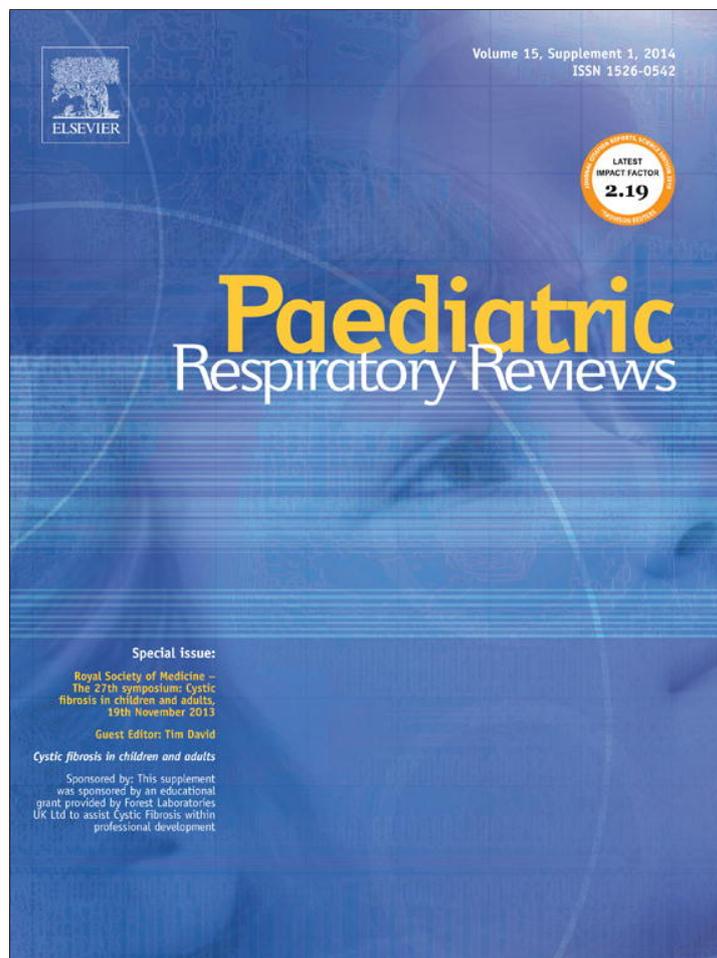


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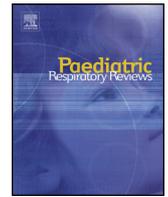
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## Paediatric Respiratory Reviews



## Personalised medicine in cystic fibrosis is unaffordable



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## SUMMARY

Personalised medicine refers to a tailored approach to treatment of an individual based on molecular analysis of genes, proteins or metabolites, and commonly involves a companion diagnostic test. It usually applies to small subsets of patients, often with rare diseases. In cystic fibrosis (CF), the best example is the CFTR (CF transmembrane conductance regulator) potentiator, ivacaftor, relevant to the 5% of cystic fibrosis patients with the p.Gly551Asp gene mutation. However the cost of personalised medicine is too high, making it unaffordable in the long term for many healthcare systems. Society needs to find a way to make personalised medicine affordable in order to not deny life-changing treatments from patients.

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## WHAT IS PERSONALISED MEDICINE?

In some ways we would like to think that all medicine is personalised, in that the doctor is treating the individual patient with therapy specific to that person's needs. However prescribing penicillin for Streptococcal tonsillitis is standard empirical therapy, and is something that would be considered for all children with that diagnosis. The level of individualisation increases if that child is treated with erythromycin because they are allergic to penicillin, and increases further still if they are given a more expensive macrolide because they always vomit with erythromycin. Of course the resistance profile of the specific Streptococcus isolated from the child's throat may alter the treatment, and here personalised medicine starts to become relevant, because a biomarker (antibiotic sensitivity) is being used to optimise the treatment. As Professor Elborn quoted "the right treatment, for the right patient, at the right time" [1].

Personalised medicine was a term first used 15 years ago, and refers to a tailored approach to treatment of an individual based on molecular analysis of genes, proteins or metabolites. It commonly involves some new technology – a companion diagnostic test, enabling a level of customisation of the treatment that was previously believed impossible. It is often used synonymously with the term stratified medicine, which in theory is the level of treatment between empirical (e.g. paracetamol for a headache) and true personalised (e.g. a cancer vaccine produced from an individual's cancer cells that will only be used to treat that

individual). An example often quoted for personalised medicine in respiratory disease is the drug crizotinib [2]. It was developed for non small cell lung cancer and was found at first to be useful only in those who are also ALK-positive (activated anaplastic lymphoma kinase gene). This led to an accelerated approval from the FDA (USA Food & Drug Administration), although unfortunately it turned out that patients can acquire resistance to the drug [3]. Use of crizotinib is better termed stratified medicine, as it is potentially useful for all ALK-positive patients. This article will discuss personalised medicine, particularly as relevant to cystic fibrosis (CF). Even though most of the examples would more accurately be described as stratified medicine, that term will not be used, in order to be consistent with the way personalised medicine is in common usage.

## PERSONALISED MEDICINE AND CF

Many CF therapies are determined by measuring biomarkers but would still not be considered as personalised medicine. For example a faecal elastase result of <15 mcg/g indicates a need for pancreatic enzyme replacement therapy, as would of course a history of pale foul-smelling fatty stools in the nappy. Knowledge of a patient's genotype has opened up new therapeutic possibilities. Although a newborn screened child homozygous for p.Phe508del is almost certainly pancreatic insufficient, giving them enzyme supplements would still not be classified as personalised medicine. Using ataluren (previously known as PTC124) for those with stop mutations (e.g. p.Gly542X), on the other hand, would be considered an example. Approximately 10% of CF patients have a mutation in which nonsense (premature stop codon) mutations in mRNA for CFTR (CF transmembrane conductance regulator) disrupt production of full length, functional

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CFTR. Ataluren has been shown to induce functional CFTR and is well tolerated [4,5], but has not proven effective enough for common usage. At the 2013 North American CF Conference it was announced that a further trial of this drug in those with the relevant genotype who are not taking inhaled aminoglycosides is planned for 2014 ([https://www.nacconference.org/art/plenaryarchives/2013\\_Ramsey.pdf](https://www.nacconference.org/art/plenaryarchives/2013_Ramsey.pdf)). Ataluren has also been considered for stop mutations in other diseases e.g. to correct nonsense BMRP2 mutations in heritable pulmonary arterial hypertension [6], and nonsense mutations in the dystrophin gene for some forms of muscular dystrophy [7].

The best example of personalised medicine in CF is the drug ivacaftor currently in clinical use for one of the gating mutations – p.Gly551Asp. It is the breakthrough small molecule potentiator therapy that produced startling improvements in sweat chloride levels, lung function and weight gain [8]. It is currently licensed for use only in those with the p.Gly551Asp mutation; but a further license has been recently approved in the USA for use in other rarer gating mutations (G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P, or G1349D). This followed initial results from the KONNECTION study, announced by Vertex Pharmaceuticals (Cambridge, Massachusetts, USA) in July 2013.

Another example involves polymorphisms rather than CFTR mutations. Severe CF liver disease (CFLD) with portal hypertension develops in 3–5% of CF patients. Severe CFLD been found to be associated with the SERPINA1 Z allele (on the  $\alpha_1$  antitrypsin gene); although only 2.2% of CF patients are carriers, their risk of developing liver disease is increased 5-fold [9]. This begs the question as to whether all CF patients should be tested for the polymorphism, and further whether those found to carry it might be offered ursodeoxycholic acid therapy – even though it has not been proven that this drug would alter the development of CFLD when given in these circumstances.

## THERANOSTICS

There is a new concept, known as theranostics, of testing a patient for possible adverse effects before starting a new treatment. The best example is the anticoagulant warfarin; there are variants of two genes, CYP2C9 and VKORC1, which account for 30–50% of the variability in dosing of warfarin [10]. There is the potential therefore of undertaking warfarin genotyping prior to starting the drug, in order to aid in optimising warfarin dosing. More relevant to CF is the antifungal agent voriconazole, which is associated with many adverse effects. A single nucleotide polymorphism for the enzyme CYP2C19 reduces its metabolism, thus increasing its plasma concentration, and making side effects more likely [11]. Patients could be tested before using this drug to ensure they are given safe doses, and so far it has been studied in CF lung transplant recipients [12]. The final example relates to the mitochondrial DNA mutation m.1555A>G, which predisposes to permanent idiosyncratic aminoglycoside-induced deafness that is independent of the dose [13]. In a UK cohort the prevalence has been found to be 1 in 385 (with a 95% confidence interval of 1 in 714 to 1 in 263). Given the multiple courses of intravenous aminoglycosides many CF patients receive over many years, there may be a case for testing all newborn screened babies, or even whole clinic cohorts. This would allow one to avoid potential harm in selected patients, although the low prevalence would call into question cost effectiveness of testing.

## IS PERSONALISED MEDICINE AFFORDABLE?

In 2011, the Hasting Center, which is a bioethics research institute, published an online essay entitled “Can we afford personalized medicine?” [14]. It led with “There are reasonable claims that personalized medicine can lower costs by specifying

which expensive treatments will or will not be beneficial. But hard data is scant and there is cause for skepticism”. Whilst a new treatment may be more cost effective if only given selectively to those most likely to benefit, it seems inevitable that this form of new treatment will be expensive, so the overall healthcare costs will rise. PriceWaterhouseCoopers published a report for investors and business leaders in 2009 on financial opportunities in personalised medicine [15]. They wrote that in the U.S., the total market for personalized medicine in 2009 was estimated at \$232 billion and was projected to grow 11% annually, nearly doubling in size by 2015, to a total of \$452 billion. The core segment of the market (comprised primarily of diagnostic tests and targeted therapies) was estimated at \$24 billion, and was expected to grow by 10% annually to \$42 billion by 2015. So whilst it may be cost effective or even good value for money, it is unlikely that the NHS will be able to afford that sum.

## COST OF TESTING

When considering cost effectiveness, the cost of the companion test must be included. The cost of genetic testing has come down markedly. The National Human Genome Research Institute ([www.genome.gov/sequencingcosts/](http://www.genome.gov/sequencingcosts/)) published how in 2001, the cost to sequence the human genome was \$100 million; by 2006 this was \$10 million; by 2008 \$1 million; by 2009 just \$100,000; and by 2011 a bargain at \$10,000. Currently it is under \$6000 and they are aiming to reach \$1000 per person sequenced. Newborn screening for CF in the UK analyses around 30 of the commonest CFTR mutations. Extended genotyping, which is required to pick up, for example, the rarer gating mutations, costs around £600 to carry out. Another example relevant to CF, as mentioned above, would be analysing one's whole CF clinic for the mutation that increases the chance of aminoglycoside-induced deafness. Although it is unlikely to be cost effective given the rarity of the mutation, one would hope the benefit to an individual of protecting their hearing, would outweigh cost considerations. However as more tests become available, healthcare costs will keep rising and inevitably become unaffordable.

## COST OF DRUGS

As mentioned above, the best example of personalised medicine in practice for patients with CF is the drug ivacaftor. It is also the best example of why personalised medicine is unaffordable. The UK list price in the British National Formulary is £182,000 per year for one patient. According to the CF Registry 2012 annual report (<https://www.cysticfibrosis.org.uk/media/316760/Scientific%20Registry%20Review%202012.pdf>), there are 471 patients with at least one p.Gly551Asp gene mutation in the UK. Currently licensed for those over 6 years of age, that means there are approximately 370 eligible patients, at a total cost of £67 million per year. Once licensed for 2 years and above (perhaps in 2015), 420 would be eligible at a cost of £76 million per year. This must be put into the context of the total UK budget for the 10,000 patients with CF being around £130 million per year (including drugs). Ivacaftor will need to be taken for life – which one would anticipate will now be extended by decades. There is no doubt that the drug is extremely effective, but is it cost effective? It has been assumed that this is the case in several reports, but this can only be an assumption, given the data are only available for 3 years of treatment. The incremental cost effectiveness ratio (ICER) for ivacaftor (at list price) is estimated to be £335,000 to £1.274 million per quality-adjusted life years (QALY); the negotiated price (see below) reduced the ICER to 85% of that cost [16]. Generally, NICE (the National Institute for Clinical Excellence) has a threshold for new drugs of £20,000 to £30,000 per QALY. Interestingly, in the US the

insurance companies and Health Maintenance Organisations, who are always concerned with cost effectiveness, approved its use quite quickly, so must believe in its cost effectiveness.

As part of the 2009 Pharmaceutical Price Regulation Scheme, the Patient Access Scheme (PAS) is an agreement reached between a pharmaceutical company and the Department of Health (with input from NICE) to improve the cost effectiveness of a drug. Clearly the scheme cannot make a drug work better, so effectively it is a mechanism to get a price reduction. A press release in December 2012 from Vertex Pharmaceuticals announced that Vertex had agreed to a PAS with the NHS, the details of which remain confidential [17]. The same month, the specialised commissioners announced that “Ivacaftor will be routinely commissioned... in accordance with the criteria outlined in this document and only if the manufacturer provides it with the discount agreed in the Patient Access Scheme” [18]. Details of the discount remain confidential, with heads of pharmacies in relevant NHS trusts signing a confidentiality agreement.

Whatever the discount, this drug remains extraordinarily expensive and unaffordable to many health services. In England, it became available in December 2012; in Scotland January 2013 (despite the Scottish Medicines Consortium not recommending its use in NHS); in Northern Ireland in March 2013; and in Wales in May 2013 (with their health minister going against the advice of the All Wales Medicines Strategy Group). It had become available first in the USA in January 2012 with Health Insurers deciding to pay for its use; the company supplied it free to a patient with no insurance and an income less than \$150,000 per year. The cost in the USA was \$294,000 per year for a patient; it is discouraging that the price has already gone up by \$17,000 per year, which totals to \$17 million per year extra for the 1000 patients receiving it. The UK price is to be reviewed in autumn 2015. These figures are clearly never going to be afforded in many countries, particularly in Eastern Europe, and patients in Australia still await a decision from their Pharmaceutical Benefits Advisory Committee in early 2014.

Ivacaftor is the most exciting therapeutic breakthrough in CF, probably of all time, and for this Vertex Pharmaceuticals should be congratulated. However there is disquiet amongst CF clinicians about the cost of this drug, and even more so amongst those responsible for funding healthcare. An editorial in *Thorax* May 2012, offered warnings about future costs of genotype-specific drugs, and suggested a patient might do better with a full time personal CF nurse, rather than the more costly ivacaftor [19]. I do not believe this (and have yet to witness one of our nurses correcting a child's sweat chloride), but nevertheless they were right to raise the issue of the tremendous costs involved. In October 2013, an editorial in the *Journal of the American Medical Association* was critical of ivacaftor's “unsustainable pricing structure” [20]. How was the price chosen? The editorial suggests that “drugs are often priced at what the market will bear” [20]. It is likely that it is no coincidence that other lifelong drugs that are aimed at small patient populations with rare diseases are all priced in a similar range. Examples are imiglucerase (Cerezyme) for Gaucher disease, and idursulfase (Elaprase) for Hunter syndrome. For a 10 year old weighing 30 kg, that is £125,000 - £250,000 per year for Cerezyme (depending on the response), and for Elaprase £260,000 per year. One must appreciate that pharmaceutical companies need to make a profit for their shareholders; and that many drugs under development never reach the market, at a financial loss to the companies (estimated that only 1 in 10,000 compounds succeed). However in the case of ivacaftor, it should be remembered that the US charity, the Cystic Fibrosis Foundation contributed \$75 million dollars towards its development to Vertex Pharmaceuticals (and its predecessor Aurora Pharmaceuticals), and made their Therapeutic Development Network available for the drug trials [20].

It would be wrong if the patients who volunteered their time and bodies for the trials, and whose families raise money for the CFF, cannot benefit from the drug. In the USA, it is said to be available to all, but there must be uninsured patients who earn too much for them to receive the drug free, yet still cannot afford to pay. It is equally wrong if patients in some countries cannot use a life-saving drug that is available to others, even though clearly there are health inequalities throughout the world. As part of the European Alliance for Personalised Medicine, a statement has been issued by members of the European Parliament - “One of our most important missions as politicians is to ensure that any citizen across the EU fully enjoys his or her right for access to high quality health care and medical products.” (<http://euapm.eu/statement-eu-parliament/>). Unfortunately, this will not be possible whilst personalised medicine remains unaffordable. In the UK, the drug eculizumab (Soliris) has been used to treat the very rare atypical haemolytic syndrome (aHUS), a genetic condition in which complement-mediated thrombotic microangiopathy leads to kidney failure. Dialysis is required and renal transplantation is not an option as a new kidney would become affected. The drug is available in the USA and Europe, but in 2013 the Department of Health refused to sanction the use of this transforming drug for all patients with the condition, and referred back to NICE (the decision is due in Spring 2014). This was despite positive recommendations in 2013 from two bodies, the Advisory Group for National Specialized Services (AGNSS) and the Clinical Priorities Advisory Group (CPAG). NHS England has agreed to fund it in the meanwhile for some of the patients, including those newly diagnosed. There are approximately 180 patients in the UK, and the drug costs £250,000 per year (totalling £45 million per year).

What next in CF? Ivacaftor hopefully is the first of many CFTR potentiators and correctors to be introduced into clinical care. At the 2013 North American CF Conference, in a plenary lecture Bonnie Ramsey predicted that in time 90% of CF patients will have small molecule therapy ([https://www.nacconference.org/art/plenaryarchives/2013\\_Ramsey.pdf](https://www.nacconference.org/art/plenaryarchives/2013_Ramsey.pdf)). If a drug is developed that corrects the commonest p.Phe508del mutation, which in the UK is present in 90% of patients, that would mean about 9000 patients could be eligible (depending on age restrictions). If this drug cost the same as ivacaftor, that would cost the health service £1.64 billion per year! In context, the UK spent £120 billion on the whole of its health care in 2011. Some say the drug would be cheaper than ivacaftor as almost twenty times more patients would be eligible to receive it. Even if the cost was halved to account for that, the bill would still be over £800 million each year. Additionally, combination therapy is currently being trialled for patients with p.Phe508del, using ivacaftor and a corrector lumacaftor together, so if that proved successful, logic would have it that two drugs cost more than one alone. It may be thought, that prices would come down in the future when the drugs are off patent, although interestingly dornase alfa is still only manufactured by the company who first produced it.

## CONCLUSIONS

Personalised medicine is undoubtedly the future direction of modern medicine. In May 2013, Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research, stated that about a third of new entities approved by the FDA last year had some type of genotyped biomarker in its marketing application. However, personalised medicine is indisputably unaffordable to most health services, thus preventing patients getting potentially curative drugs. Society needs to make it affordable as it is unethical and immoral to deny life-changing treatments from our patients.

**DECLARATION OF INTEREST**

IBL gave 3 paid lectures on behalf of Vertex Pharmaceuticals in 2013.

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