UCL SCHOOL OF PHARMACY

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Medicines for the Few and the Many

Medicines for rare diseases – which in total directly affect 6 per cent of the UK population – are already making important contributions to improving health and well-being. But there is a growing requirement for novel systems for developing treatments for very rare and ultra-rare disorders.

New approaches to whole genome screening for new-borns and assuring timely NHS patient access to innovative 'orphan' therapies are also needed.

Summary

Rare disease definitions vary. Conditions with a prevalence of less than 1 in 2000 people are normally seen as rare. As defined here those with a prevalence of under 1 in 10,000 but more than 1 in a million may be regarded as very rare while those with a prevalence of 1 in a million or less are ultra-rare.

Rare diseases are by definition uncommon. But there are some 7,000 rare disorders in today's medical literature. In aggregate they directly affect around 6 per cent of the population and approaching 20 per cent directly and indirectly. Very rare and ultra-rare conditions alone directly affect about 1 person in every 100. These figures indicate a major societal burden.

Some rare disorders can now be much more effectively treated than when the NHS was first established. Technologies like gene therapies promise further gains. However, most people affected by rare diseases remain at high risk of misdiagnosis, late diagnosis and inappropriate or inadequate treatment. Another reason why enhancing rare disease research and services is an important health policy goal is that as complex diseases like cancers are becoming better understood more rare sub-types requiring specific treatments are being identified.

Medicines required in low volumes have high unit costs and hence high prices. This may make them seem unaffordable in the short term, even when they can in the longer term offer important health gains at an acceptable overall cost. At present total spending on medicines for rare diseases represents only 0.1 per cent of UK GDP. If this spend were to double it could still be afforded, should decision makers choose.

In the US, the EU and the UK provisions are in place for allowing companies that invest in proving the safety and value of rare disease medicines exclusive use of the data they generate to gain marketing authorisations for up to 10 years. This incentive helps drive investment in 'common' rare conditions and should from a public interest viewpoint be maintained. Yet as opportunities for developing effective treatments for very rare and ultra-rare conditions increase it presently appears unlikely there will be sufficient incentive for commercial investors to channel funds into translating basic advances into licensed treatments for very/ultra low volume indications. If policy makers wish Britain to be a global life sciences centre addressing this problem should be seen as an opportunity.

Extending whole genome screening for new-borns in order to permit the early and accurate diagnosis of inheritable disorders also deservers prioritisation. Recent changes in the ways in which organisations such as the MHRA and NICE work ought to allow NHS patients better access to 'orphan' treatments. But there are concerns about issues like tight restrictions on allowing rare disease therapies to be evaluated via NICE's Highly Specialised Technology assessment process and curbs on permitting more to be paid per QALY gained in areas where costs are high and suffering is most severe, as compared with QALYs gained elsewhere.

UK public and patient interests will be served by finding incremental ways of enabling agencies such as NICE to work more flexibly. However, the process of valuing innovative treatments before NHS service users can access them may in future need to be amended or radically simplified. One possible reform might involve indication based pricing. This could allow more to be paid for given therapies when they are used to treat rare as opposed to commonly occurring indications. Another might be the introduction of free pricing for 'orphan' disease medicines at the time of launch, followed by controls as needed in subsequent years. This should accelerate patient access. ►

The UK also has additional opportunities to lead progress on forming close working partnerships between grant funded researchers working in settings such as Universities and NHS hospitals and scientists and other contributors working in commercial environments, aimed at developing new very low volume use treatments and making them affordably available. A national consultation on what policies can most realistically achieve this end is needed to bring patient representatives and other stakeholders in the public and private sectors together to raise the quality of public policy debate and build a common focus on achieving shared health gain goals.

Introduction

During the last 100 years medicines and vaccines have, with advances in areas like education, food supply, contraception and surgery, permitted major advances in life expectancy, nationally and globally. Babies born in Britain at the start of the 1920s on average lived for just over 50 years. By 1950 this figure had risen to 65 years. Despite recent setbacks associated with social and economic equities (Marmot at al, 2020) it is today about 80 years. Since the Second World War around half the life expectancy gains achieved have been due to more effective health care. But as the common causes of early death and disability have been understood and better controlled other, individually rare, forms of ill-health have emerged as important challenges to wellbeing.

The speed at which publicly and privately funded researchers and pharmaceutical manufacturers developed and, at least in more prosperous settings, successfully supplied populations with vaccines and drugs for the prevention and treatment of Covid 19 illustrates the fact that humanity is now better able to protect itself from infections than ever before. This is also true for non-communicable conditions, including many cardiovascular disorders, neurological diseases and cancers. Given adequate investments in basic science, ongoing biopharmaceutical innovation and universal health care, the development of increasingly precise treatments that can directly influence processes like gene expression and immune responses could in the second half of this century mean that nearly everyone will have a fair chance of living in good health until their 80s or beyond (Peto, 2014).

Advances in the biological and allied sciences needed for continuing therapeutic progress will also open the way to other beneficial innovations, including technologies needed for sustainable food and energy production and the control of global warming. In the UK the publication of policies for strengthening the life science industrial base and the further development of genetics and genomics (see, for example, *Genome UK: the future of healthcare* [2020] and *Life Sciences Vision* [2021]) reflect reasons for optimism about the future.

However, despite long term hopes there are many immediate barriers to be overcome if the health and social development potential of today's opportunities is to be realised. These range from finding better ways of making new medicines and technologies available to minority populations and in low and middle income nations to meeting the costs of R&D in high-income countries. Some advances in rare disease therapies are at risk of being judged unaffordable for everyone even in the most affluent communities At a time when – particularly in the light of recent events in the Ukraine – there are demands for increased defence spending coupled with rising living costs, downward funding pressures on health related investment in Britain and elsewhere may be especially likely to impact isolated minorities and industries thought to be unpopular with voters.

Some critics say or imply that new medicines, and particularly those for rare conditions, are over-priced and that pharmaceutical companies make excessive overall profits. It is also on occasions claimed that private sector innovators unfairly benefit from using knowledge gained from publicly funded research without directly paying for it, while also making too little effort to develop medicines aimed at satisfying unmet needs outside those fields most likely to generate profit (Mazzucato and Li, 2020). Such commentators may also say that the existing market-based system of pharmaceutical innovation is 'broken' and that a radically new publicly directed model must be established in order to assure the appropriate provision of valuable new therapies.

Against this, this UCL School of Pharmacy Policy Briefing explores questions relating to the future of the UK and wider global pharmaceutical industry with special reference to the discovery and equitable supply of treatments for low prevalence 'orphan' diseases. Markets for medicines and vaccines are, like those for health and social care in general, inherently imperfect. Yet the analysis offered here concludes that, in part because of the regulatory and universal health care systems found in settings like Western Europe, the current mixed publicly and privately funded model of pharmaceutical innovation is serving most public interests. It is neither 'broken' nor unaffordable.

There is, for example, evidence that in countries like the UK NHS medicine costs have not risen as a proportion of total health spending in recent decades (Taylor, 2020). Despite the negative impacts the Covid-19 pandemic and Brexit have had on the economy and the NHS in the last two years this still appears to be the case. Notwithstanding uncertainties which ongoing research on topics such as the proportion of GDP now being spent on health will resolve, it remains almost certain that the percentage of total health budgets allocated to pharmaceuticals has fallen in this country and Western Europe as a whole since the start of this century (Espin et al, 2018).

From a political perspective it is also relevant that a majority of the British population believes that pharmaceutical companies make important positive contributions to

society. However, there are some pharmaceutical market failings that are both undesirable and correctable. The types of reform likely to serve public interests range from finding more robust ways of financing the development of new treatments for very rare diseases and promoting better co-ordinated partnerships between publicly funded researchers undertaking basic and early stage research in institutions such as Universities and commercially supported scientists involved in product development.

This UCL School of Pharmacy Policy Briefing begins with an outline of how orphan diseases are defined and why as science has advanced and the health of communities has improved they have become increasingly important. It then discusses issues relating to the costs and benefits of medicines research and supply before going on to consider the types of development that could in the age of cell, gene, RNA/DNA based and other advanced medicinal products support faster therapeutic progress, both nationally and globally.

The emergence of improving rare disease treatment as a major public health challenge

Despite 'breakthroughs' such as the advent of smallpox vaccination at the beginning of the nineteenth century and the introduction of rabies immunisation towards its end, the discovery of insulin at the start of the 1920s and the marketing of sulphonamide antibiotics in the 1930s, it was not until after World War 2 that – even in countries like Britain – novel medicines and vaccines began to generate large health improvements. Until then the health gains derived from factors like clean water, improved household hygiene, access to contraception and enhanced nutrition played key roles in driving the transition from high infant death rates and short life expectancies to significantly longer average life spans.

Since the 1950s important medical advances have been made in areas like diabetes care and cardiovascular disease prevention and treatment, and to a lesser but significant extent in fields such as cancer and the control of conditions like multiple sclerosis and the dementias. However, the extent of the progress due to pharmaceutical interventions alone should not be overstated. For example, the benefits achieved because of drugs used in treating established cancers have so far been limited as compared with those from early stage diagnosis followed by timely surgery or the health benefits stemming from reduced rates of tobacco smoking. This means that continuing biopharmaceutical innovation is needed to deliver the health gains still desired by many individuals and families at risk of premature death and long term disabilities.

The medicines currently in use typically act in intermediate ways (by, for instance, affecting the sensitivity of receptors on the surfaces of cells) rather than affecting the molecular-

Box 1. Preventing Health and Medicines Market Failures

Market economists believe that in markets that are functioning well the self-interested pursuit of profit within the law by individuals and organisations leads to optimal society-wide resource use. But in complex areas such as health and social care multiple regulatory and economic interventions are needed to protect public and patient interests and promote efficiency. Within the health sector, the market for innovative medicines – which are often seen as public goods to which all in need are entitled being supplied by private companies charged with maximising investor returns – is at risk of various forms of failure. This means that without complex interventions important opportunities for welfare gain could be lost, not so much because of fault on the part of individual actors but the inherent nature of the context in which they are working.

At the world-wide level, providing therapies for tropical diseases has exemplified this point. The fact that, despite the high prevalence of many such conditions, the individuals and populations requiring effective treatments were and still are typically poor and often unable to access good health care has meant that would-be innovators have been unable to attract 'risk' capital. This led to neglected R&D opportunities. Even when (as with HIV at the start of this century) treatments existed they were not widely available to those who could benefit from them most. Significant efforts have in the last two decades been made to correct such failings by governmental, industrial and voluntary aid organisations, as well as local actors. But there remains a considerable problem to be overcome, not least because as the populations of less developed countries age they becoming increasingly affected by cardio-vascular disorders and cancers.

A more specific illustration of pharmaceutical market failure is that of antibiotic research and innovative product supply. Because of the resistance threat clinicians and health policy makers want advanced new products to be held in reserve, and used only in very low volumes when absolutely necessary. But this has discouraged commercial (and some argue public) investment in timely antibiotic development. Once again, innovative approaches to resolving such problems have now emerged, as has recently been the case with NHS England's antimicrobial purchasing strategies. Yet here again significant challenges remain, even in this comparatively straightforward context.

The risk of rare disease and even more critically very rare and ultra-rare disease treatment market failures exists in all social settings, rich and poor. It is fundamentally a function of low volume demand and the necessary day-to-day focus of health care funders and commercially funded pharmaceutical innovators alike on balancing short term local costs and returns, as opposed to pursuing long term global public interests. In such circumstances seeking to attribute blame has little utility other than to attract attention to the problem. Solutions demand ways of promoting investment in basic and translational R&D, promoting universal health care, increasing diagnostic capacities and instituting more appropriate drug purchasing strategies.

level causes of disease. This often means that only partially satisfactory treatment outcomes are achieved. The promise of therapies acting in more fundamental ways is that they will in time enable people either to avoid symptomatic illness altogether or to fully recover good health. Part of the reason that previously neglected rare diseases (as opposed to neglected tropical diseases – see Box 1) have become a greater focus of medical and biopharmaceutical attention is that many of them are now known to be caused by gene variations that are potentially treatable, given further investments in basic and applied science and health care delivery.

The definition of rare disease is arbitrary and varies between countries. The available data indicates that a little over 70 per cent of such conditions (and especially those with ultra-low incidence and prevalence rates) are the result of single gene or related inheritable defects (Wakap et al, 2020).

In the UK it was recognised in as long ago as the 1970s that medicines that are used in very low volumes face special problems in relation to meeting the costs of licensing and supplying them at affordable unit prices (Mikami, 2019). However, the United States was the first nation to introduce legislation designed to protect society against the danger of markets failing to adequately incentivise rare disease R&D investment. The 1983 Orphan Drugs Act (the ODA, which was subsequently complemented by interventions designed to encourage or require investment in children's medicines) defined rare illnesses as those affecting less than 200,000 American citizens at any given time. This was originally equivalent to a maximum prevalence rate of around 9 per 10,000 people but on the basis of today's US population the implied figure is close to 6 per 10,000.

In the US market (which accounts for over 40 per cent of world medicine sales by value) the ODA – which can also apply to treatments for more prevalent conditions if their development cannot be supported by normal financing mechanisms – awards rare disease treatment makers 7 years exclusivity relating to the use of trial and allied data generated by them in order to license a treatment for orphan indications. The public interest linked purpose of this is to for a short period stop innovators from being exposed to low cost competition from producers who have not invested in developing the product in question for orphan use. This applies even in circumstances where patent protection is not available.

Equivalent European Union regulations were introduced in 2000 and, in the case of children's medicines, 2006. The EU defines rare diseases as affecting fewer than 5 in 10,000 Europeans at any one point in time and offers suppliers of licensed orphan products 10 years of marketing exclusivity. This may appear to provide more incentive to invest than the US legislation. But the overall value of the EU's pharmaceutical market is (at in the order of 25 per cent of global pharmaceutical sales) around a third less than that of the US, despite the latter's population being only two thirds the size.

In many if not all European Member States local cost control mechanisms temper the financial benefits of extended exclusivity periods (and other forms of IP protection) aimed at fostering R&D investments. The demands and preferences of US patients and prescribers are currently the greatest single influence on global patterns of medicines development. The direction of more fundamental research is predominately influenced by public expenditure decisions, although here again America remains the largest global funder in areas ranging from improving cancer care to understanding and treating rare and very rare disorders. The latter may be defined as having a prevalence of less than 1 in 10,000 while ultra-rare conditions are 1 in a million occurrences – see Box 2.

Box 2. Defining rare, very rare and ultra-rare diseases

In Europe and the US rare diseases are normally defined as having a point prevalence of up to between 5 and 7 per 10,000 people. This implies that at any one time in a country the size of the UK a single rare disease could – at maximum – directly affect some 40,000 individuals. (For reference, around 25,000 people in the UK are living with the blood cancer myeloma at any one time and in the order of 50,000 have a form of muscular dystrophy, of whom 2,500 have Duchenne MD.) However, the prevalence of the great majority of the 7,000 or so rare disorders now known is much lower. A very rare disease with a prevalence of 1 in 50,000 directly affects around 1000 people in the UK at any one time and for ultra-rare conditions the equivalent figure is around 50.

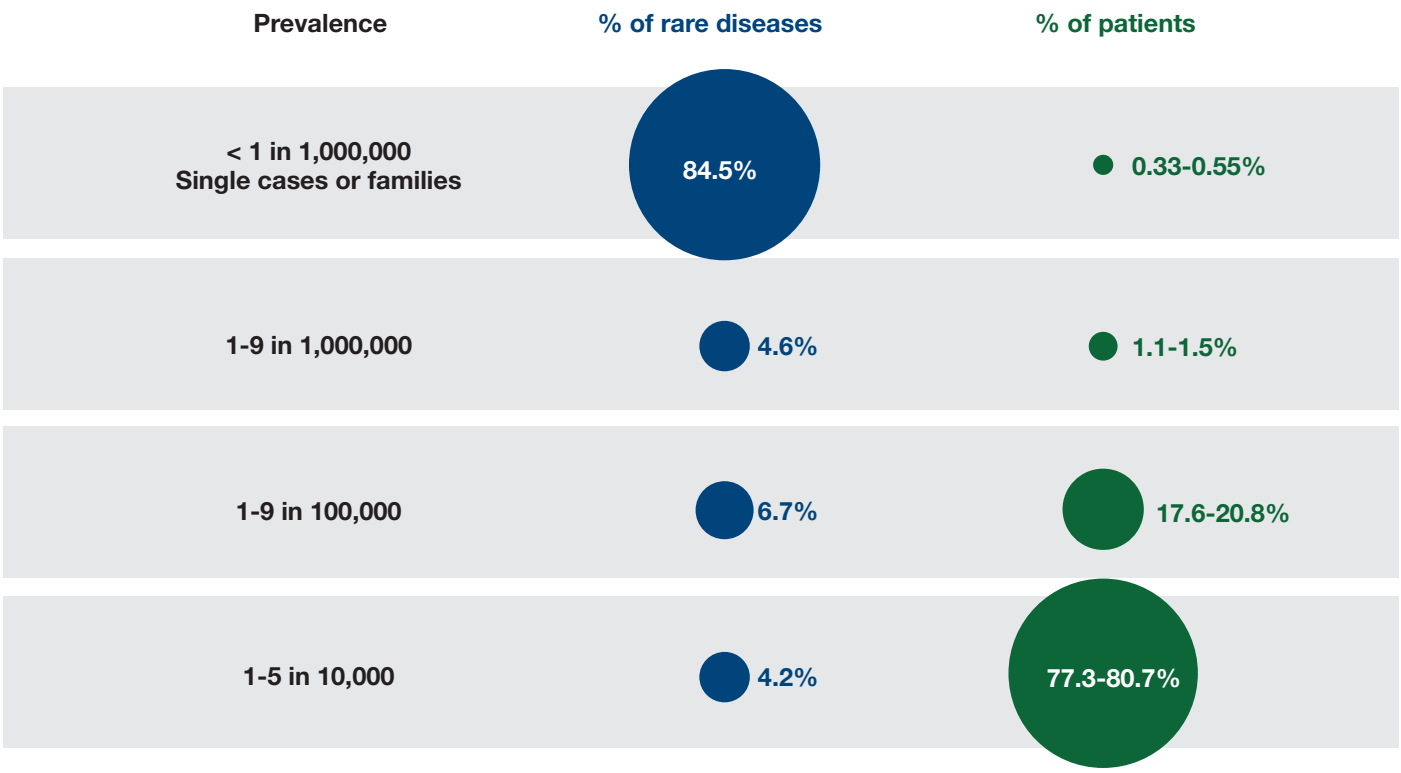
Diseases that have short survival durations and high mortality rates have lower prevalence rates than those which permit longer survival. This may mean that on occasions it is also appropriate to take into account incidence rates when judging the total burden imposed by rare diseases on individuals and families. The fact that as survival for given conditions improves their prevalence will also rise and with it on occasions the extent of some forms of distress may also need to be taken into account when deciding which treatments qualify for evaluation via the NICE HST process. Currently, the HST entry ceiling is 300 anticipated patients.

This is a complex field. Many caveats and additional considerations would need to be taken into account for a comprehensive overview of the rare disease research and care arena to be presented. But for the purposes of this Policy Briefing key issues include:

- The number of known rare diseases is presently increasing by some 200 a year. Hence whatever the formal definition employed it is not possible to say exactly how many orphan conditions exist. A commonly quoted total is now 7,000. Individual rare disorders have by definition limited significance in overall public health terms. But in aggregate some 6 per cent of the population of countries like the US and the UK has a rare disease at any one time. If those indirectly affected (including parents, siblings and partners) are included this proportion rises to about 20 per cent, or one in every five people.

Figure 1. Rare Diseases by Point Prevalence Rates

Sources: Neez et al, 2021 and Wakap et al, 2020
(NB Not to scale)



- If narrowly defined, static and short term oriented methods of valuing treatments for rare conditions are used then their perceived worth will often seem low relative to the costs of developing them, despite the individual suffering they may relieve. But if it is accepted that research and development conducted in one area can have spill-over effects in others and that over time the unit cost of supplying innovative treatments falls while the numbers of people directly and indirectly benefiting rises cumulatively then a more positive picture of the benefits of investing in novel rare disease therapies emerges. Health service budget holders are likely to favour a cost minimising approach to valuing new products. Yet this may not be consistent with long term public interests, particularly if advances pioneered in areas like gene therapies for rare diseases or rare sub-types of common disorders prove to have important applications outside health care.

- Of the estimated total of 7,000 known rare diseases (of which only 5 per cent or so presently have satisfactory treatments) just 150 of the most common ones account for over 80 per cent of all recorded cases – see Figure 1 (Hutchings, 2021; Neez et al 2021). To date most public and private R&D spending is – and from a simple utilitarian perspective desirably – concentrated on the limited number of commonly occurring rare diseases. Even in this context there can be significant problems in areas like finding sufficient numbers of patients to take part in clinical trials and organising them internationally. But with very rare and ultra-rare disorders such difficulties are much greater. Organisations like Universities should be well placed to conduct fundamental research and identify potential treatment strategies. Yet when such progress has been achieved there is an arguable need for new ways of providing patients with affordable access to approved therapies.

With regard to this last area the European Commission has recently been seeking to further develop its Pharmaceutical Strategy. As part of this it in 2021 published proposals on amending its orphan disease and paediatric disease regulations. It has also undertaken consultations with stakeholders. The Commission's findings are consistent with the view that the existing regulations have encouraged research and development leading to treatments for more commonly occurring rare diseases and childhood disorders but that there is still much unmet need.

For example, there are concerns that more could be done to develop medicines for children living with cancers (in the US novel medicines manufacturers are obliged rather than just incentivised to invest in this field) together with those relating to the requirements of individuals with very and ultra-rare disorders. The total number of people directly affected by these conditions is around 1 per cent of the European population, rising to 3-4 per cent when parents and other family members are added. From a Rawlsian justice perspective (which focuses on fairness for those with the greatest need as distinct from maximising the happiness of the majority) this is indicative of a major problem.

The Commission's proposals for reform (which are yet to be published in final form) include strengthening Europe's paediatric medicines regulations to bring them more into line with US legislation and placing an increasing focus on meeting unmet medical needs. However, some commentators fear

that interventions will also involve reductions in the period of marketing exclusivity granted to products for rare conditions which already have at least partially effective treatments available. A risk to avoid is weakening performance in the areas where the present system is working satisfactorily without strengthening investment incentives in areas where they have proved inadequate.

The UK's rare diseases policies

Largely because of lobbying by Americans living with rare diseases and the institutional efforts of the non-profit coalition NORD (the National Organisation for Rare Diseases, which was originally created at the start of the 1980s) the Rare Disease Act passed into US law in 2002. This established the NIH's Office of Rare Diseases, which co-ordinates America's rare condition research agenda and supports individual projects. This legislation, along with the work of the at that time newly founded European Organisation for Rare Diseases (EURORDIS), also helped raise European awareness of the burdens associated with orphan diseases.

The European Commission adopted a Communication called *Rare Diseases: Europe's Challenges* in 2008. This opened the way for the EU Council to adopt a Recommendation on rare diseases. It contained a variety of action points, including the establishment of the European Project for Rare Diseases National Plans Development, or EUROPLAN. It was responding to that which in 2013 led to the publication of the *UK Strategy for Rare Diseases*. However, it was not until 2018 that NHS England produced its *Implementation Plan for the UK Strategy for Rare Diseases*.

Following this, 2021 saw the publication of the *UK Rare Diseases Framework*. The latter embodied a commitment that the four UK nations would each develop relevant action plans, ideally before the end of that year. NHS England published its *England Rare Diseases Action Plan* early in 2022. Similar documents have also been released in Northern Ireland and Wales, and Scotland (see Box 3) is due to publish its action plan before the summer of 2022.

Recent progress is to be welcomed. Yet overall this record suggests that in the past British policy makers, perhaps because of the widespread confidence the electorate has had in the ability of the NHS to meet all needs coupled with a tradition of Benthamite political thought, have not given '*the orphan disease problem'* the degree of attention it has received in some other developed nations.

However, British political leaders now appear increasingly aware of rare disease linked distress and the need to raise standards of care, particularly for individuals and families living with combinations of social disadvantages and rare illnesses. The 2021 UK framework outlined four national priorities:

- enabling patients get an accurate diagnosis in a timely manner;
- increasing awareness of rare diseases and their high aggregated prevalence among health professionals;
- improving care co-ordination; and
- enhancing access to specialist care, treatment and drugs.

Box 3. Rare Disease Progress in Scotland

Although the Scottish Action Plan is as yet (as of May 1st 2022) to be published a new Scottish Rare Disease Implementation board (RDIB) and a Patient Voices Advisory Group have been established, following the publication of the UK Rare Diseases Framework. Sub-groups have already been convened on care coordination and improving diagnostic services. It is anticipated by Genetic Alliance UK that the Scottish Action Plan will outline further developments related to the Scottish Strategy for Genomics, including increased financial investments and greater focus on whole exome sequencing.

Public Health Scotland has recently been instrumental in establishing the Congenital Condition and Rare Diseases Registration and Information Service for Scotland (CARDRISS). This has been designed to gather information on all babies affected by a major structural or chromosomal anomaly or recognised syndrome. CARDRISS data should cover all babies known to be affected by inherited endocrine, metabolic, and haematological conditions, including those identified via the new-born blood spot (NBS) screening programme.

The specific actions needed to deliver progress across these interlinked fronts are not explored in detail here. However, from a health policy perspective there are several points worth special emphasis. The first is that the British health care model has traditionally relied on the skills of general medical practitioners who know their patients relatively well to differentiate between commonly occurring conditions that are self-limiting or can be successfully treated in the primary care setting and those that ought to be referred to more narrowly specialised clinicians.

This approach has many advantages. Yet as experience in the area of cancer care illustrates, desires for cost restraint – which in the UK appear linked to the fact that the NHS is directly tax funded – may on occasions have discouraged GPs and their colleagues from sending patients for diagnostic testing and/or specialist investigation when that would have served their best interests. Even today such problems can adversely affect care quality, perhaps especially in circumstances where patients no longer enjoy personal relationships with their primary care doctors.

By definition, individual rare diseases are not frequently encountered by GPs or most hospital staff, who understandably tend to focus on more commonly encountered problems. This can mean that it takes a long period for correct diagnoses to be made. A survey conducted in the summer of 2020 (Genetic Alliance, 2020) found that many individuals and families affected by rare diseases experience considerable and prolonged distress while seeking to find out what is causing their ill-health. Around half of all respondents had been misdiagnosed

Figure 2. The Frequency with which People Living with a Rare Condition Report Misdiagnoses

Source: Genetic Alliance UK, 2020

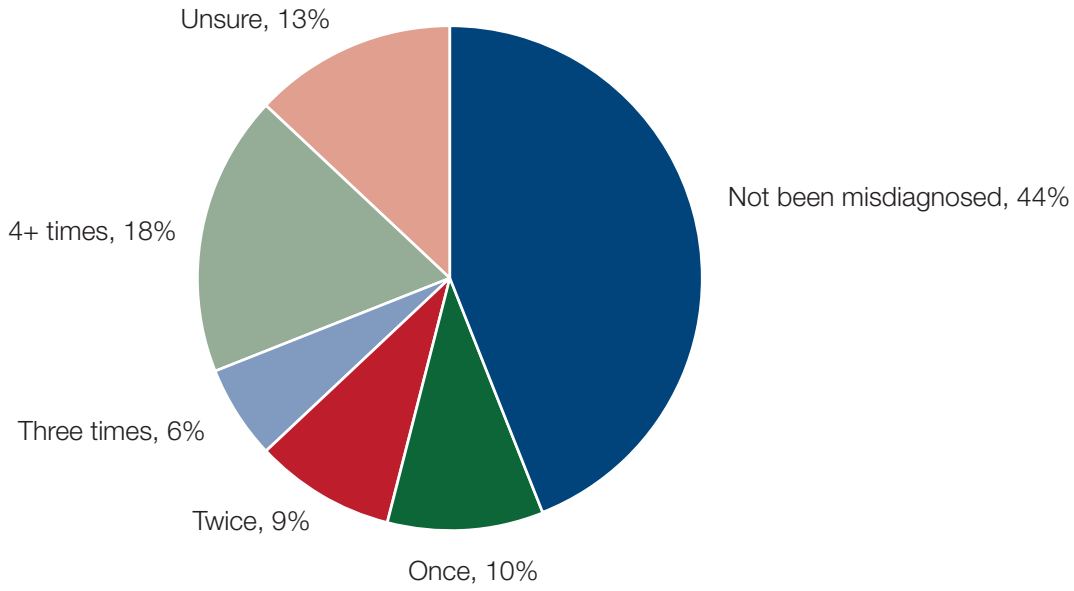
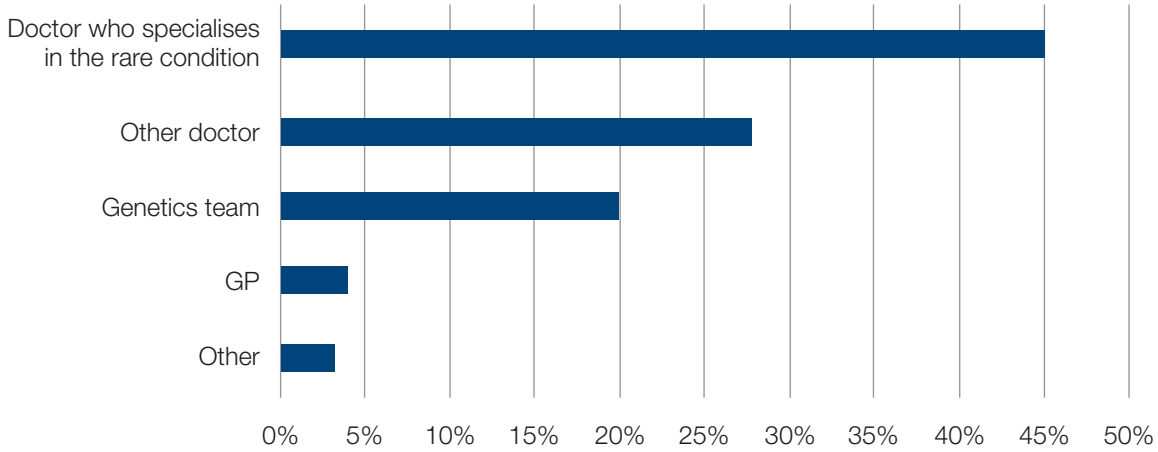


Figure 3. Health Professionals Reported by Patients as Diagnosing Rare Diseases

Source: Genetic Alliance UK, 2020



before ultimately having their condition accurately identified, normally by a specialist doctor or a member of a genetics team – see Figures 2 and 3.

In future the development of digital data sets coupled with the extended use of artificial intelligence-driven diagnostic support systems, greater access to whole genome based screening and other forms of testing and the appropriate use of innovations like video based consultations should help to increase rates of early diagnosis. But the difficulty of achieving this in not only the rare disease context but also in fields such as oncology should not be underestimated (HCHSC, 2022). The impacts of the Covid pandemic, coupled with other economic challenges affecting the UK and problems in areas such as workforce shortages and health sector staff training, will mean that progress proves considerably slower than patients and their representatives hope for unless informed decisions are made to swiftly improve services in fields such as neonatal genetic and other forms of screening for problems like, for instance, SMA – see Box 4.

Poor or inadequate health and social care co-ordination is another instance of a challenge that is important to overcome not only for improving rare disease outcomes but in all forms of long term condition care. It is also one where once again the centrality of personal relationship based primary care in the traditional British model needs recognition, along with systematic investment in building better functional linkages between GP practice services and all other forms of community support and specialist level medical care.

There is evidence that the stresses of living with rare diseases can, especially when combined with diagnostic uncertainties and fragmented health and social care provision, be a potent source of psychological distress and mental ill-health (Genetic Alliance, 2018). This hazard is on occasions amplified by anxieties surrounding limited access to therapies provided by the NHS, even after a correct diagnosis has been made and a licence granted for the indication in question.

Box 4. Spinal Muscular Atrophy (SMA)

Spinal Muscular Atrophy is known to affect 1 in every 10,000 new-borns or 70 babies a year in the UK, although one person in every 40 carries relevant mutations in the SMN (Survival Motor Neurone) 1 gene. These reduce or stop the production of a protein required by motor neurones in the spine. Neuronal deaths cause loss of muscle power in the upper arms and legs. In untreated severe cases SMA is fatal in infancy or childhood.

For the disease to occur abnormal SMN 1 genes must be inherited from both parents. Before the genetics of the condition (which also involve variations in the functioning of a gene called SMN 2) were understood SMA was divided into five types, ranging from 0 (prenatal onset) and type 1 (onset within six months of birth) to 4 type (adult onset). The earlier the onset the more severe the condition was found to be.

Since 2016 three novel treatments have been licensed in the US and elsewhere, the actions of which can raise SMN 2 linked protein production. This has radically improved the outlook for babies with SMA. If progress in areas such as gene therapy continues even better outcomes may in time be achievable. But realising this promise will demand increased investment in early diagnosis, because once neurological damage has been incurred it cannot be repaired. Although a pilot new-born screening programme was recently launched in Oxford the NHS does not as yet routinely provide pre-symptomatic SMA testing for new-borns, unlike health services in countries such as France – see main text. Further, few adults know whether they are carriers of relevant mutations.

As with cancer care, prolonged and sometimes controversial negotiations relating to the prices and/or overall costs of rare disease treatments (past instances include delays relating to the provision of medicines for Cystic Fibrosis and Morquio syndrome) may – regardless of who or what might have been at fault – undermine public trust in the NHS and cause community-wide dismay, in addition to avoidable physical, psychological and financial harm to already distressed patients and families.

The ways in which the chance of such service failures occurring might in future be reduced as more gene, cell-based and other advanced therapies are introduced are discussed later in this UCL School of Pharmacy Policy Briefing. But in order for public interests in areas such balancing measures aimed at drug and other forms of health and social care cost minimisation against the value of incentivising ongoing innovation and optimising individual care to be adequately appreciated issues relating to the economics of pharmaceutical innovation and the methods by which medicines spending is controlled in Britain and elsewhere are initially reviewed.

The economics of pharmaceutical innovation

In the mixed public/private model of biopharmaceutical, diagnostic and wider therapeutic discovery, development and supply that has evolved in countries such as Great Britain and the United States fundamental – basic knowledge generating – research is typically financed by government grants, charities and philanthropic donations. Once published it is usually free for all to use. By contrast, product generating research and development is much more likely to be commercially funded from venture capital or the sales of existing patented and other intellectual property right protected items. In essence, tomorrow's scientific knowledge is paid for by today's taxes and (albeit sometimes fiscally incentivised) gifts, while developing tomorrow's science based medicinal and related products is paid for via temporary premiums on the prices of today's branded therapies.

From a public policy perspective one of the strengths of patents is that they discourage secrecy by demanding the publication of how useful items can be made and used. At the same time a weakness of raising taxes is that they may be resented by voters, albeit patients and health care funders are also likely to object to paying more than they believe is necessary for items like medicines. Some critics of the present biopharmaceutical innovation model claim, as noted at the start of this Briefing, that privately owned pharmaceutical companies do not pay for the publicly funded knowledge they use, and are consequently asking communities to 'pay twice' for the medicines and vaccines they provide.

Such charges risk building unjustified resentment and destructive conflict. The reality is that commercial companies of all types contribute to the government incomes needed to fund research in a variety of ways, including via the salaries of the staff for whom they create employment. Research based pharmaceutical companies may also on occasions directly support fundamental research. Successful pharmaceutical companies are profitable. Yet suggestions that the public is 'paying twice' for their products lacks serious substance.

In overall terms, pharmaceutical innovation and supply is characterised by high fixed costs of development (including 'sunk' spending on, for instance, clinical trials and obtaining marketing authorisations) counterbalanced in many instances by low marginal production costs. This helps to explain why the unit prices of new medicines at the time of their launch (when volume sales are limited and knowledge about their optimal use incomplete) are typically up to 100 fold greater than they are when products have matured and are being offered as proven generics. Cost disparities of this magnitude can on occasions be taken as evidence of excessive profit taking. But their existence means that despite ongoing innovation overall pharmaceutical costs tend to stay stable as a proportion of total health care costs because as they age initially expensive innovations become low cost 'tried and tested' therapies.

This dynamic makes new pharmaceutical treatments much more cost effective for communities than static cost benefit analyses conducted when novel therapies are first being

introduced may indicate. However, in the case of rare and very rare disease treatments the picture can differ, especially with those that like cell and gene therapies are at the margin relatively costly to make. Treatments with the potential to confer benefits over whole lifetimes can also be difficult to value, not least because of disputes about what if any discount rate it is appropriate to apply to anticipated health gains.

There is evidence that, because of factors such as trial sizes being relatively small, the costs of developing and marketing a rare disease medicine may only be a third or less of those incurred for a 'common use' pharmaceutical product (Berdud et al, 2020). However, very low case numbers are still likely to mean that exceptionally high unit prices have to be charged at the time of launch if investor expectations are to be met. In the case of orphan treatments that are not discovered to have other more prevalent indications it is also the case that there will not be longer term opportunities to generate savings to significantly increased production scale.

In the case of very and ultra-rare disease treatments it has been calculated that payers would initially need to pay in the order of £1 million per QALY (quality adjusted life year) gained to allow levels of return associated with novel therapies supplied in average volumes (Berdud et al, 2020). This might be possible to achieve in sections of the US and parts at least of some other markets. Yet the policy context prevailing in Britain means that organisations such as NICE and NHS England and their equivalents elsewhere in the UK are unable accept such a cost. Key questions therefore relate to the extent to which rare disease treatment development and supply costs can be reduced and whether purchasers and providers can agree UK prices which are seen as affordable by the Treasury and regarded by investors as sufficient to attract continuing private (and public) investment.

Adequate returns?

Figures 4 and 5 are based on OECD data up to 2017 and 2018. They show that in the decade or so before the start of the Covid 19 pandemic spending on pharmaceuticals across the OECD as a whole was falling both absolutely and relative to total health care spending. The present situation is subject to uncertainties because of Covid 19. However,

Figure 4. Pharmaceutical spending as a percentage of all health spending in selected countries in 2018 or nearest year

Source: OECD 2019a

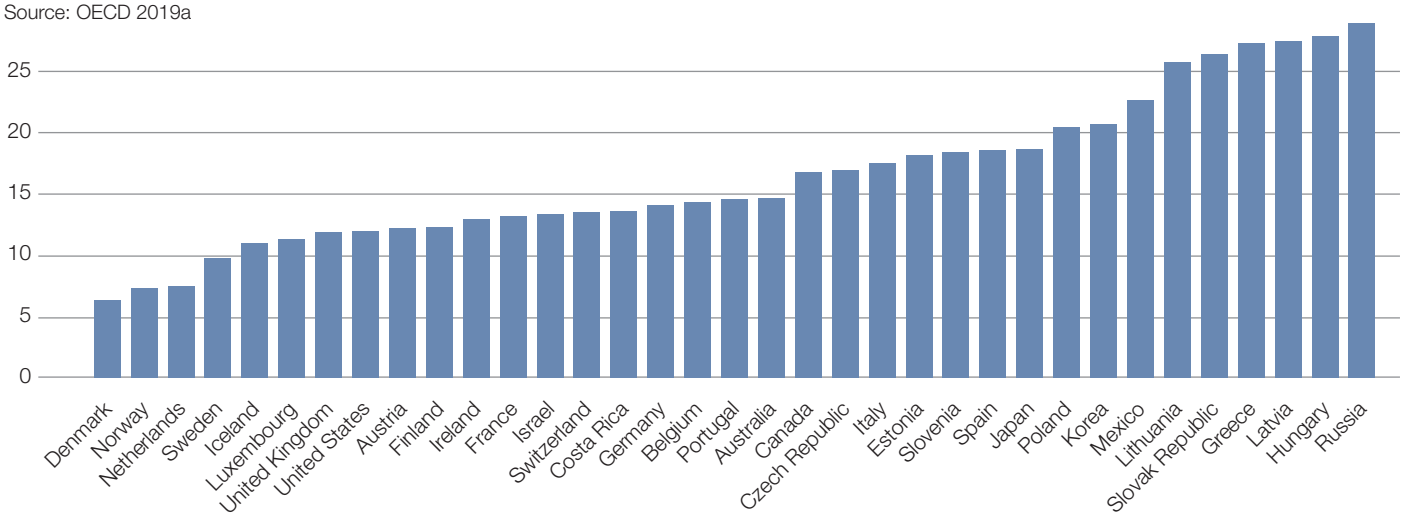
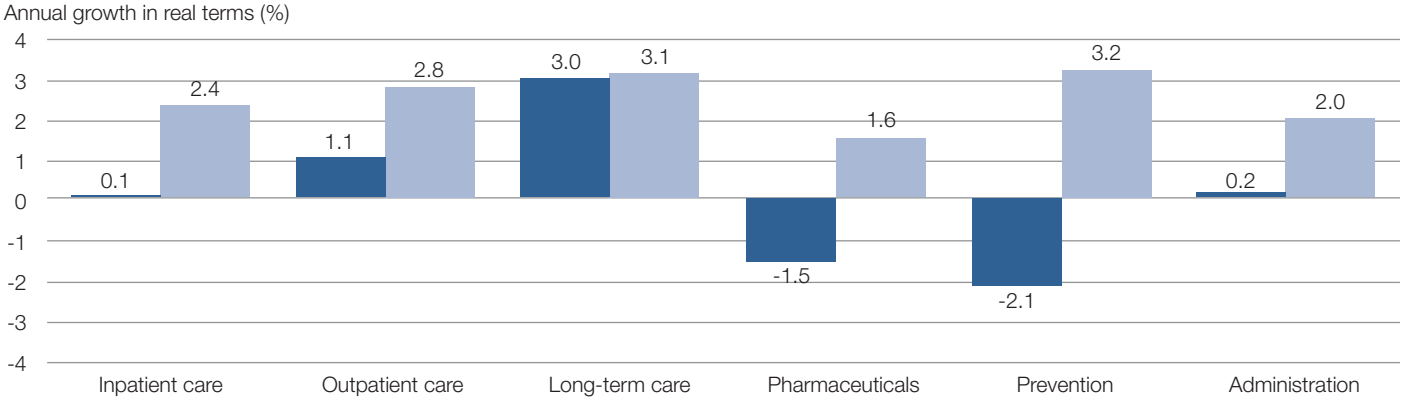


Figure 5. Annual growth in health expenditure for selected services (real terms) based on the Organisation for Economic Co-operation and Development (OECD) average for 2009–2013 (dark blue) and 2013–2017 (light blue)

Source: OECD 2019b



the OECD also estimated that in 2018/19 the UK spent just 12 per cent of its total health budget on medicines and allied goods. The percentage of the UK's GDP spent on health care was (including private outlays) around the OECD average.

Other sources indicate that when all discounts and repayments are taken into account NHS pharmaceutical outlays are closer to 10 per cent of its overall spending (ABPI, 2021). Of this proportion about 8 per cent (that is, about 1 per cent of NHS spend and 0.1 per cent of GDP) is attributable to rare condition treatment costs (Hutchings, 2021). Regarding levels of return, European Commission supported research has suggested that overall pharmaceutical industry profitability is, when adjusted for risk, comparable to that for other industries while the ratio of pharmaceutical R&D investment spending to total sales is higher for pharmaceutical companies than other sectors. The Commission has also found that pharmaceutical R&D investment in the EU remains below that recorded in the US. (See, for example, Grassano et al, 2021; Lundeby-Grepstad et al, 2014).

One reason for the differences between the US pharmaceutical sector and its counterparts in Europe relates to the more diverse nature of the American health care system and the absence of nationally imposed price controls. The US spends about twice as much per head on medicines than the UK. This is only in part a reflection of the fact that America devotes more of its greater wealth (some 17 per cent of GDP) to health care than does Britain (10 per cent of GDP).

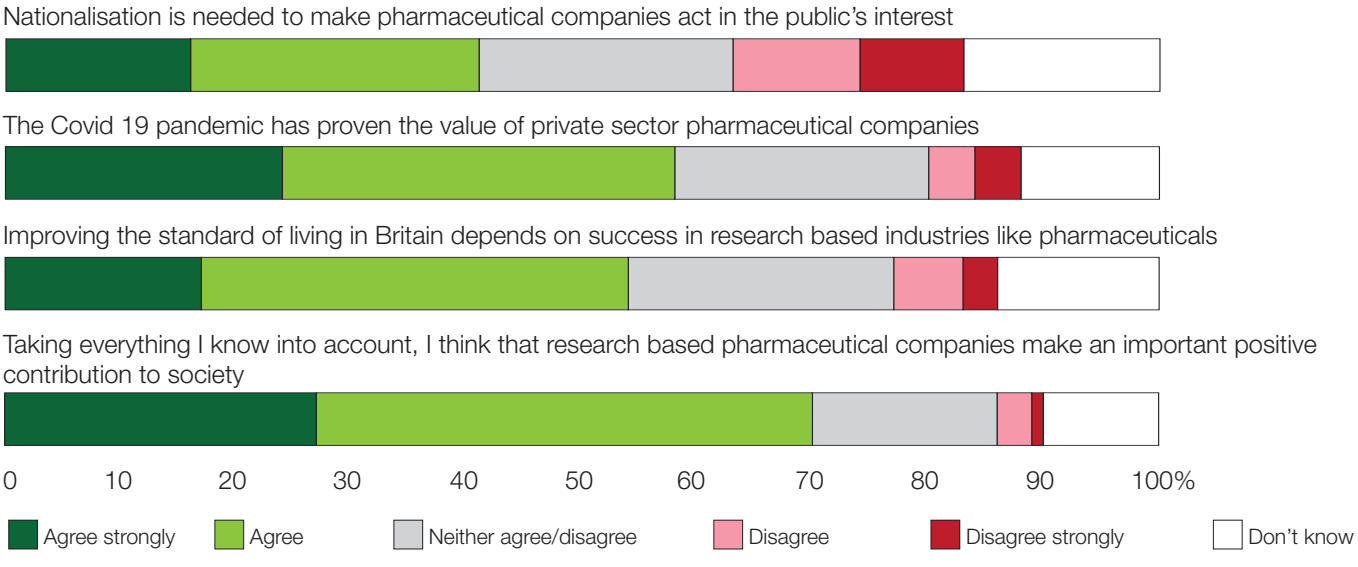
In both the US and the UK there is conventional price competition between generic medicines and also between intellectual property right protected products with the same or similar indications. Its drivers include institutional formularies and professional judgements about value as well as (in the US) limits on patient willingness and abilities to pay. However, partly because there are multiple imperfections in markets for innovative pharmaceuticals the UK has additional pharmaceutical price and total cost controls provided via:

- **VPAS, the Voluntary Price and Access Scheme for Branded Medicines.** This has been a UK wide arrangement which amongst a variety of effects limits the total amount paid for NHS pharmaceuticals. VPAS will end in 2023.
- **The work of NICE and equivalent bodies, most notably the Scottish Medicines Commission.** In addition to producing clinical guidelines the National Institute for Health and Social Care Excellence conducts cost-effectiveness studies on individual or groups of medicines and recommends whether they are sufficiently cost effective for NHS use. This can drive discounting via arrangements such as Patient Access Schemes (PASs) and Managed Entry Agreements (MEAs). The recent NICE methods and process review (see NICE, 2022) has been welcomed in that it promises greater flexibility in relation to determining the affordability of medicines for rare diseases. But concerns remain as to what extent this will provide NHS patients with rare diseases with the same level of access as that enjoyed in countries like Germany and better served sections of the US community.
- **Interventions by NHS England.** Central NHS purchasers of medicines, of which by far the largest is NHS England, can in some circumstances require further price cuts and/or phase the introduction of novel therapies. In England, the Budget Impact threshold for this is £20 million a year. Tendering based approaches may also be employed to drive down the costs of medicines with the same or overlapping indications.

UK public opinion as to the value of the pharmaceutical industry is more positive than is sometimes assumed. For instance, in 2021 70 per cent of British adults agreed with the statement '*taking everything I know into account, I think that research based pharmaceutical companies make an important positive contribution to society*' – see Figure 6.

Figure 6. UK Public Attitudes Towards the Pharmaceutical Industry, May 2021

Source: Taylor et al, 2021



There is also majority public support for the beliefs like '*the NHS should pay as much for new anticancer medicines as is paid in leading EU countries like France and Germany'* although there is also evidence of widespread lack of knowledge about the effectiveness of NHS medicine cost controls (Taylor et al, 2021).

Demands for more effort to minimise NHS medicine costs are perhaps to be expected in any circumstance. However, such actions could have counterproductive effects on investment in areas such as rare disease R&D. The UK can already claim to have the lowest *de facto* medicine prices of any nation with a strong record in biomedical R&D. A more positive approach might be to promote informed trust in the NHS and its capacities to control costs while working coherently to identify areas in which undue austerity may be threatening long term public interests in health and wealth generation.

Policy opportunities

At present in the order of 30 per cent of babies born with rare disorders (which amongst those with a genetic cause may be inherited or may on occasions occur spontaneously) die before their fifth birthdays (Lancet, 2019). Others live on with significant disabilities that affect their wellbeing and that of their families. Developing effective treatments has the potential to relieve suffering and reduce costs. It should in time generate social as well as financial benefits for large numbers of people, not least because of 'spill over' effects between rare disease related scientific advances and other fields.

Britain could play a leading role in pursuing such progress. However, the UK economy is facing severe challenges. The combination of Brexit linked losses, Covid 19 impacts and the consequences of the Russo-Ukrainian war are increasing the costs of living and it has also become increasingly difficult for the NHS and its social care partners to achieve desired standards. Proposals for strengthening incentives to conduct rare and very rare disease R&D and improve NHS and allied services for those with such disorders need to be grounded in the fact that there will, probably throughout the current decade, be powerful pressures to curb spending on items such as pharmaceutical and medical interventions that are regarded as cost increasing.

These are likely to be most acute in fields which are not in the public eye and where better services are seen by policy makers and/or the electorate as benefiting only small numbers of people. Downward pressures are also likely to be strong in contexts in which unfair profits are widely thought by voters to be being made. This implies that individuals and organisations wishing to defend the interests of people with unmet medical and social needs associated with rare diseases should work to raise awareness of the inequitable distress they cause and the fact that in total they directly and indirectly (typically via parental and other family associations) affect one person in every five in countries like the UK.

With regard to providing access to those in need of better rare disease treatments efforts should also be made to enhance public trust in the NHS's capacity to control pharmaceutical costs and prevent unfair profit-taking. As previously evidenced, pharmaceutical spending has not risen faster than total health service outlays in recent decades in the UK or many other parts of Europe (Espin et al, 2018). From a long term public interest perspective the risk of the NHS spending too little on innovative therapies relative to their worth is arguably as great as that of spending too much on them.

Investing in neonatal genetic screening

Not all rare diseases have their origins in genetic differences or other impairments detectable early in life. Further, of those that are caused by recessive or – rather less frequently – dominant gene abnormalities relatively few presently have specific treatments. Even so, there are already estimated to be 200-300 rare disorders that could be identified via neonatal genetic screening in order to avoid the harms caused by diagnostic delays and allow significantly more effective management. Some rare disorders may be diagnosable via abnormal proteins or protein levels in the blood of new-borns.

Presently nine conditions are included in the UK's heel-prick blood spot based screening programme – see Box 5. But as already noted in the context of Spinal Muscular Atrophy, this country has to date taken a relatively conservative approach. New Zealand's equivalent to the British heel-prick programme seeks to identify over 20 conditions. In parts of the US this figure is about 40.

The UK's record to date can be seen as consistent with, until recently at least, NHS policy makers attaching limited priority to diagnosing rare disorders before there is definitive proof that enhanced rates would lead to conventionally defined medical and economic gains within set affordability parameters. This might well be partly because of fears of generating demands for interventions not yet regarded as cost effective in Britain.

Such caution will, even when justified by ethical concerns, inevitably lead to delayed diagnoses. Yet attitudes may now be changing, not least amongst politicians aware of constituents' distress and the future promise of gene and other advanced biomedical therapies to (given ongoing scientific advances) effectively prevent or cure previously untreatable disorders.

In late 2021 Genomics England announced its support for a pilot research project to examine the use of whole genome sequencing to find and open the way to treating rare genetic diseases in babies (Genomics England, 2021). Some critics have said that they regard this initiative as more concerned with building data sets than optimising care. A variety of other concerns exist. But against this there is considerable potential for preventing harm and neonatal genetic screening is an area where the UK is well placed

Box 5. Conditions Screened for via the UK's New-born Heel-Prick Programme

The New-born Blood Spot (NBS) screening programme currently seeks to identify nine rare conditions, namely:

- **Sickle cell disease (SCD).** This presently affects about 1 baby in every 2,800 in the UK. In total there are now around 15,000 people known to be living with SCD in this country.
- **Cystic Fibrosis (CF).** Britain has one of the highest rates of Cystic Fibrosis – which is principally caused by functional deficits in the CF transmembrane conductance regulator (CFTR) gene – in the world. About 1 in 2,500 babies are born with the condition and some 10,000 people are currently living it in the UK. New therapies are significantly improving CF outcomes.
- **Congenital hypothyroidism (CHT).** There are various forms of hypothyroidism which affect people across the age spectrum. Primary congenital hypothyroidism, which is what the NBS aims to identify, affects 1 birth in 2000. Timely treatment with thyroxin prevents physical and learning difficulties from occurring.
- **Phenylketonuria (PKU).** This metabolic disorder affects 1 in every 10,000 UK new-borns, who to suffer the condition must have two abnormal copies of the phenylalanine hydroxylase (PAH) gene. PKU can be treated by a mix of dietary and pharmacological interventions.
- **Medium-chain acyl-CoA dehydrogenase deficiency (MCADD).** This also affects 1 in every 10,000 babies. Symptoms include exhaustion, vomiting and fitting. Without appropriate care MCADD is life threatening, although with specialist dietary and allied support it is normally well managed.
- **Maple syrup urine disease (MSUD).** The incidence of MSUD in UK new-borns is approximately 1 in 150,000. Lack of a functional enzyme needed to break down amino acids in substances such as milk puts babies at risk of brain damage. Management is presently via dietary modification.
- **Isovaleric acidaemia (IVA).** This is another genetic disorder affecting the metabolism of an amino acid (leucine) found in milk which has an incidence of about 1 in 150,000. Treatment is again based on special diets.
- **Glutaric aciduria type 1 (GA1).** About 1 in every 300,000 new-borns (or two or three per year in the UK) has GA1 resulting from the lack of an enzyme needed to break down glutaric acid. When the disease is identified early dietary modification can prevent harm.
- **Homocystinuria (HCU).** The NBS programme identifies pyridoxine unresponsive HCU, an ultra-rare disorder with an incidence of approaching 1 in every 600,000 UK babies. Without effective dietetic management levels of homocysteine and methionine rise and cause brain damage.

to lead global development. It is likely that many parents would if given the choice support extended testing for rare disorders even if treatments have not yet been developed or made available via the NHS.

The continuing evolution of NICE

The processes of medicines evaluation, purchasing and supply vary between nations. They reflect the wider medical and health care models and overall cultures in which they take place. The reasons why US approaches to issues such as limiting pharmaceutical costs and assuring equitable access differ markedly from those in the UK are more complex than the range of factors typically considered by health economists might suggest. Nevertheless, improving the extent and timeliness of rare disease and other types of treatment in the UK will demand understanding and refining the methods used by NICE and related bodies and optimising their application, alongside a willingness on the part of political leaders to when appropriate change the restraints within which the NHS operates.

The creation of NICE at the start of the first Blair administration involved an acceptance that the market for new medicines is highly imperfect and a belief that government ought to create a system for determining the 'value based' prices that the NHS as a monopsony (dominant single) purchaser should pay. It is debatable whether the arrangements introduced at the end of the 1990s are in reality better able to protect public interests in medicines affordability on the one hand and the support of innovation and industrial success on the other than those previously in place. Yet successful work on tasks such as creating clinical guidelines has been undertaken and the 'cost per QALY' approach originally pioneered by economists at the University of York provides, despite significant weaknesses, a coherent means of assessing the value of novel medicines that should provide a basis for informed dialogue.

A pragmatic conclusion to draw is that emphasis should be given to the incremental improvement of how NHS and allied agencies approve, value, purchase and supply medicines for rare diseases. The MHRA has expressed a desire to make licensing products for low prevalence indications and hence low volume use as flexible and pragmatic as possible. This needs to be matched by effective efforts to minimise delays between marketing application approvals and the subsequent agreement of prices acceptable to innovators and judged sufficiently cost effective to permit provision to NHS patients.

Following the recent NICE methods and processes review there has been progress in areas such as managing evidential uncertainties and enabling (very) rare disease products required by no more than 300 patients to be evaluated via the HST (Highly Specialised Technology) path. The use of a revised 'severity modifier' (in essence, a QALY affordability threshold adjuster) to allow more products

capable of meeting serious unmet medical need to be given the degree of priority previously reserved for life-extending anti-cancer treatments is also to be welcomed. However, areas of concern remain, including:

- the fact that significant numbers of innovative, low volume indication medicines for conditions affecting more than 300 people in this country will not qualify for HST evaluations but will nevertheless be unsuitable for the standard STA (Single Technology Assessment) process. Allied to this there are anxieties about the number of HST evaluations NICE is resourced to undertake at any one time;
- the apparent Treasury refusal to permit NICE to lower the discount rates it applies to future costs and health benefits from 3.5 per cent to 1.5 per cent. The resultant bias towards short-termism particularly disadvantages patient groups that could benefit from 'once off' gene therapies for conditions like, for instance, sickle cell disease; and
- the application of an 'opportunity cost neutral' approach to introducing the new severity modifier. This can be seen as meaning that money previously allocated to facilitating the introduction of anti-cancer treatments will be spread further to include severe non-cancer conditions. If maintained over time this strategy will significantly dilute the impact of the new modifier in the rare disease context while threatening some cancer patients' interests.

There are many detailed questions to be analysed in these and related contexts. At a high level they relate to how Ministers expect agencies such as NICE to exercise their duty to defend public interests in biomedical innovation in ways that adequately offset short term pressures for NHS cost minimisation, and how in a democratically accountable system responsibilities for deciding NHS affordability thresholds for therapies for previously untreatable rare diseases can best be discharged. At present this is done in a far from transparent manner which some fear is not subject to informed political control. This raises barriers to optimally combining the pursuit of science, industrial, health and other policy objectives.

At some future point it may be in the interest of NHS patients and the wider public to ask fundamental questions about whether current ways of determining what should be paid by the health service for innovative treatments at the point of market entry should be radically simplified or otherwise reformed. It might, for instance, prove desirable to introduce indication based pricing (that is, varying the permitted prices for a given active entity used for differing conditions) or a German-style drug introduction model. The latter could in outline permit free or relatively free pricing at the time of launch as soon as possible after the receipt of a marketing authorisation (as did the UK system until 1999), followed later by price reductions or a product 'de-listing' if subsequently judged appropriate on cost effectiveness grounds.

From a patient-centred perspective such options have considerable attractions. But in the immediate future enabling the existing system to work more rapidly and in an optimally informed way is the most viable path forward. Many rare disease treatments now become available in the UK and other settings as a result of Managed Entry Agreements (MEAs) negotiated between their producers and institutional or national payers. At present establishing these can be a time consuming and poorly structured process. The use of a validated, systematic, framework for guiding the formation of MEAs could serve to speed their agreement (Whittal et al, 2022). Nevertheless, if payers and producers lack flexibility and genuine commitment to meaningful dialogue avoidable delays and needless distress will still occur.

A new model for developing very rare and ultra-rare disease treatment innovations?

The view underpinning this UCL School of Pharmacy Policy Briefing is that in most instances the mixed model of publicly and privately funded biopharmaceutical innovation that exists in countries such as those of Western Europe and North America is serving public interests relatively well. To describe it as broken would be misleading although, as with any evolving entity, improvements should be made on a continuing basis.

At the global level there are major inequities between rich and poor nations regarding access to all types of goods and services, including professionally delivered health care and life-saving and life-changing medicines. Within industrially advanced and economically less advantaged nations alike there are also important challenges with regard to treating rare diseases effectively and equitably, and failings to be overcome in relation to funding R&D into very rare and ultra-rare diseases that are currently untreatable. As the complex conditions of later life are becoming better understood similar challenges are occurring in relation to developing therapies for low prevalence sub-types of common disorders like cancers.

The UK alone cannot change the realities of world-wide resource distribution, even though it has had a comparatively good record in funding international health initiatives and agencies like the World Health Organisation. Yet it is well-placed at this point in history to help speed developments in genomics and the creation of gene, cell-based and other adavanced therapies and diagnostics in order to provide lasting solutions to disease related threats.

Observers may disagree as to the extent of their adequacy, but significant incentives already exist to encourage R&D investments aimed at discovering new treatments for high prevalence disorders and the more commonly occurring rare diseases affecting the world-wide population. This clearly is not the case for very rare and ultra-rare conditions, despite the fact that in aggregate they directly affect one in every 100 UK citizens. In this context a broadly defined

global market failure can be said to exist. Finding solutions to this problem is an important policy challenge.

Universities and allied public and charitable fund receiving bodies in the UK and elsewhere are undertaking fundamental research relevant to developing better rare illness treatments. At present this effort may seem fragmented and in the case of many very rare and ultra-rare conditions there is still a lack of fundamental scientific insight into their underlying mechanisms coupled with funding limitations. Nevertheless, the value of what is already being achieved deserves recognition. In UCL, for example, work on conditions such as Bardet-Biedl syndrome is helping to make more effective therapies possible – see Box 6.

However, even when early stage discoveries have been made there is in many instances a lack of resources for translating pioneering work by academics and clinicians into appropriately approved treatments capable of meeting patients' needs. It is not possible to identify here precisely what should be done to improve this situation or specify the extent to which Britain ought to take action unilaterally or seek to do so in partnership with, for example, Commonwealth nations like Canada and India or with the European Union or US institutions such as the National Institutes of Health's Office of Rare Diseases. But in overall terms there is a case for channelling additional government resources into creating an integrated very rare disease innovation support system while maintaining the incentives already in place for investing in rare disease therapies in the UK and elsewhere. Such a model could combine measures aimed at minimising rare disease treatment development costs with new ways of facilitating co-operation between Universities, centres of clinical excellence and research based pharmaceutical companies.

As patient numbers permit, one goal of such a reform could be to encourage the enhanced use of 'real world' evidence gathering and/or innovative trial approaches, including the platform designs employed in the UK recently in the Covid 19 context (Normand, 2020) and in the United States to test alternative Motor Neurone Disease (ALS) treatments (see Sean M. Healey & AMG Center for ALS, 2022). A second might be to provide risk capital on a non-market grant or subsidised basis in return for ensuring that new treatments are made available at close to the cost of manufacturing.

Establishing such an initiative and instituting the cultural changes needed to accompany it would not be straightforward. An initially viable step might be to organise a national consultation process on the introduction of a new model for fostering very and ultra-rare disease treatment innovations. This would serve to bring interested parties ranging from rare disease service users to industrialists, academics and health sector staff together in ways designed to raise the level of public policy debate and focus on seeking the long-term common good nationally and globally, rather than merely encouraging the articulation of near-term sectional interests.

Box 6. Understanding and Treating Ciliopathies

Motile and non-motile (or primary) cilia protrude from the surfaces of many cells, including neurones. These antenna-like structures were once regarded as vestigial but are now known to act as sensory organelles and to play an important part in fields such as inter-cellular communications. Ciliopathies are diseases that arise from cilial dysfunctions.

At the UCL Great Ormond Street Institute of Child Health Professor Phil Beales and his colleagues research the causes of and treatments for rare illnesses with a special focus on the ciliopathies. For instance, he first hypothesised and subsequently showed that non-motile cilial abnormalities underpin Bardet-Biedl Syndrome (BBS). Professor Beales has also played a central role in discovering its genetic causes.

BBS, which has a known prevalence of around 1 in 100,000 in an average North American or European population, gives rise to many symptoms and can be life-shortening. It is normally diagnosed in childhood or shortly afterwards. It causes progressive loss of night and peripheral vision due to retinitis pigmentosa, together with problems like obesity, kidney disorders, cardiomyopathy and developmental disabilities.

Similar disabilities characterise other ciliopathies, examples of which range from Joubert Syndrome to Polycystic Kidney Disease (PKD). Joubert Syndrome is believed to affect around 1 in 80,00 new-borns and presently lacks disease modifying as distinct from symptom relieving treatments. Most of those living with Joubert Syndrome do not survive beyond their first decade and the overall prevalence is consequently very low. By contrast the number of people with PKD in the UK may well exceed 50,000.

Conclusion

As the health of communities has improved and fundamental scientific understanding of disease causes has increased, enhancing the treatment of rare conditions and low prevalence sub-types of common disorders has become a significant policy challenge. This is most likely to be recognised in societies that see addressing the needs of minorities suffering very severe forms of illness and disability as being as important as promoting 'the greatest good for the greatest number'. Yet it is worth stressing that in aggregated terms the total number of infants, children and adults living with rare conditions in the UK is approaching 4 million. The wellbeing of relatives can also be seriously affected.

Since the start of this century important progress has been made in treating more frequently occurring 'orphan' conditions such as some types of leukaemia and cystic fibrosis. But well over ninety percent of rare conditions still lack definitive or satisfactory treatments. The rarer the condition the higher is this risk.

There is a danger that even if biological and allied progress in areas such as genetics fulfils its promise to make the development of more effective therapies and accurate

diagnostic tests possible, such advances will be unduly slow to translate into therapies available to patients. Sub-optimal organisational and economic arrangements can add to avoidable inequities and threaten public confidence in institutions such as the NHS. This in turn could in the long term paradoxically increase the costs of health and social care while causing particular harm to many of society's least advantaged members.

But despite past failures and current financial challenges, UK policy makers have significant opportunities to promote the early diagnosis of and better treatment for rare diseases. Politicians of all parties, together with most voters, agree that the UK should seek to build its position as a world leader in the life sciences, in both the academic and industrial contexts. This is demonstrated by, for instance, the work of the Accelerated Access Collaborative. Playing a stronger role in rare disease treatment improvement could prove central to achieving this end. It will demand continuing efforts to align economic incentives and financial support systems with the nation's physical and human capabilities.

In order to encourage rare disease research funded by independent commercial agencies such as pharmaceutical companies there needs in the UK and elsewhere to be a shared preparedness to, as and when innovative therapies become available, pay prices sufficient to incentivise ongoing R&D. It is also important to avoid needless local delays between licensing and uptake by health care providers. Despite their strengths it does not always appear that the English and other UK systems presently in place have the flexibility to deliver this in the context of supplying very low volume treatments. Charges of 'penny pinching' or undue evaluation process complexity can, justified or not, undermine investor confidence as well as patient trust.

To further strengthen the academic base and deliver enhanced therapies for very rare and ultra-rare conditions there is also a need to find solutions to problems in areas where private sector led action is not seen as commercially viable. A well co-ordinated national programme funded to foster both fundamental and translational research in selected areas and make innovative very rare disease therapies available to the public at a cost acceptable to the NHS would help address such challenges.

Other ways of providing better rare disease treatment and achieving desired outcomes range from extending access to population-wide and where appropriate targeted whole genome (or exome) and proteomic screening through to enhancing psychological and social care. Some may argue that such developments are not affordable at present. Yet if Britain does not act others almost certainly will, leading to the danger of this country falling progressively behind. If the UK is to maintain standards of health and social care in line with changing public expectations and continue building its life science based research and industrial capacities in order to earn its future living in the world there is a powerful case for concluding that the nation cannot afford not prioritise finding better ways of treating all forms of rare disease.

References

ABPI (2021) *NHS Medicines Spend*. Available at https://www.abpi.org.uk/value-and-access/uk-medicine-pricing/nhs-medicine-spend/

Berdud M., Drummond M. and Towse A. (2020) Establishing a reasonable price for an orphan drug. *Cost Effectiveness and Resource Allocation* 18: 31

Commission of the European Communities (2008) Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases - Europe's challenges {SEC(2008)2713} {SEC(2008)2712} Available at EUR-Lex - 52008DC0679 - EN - EUR-Lex (europa.eu)

DBEIS, DHSC and OLS (2020) *Genome UK: the future of healthcare. Policy paper.* Available at Genome UK: the future of healthcare - GOV.UK (www.gov.uk)

DBEIS and OLS (2021) *Life Sciences Vision.* Available at Life Sciences Vision (publishing.service.gov.uk)

DHSC (2021) *UK Rare Diseases Framework. Policy Paper .* Available at The UK Rare Diseases Framework - GOV.UK (www.gov.uk)

DHSC (2022). *England Rare Diseases Action Plan 2022*. Available at England Rare Diseases Action Plan 2022 - GOV.UK (www.gov.uk)

Department of Health (2013). *The UK Strategy for Rare Diseases.* Available at UK_Strategy_for_Rare_Diseases.pdf (publishing.service.gov.uk)

Espin J., Schlander M., Godman B. et al (2018). Projecting Pharmaceutical Expenditure in EU5 to 2021: adjusting for the impact of discounts and rebates. *Applied Health Econ and Health Policy* 16, 808-817

Genetic Alliance (2020). *Rare Experience 2020*. Available at Rare-Experience-2020-Report-.pdf (geneticalliance.org.uk)

Genetic Alliance UK (2018) *Living with a Rare Condition: the Effect on Mental Health.* Available at living-with-a-rare-condition-the-effect-on-mental-health-pdf.pdf (raredisease.org.uk)

Genetic Alliance UK (2022). *Good Diagnosis.* Available at Rare-Disease-UK-Good-Diagnosis-Report-2022-Final.pdf (geneticalliance.org.uk)

Genomics England (2021). *Newborn Genomes Programme*. Available at Newborns-Vision-Final_SEP.pdf

Grassano, N., Hernandez Guevara, H., Fako P. et al (2021). *The 2021 EU Industrial R&D Investment Scoreboard.* Available at The 2021 EU Industrial R&D Investment Scoreboard | IRI (europa.eu)

House of Commons Health and Social Care Committee (2022) *Cancer Services*. Available at Cancer services (parliament.uk)

Hutchins A. (2021) *How did we get here and where do we go now? An economists perspective on EU orphan drug policy.* London: Dolon Ltd. Available at How-did-we-get-here-and-where-do-we-go-now.pdf (dolon.com)

Lancet Diabetes and Endocrinology (2019). Spotlight on Rare Diseases*. Lancet Diabetes and Endocrinology, Editorial,* 7, 2, 75

Lundeby-Grepstad M., Tordrup D., Craig T. et al. (2014) *Patients Needs, Medicines Innovation and the global Publics Interests*. London: the UCL School of Pharmacy. Available at Patients' Needs Medicines Innovation and the Global Public's interests.pdf (iapo.org.uk)

Marmot M., Allen J., Boyce T. et al (2020*). Health Equity in England : the Marmot Review 10 Years On*. London: Institute of Health Equity. Available at https://www.health.org.uk/publications/reports/the-marmot-review-10-years-on

Mazzucato M. and Li H. L. (2020). *A market-shaping approach for the biopharmaceutical industry: governing innovation towards the public interest.* UCL Institute for Innovation and Public Purpose, Working Paper Series (IIPP WP 2020-21). Available at https://www.ucl.ac.uk/bartlett/public-purpose/publications/2020/dec/market-shaping-approach-biopharmaceutical-industry

Mikami K (2019). Orphans in the Market: The History of Orphan Drug Policy. *Social History of Medicine* 32, 3, pp 609–630

Neez E., Gentilini A. and Hutchings A. (2021) *Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions.* Dolon Ltd/EFPIA. Available at Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions (efpia.eu)

NHS England (2018). *Implementation Plan for the UK Strategy for Rare Diseases.* Available at implementation-plan-uk-strategy-for-rare-diseases.pdf (england.nhs.uk)

NICE (2022). *NICE Health Technology Evaluations: the Manual*. Available at Introduction to health technology evaluation | NICE health technology evaluations: the manual | Guidance | NICE

Normand S-L T (2021). The Recovery Platform. *N Engl J Med* 2021; 384:757-758

OECD (2019a) OECD Health Statistics. OECD

OECD (2019b) Health at a Glance 2019: OECD Indicators. OECD Publishing. Available at Health at a Glance 2019 : OECD Indicators | OECD iLibrary (oecd-ilibrary.org)

Peto R (2014) Harveian Oration 2012: Halving premature death. *Clinical Medicine* 14, 6: 643–57

Sean M Healey & AMG Center for ALS (2022). *The Healey ALS Platform Trial*. Available at HEALEY ALS Platform Trial (massgeneral.org)

Taylor D.G. (2020) The political economics of cancer drug discovery and pricing. *Drug Discovery Today.* 25 (12): 2149–2160

Taylor D., Heller M. and Emberton M (2021) *British Public Attitudes towards Cancer Research and Treatment in 2021. London: the UCL School of Pharmacy.* Available at vfr_web_edition_british_public_attitudes_towards_cancer_research_and_treatment_in_2021_latest_version.pdf (ucl.ac.uk)

Wakap N. S., Lambert D.M., Olry A. et al (2020) Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet* 28:165–173. doi: 10.1038/s41431-019-0508-0

Whittal A., Jommi C., De Pouvourville G. et al (2022). Faciliating More Efficient Negotiations for Innovative Therapies: A Value-Based Negotiation Framework. *International Journal of Technology Assessment in Healthcare* 38 (1), e23, 1-8

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