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Corresponding Author: Prof. Nicky Britten, PhD

Corresponding Author's Institution: University of Exeter

First Author: Nicky Britten, PhD

Order of Authors: Nicky Britten, PhD; Catherine Pope, PhD; Susan Halford , PhD; Luca Richeldi , MD

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Title: What if we made stratified medicine work for patients?

Authors

Nicky Britten, PhD, Professor of Applied Health Care Research, University of Exeter Medical School, Institute of Health Research, Exeter EX1 2LU
Email: N.Britten@exeter.ac.uk. Tel: 01392 724851 **(corresponding author)**

Catherine Pope, PhD, Professor of Medical Sociology, Faculty of Health Sciences, University of Southampton, Southampton, SO17 1BJ

Susan Halford, PhD, Professor of Sociology, Faculty of Social and Human Sciences, University of Southampton, Southampton, SO17 1BJ

Luca Richeldi, MD, Professor of Respiratory Medicine, University of Southampton / University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, SO16 6YD

Stratified medicine is the ultimate medical advance - the targeting of medicines and other interventions according to biological characteristics of subgroups of patients. The UK Medical Research Council promises that "Ultimately stratified medicine will ensure that the right patient gets the right treatment at the right time"[1] and the Academy of Medical Sciences has argued that it will "revolutionise the treatment of disease".[2] We seek to expand this debate by moving beyond the narrow confines of biomarkers and genomics and exploring what genuinely patient-focussed stratified medicine might look like.

Stratified medicines are a serious challenge to evidence-based medicine. Even the best evidence offers a 'one size fits all' solution. Research tells us which drugs have proven safe and effective for a particular *disease*, but crucially – as physicians are quick to point out – not whether they will work for a particular *patient*. Medicines are not effective for everyone. Some people will experience adverse reactions while others will not. Sometimes medicines work brilliantly, but in other cases, they do not. Rather than waste money and time, and cause unnecessary suffering, it would be preferable to give medicines only to those people who will benefit from them. This is the challenge, and the promise, of stratified medicine.

Thus far much of the debate and exploration of the potential of stratified medicine has been concerned with identifying genetically defined population subgroups who might benefit from particular interventions. This has proven incredibly useful: advances in developing anti hepatitis C treatments, based on the use of biomarkers, has allowed targeting of interventions for patients who can benefit. However, we want to take a broader view of what stratified medicine could offer if it focussed on the patient as well as biology using the exemplar of idiopathic pulmonary fibrosis (IPF).

IPF is a devastating disease that results in death within a few years of diagnosis, with a prognosis worse than many cancers. The rate of disease progression is uncertain, but it is severely debilitating, painful and frightening for patients and their carers. PF has been described as 'like drowning in your own lungs'. Prevalence estimates vary according to the definitions used, but range from 1.25 to 23.4 cases per 100,000 population, and annual incidence may be 7.4 per 100,000 population. IPF rates are higher among men, and it is a condition that, whilst rare, seems to be on the increase [3]. The need to palliate symptoms, and the lack of robust measures of long-term clinical outcomes has hindered development of novel therapeutics. Medical intervention and management is further confounded by an inability to predict natural history of the disease. Non-pharmacological treatments include pulmonary rehabilitation, oxygen, and, in some selected cases, lung transplant surgery. Currently available medications include pirfenidone and nintedinib (the latter is currently still unlicensed in the UK). These medicines do not work for everyone with IPF and only reduce the rate of progression of the disease; as a consequence, some patients find that side effects of these drugs, which range from nausea, diarrhoea, vomiting, and photosensitivity to chronic pain and fatigue, are worse than the disease.[4 5]

Stratified medicine could revolutionise treatments for IPF. There are familial patterns in disease and data on sporadic forms that suggest that genomic factors may account for up to one third of the risk.[6] Further work is being done experimenting biomarkers that could support earlier, better diagnosis, and help predict prognosis.[7] In short, IPF is a strong candidate for the development of stratified medicine and one that the major pharmaceutical companies and patient lobby groups are keen to pursue.

But stratification need not be limited to genomics and biomarkers alone. The development of stratified medicine is a social process as well as a biochemical one. We advocate a conceptual broadening of 'stratification' to include patient perspectives and experiences. Stratified medicine must recognise that the factors shaping differential outcomes within patient groups are heterogeneous, complex and under-recognised in conventional biomedical approaches. What 'works' according to randomised controlled trials is not a useful indicator of what will be embedded in everyday practice by patients or physicians.[8] For example, some patients will not follow treatment regimens if side effects are unacceptable, the treatment burden too onerous, or normal life rendered impossible. If we can predict who these individuals are we can offer more meaningful interventions. In the case of IPF, the risk of a specific side effect (e.g. photosensitivity or diarrhoea) may be extremely debilitating to one patient but a lesser concern for another. Research [9] shows us that patients make trade-offs between symptom states, duration, and quality of life. If we could harness stratified medicine to capture the parameters offered by different medicines this would aid shared decision-making.

For medicine to deliver on its promise we need to recalibrate stratification according to wider criteria that combine biomedical markers with the patient experience. This requires a move outside the laboratory and into social science. We need approaches [10,11] that illuminate the burden of treatment [12] and the complex decision-making surrounding medicine taking.[13] We need to uncover the meaning of stratified medicines for patients and their carers. If we could identify biomarkers that predict the progression of IPF and response to treatment based on endotypes, *and* integrate this knowledge with a patient-focus on quality of life and experience of treatment we would be far closer to delivering the 'right medicine to the right patient at right time'.

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