for example, single-nucleotide mutations in *ERBB2* have been found in breast cancers[6] that do not have amplified *ERBB2*, and in lung adenocarcinomas[7].

The rapid development of therapeutics targeting specific cancer-associated proteins has coincided with the rise in DNA sequencing of tumours. In the past decade, the genomic alterations in tens of thousands of cancers have been characterized at single-nucleotide resolution. This has revealed that cancer-associated genes can be altered in myriad ways and that such alterations can be found in primary tumours that arise in many different tissues. However, such variability makes it hard to predict whether a specific drug will have an effect on a patient's cancer; this, in turn, complicates the decision of who to enrol in a clinical trial. One approach to this problem involves introducing the mutated genes in question into preclinical model systems such as genetically engineered mice or cell-line models, but these models are not practical for large-scale investigations of many different gene alterations in different tissue types.

The design of clinical trials testing targeted therapeutics has changed substantially in the era of cancer genomics. Early-phase trials, in particular, now often include people who have an altered target gene, regardless of the tissue in which the tumour is present. These 'basket' trials seek to identify the combination of mutations and tissues that respond to treatment, offering the opportunity, if a trial progresses to a later stage, to focus on tumours in those tissues that are most likely to respond.

The ability of neratinib to target tumours with *ERBB2* mutations had been demonstrated[6] in human-tumour samples transplanted into mice. Hyman *et al*. used a basket-trial approach to test the effects of the drug on many patients with known tumour-driving *ERBB2* mutations; they also examined its effects on a small number of patients who had either rare *ERBB2* mutations or mutations in *ERBB3*, the gene that encodes HER3 and that has also been linked to tumour growth[8]. An interesting feature of the trial design is that it included people with mutations that had not previously been tested for a response to the drug. Some tumour types studied by Hyman and colleagues were not represented in sufficient numbers for the team to assess whether treatment had had a statistically significant effect, and enrolment in the trial is continuing for specific tissues.

The authors found that the effect of neratinib therapy varied in different mutational and tissue contexts. For example, some people who had breast, small-cell lung, cervical, biliary or salivary cancers, and who had certain *ERBB2* mutations, responded to the treatment; the greatest effect was observed for breast cancers containing amino-acid alterations in the extracellular or kinase domains of HER2 (Fig. 1). Several patients with previously uncharacterized *ERBB2* variants responded to neratinib, supporting the role of these mutations as tumour drivers. Neratinib had no effect on tumours with *ERBB3* mutations, nor did it affect colorectal or bladder cancers that had *ERBB2* mutations. The bladder-cancer result is consistent with previous studies[9,10] in which HER2 targeting did not affect this type of cancer. Lack of response to neratinib provides circumstantial evidence that rare alterations in *ERBB2* are unlikely to be tumour drivers.

Hyman and colleagues' results indicate that preclinical model studies, such as those suggesting that *ERBB3* can drive tumour growth[8], can sometimes be misleading when trying to infer what happens in a human tumour. This might be because of how the overall genomic context influences the effect of a mutation. A tumour that has an altered target gene could also have alterations in other cancer-promoting genes. Another source of inconsistency between human and mouse studies might be the particular tissue context.

Finally, the genomic heterogeneity of tumour cells (the presence of groups of cells in the tumour that contain different genetic alterations) might be important in determining treatment response. Sequencing analysis conducted by Hyman and colleagues for certain *ERBB2* mutations demonstrated that most patients whose *ERBB2* mutations were present in all the tumour cells responded to neratinib, whereas those with *ERBB2* mutations in only a subset of the tumour cells did not respond.

The authors noted that response to treatment could be affected by the particular genetic mutation, the location of the tumour and the specific pattern of other mutated cancer-associated genes present. This will probably hold true for most, if not all, future basket trials of targeted inhibitor therapies and is quite instructive for such studies. More-complete genomic characterization of tumours, beyond the gene(s) being targeted, will be needed to determine the genomic context linked to response or resistance to treatment. The genomic profiles and therapeutic-response data from basket trials such as this one should be made publicly available as a way of improving the design of clinical trials of other agents. Such data sets might contribute to the development of diagnostics that enable the precise identification of those patients who are most likely to benefit from targeted treatment. The data could also help to streamline the design of clinical trials and thereby hasten cancer therapeutics towards regulatory approval. ■

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CLIMATE SCIENCE

Fossil-fuel subsidies assessed

Many governments subsidize the production and consumption of fossil fuels. Contrary to expectation, a study finds that removing these subsidies would only modestly reduce global carbon dioxide emissions. SEE LETTER P.229

IAN PARRY

The 2015 Paris climate agreement was signed by 195 countries, with most pledging to reduce their emissions of carbon dioxide and other planet-warming gases. Many countries have a long history of subsidizing fossil fuels, and it seems logical that removing these subsidies — as the G20 group of nations has agreed to do — would help them to achieve their Paris climate commitments. However, on page 229, Jewell *et al.*[1] report a comprehensive and convincing analysis suggesting that reforming these subsidies would cause only a modest reduction in global CO_2 emissions. Nevertheless, I think that there is an urgent need for broader reform of fossil-fuel prices to fully reflect the costs associated with global warming and other environmental considerations.

Subsidy reform would increase domestic fossil-fuel prices to match the production costs. Its impact on the climate would therefore depend on how energy demand is affected by

these higher fuel prices — for example, through people driving less, power generators switching to cleaner fuels such as those from renewable energy sources, and households and businesses adopting energy-saving technologies. Because these responses are inherently uncertain, Jewell *et al.* used five different models to assess the consequences of subsidy reform. These models compared projections of fuel use and CO_2 emissions with and without subsidy reform by region or country, using diverse assumptions about future economic growth, technological trends, energy prices and so on.

The authors found that removing all fossil-fuel subsidies would have a limited impact on global energy demand by 2030 (a reduction of about 1–4%). In addition, the share of energy from renewable sources would rise by less than 2%, and global CO_2 emissions would fall by only 1–4% (under both low and high oil prices). Consequently, in most regions, the CO_2 reduction from subsidy reform would fall far short of what is needed to meet the Paris climate pledges (Fig. 1). The exceptions are regions such as Russia, the Middle East and North Africa, where subsidies are heavily concentrated and pledges are less ambitious.

There are two main reasons for the generally modest impact of subsidy reform on CO_2 emissions. The first is that coal (the fossil fuel that emits by far the most CO_2 per unit of energy) currently receives little subsidy. Instead, 60% of subsidies are for oil, and the remainder is largely for natural gas and for the electricity generated from fuels (see Figure 2a of the paper[1]). The second reason is that global subsidies have declined sharply, from US$570 billion in 2013 to $330 billion in 2015.

However, I think that reform of fossil-fuel prices needs to go well beyond aligning them with production costs. Fuel prices should also reflect the consequences of their use for global warming and other environmental considerations, such as the costs of deaths resulting from air pollution and, in the case of road fuels, traffic congestion and accidents. Furthermore, prices for fuels purchased by households should include the general sales or value-added taxes that are applied to other consumer products.

A study[2] in 2017 estimated that if fossil-fuel subsidies had been defined more broadly to reflect undercharging for environmental costs and general taxes, as well as production costs, these subsidies would have totalled $5.3 trillion in 2015 (6.5% of global gross domestic product). Furthermore, the study suggested that if prices had fully accounted for production costs, global and domestic environmental impacts and general taxes in 2013, global CO_2 emissions would have been 21% lower than they were, air-pollution deaths associated with fossil fuels would have been 55% lower, and government revenues as a percentage of gross domestic product would have been 4% higher.

Broader reform of fossil-fuel prices is therefore urgent for both developed and developing countries. However, such a reform must be carefully crafted to enhance the prospects for success. A comprehensive plan should be developed, in consultation with stakeholders, that has clear goals and timetables. It should specify the taxes to be cut or the public investment programmes to be expanded, using revenue raised by fuel-price reform. In addition, there should be measures to compensate low-income households for the effects of higher energy prices and to help workers who might lose their jobs in energy-intensive industries.

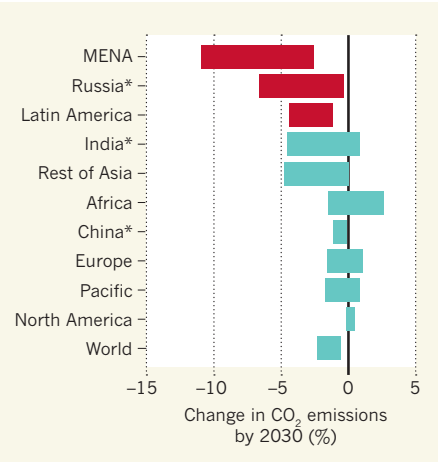

Figure 1 | Impact of fossil-fuel-subsidy reform. Fossil fuels are subsidized in many countries, and it was thought that removing these subsidies would lead to a substantial reduction in carbon dioxide emissions. However, Jewell *et al.*[1] report an analysis suggesting that the resulting change in CO_2 emissions by 2030 would be modest. The exceptions are regions in which current subsidies are heavily concentrated (shown in red), such as the Middle East and North Africa (MENA). The bars denote the range of emission changes predicted (under low oil prices), and asterisks indicate regions that constitute more than the designated country. (Adapted from Fig. 3b of ref. 1.)

Researchers and international organizations (such as the International Monetary Fund, World Bank and the Organisation for Economic Co-operation and Development) have an important role in providing information and guidance to help policymakers drive forward subsidy reform and communicate the case for reform to the public. The information required includes the fossil-fuel prices that countries should adopt, both to meet their Paris climate pledges and to reflect the broader environmental costs.

But it also includes the effect of reform on energy systems, the economy, fiscal balances and vulnerable groups, and the trade-offs between higher fuel prices and other policy approaches, such as requirements for energy efficiency and renewable fuels. Analysis of ongoing reform experiences in different countries could also help governments to navigate around the political obstacles.

Rigorous studies, such as that by Jewell and colleagues, are essential. But there is a need to focus these studies on the broader reform issues discussed here, for which the stakes are especially high. ■

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BIOMECHANICS

Evolutionary race as predators hunt prey

Remote-sensing data for wild animals such as lions reveal that predators and prey optimize manoeuvrability rather than speed during the hunt. SEE ARTICLE P.183

ANDREW A. BIEWENER

The survival of predators and prey depends on their respective abilities to successfully chase food and escape capture, thereby exerting strong selective pressure on their running ability and behavioural strategies. Perhaps nowhere on Earth does this play out more dramatically than on the African savannah, where the fastest terrestrial predators chase their fleet-footed prey. Yet direct measures of the key factors driving this type of hunt performance in the wild are difficult to obtain. On page 183, Wilson *et al.*[1] report findings from their use of data-capturing collars to track the movement dynamics of wild animals in Botswana during hunts. The authors also conducted computer modelling of predator–prey interactions and carried out laboratory tests to assess the properties of the animals' muscles.

In recent years, the ability to use remote-sensing devices under natural field