Maybe a two strikes and you are out policy should also be applied to an intubation technique.

In the PeDI registry, the choice of airway management was at the discretion of the individual anaesthesiologist, who took into account not only patient factors, personal preferences and tradition of the institution, but also teaching factors. There is no one-size-fits-all approach in paediatric anaesthesia, which makes the paediatric difficult airway especially hard to study.[4] Neither the success rates of the different intubation techniques (eg, direct laryngoscopy, video laryngoscopy, or fiberoptic) nor the different operator groups (eg, trainee, consultant, or nurse anaesthetist) can be compared in this registry because the underlying patient subgroups are probably very different. For example, a patient with a known impossible direct laryngoscopy is more likely to be planned to receive a fibreoptic intubation next time. Videolaryngoscopy might have been chosen because direct laryngoscopy is difficult or for teaching reasons to supervise a trainee. Consultants are more likely to intubate more difficult patients on the first attempt compared with trainees.

What questions remain—where to next? Which technique should we use in which age group and for which pathology? The one, we most commonly use, the direct laryngoscopy? The fancy one with the beautiful pictures, the videolaryngoscopy, but linked to longer tracheal intubation times and higher failure rates?[5] Or the gold standard, the fibreoptic intubation, which requires significant time and skills in case of an emergency? What endpoints are important? A beautiful view or a tube in the trachea? If videolaryngoscopy, which one of the many types on the market should we use? To answers these, multicentre randomised controlled trials will be needed.

Data collected by PeDI could help with the planning of a large randomised controlled trial, and the collaboration established through the registry could serve as a basis for obtaining higher level evidence. Large randomised controlled trials would eliminate a lot of the bias inherent in registries and would provide answers about how to manage difficult airways in paediatric anaesthesia.

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We declare no competing interests.

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Whole-genome sequencing of *Mycobacterium tuberculosis* for rapid diagnostics and beyond

Published Online December 3, 2015 http://dx.doi.org/10.1016/S2213-2600(15)00510-X

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In *The Lancet Respiratory Medicine*, Louise Pankhurst and colleagues[1] establish the feasibility of adoption of whole-genome-sequencing (WGS) for routine diagnosis of and drug susceptibility testing for *Mycobacterium tuberculosis* in well resourced settings with a low tuberculosis burden. Within the context of this impressive study, this international team of researchers show the favourable performance and costs of WGS-based species identification and prediction of drug susceptibility. The availability of WGS led to earlier diagnosis of multidrug resistance than with routine laboratory diagnostics for one patient, and WGS also led to the identification of a new suspect transmission cluster. This effort needed substantial coordination across eight participating international centres and development of new data and bioinformatics infrastructure. As such, the findings provide an important proof of principle that WGS methods can provide an attractive alternative to conventional approaches for routine diagnosis and drug susceptibility testing and that the information made available by routine WGS can improve understanding of transmission beyond what might be possible with molecular genetic tests.

Although Pankhurst and colleagues map a way forward for expanded use of WGS as a routine method

for diagnosis of tuberculosis, several important challenges exist that limit the effect of WGS used in the manner described in the study. First, although early identification of drug resistance by WGS could have an important effect on the treatment outcome for individual patients[2] and on reduction of onward transmission of resistant strains, the approach described by Pankhurst and colleagues needs a positive culture to be obtained before DNA isolation and WGS. This approach is appealing because attempting to do WGS for detection of *M tuberculosis* and identification of drug resistance-associated mutations directly from sputum is challenging,[3] and doing these tests on all sputum samples collected from patients who might have tuberculosis (not just those that exhibit growth in selective culture) would inflate WGS costs tremendously. However, a need for culture before WGS adds substantial delay to detection of resistance compared with commercially available tests done directly on sputum in a matter of hours, such as cartridge-based nucleic acid amplification tests like Cepheid Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA).[4] In some settings, GeneXpert could be used for early identification of rifampin resistance, with WGS (as was done by Pankhurst and colleagues) providing a comprehensive picture of susceptibility, allowing individualisation of second-line treatment.

Second, although WGS can play a part in identification or exclusion of transmission between individuals and can, in some circumstances, suggest directionality of transmission, little evidence exists that routine use of genotyping has helped to curb transmission,[5] although ruling out of transmission has probably averted unnecessary contact tracing efforts. Although we are optimistic that improved characterisation of transmission patterns will ultimately result from incorporation of WGS data into transmission studies, whether this information can be effectively used to avert transmission events that would have occurred in the absence of such information remains to be seen.

Third, we note that Pankhurst and colleagues included eight international study sites with state-of-the-art facilities and low throughput of samples; across these sites, 171 *M tuberculosis*-positive samples were identified with WGS. As Pankhurst and colleagues note, scaling up of WGS technologies to much larger numbers of samples within centres with less advanced infrastructure than those in this study is challenging because of the need for sequencing and data infrastructure along with bioinformatics expertise.

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We believe that this study represents a major step forward in the effort to use WGS as a method for routine diagnosis and are optimistic that WGS infrastructure will have positive effects beyond diagnosis. Methods to infer patterns of transmission from sequence data are being improved, but use of these methods to inform realtime tuberculosis control will need more robust analytical methods than those at present and systems allowing rapid dissemination of WGS data and associated metadata to public health authorities.[6–9] If efforts to link WGS data to de-identified metadata and make these available are successful,[10,11] the scientific community will be able to expand the already growing database relating sequences to resistance profiles and continue to improve prediction of resistance from sequences.[12–14]

The costs of sequencing are likely to continue to decrease, and the capabilities of sequencing-based technologies will probably continue to improve. Both of these factors make adoption of WGS infrastructure appealing beyond the slight cost benefit reported in this study. Exciting approaches to the challenge of sequencing directly from sputum (without waiting for culture) have already yielded promising results.[3,15] These approaches, together with deep sequencing, could improve detection of minority variants in sputum, further improving characterisation and understanding of both transmission and resistance and needing essentially the same WGS infrastructure.

In principle, WGS methods offer the ability to customise treatment regimens on the basis of rapidly obtained knowledge of individual resistance profiles to understand when and where transmission is taking place and characterise the acquisition and transmission of drug resistance in real time. Pankhurst and colleagues have shown a proof of principle that a move to WGS technologies is feasible in high-income settings; ultimately, expanded adoption of WGS, if effectively combined with data deposition and sharing, could be a major step towards realisation of the promised benefits of sequencing technologies for improvement of understanding and control of tuberculosis.

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We declare no competing interests.

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What if we made stratified medicine work for patients?

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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-focused 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 treatments for hepatitis C, based on the use of biomarkers, have allowed targeting of interventions for patients who can benefit. However,