inhaled corticosteroids, such as leukotriene inhibitors or slow-release theophylline? A small study[9] showed that add-on montelukast to low-dose budesonide was better than add-on tiotropium in terms of control of asthma and FEV_1. Further studies are needed.

Addition of tiotropium to combined inhaled corticosteroids and LABA could also be an alternative approach at step 4 of the GINA guidelines (when medium-dose or high-dose inhaled corticosteroid with LABA is used), and already many such patients with uncontrolled asthma are being prescribed add-on tiotropium. These emerging beneficial effects of tiotropium in patients with asthma should give encouragement for other LAMAs that are now established for use in patients with COPD to be tested in asthma. At present, another LAMA—umeclidinium—has undergone phase 2 trials in patients with asthma, but the results have not yet been published (ClinicalTrials.gov, number NCT01573624). A study of glycopyrolate bromide in combination with inhaled corticosteroid and LABA in patients with asthma is ongoing (NCT02127866).

The adverse and severe adverse effects recorded in Kerstjen and colleagues' studies were similar between the two tiotropium groups, salmeterol, and placebo, as has been reported in other trials of tiotropium delivered by the Respimat Softmist inhaler for asthma. Debate is ongoing about the risk of mortality with treatment with tiopropium Respimat inhaler in patients with COPD, in particular in those with cardiovascular disease and cardiac arrhythmias.[10,11] A note of caution should be taken regarding chronic use of this treatment in patients with asthma with such a cardiac background.

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Whole-genome sequencing in critically ill infants and emerging ethical challenges

Several of the authors of Laurel Willig and colleagues' report[1] in *The Lancet Respiratory Medicine* have previously described their concerns that the use of whole-genome sequencing and other next-generation sequencing in clinical care could give rise to various novel ethical challenges, but that "the ethical issues that arise from new uses of new technologies…cannot be understood until the technologies are deployed in the real world."[2] Other authors, myself included, have put forward perspectives on the potential ethical challenges that could arise with implementation of whole-genome sequencing.[3] With the findings described by Willig and colleagues, several of these potential ethical challenges of applying whole-genome

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sequencing in clinical care, particularly the care of critically ill infants, are beginning to emerge.

In their compelling report, Willig and colleagues describe that a rapid whole-genome sequencing technique and service (STATseq) can be effectively used to alter the care of selected critically ill neonates and infants. Whole-genome sequencing has previously been piloted in critically ill infants because more than 20% of deaths in infants are caused by chromosomal abnormalities, congenital malformations, deformations, and genetic diseases;[4] many of the 3528 monogenic diseases of known cause are present during the first 28 days of life; and neonatal intensive care units (NICUs) are thought to be suitable for early adoption of genomic medicine because extraordinary interventional efforts are customary and innovation is encouraged.[5] Whole-genome sequencing has been used to search for diagnoses in critically ill infants with suspected neurodevelopmental disorders,[5] dystonia,[6] and congenital cardiac disease.[7] Proof-of-concept of the usefulness of whole-genome sequencing to diagnose suspected genetic disease has already been shown in the acute care setting of the NICU[8] and, together with the findings from Willig and colleagues' study, suggest that whole-genome sequencing is no longer a theoretical care choice. Infants in acute care and the NICU environment are in need of the diagnostic methods provided by the introduction of genomic medicine because "rapid diagnosis is critical for timely delivery of interventions" and also because diagnosis can avoid futile intensive care.[8] Thus, genomics is potentially highly relevant for critically ill neonates and infants.

However, the whole-genome sequencing technology is novel. Whole-genome sequencing is intended to be predictive of the short-term and long-term functioning of an entire genome, as opposed to older genetic and genomic testing that examined single genes or gene clusters, and ethical considerations affect all steps in the implementation of a whole-genome sequencing programme including test design, patient selection, consent, sequencing analysis of patient DNA and delivery of results to the patient and family.[2] How to best select patients and provide appropriate whole-genome sequencing services to them still needs to be defined. Willig and colleagues chose to assess parent–child trios for children suspected by their clinicians to have monogenic disorders of an unknown genetic cause; children with signs and symptoms suggesting an elusive underlying genetic cause and whose clinicians were beginning to pursue a diagnostic odyssey. The patients were nominated by their treating clinicians and the nomination for study was reviewed before the research team decided to apply whole-genome sequencing in the patient (that a selection bias might account for some of the benefits with whole-genome sequencing in this study is noted by the investigators in their discussion). Interestingly, only half the nominated families enrolled in the study and Willig and colleagues cited parental refusal as a major reason. Parental perceptions of whole-genome sequencing and genomics in general, since analysis of parent–child trios involves the parents or families as study subjects, might need to be more carefully investigated as whole-genome sequencing is used in clinical care.

Additionally, use of whole-genome sequencing increases the focus on previously identified ethical and social issues surrounding the return of results, particularly the return of so-called incidental findings.[9] Willig and colleagues reported no incidental findings but by identifying all variants in a genome, it is no longer a question of whether incidental findings or clinically useful results will be found, but rather how many such results will be identified.[10] What to do with these findings is a challenge that still needs to be addressed.

The findings from whole-genome sequencing might have the potential to be used as justification to remove some therapeutic options, to decide that other options are futile, and possibly to ration scarce resources, such as organ transplantation, to one patient over another.[3] Willig and colleagues drew attention to four cases of genomics leading to life-prolonging outcomes. The data in their report, however, describe more starkly that both overall mortality was higher in the children diagnosed with whole-genome sequencing (57% *vs* 21% in children who were enrolled but did not have a genetic diagnosis) and, notably, that palliative care was instituted in almost a third of the children diagnosed with whole-genome sequencing (as opposed to none of the children who remained undiagnosed). Whether this should be thought of as a benefit or a burden of whole-genome sequencing might vary for different patients but it clearly warrants closer examination.

As Willig and colleagues show, the implementation of whole-genome sequencing to clinical care potentially offers great clinical benefits; the ethical challenges emerging with whole-genome sequencing will require some study and guidance.

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Efficacy endpoints for idiopathic pulmonary fibrosis trials

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Despite groundbreaking advances in the development of treatments for idiopathic pulmonary fibrosis, many questions remain unanswered—eg, what causes this deadly disease and what represents a clinically meaningful benefit for patients? Since idiopathic pulmonary fibrosis is a progressive and ultimately fatal disorder, with survival worse than many types of cancer,[1] translating meaningful benefit into prolonged survival seems obvious. However, international debate on the benefits and drawbacks of using mortality as the primary efficacy endpoint in clinical trials in idiopathic pulmonary fibrosis has been active and sometimes heated.[2–4] The feasibility of mortality trials in patients with idiopathic pulmonary fibrosis (or, at least, in early or intermediate stages of the disease) has been challenged by analyses of large clinical trials.[5] Yet, this discussion seemed anachronistic on Oct 15, 2014, when two drugs—nintedanib and pirfenidone—were approved simultaneously by the US Food and Drug Administration (FDA) for treatment of idiopathic pulmonary fibrosis.

The FDA's decision was based on the effect of these drugs on lung function, measured as a decline in forced vital capacity (FVC), making reduction in mortality seem redundant as an endpoint, at least with respect to drug approval. However, the FDA looked at the mortality data very carefully.[6] In all the trials that assessed the two approved drugs, mortality was a secondary endpoint: although none of the individual studies was powered to show a significant reduction in mortality, for both drugs, a non-significant improvement in survival was seen. These results lend support to the intuitive idea that, in a disease such as idiopathic pulmonary fibrosis that is restricted to the lungs, preserving lung function would ultimately translate into a survival benefit. However, the threshold for a clinically meaningful decline in FVC