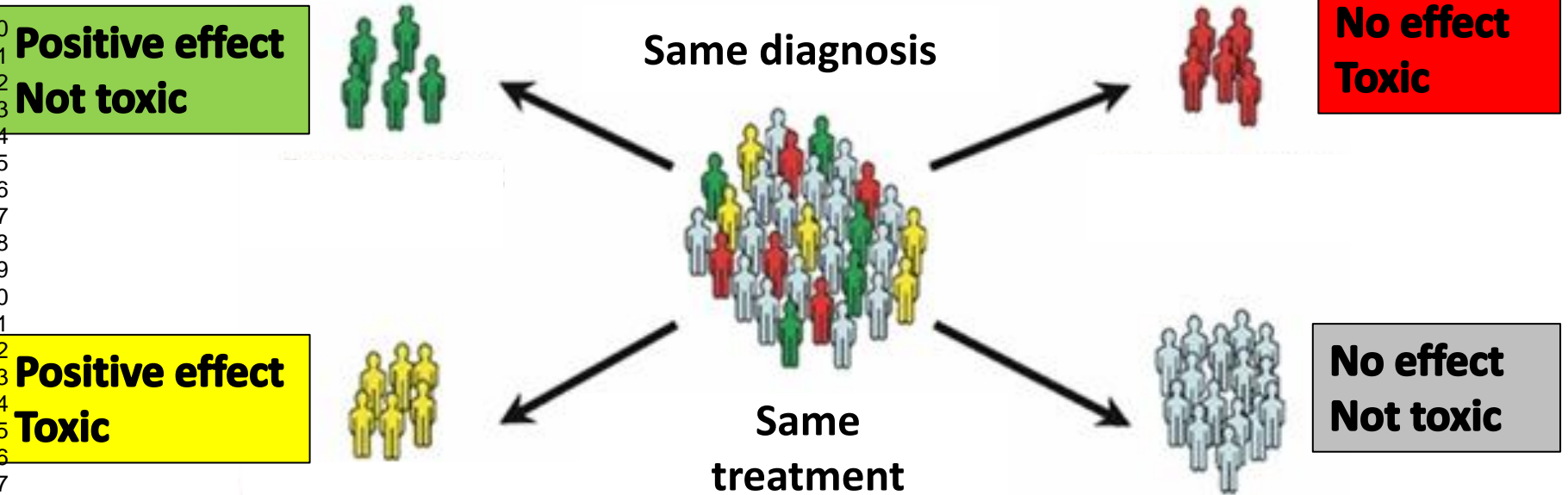


Figure 1

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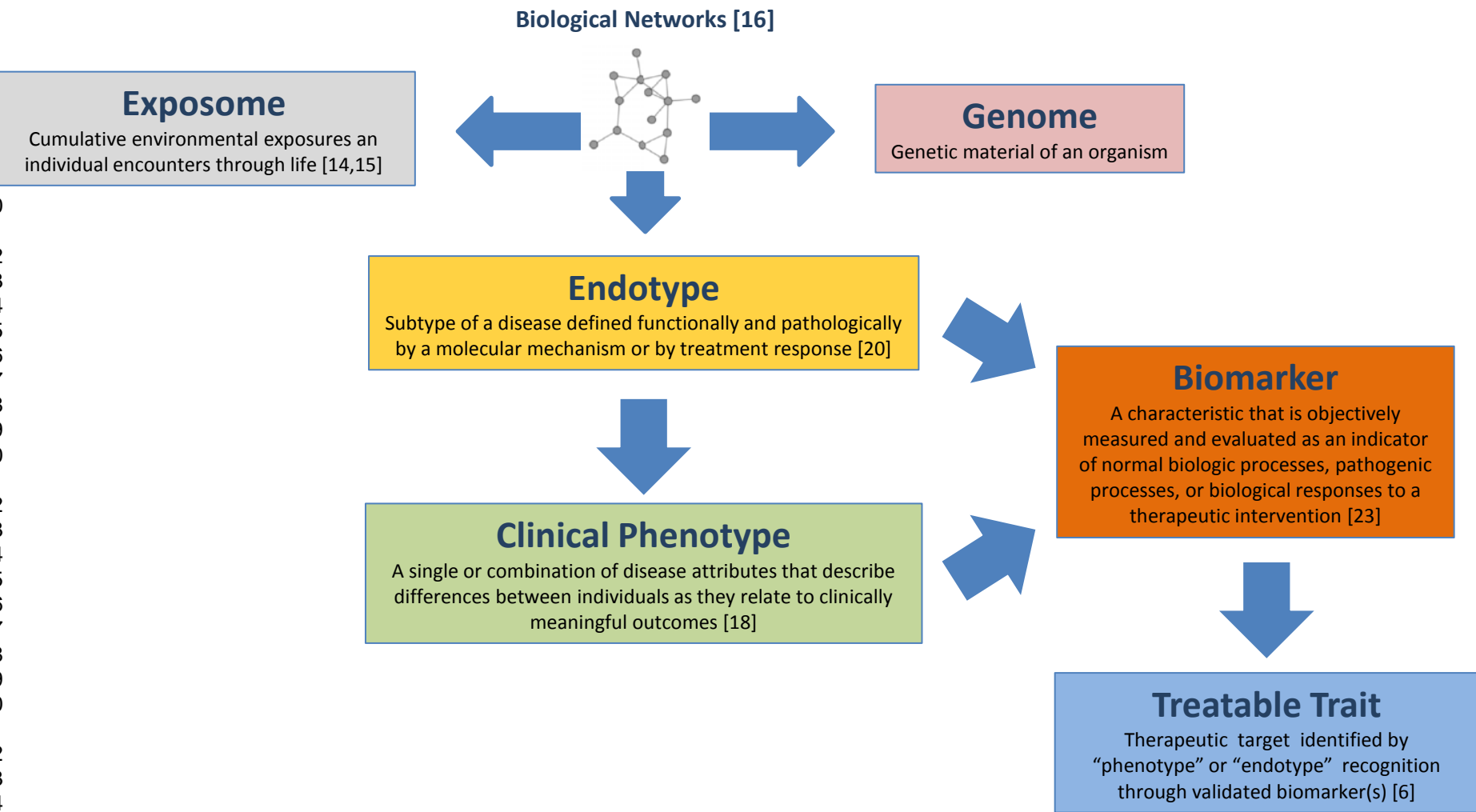


Figure 2

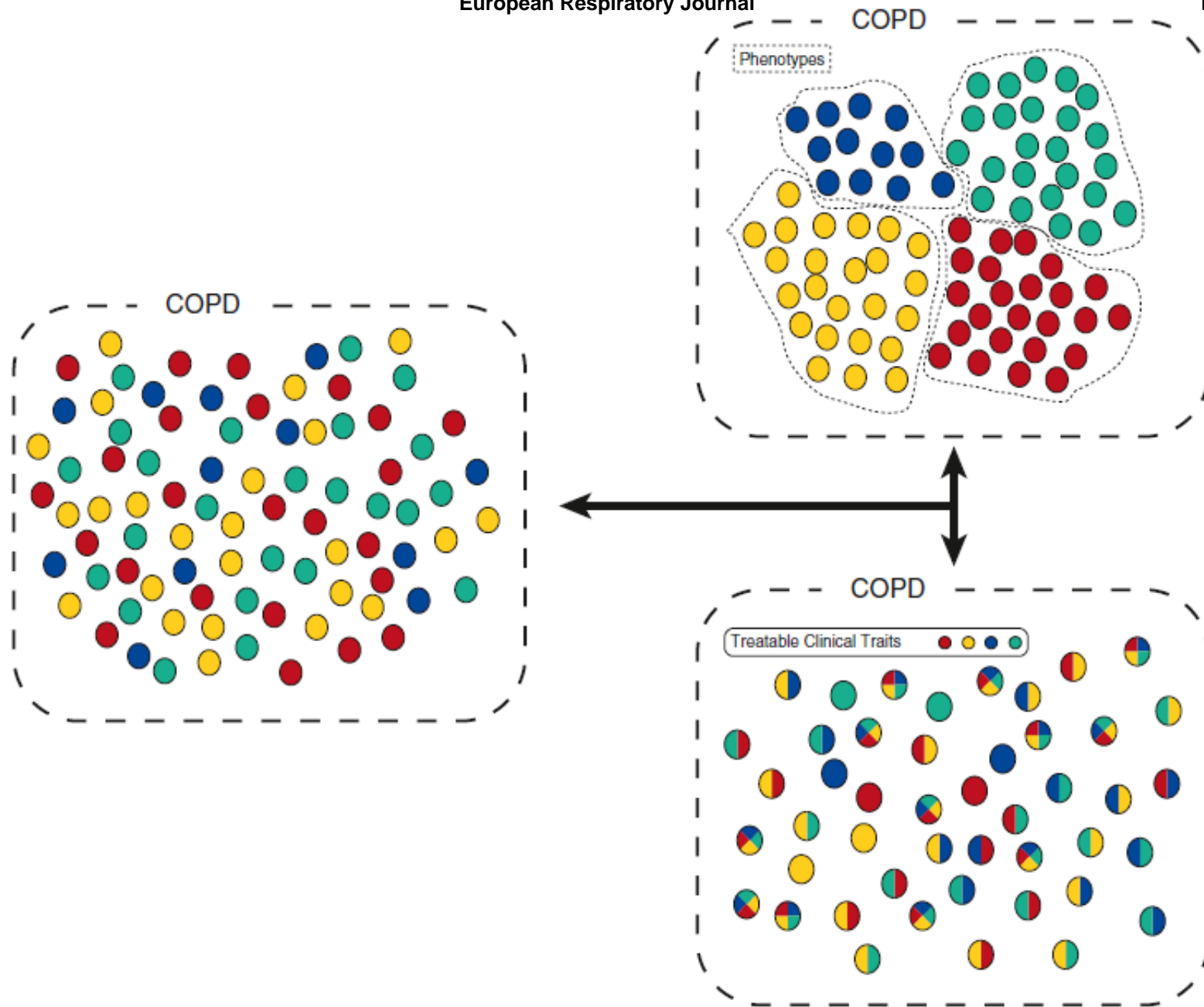


Figure 3

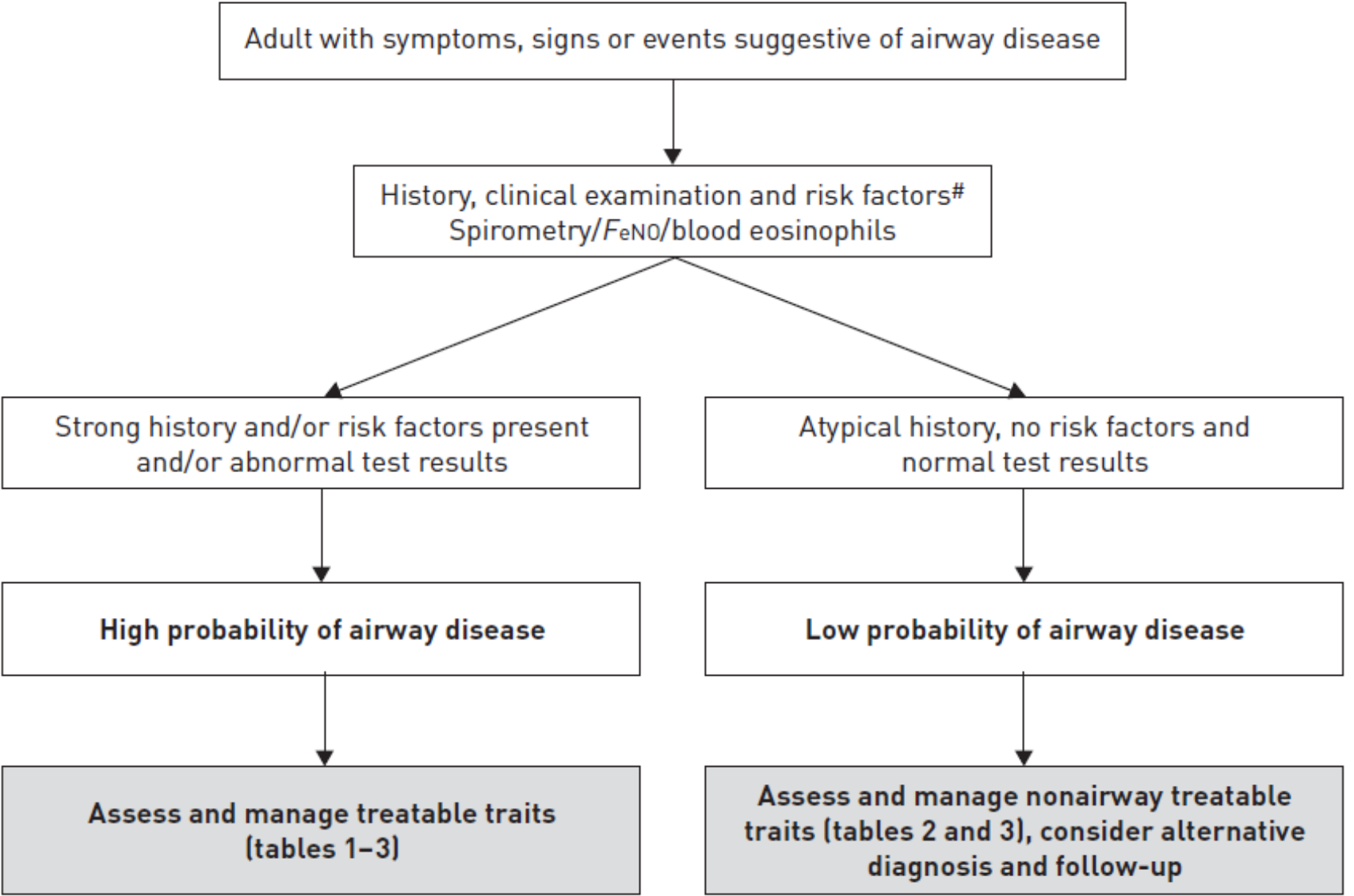


Figure 4

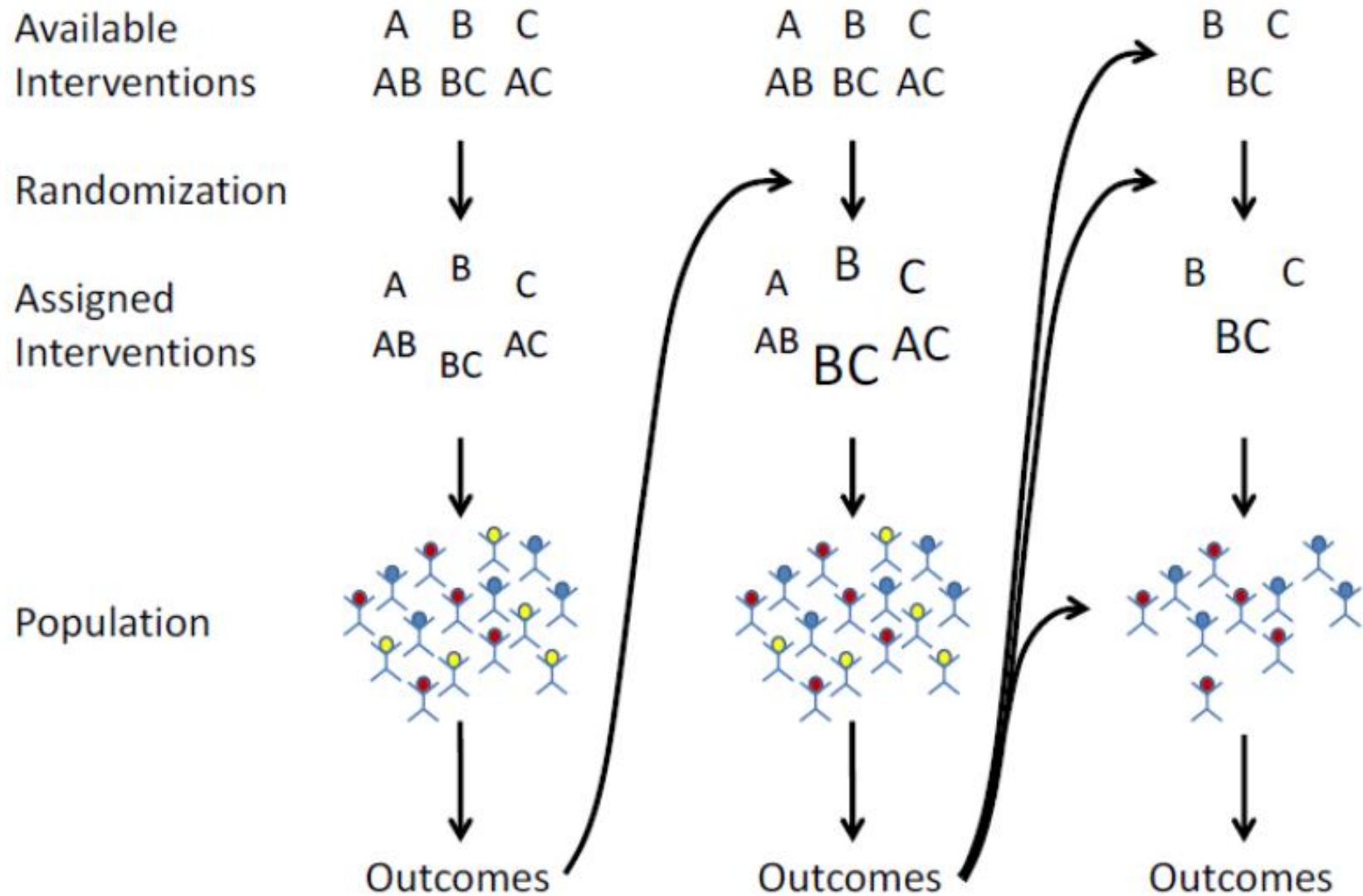


Figure 5