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Early Returns From the Era of Precision Medicine

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The era of precision medicine has arrived. A large share of new pharmaceuticals are tested and approved on the basis of biomarkers. Pharmacogenomics—the tailoring of drugs to patients based on one or more biomarkers—is used in conditions as diverse as HIV and thromboembolism.

Precision medicine raises hopes for patients and fears for those who try to ride herd on health care spending. Will patients finally live longer and healthier lives? Will society be able to afford it? Surprisingly, at this point, personalized medicine has had less effect on both health and medical spending than either its strongest backers hoped or its most apprehensive actuaries feared.

**Precision Oncology**

Oncology has been the primary focus of precision medicine. One recent analysis by the IQVIA Institute found that 97 new anticancer medications have been approved since 2011. A 2018 study published in *JAMA Oncology* found that 31 genome-targeted or genome-informed anticancer drugs were in use as of January 2018.

Precision oncology has had some major successes. Imatinib has a 95% response rate in patients with chronic myeloid leukemia and extends quality-adjusted life by about 9 years; venetoclax has an 80% response rate in patients with chronic lymphocytic leukemia who have a 17p deletion. The new chimeric antigen receptor T cell (CAR-T) therapy tisagenlecleucel has a 62% remission rate at 24 months among patients with acute lymphoblastic leukemia.

And yet, the overall effect of precision medicine on care for patients with cancer has been modest. The 2018 *JAMA Oncology* study estimates that only 8% of patients with cancer are eligible for precision medications approved as of January 2018 and only 5% would actually benefit from them. Even among patients who respond, incremental survival provided by many drugs is measured in months. Partly because of cost-effectiveness concerns, of the 54 new anticancer drugs launched between 2013 and 2017, only 80% were available in Germany by the end of 2018 and only 69% were available in France (96% were available in the United States).

**The Effect on Cost**

Economists were uncertain about the effect of precision medicine on costs. Because precision medicines are expensive to produce, they need to be priced higher. Furthermore, patients and insurers are willing to pay more for a precision-medicine drug that is more likely to work. On the other hand, precision medicine reduces the proportion of patients with a cancer type using each medication.

To date, total spending on anticancer drugs has been relatively modest. Although inflation-adjusted spending on anticancer drugs increased by $30 billion between 2011 and 2018, this is only 6% of the total increase in personal health care spending over the period. Given that administrative
expenses cost an estimated 4 times the amount spent on anticancer drugs, one should be cautious about focusing excessively on the cost of precision medicine.

A better metric than total spending is cost-effectiveness: do the benefits of the drugs outweigh the cost? The “drug abacus” tool developed by Memorial Sloan Kettering Cancer Center, which evaluates the cost-effectiveness of 52 anticancer drugs approved between 2001 and 2013, estimates that only a handful of new drugs are worth the cost at conventional valuations of life. If anticancer drugs were priced based on cost-effectiveness criteria, spending would fall by 30%.

One important feature of personalized oncology is that use of anticancer drugs seems to be limited primarily to the indication for which the drug was approved. Many anticancer drugs are tested in metastatic cases first; clinical trial recruitment is easier and the time from initiation of therapy to a meaningful end point is shorter. Drugs are then sometimes used off-label to treat earlier-stage cancers or certain other cancer types, even before clinical trials are conducted or completed. Thus, off-label use has been estimated as high as 30% of use for some anticancer agents.

For new therapies, however, insurers are commonly imposing prior-authorization requirements that limit use to patient populations for which drugs have been approved. Medicare requires that off-label uses of anticancer drugs be supported by at least 1 compendium. Similarly, United Healthcare requires adherence to National Comprehensive Cancer Network (NCCN) guidelines before anticancer drug approval or off-guideline care only with specific rationale. The IQVIA Institute estimates that 87% of newly approved anticancer drugs are used by fewer than 10,000 patients annually.

The treatments’ complexity may also limit use. Oncologists outside of academic medical centers are not always aware of the new therapies and guidelines can be slow to change. Diagnostics required to use targeted medications are not available everywhere. Involving patients in the decision-making can be complex. And high cost sharing contributes to limiting use. Many anticancer agents are in specialty tiers of formularies for which patient cost sharing is high. This is a particular challenge for patients enrolled in Medicare Part D, which has no out-of-pocket limit.

Until very recently, the trend in pricing of anticancer drugs had been fairly constant. Between the mid-1990s and the mid-2010s, launch prices of anticancer drugs rose roughly $8500 per year. The past few years have seen significant outliers from this trend, however. The highest prices have been for new CAR-T therapies: $475,000 for tisagenlecleucel and $373,000 for axicabatogene ciloleucel (though these pale in comparison to the $2.1 million list price for onasemnogene abeparvovec to treat spinal muscular atrophy in young children). Because these drugs are personalized to each patient, it is natural that they should cost somewhat more than other medications. More importantly, their high price reflects high effectiveness. The Institute for Clinical and Economic Review estimates that both medications are cost-effective even at these prices. Whether the trend toward a newer, higher price level for anticancer drugs continues or whether these prices are an aberration applying only in selected cases is not known.

Flash Points
Not surprisingly, insurers and pharmaceutical companies are clashing over coverage of expensive new therapies. In response to insurers raising the out-of-pocket cost for expensive drugs, pharmaceutical companies have responded with co-pay coupons for privately insured individuals (they are illegal for Medicare and Medicaid beneficiaries). For example, a drug treatment with a $25,000 total cost might have a $500 co-pay. The pharmaceutical company might offer a coupon to the individual worth $450, effectively cutting the out of pocket cost to $50. Not to be defeated, many insurance companies have enacted policies that coupons used for co-pays do not count towards deductibles or out-of-pocket maximums. Effectively, the patient can use a coupon at the point of sale, but they have to make up for it with increased co-payments later on.

Refereeing this conflict is difficult. Pharmaceutical companies note that insurers may not have the best interests of sick patients in mind. It is far easier to make sick people pay when they need care than to raise premiums on everyone. Insurance companies respond that low co-pays lead to higher prices for medications and to shifts from less expensive to more expensive medications, even if cheaper drugs have similar efficacy.

One way policy can help is by encouraging more price competition. Compared with Europe, the United States has been very slow in approving “biosimilars” (the biological equivalent of generic drugs). And litigation has kept even some approved biosimilars off the market. Accelerating the review time for new, competing medications would also help. And the rush into precision care—more than 400 immunotherapy drugs are in development—may limit the profits that can be made. The more drugs there are in a particular therapeutic area, the more competitive pricing.

The precision medicine era is a test of the health system and the biomedical innovation system. Can we turn the revolution in knowledge of the human body into meaningful improvements in population health at appropriate prices? The outcome of this test is immensely important for society.