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The Health Impact of, and access to, New Drugs in Korea

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We perform an econometric assessment of the role that pharmaceutical innovation—the introduction and use of new drugs—has played in improving the health of Koreans, by investigating whether diseases for which more new drugs were launched had larger subsequent increases in longevity and smaller subsequent increases in hospitalization. Drugs launched during 1993-2012 are estimated to have increased mean age at death from all diseases by 1.71 years between 1995 and 2015 and 1.09 years between 2005 and 2015. We also estimate that new drugs increased the five-year relative survival rate from all cancers combined by 23.2 percentage points—78.5% of the total increase—between 1993-1995 and 2011-2015, and that new drugs launched during 2008-2010 reduced the number of hospital days in 2017 by 13.0 million.
If the drugs launched during 2003-2012 had had no effect on other medical expenditure in 2015, the cost per life-year gained would not have exceeded 6332 USD. Therefore, even if we ignore the effect of new drugs on hospital utilization, the drugs launched during 2003-2012 were very cost–effective, overall. When reduced hospital utilization is accounted for, the evidence indicates that, in the long run, pharmaceutical innovation was cost-saving as well as life-year saving.

Keywords: Longevity, Pharmaceutical, Innovation, Korea, Hospitalization, Cancer
JEL Classification: J11, O33, L65

I. INTRODUCTION

The health status of Koreans has improved significantly during the past few decades. Life expectancy at birth increased from 78.17 years in 2005 to 82.02 years in 2015. Yang et al. (2010) concluded that rapid increases in life expectancy in South Korea during the period 1970-2005 were mostly achieved by reductions in infant mortality and in diseases related to infections and blood pressure. But reductions in infant mortality account for a very small part of recent increases in life expectancy at birth. The ratio of the 1999-2009 increase in life expectancy at age 1 to the 1999-2009 increase in life expectancy at birth was 96% for males and 93% for females (Statistics

Korea, 2010). Also, the 5-year relative survival rate of Korean patients diagnosed with cancer increased from 41.2% in 1993-1995 to 70.7% in 2011-2015 (Jung et al., 2018).

The purpose of this study is to assess econometrically the role that pharmaceutical innovation—the introduction and use of new drugs—has played in improving the health of Koreans. During the period 1988-2018, 775 new drugs (new molecular entities[1]) were launched in Korea: about 25 new drugs per year, on average.[2] The vast majority of new drugs launched in Korea were developed in other countries. Hence if life-years were gained by Koreans from the launch of new drugs, they might be considered "gains from international trade."

Longevity increase is a very important part of economic growth, broadly defined. Nordhaus (2005) argued that "improvements in health status have been a major contributor to economic welfare over the twentieth century. To a first approximation, the economic value of increases in longevity in the last hundred years is about as large as the value of measured growth in non-health goods and services." There is a consensus among macroeconomists that technological progress (which includes the introduction of new products) is the principal source of economic growth. Jones (2002) argued that "long-run growth is driven by the discovery of *new ideas* throughout the world."[3] Aghion and Howitt (2005) said that "technological progress, the mainspring of long-run economic growth, comes from innovations that generate *new products*, processes and markets." Grossman and Helpman (1991) developed "a model of repeated *product improvements* in a continuum of sectors. Each product follows a

[1] New Molecular Entities (NMEs) are compounds that emerge from the process of medicine discovery, that are not a version or derivative of an existing, previously investigated/approved substance. They have promising activity against a particular target thought to be important in a disease. <https://www.eupati.eu/glossary/new-molecular-entity/> (accessed February 21, 2020) Here are 3 examples of NMEs: (1) Tenofovir, a medication used to treat chronic hepatitis B and to prevent and treat HIV/AIDS, was approved for use in the United States in 2001, and first sold in Korea in 2012. (2) Linagliptin, a medication used to treat diabetes mellitus type 2, was approved for medical use in the United States in 2011, and first sold in Korea in 2016. (3) Sofosbuvir, a medication used to treat hepatitis C, was approved for medical use in the United States in 2013, and first sold in Korea in 2016.

[2] These figures refer to the number of post-1981 new chemical entities (NCEs) launched in Korea. A post-1981 NCE is an NCE that was first launched anywhere in the world after 1981.

[3] The discovery of new ideas could increase economic output for two different reasons. First, output could simply be positively related to the quantity (and variety) of ideas ever discovered. Second, output could be positively related to the (mean or maximum) quality of ideas ever discovered, and new ideas may be better (of higher quality), on average, than old ideas.

stochastic progression up a quality ladder." Bresnahan and Gordon (1996) said that "*new goods* are at the heart of economic progress." As noted by Jovanovic and Yatsenko (2012), in "the Spence–Dixit–Stiglitz tradition…*new goods* [are] of higher quality than old goods" [emphasis added].

Most scholars agree with Jones' (1998, pp. 89-90) statement that "technological progress is driven by research and development (R&D) in the advanced world." Dorsey et al. (2010) showed that, in 2008, 88% of private U.S. biomedical research expenditure was funded by pharmaceutical and biotechnology firms; the remaining 11% was funded by medical device firms.

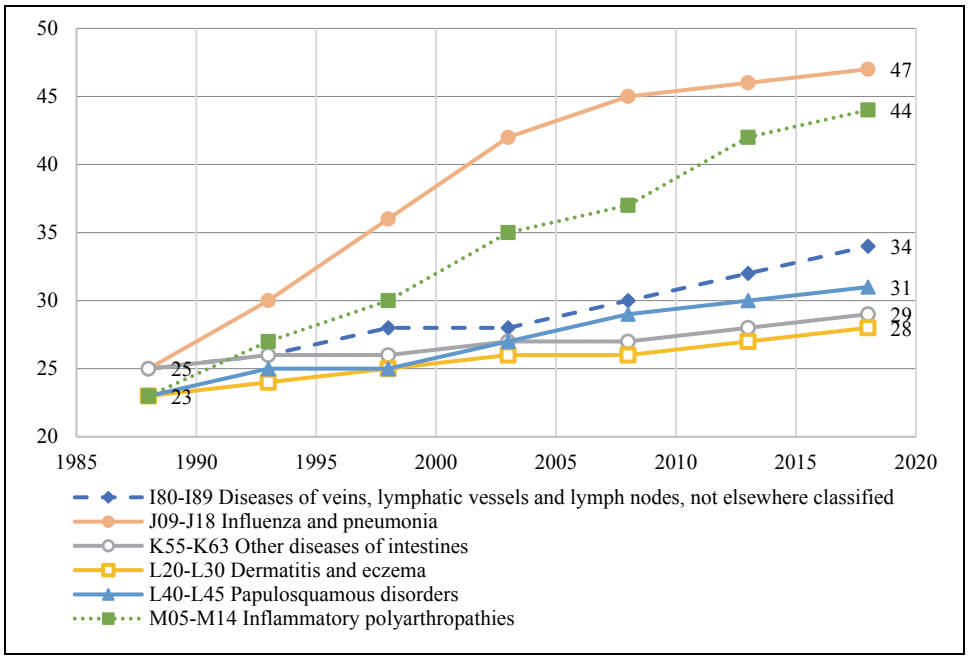
The analysis will be performed using a difference-in-differences (or two-way fixed effects) research design: we will investigate whether diseases for which more new drugs were launched had larger subsequent increases in longevity and smaller subsequent increases in hospitalization. This design controls for the effects of general economic and societal factors (e.g. income, education, and behavioral risk factors), to the extent that those effects are similar across diseases, e.g. smoking increases mortality from respiratory and cardiovascular disease as well as lung cancer, and education reduces mortality from all diseases.

The number of new drug launches varied considerably across diseases. For example, as shown in Figure 1, during the period 1988-2018, 22 new drugs for treating influenza and pneumonia, and 21 new drugs for treating inflammatory polyarthropathies, were launched. Only 5 new drugs for treating dermatitis and eczema, and 4 new drugs for treating other diseases of intestines (ICD-10 block K55-K63), were launched.

We will analyze the impact that new drug launches had on three important health outcomes: (1) mean age at death from all types of diseases; (2) cancer survival rates; and (3) hospitalization from all types of diseases. We will also provide evidence about how access to new drugs in Korea compares to access in other "high-income" (as defined by the World Bank) countries.

In the next section, we will describe the econometric models that we will use to assess the role that pharmaceutical innovation played in reducing mortality and hospitalization in Korea. The data sources used to estimate these models are discussed on Section III. Empirical results are presented in Section IV. Some implications of the estimates, and evidence about access to new drugs in Korea, are discussed in Section V. Section VI provides a summary.

Figure 1. Number of Drugs used to Treat 6 Diseases ever Launched in Korea, 1988-2018



Source: Author's calculations based on data contained in Theriaque database and IQVIA New Product Focus and MIDAS databases.

II. METHODS

1. Mean Age at Death from All Types of Diseases

To assess the impact that pharmaceutical innovation had on mean age at death from all types of diseases, we will estimate models based on the following 2-way fixed effects equation:

$$AGE\_DEATH_{dt} = \beta_k \, CUM\_DRUG_{d,t-k} + \alpha_d + \delta_t + \varepsilon_{dt} \qquad (1)$$

where

AGE_DEATH_{dt} = mean age at death from disease d in year t (t = 1995, 2005, 2015)

$CUM\_DRUG_{d,t-k} = \sum_m IND_{md} LAUNCHED_{m,t-k}$ = the number of chemical substances to treat disease d that had been launched in Korea by the end of year t-k (k = 0, 1, 2,…)

IND_{md} = 1 if chemical substance m is used to treat (indicated for) disease d [4]
= 0 if chemical substance m is not used to treat (indicated for) disease d

$LAUNCHED_{m,t-k}$ = 1 if chemical substance m had been launched in Korea by the end of year t-k
= 0 if chemical substance m had not been launched in Korea by the end of year t-k

α_d = a fixed effect for disease d

δ_t = a fixed effect for year t

Eq. (1) may be considered a health production function (Koç, 2004), and the number of chemical substances ever launched may be considered a measure of the stock of pharmaceutical "ideas."

The measure of longevity that is the dependent variable in eq. (1) is mean age at death. An alternative, and better known, measure of longevity is life expectancy at birth.[5] Mean age at death can be computed for specific diseases, whereas life expectancy at birth cannot. However, the 2005-2015 change in life expectancy at birth is strongly positively correlated (p-value < .0001) across countries with the 2005-2015 change in mean age at death (from all diseases combined). Appendix Figure 1 shows a bubble plot of this relationship based on data for 35 European countries.

The launch of a drug indicates that patients *could* have been treated with that drug, not necessarily that patients *were* treated with that drug. We would prefer to estimate models in which the explanatory variables measured the drugs *actually used* to treat

[4] Many drugs have multiple indications: 50% of drugs have 2 or more indications (causes of disease in the WHO Global Health Estimates disease classification), and 7% of drugs have 5 or more indications.

[5] Mean age at death represents the actual mean age at which patients died in a given year. Life expectancy at birth represents the hypothetical mean number of years until death of patients born in a given year.

patients, by disease, and year. We have annual data for 2007-2017 on the utilization of each drug in Korea. However, many drugs have multiple indications—50% of drugs have 2 or more indications (causes of disease in the WHO Global Health Estimates disease classification), and 7% of drugs have 5 or more indications—and our data do not enable us to determine how often each drug was used for each of its indications.

Since patients can access drugs that have been included in the National Health Insurance System (NHIS) of Korea with less financial burden, it might also be preferable to replace $CUM\_DRUG_{d,t-k}$ with $CUM\_NHIS_{d,t-k}$, where $CUM\_NHIS_{d,t-k}$ = the number of chemical substances to treat disease d that had been included in the NHIS by the end of year t-k. Unfortunately, we were unable to obtain data on the year in which each chemical substance was included in the NHIS.[6] But $CUM\_DRUG_{d,t-k}$ is likely to be fairly highly correlated with $CUM\_NHIS_{d,t-k}$.

Since our drug launch variables are imperfect measures of exposure to pharmaceutical innovation, the estimated coefficients on those variables are likely to be biased towards zero, and our estimates of the number of life-years saved by new drugs are likely to be conservative. Here is the first paragraph of the eminent MIT econometrician Jerry Hausman's (2001 p. 57) article on mismeasured variables in econometric analysis:

> The effect of mismeasured variables in statistical and econometric analysis is one of the oldest known problems, dating from the 1870s in Adcock (1878). In the most straightforward regression analysis with a single regressor variable, the least squares estimate is downward biased in magnitude toward zero. While a mismeasured right-hand side variable creates this problem, a mismeasured left-hand side variable under classical assumptions does not lead to bias. The only result is less precision in the estimated coefficient and a lower t-statistic.

Due to data limitations, $CUM\_DRUG_{c,t-k}$ is the only disease-specific, time-varying regressor in eq. (1). If the data were available, we would like to include other regressors in eq. (1), e.g. the number of non-pharmaceutical medical innovations (e.g. medical device innovations) that had been launched in Korea.[7] Failure to control for non-

[6] Those data may be available upon request to the NHIS.

[7] Some major studies have not found there to be health benefits of some nonpharmaceutical innovations. A large U.S. government study found that drug therapy alone may save lives as effectively as bypass or stenting procedures (Kolata, 2019). Also, data from the Prostate, Lung, Colorectal and Ovarian randomized screening trial showed that, after 13 years of follow up, men who underwent annual prostate cancer screening with prostate-specific antigen testing and digital

pharmaceutical medical innovation (e.g. innovation in diagnostic imaging, surgical procedures, and medical devices) is also unlikely to bias estimates of the effect of pharmaceutical innovation on the burden of disease, for two reasons. First, as noted earlier, 88% of privately-funded U.S. funding for biomedical research came from pharmaceutical and biotechnology firms (Dorsey et al., 2010).[8] Second, previous research based on U.S. data (Lichtenberg, 2014a; 2014b) indicated that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation. Third, a study of pharmaceutical innovation and longevity growth in 30 developing and high-income countries during the period 2000-2009 (Lichtenberg, 2014c) found that controlling for ten other potential determinants of longevity change (real per capita income, the unemployment rate, mean years of schooling, the urbanization rate, real per capita health expenditure (public and private), the DPT immunization rate among children ages 12-23 months, HIV prevalence and tuberculosis incidence) *increased* the estimated effect of pharmaceutical innovation on life expectancy by about 32%.

We will use data for three years: 1995, 2005 and 2015.[9] Substituting the first and last values of t into eq. (1) yields:

$$AGE\_DEATH_{d,1995} = \beta_k \, CUM\_DRUG_{d,1995\text{-}k} + \alpha_d + \delta_{1995} + \varepsilon_{d,1995} \quad (2)$$

$$AGE\_DEATH_{d,2015} = \beta_k \, CUM\_DRUG_{d,2015\text{-}k} + \alpha_d + \delta_{2015} + \varepsilon_{d,2015} \quad (3)$$

Subtracting eq. (2) from eq. (3) yields:

$$\Delta AGE\_DEATH_d = \beta_k \, \Delta CUM\_DRUG\_k_d + \delta + \varepsilon_d' \quad (4)$$

where

rectal examination had a 12 percent higher incidence of prostate cancer than men in the control group but the same rate of death from the disease. No evidence of a mortality benefit was seen in subgroups defined by age, the presence of other illnesses, or pre-trial PSA testing (National Cancer Institute, 2012).

[8] Much of the rest came from the federal government (i.e. the NIH), and new drugs often build on upstream government research (Sampat and Lichtenberg, 2011). The National Cancer Institute (2019) says that it "has played a vital role in cancer drug discovery and development, and, today, that role continues."

[9] 1995 and 2015 are the first and last years for which the ICD10 disease classification was used in available Korean mortality data.

$$\Delta AGE\_DEATH_d = AGE\_DEATH_{d,2015} - AGE\_DEATH_{d,1995}$$

$$\Delta CUM\_DRUG\_k_d = CUM\_DRUG_{d,2015-k} - CUM\_DRUG_{d,1995-k}$$

$$\delta = \delta_{2015} - \delta_{1995}$$

$$\varepsilon_d' = \varepsilon_{d,2015} - \varepsilon_{d,1995}$$

Eq. (4) is a simple regression of the 20-year (1995-2015) *change* in mean age at death from disease d on the change in the number of drugs that were used to treat disease d that had ever been launched k years earlier, i.e. on the number of drugs used to treat disease d that were launched during the years 1995–k+1 to 2015-k.[10] The intercept of eq. (4) is an estimate of the change in mean age at death in the absence of pharmaceutical innovation (i.e. if mean (ΔCUM_DRUG_k) = 0), so [mean (ΔAGE_DEATH) - δ] is an estimate of the increase in mean age at death attributable to pharmaceutical innovation. To address the issue of heteroskedasticity, eq. (4) will be estimated by weighted least squares, weighting by $1/((1/N\_DEATHS_{d,1995}) + (1/N\_DEATHS_{d,2015}))$, where N_DEATHS_{dt} = the number of deaths caused by disease d in year t. The diseases are ICD-10 blocks, e.g. I00-I02 Acute rheumatic fever or J09-J18 Influenza and pneumonia).

In addition to estimating models of the 20-year (1995-2015) change in mean age at death, we will estimate models of the 10-year (2005-2015) change in mean age at death.

There is likely to be a lag between the launch of a new drug and its maximum impact on mean age at death. Utilization of recently-launched drugs tends to be much lower than utilization of drugs launched many years earlier. Evidence about the shape of the drug-age (number of years since launch) drug-utilization profile can be obtained by estimating the following equation:

$$\ln(N\_SU_{mn}) = \rho_m + \pi_n + \varepsilon_{mn} \quad (5)$$

where

N_SU_{mn} = the number of standard units of molecule m sold in Korea n years after it was first launched (n = 0, 1,…, 20)

[10] The parameter δ in eq. (4) is an estimate of the change in mean age at death in the absence of any drug launches between 2005 – k and 2015 – k.

ρ_m = a fixed effect for molecule m

π_n = a fixed effect for age n

The expression $\exp(\pi_n - \pi_{10})$ is a "relative utilization index": it is the mean ratio of the quantity of a drug sold n years after it was launched to the quantity of the same drug sold 10 years after it was launched. We estimated eq. (5), using annual data for the period 2007-2017 on 631 molecules. Estimates of the "relative utilization index" are shown in Figure 2. These estimates indicate that utilization of a drug reaches a peak about 16-18 years after it was launched. It is used about twice as much then as it was 3-4 years after launch.[11,12]

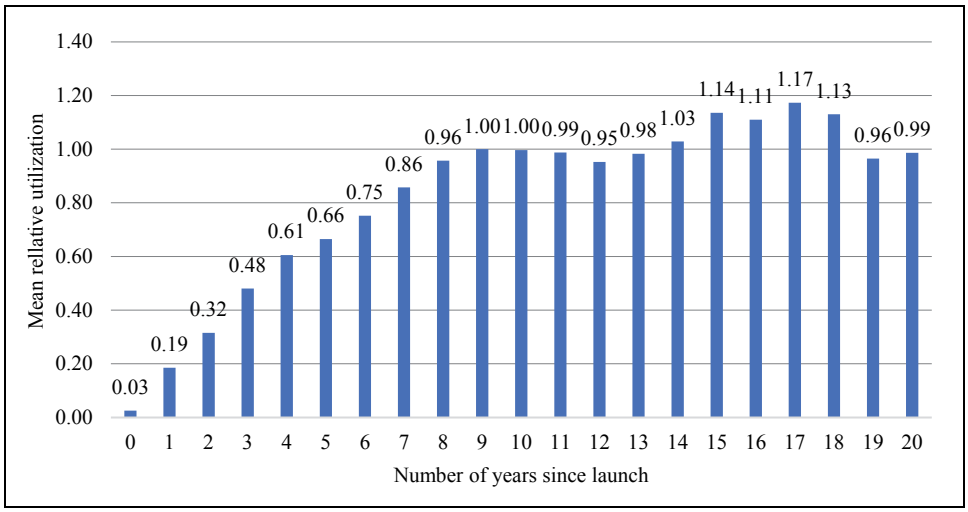
Due to gradual diffusion of new drugs, the maximum impact of a drug on mean age at death is likely to occur years after it was launched, but the peak effect could occur either more than or less than 16-18 years after launch. The lag might be longer because some drugs for chronic diseases (e.g. statins) may have to be consumed for several years to achieve full effectiveness. But the lag might be shorter because the impact of a drug on mean age at death is likely to depend on its quality (or effectiveness) as well as on its quantity (utilization), and drugs launched more recently are likely to be of higher quality than earlier-vintage drugs.[13]

[11] The estimate of a 16-18 year lag from drug launch to peak drug utilization in Korea is 8 years longer than the average 8-10 year lag in 22 countries (Australia, Austria, Belgium, Brazil, Canada, Switzerland, Chile, Colombia, Germany, Ecuador, Spain, Finland, France, United Kingdom, Ireland, Italy, Japan, Mexico, Portugal, Singapore, Sweden, and the U.S.) estimated in Lichtenberg (2018).

[12] Diffusion of cancer (WHO ATC anatomical main group L) drugs is slower than diffusion of drugs in general: cancer drugs are used 6 times as much 16-18 years after launch as they are 3-4 years after launch.

[13] The impact on mortality may depend on the interaction (quantity * quality) of the two variables. The mortality impact will increase with respect to drug age (time since launch) if the rate of increase of quantity with respect to age is greater than the rate of decline of quality with respect to age; otherwise the mortality impact will decline.

Figure 2. Mean Ratio of Quantity of a Drug Sold k Years after Launch to Quantity of the Same Drug Sold 10 Years after Launch



2. 5-year Relative Cancer Survival Rates

To assess the impact that pharmaceutical innovation had on 5-year relative cancer survival rates, we will estimate models based on the following 2-way fixed effects equation:

$$\ln(SURV_{st}/(1 - SURV_{st})) = \beta_k \ln(CUM\_DRUG_{s,t-k}) + \alpha_s + \delta_t + \varepsilon_{st} \quad (6)$$

where

$SURV_{st}$ = the 5-year relative survival rate of patients diagnosed with cancer at cancer site s (breast, colon, lung, etc.) between year t and year t+2 or t+4 (t = 1993, 1996, 2011)[14]

$CUM\_DRUG_{s,t-k}$ = the number of chemical substances to treat cancer at site s that had been launched in Korea by the end of year t-k (k = 0, 1, 2,…)

[14] The survival rates cover three periods: patients diagnosed in 1993-1995, 1996-2000, and 2011-2015.

The following model of the 19-year (1993-1995 to 2011-2015) *change* in the log-odds of cancer survival can be derived from eq. (6):

$$\ln(SURV_{s,2011}/(1-SURV_{s,2011})) - \ln(SURV_{s,1993}/(1-SURV_{s,1993})) = \beta_k [\ln(CUM\_DRUG_{s,2011-k}) - \ln(CUM\_DRUG_{s,1993-k})] + \delta + \varepsilon_s' \quad (7)$$

We will also estimate a similar model of the 15-year (1996-2000 to 2011-2015) change in the log-odds of cancer survival. To address the issue of heteroskedasticity, eq. (7) will be estimated by weighted least squares, weighting by $1/((1/INCIDENCE_{s,1999}) + (1/INCIDENCE_{s,2015}))$, where $INCIDENCE_{st}$ = the age-standardized incidence rate of cancer at site s in year t. Jung et al. (2018)'s cancer site classification will be used.

3. Hospital Utilization

Studies have shown that new drugs for Crohn's disease, transthyretin amyloid cardiomyopathy, and some types of cystic fibrosis have reduced hospitalization:

- Data from the Phase 3 IM-UNITI study showed that treatment with ustekinumab lowered the risk of Crohn's disease (CD)-related hospitalization, surgery, and the need for alternative biologic therapy in patients with moderate-to-severe CD when compared with placebo. At 2 years, patients in the ustekinumab q12w group were 52% less likely to be hospitalized or require surgery vs patients in the placebo group (hazard ratio [HR] 0.477; 95% CI, 0.238, 0.957; P =.033). Patients in the ustekinumab q8w group were 40% less likely to be hospitalized or require surgery (HR 0.601; 95% CI, 0.411, 0.879; P =.006).[15]
- A phase three clinical trial has shown that tafamidis significantly reduces deaths and hospitalizations in patients with transthyretin amyloid cardiomyopathy, a progressive form of heart failure. Compared to a placebo, the drug reduced deaths by 30 percent and reduced cardiovascular-related hospitalizations by 32 percent.[16]
- Ivacaftor is a small molecule drug originally developed to treat the G551D CFTR gene variant that causes about 3-4% of Cystic fibrosis (CF) cases. Inpatient

[15] <https://www.empr.com/news/stelara-ustekinumab-crohns-disease-hospitalization-surgery-reduction-im-uniti/article/770888/> (accessed February 21, 2020)

[16] <https://www.nyp.org/news/Drug-Reduce-Deaths-Hospitalizations-Underdiagnosed-Heart-Failure> (accessed February 21, 2020)

admissions decreased by 55% from 0.57 inpatient admissions per person-year pre-ivacaftor to 0.26 admissions post-ivacaftor, with similar decreases for children and adults.[17]

Other studies have provided more general evidence about cost offsets from prescription drug innovation. Lichtenberg (2009) analyzed the impact of pharmaceutical innovation on hospitalization for a single (albeit important) disease—cardiovascular disease—in 20 OECD countries during the period 1995-2003. Lichtenberg (2014d) analyzed the impact of pharmaceutical innovation on hospitalization for 131 medical conditions in a single country—the United States—during the period 1996-2010. The measure of pharmaceutical innovation used in both studies was the mean *vintage* of prescription drugs, i.e. the utilization-weighted mean world launch year (or FDA approval year) of drugs consumed. Both studies found that pharmaceutical innovation reduced hospitalization, and that the reduction in hospital cost from the use of newer drugs was considerably greater than the innovation-induced increase in pharmaceutical expenditure.

To assess the impact that pharmaceutical innovation had on hospital utilization in Korea, we will estimate models based on the following 2-way fixed effects equation:

$$\ln(DAYS_{dt}) = \beta_k \ln(CUM\_DRUG_{d,t-k}) + \alpha_d + \delta_t + \varepsilon_{dt} \quad (8)$$

where

$DAYS_{dt}$ = the number of days of hospital care[18] provided to patients with diagnosis d in year t (t = 2014, 2017)[19]

The following model of the 3-year *change* in hospital utilization can be derived from eq. (8):

[17] <https://blogs.cdc.gov/genomics/2018/05/08/evaluating-the-impact/> (accessed February 21, 2020)

[18] The number of days of hospital care equals the number of hospital discharges (or admissions) times average length of stay.

[19] Due to a change in the data source, there was a break in the hospital time series in 2014. From 2014, administrative data (the Health Insurance Review & Assessment Service, Statistics of Health Care Utilization) were used. Until 2013, patient survey data (The Patient Survey Report, produced by the Korea Institute for Health and Social Affairs, Ministry of Health and Welfare) were used. See OECD (2019a).

$$\Delta\ln(DAYS_d) = \beta_k \, \Delta\ln(CUM\_DRUG\_k_d) + \delta + \varepsilon_d \text{‘} \quad (9)$$

where

$$\Delta\ln(DAYS_d) = \ln(DAYS_{d,2017}) - \ln(DAYS_{d,2014})$$

$$\Delta\ln(CUM\_DRUG\_k_d) = \ln(CUM\_DRUG_{d,2017\text{-}k}) - \ln(CUM\_DRUG_{d,2014\text{-}k})$$

Eq. (9) will be estimated by weighted least squares, weighting by $1/((1/DAYS_{d,2014}) + (1/DAYS_{d,2017}))$. The disease classification is the Eurostat/OECD/WHO *International Shortlist for Hospital Morbidity Tabulation* (OECD, 2019b).

III. DATA SOURCES

Drug launch data. Data on the years in which post-1981 new chemical entities were first launched in Korea were obtained from IQVIA's *New Product Focus* database. Coverage of Korea began in 1988.

Drug indications data. Indications (coded by ICD-10) of chemical substances were obtained from Thériaque, a database produced by the French Centre National Hospitalier d'Information sur le Médicament (2019).[20]

Drug utilization and expenditure data. Data on the quantity (number of standard units) and value (in USD) of prescription drugs sold in Korea, by chemical substance and year (2007-2017) were obtained from the IQVIA MIDAS database. By combining MIDAS data on which drugs were sold in 2015 and *New Product Focus* data on new drug launches during 1988-2015, we can estimate ("backcast") the number of drugs that had ever been launched for each disease by the end of each year (1987-2015).

Mortality from all diseases. Data on mean age at death and the number of deaths were constructed from data obtained from the WHO's Cause of Death Query online database (World Health Organization, 2019), a web-based system for extracting trend series detailed cause-of-death data. Mean age at death increased from 63.6 in 1995 to 68.7 in 2005 and to 73.3 in 2015. Data on mortality and the number of drugs ever launched, by ICD-10 block, are shown in Appendix Table 1.

Cancer survival and incidence. Data on cancer survival and incidence rates, by cancer site and year, were obtained from Jung et al. (2018). Data on cancer survival and

[20] Thériaque provides data only on labeled indications; it does not provide data on off-label indications.

incidence rates and the number of drugs ever launched, by cancer site, are shown in Appendix Table 2.

Hospitalization data. Data on the number of hospital discharges and average length of stay, by diagnosis and year (2014-2017), were obtained from the *OECD Health Statistics database* **(**OECD, 2019c). Data on hospital utilization and the number of drugs previously launched, by diagnosis, are shown in Appendix Table 3.

IV. EMPIRICAL RESULTS

1. Mean Age at Death from All Types of Diseases

Estimates of the parameter β_k from the model of the 20-year (1995-2015) change in mean age at death from all diseases (eq. (4)) are presented in rows 1-8 of Table 1. Each estimate is from a separate model. The table shows estimates for 8 values (k = 0, 1,…, 6, 7) of the lag (k) from cumulative drug launches to mean age at death. All 8 estimates are positive and statistically significant (p-value < .05).[21] The largest, and most significant, estimate is for k = 3: the 1995-2015 change in mean age at death from a disease is most strongly related to the 1992-2012 change in the number of drugs used to treat the disease ever launched, i.e. to the number of drugs launched during 1993-2012.

The weighted (by $1/((1/N\_DEATHS_{d,1995}) + (1/N\_DEATHS_{d,2015}))$) mean value of ΔAGE_DEATH is 8.39, and the intercept of eq. (4) when k = 3 is 6.67, so the 1995-2015 increase in mean age at death attributable to drugs launched during 1993-2012 is 1.71 (=8.39 – 6.67) years. This is about one fifth (20.4%) of the actual increase in mean age at death during that period. There were 275,854 deaths in Korea in 2015. If drugs launched during 1993-2012 did not affect the total number of deaths or their distribution across diseases, those drug launches increased the number of life-years (or reduced the number of life-years lost) in 2015 by 472,990 (= 1.71 years * 275,854 deaths).

[21] Since Korean drug launch data are not available for years prior to 1988, the longest lag we can estimate is 7 years.

Table 1. Weighted Least-squares Estimates of the Parameter β_k from the Model of the Change in Mean Age at Death from All Diseases (eq. (4)): $\Delta AGE\_DEATH_d = \beta_k \Delta CUM\_DRUG\_k_d + \delta + \varepsilon_d$'

row	k	β_k	Standard Error	t Value	Pr > |t|
Dependent variable: change in mean age at death, 1995-2015					
1	0	**0.123**	**0.060**	**2.06**	**0.0415**
2	1	**0.134**	**0.059**	**2.26**	**0.0258**
3	2	**0.117**	**0.056**	**2.10**	**0.0383**
4	3	**0.144**	**0.055**	**2.61**	**0.0104**
5	4	**0.127**	**0.052**	**2.45**	**0.0158**
6	5	**0.122**	**0.050**	**2.45**	**0.0159**
7	6	**0.120**	**0.049**	**2.42**	**0.0171**
8	7	**0.110**	**0.048**	**2.30**	**0.0236**
Dependent variable: change in mean age at death, 2005-2015					
9	0	**0.192**	**0.058**	**3.32**	**0.0013**
10	1	**0.181**	**0.053**	**3.42**	**0.0009**
11	2	**0.178**	**0.051**	**3.52**	**0.0007**
12	3	**0.208**	**0.056**	**3.73**	**0.0003**
13	4	**0.204**	**0.058**	**3.51**	**0.0007**
14	5	**0.177**	**0.052**	**3.43**	**0.0009**
15	6	**0.162**	**0.045**	**3.60**	**0.0005**
16	7	**0.133**	**0.043**	**3.10**	**0.0025**

N = 104.

Estimates in bold are statistically significant (p-value < .05).

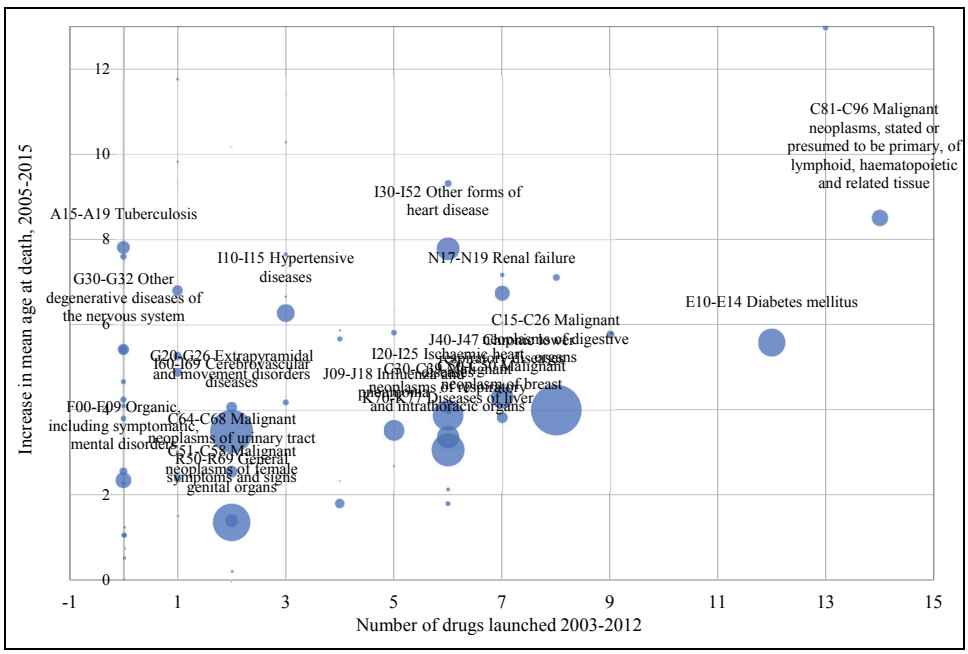
In rows 1-8, observations are weighted by $1/((1/N\_DEATHS_{d,1995}) + (1/N\_DEATHS_{d,2015}))$, where N_DEATHS_{dt} = the number of deaths caused by disease d in year t. In rows 9-16, observations are weighted by $1/((1/N\_DEATHS_{d,2005}) + (1/N\_DEATHS_{d,2015}))$.

Estimates of the parameter β_k from the model of the 10-year (2005-2015) change in mean age at death from all diseases are presented in rows 9-16 of Table 1. Once again, all 8 estimates are positive and statistically significant (p-value < .01), and the most significant, estimate is for k = 3: the 2005-2015 change in mean age at death from a disease is most strongly related to the 2002-2012 change in the number of drugs used to treat the disease ever launched, i.e. to the number of drugs launched during 2003-2012. Figure 3 is a bubble plot of the correlation across diseases between the number of drugs launched during 2003-2012 and the 2005-2015 increase in mean age at death. The estimate of β_3 in row 12 is 45% larger than the estimate of β_3 in row 4. A possible explanation for this is that the average quality of drugs launched during 2003-2012 was higher than the average quality of drugs launched during 1993-2002.

The weighted (by $1/((1/N\_DEATHS_{d,2005}) + (1/N\_DEATHS_{d,2015}))$) mean value of ΔAGE_DEATH is 4.14, and the intercept of eq. (4) when k = 3 is 3.05, so the 2005-

2015 increase in mean age at death attributable to drugs launched during 2003-2012 is 1.09 (= 4.14 – 3.05) years.[22] Drugs launched during 2003-2012 are estimated to have increased mean age at death by slightly more than one year between 2005 and 2015. This is about one fourth (26.3%) of the actual increase in mean age at death during that period. If drugs launched during 2003-2012 did not affect the total number of deaths or their distribution across diseases, those drug launches increased the number of life-years (or reduced the number of life-years lost) in 2015 by 300,057 (= 1.09 years * 275,854 deaths).

Figure 3. Correlation across Diseases between Number of Drugs Launched during 2003-2012 and 2005-2015 Increase in Mean Age at Death



Bubble area is proportional to (1/((1/N_DEATHS$_{d,2005}$) + (1/N_DEATHS$_{d,2015}$))), where N_DEATHS$_{d,t}$ = the number of deaths due to disease d in year t.

[22] This figure is fairly similar to Lichtenberg's (2014c) 1.27-year estimate of the 2000-2009 increase in life expectancy at birth in 30 developing and high-income countries attributable to pharmaceutical innovation. That study was based on aggregate country-level data on all diseases combined, and the pharmaceutical innovation measure was the increase in the fraction of drugs consumed that were launched after 1990.

2. 5-year Relative Cancer Survival Rates

Estimates of the parameter β_k from the model of the 19-year (1993-1995 to 2011-2015) change in the log-odds of cancer survival (eq. (7)) are presented in rows 1-7 of Table 2. For $k \leq 3$, the estimates are not statistically significant. However, the estimates of β_4, β_5 and β_6 are positive and highly significant.[23] The 19-year change in the log-odds of cancer survival is most strongly related to the log change in the number of drugs ever launched 6 years earlier. Figure 4 is a bubble plot of the correlation across cancer sites between the 1988-2003 log change in the number of drugs ever launched and the log change in the 5-year relative survival rate, 1996-2000 to 2011-2015.

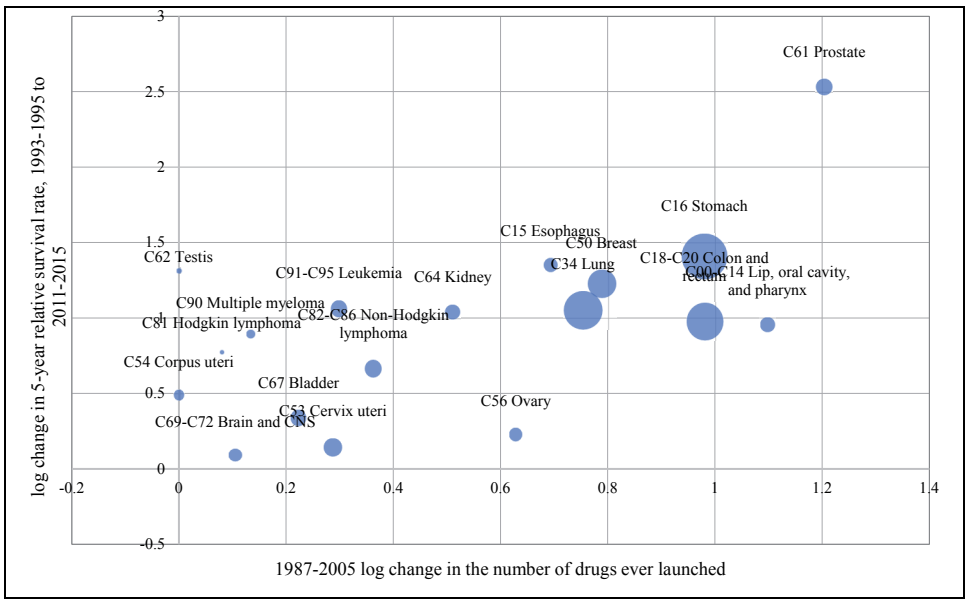
Table 2. Weighted least-squares estimates of the parameter β_k from the model of the the long-run change in the log-odds of cancer survival (eq. (7)):
$\ln(SURV_{s,2011}/(1 - SURV_{s,2011})) - \ln(SURV_{s,t0}/(1 - SURV_{s,t0})) = \beta_k [\ln(CUM\_DRUG_{s,2011-k}) - \ln(CUM\_DRUG_{s,t0-k})] + \delta + \varepsilon_s$'

row	k	β_k	Standard Error	t Value	Pr > |t|
		1993-1995 to 2011-2015			
1	0	0.239	0.329	0.73	0.4761
2	1	0.314	0.317	0.99	0.3349
3	2	0.051	0.309	0.17	0.8697
4	3	0.052	0.310	0.17	0.8689
5	4	**0.905**	**0.267**	**3.38**	**0.0038**
6	5	**0.896**	**0.268**	**3.34**	**0.0041**
7	6	**1.104**	**0.270**	**4.09**	**0.0008**
		1996-2000 to 2011-2015			
8	0	0.347	0.288	1.20	0.2439
9	1	0.278	0.285	0.97	0.3427
10	2	0.264	0.280	0.95	0.3567
11	3	0.201	0.270	0.74	0.4674
12	4	0.311	0.259	1.20	0.2449
13	5	0.211	0.270	0.78	0.4456
14	6	0.414	0.321	1.29	0.2136
15	7	**0.967**	**0.205**	**4.71**	**0.0002**
16	8	**0.952**	**0.204**	**4.66**	**0.0003**
17	9	**1.087**	**0.248**	**4.39**	**0.0005**

N = 18.
Estimates in bold are statistically significant (p-value < .01).
Observations are weighted by $1/((1/INCIDENCE_{s,1999}) + (1/INCIDENCE_{s,2015}))$, where $INCIDENCE_{st}$ = the age-standardized incidence rate of cancer at site s in year t.

[23] Because data on Korean drug launches before 1988 are not available, it is not possible to estimate models for k > 8.

Figure 4. Correlation across Cancer Sites between the 1987-2005 Log Change in the Number of Drugs ever Launched and the Log Change in the 5-year Relative Survival Rate, 1993-1995 to 2011-2015



Bubble area is proportional to by $1/((1/INCIDENCE_{s,1999}) + (1/INCIDENCE_{s,2015}))$, where $INCIDENCE_{st}$ = the age-standardized incidence rate of cancer at site s in year t.

Between 1993-1995 and 2011-2015, the five-year relative survival rate from all cancers combined increased by 29.5 percentage points, from 41.2% to 70.7%. The estimate of β_6 in row 4 of Table 2 indicates that 78.5% of this increase in the log-odds of survival was due to new drug launches during 1988-2005.[24] Hence, we estimate that new drugs launched during 1989-2003 increased the five-year relative survival rate from all cancers combined by 23.2 percentage points (= 78.5% * 29.5 percentage points).

[24] The weighted mean of the dependent variable of eq. (7) is 1.086. The intercept of eq. (7) when k = 6 is 0.234. This is an estimate of the 19-year change in the log-odds of cancer survival in the absence of any increase in the number of drugs ever launched 6 years earlier (when $[\ln(CUM\_DRUG_{s,2011-6}) - \ln(CUM\_DRUG_{s,1993-6})] = 0$). Hence the fraction of the increase in the log-odds of survival that was due to new drug launches during 1988-2005 is 78.5% (= 1 – (0.234/1.086)).

Estimates of the parameter β_k from the model of the 15-year (1996-2000 to 2011-2015) change in the log-odds of cancer survival (eq. (7)) are presented in rows 8-17 of Table 2. For $k \leq 6$, the estimates are not statistically significant. However, the estimates of β_7, β_8 and β_9 are positive and highly significant. The 15-year change in the log-odds of cancer survival is most strongly related to the log change in the number of drugs ever launched 7 years earlier. Between 1996-2000 and 2011-2015, the five-year relative survival rate from all cancers combined increased by 26.7 percentage points, from 44.0% to 70.7%. The estimate of β_7 in row 15 of Table 2 indicates that 75.7% of this increase in the log-odds of survival was due to new drug launches during 1990-2004. Hence, we estimate that new drugs launched during 1990-2004 increased the five-year relative survival rate from all cancers combined by 20.2 percentage points (= 75.7% * 26.7 percentage points).

3. Hospital Utilization

Estimates of the parameter β_k from the model of the 2014-2017 log change in hospital utilization (eq. (9)) are presented in Table 3. When $k \leq 5$, the estimate is not statistically significant, but when $6 \leq k \leq 9$, the estimates are negative and highly significant. The growth in the number of hospital days is inversely related across diseases to the growth in the number of drugs that had ever been launched 6-9 years earlier. It is most strongly related to the growth in the number of drugs that had ever been launched 7 years earlier. Figure 5 is a bubble plot of the correlation across diseases between the 2007-2010 log change in the number of drugs ever launched and the 2014-2017 log change in the number of hospital days.

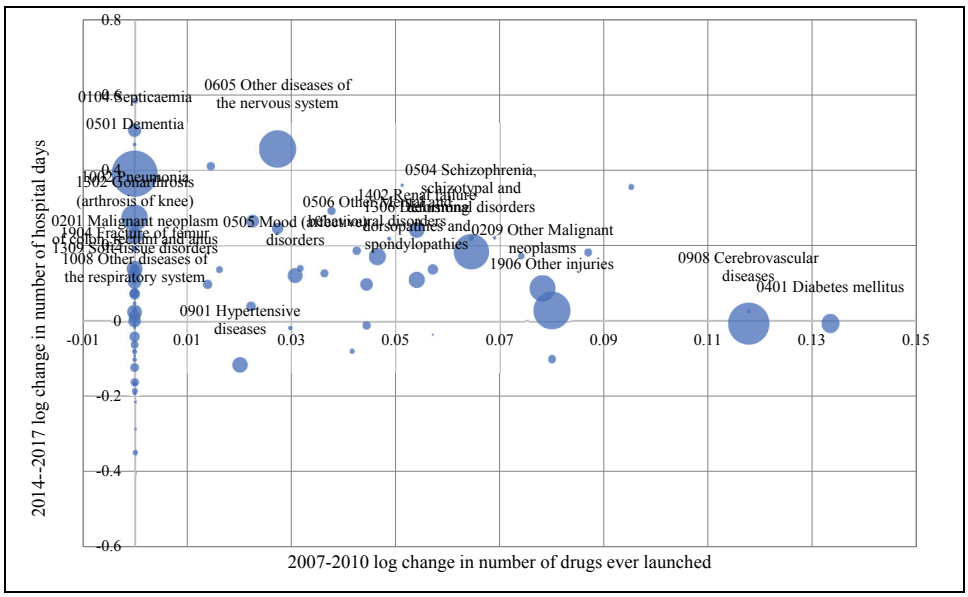
Between 2014 and 2017, the number of hospital discharges increased by 7%, from 8.20 million to 8.74 million, average length of stay increased by 9%, from 17.0 to 18.5 days, and the number of hospital days increased by 16%, from 139.4 million to 161.7 million. Our estimates imply that, if no new drugs had been launched during 2008-2010, the number of hospital days would have increased even more during 2014-2017, and the number of hospital days in 2017 would have been 8.1% higher than it actually was. We estimate that the new drugs that were launched during 2008-2010 reduced the number of hospital days in 2017 by 13.0 million (= 8.1% * 161.7 million).

Table 3. Weighted least-squares estimates of the parameter β_k from the model of the 2014-2017 log change in hospital utilization (eq. (9)):
$\Delta\ln(DAYS_d) = \beta_k \Delta\ln(CUM\_DRUG\_k_d) + \delta + \varepsilon_d$‘

k	β_k	Standard Error	t Value	Pr > |t|
0	-1.217	1.493	-0.82	0.4172
1	2.055	1.212	1.70	0.0933
2	-0.165	0.631	-0.26	0.7941
3	0.626	0.558	1.12	0.2651
4	-0.717	0.441	-1.63	0.1073
5	-0.656	0.418	-1.57	0.1201
6	**-1.004**	**0.279**	**-3.60**	**0.0005**
7	**-1.725**	**0.330**	**-5.22**	**<.0001**
8	**-1.702**	**0.337**	**-5.05**	**<.0001**
9	**-0.952**	**0.323**	**-2.95**	**0.0041**
10	-0.649	0.334	-1.95	0.0547

N = 92.
Estimates in bold are statistically significant (p-value < .01).
Observations are weighted by $1/((1/DAYS_{d,2014}) + (1/DAYS_{d,2017}))$, where $DAYS_{dt}$ = the number of days of hospital care provided to patients with diagnosis d in year t.

Figure 5. Relationship across Diseases between 2007-2010 Log Change in Number of Drugs ever Launched and 2014-2017 Log Change in number of Hospital Days



Bubble size is proportional to $1/((1/DAYS_{d,2014}) + (1/DAYS_{d,2017}))$, where $DAYS_{dt}$ = the number of days of hospital care provided to patients with diagnosis d in year t. To improve legibility, only the 20 largest diseases are labeled.

V. DISCUSSION

We estimated that drugs launched during 2003-2012 (which increased the number of drugs that had ever been launched between the end of 2002 and the end of 2012) increased mean age at death by 1.09 years between 2005 and 2015, and that they reduced the number of life-years lost in 2015 by 300,057. IQVIA data indicate that 2015 expenditure on drugs launched during 2003-2012 was 1.90 billion USD.[25] Hence if the drugs launched during 2003-2012 had had no effect on other medical expenditure in 2015, the cost per life-year gained would not have exceeded 6332 USD (= 1.90 billion USD / 300,057 life-years).[26]

As noted by Bertram et al. (2016), authors writing on behalf of the WHO's *Choosing Interventions that are Cost–Effective* project (WHO-CHOICE) suggested in 2005 that "interventions that avert one disability-adjusted life-year (DALY) for less than average per capita income for a given country or region are considered very cost–effective; interventions that cost less than three times average per capita income per DALY averted are still considered cost–effective."[27] Korea's per capita GDP was 27,105 USD in 2015, so these estimates indicate that, even if we ignore the effect of new drugs on hospital utilization, the drugs launched during 2003-2012 were very cost-effective, overall.

When the effect of new drugs on hospital utilization is accounted for, the evidence indicates that, in the long run, pharmaceutical innovation was cost-saving as well as life-year saving. We estimated that, if no new drugs had been launched during 2008-2010, the number of hospital days in 2017 would have been 8.1% higher than it actually was. It is reasonable to assume that hospital expenditure in 2017 would have

[25] This is 15% of IQVIA's estimate of total pharmaceutical expenditure in 2015: 12.98 billion USD. According to the International Federation of Pharmaceutical Manufacturers & Associations (2017), total sales of prescription drugs in Korea in 2014 was 12.67 billion USD.

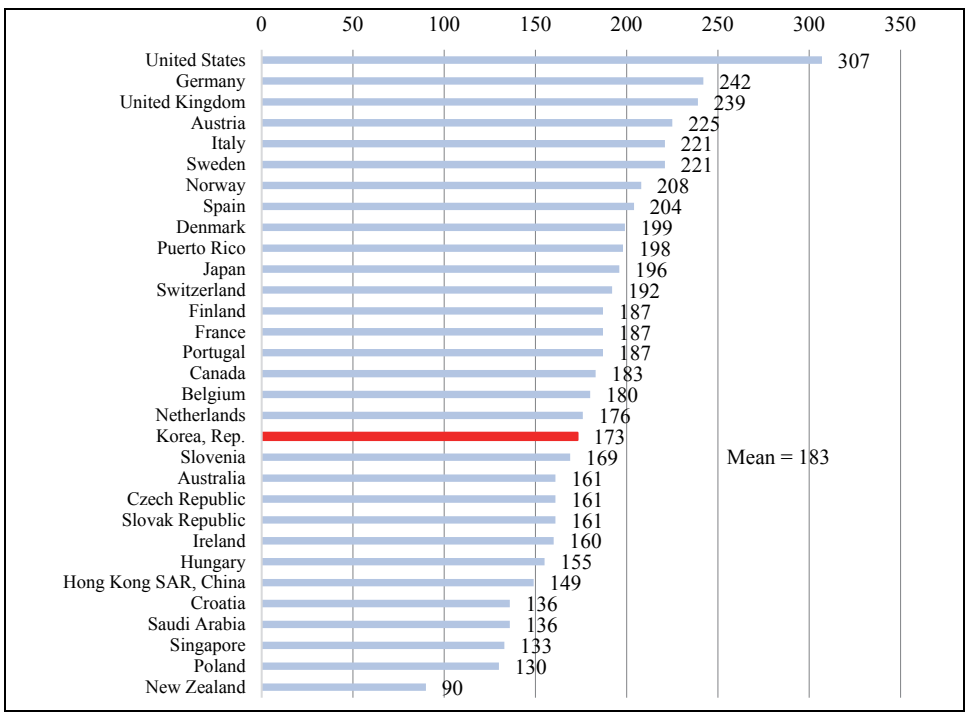
[26] This calculation does not account for the fact that expenditure on other (older) drugs may have been reduced by the use of these drugs.

[27] Other authorities use reasonably similar cost-effectiveness thresholds. The U.K. National Institute for Health and Care Excellence (2019) says that, "in general, interventions with an ICER [Incremental Cost-Effectiveness Ratio] of less than £20,000 per QALY gained are considered to be cost effective." The U.S. Department of Veterans Affairs Health Economics Resource Center (2019) says that "a cost-effectiveness analysis may indicate that Drug A is a good value relative to Drug B, because it has an incremental cost-effectiveness ratio (ICER) of $40,000 per Quality-Adjusted Life Year."

been 8.1% higher than it actually was. 2017 expenditure on inpatient curative and rehabilitative care was 37.4 billion USD, so new drugs launched during 2008-2010 may have reduced 2017 hospital expenditure by 3.0 billion USD (= 8.1% * 37.4 billion USD). This figure is 10.5 times as high as 2017 expenditure on drugs launched during 2008-2010 (287 million USD).[28]

We conclude by comparing the extent of access to new drugs in Korea to the extent of access in other high-income countries. One measure of access is the number of post-2005 new chemical entities (NCEs) sold. As shown in Figure 6, 173 post-2005 NCEs were sold in Korea in 2018. The average number of post-2005 NCEs sold in 31 high-income countries was 183. Korea ranked 19 out of 31 countries.

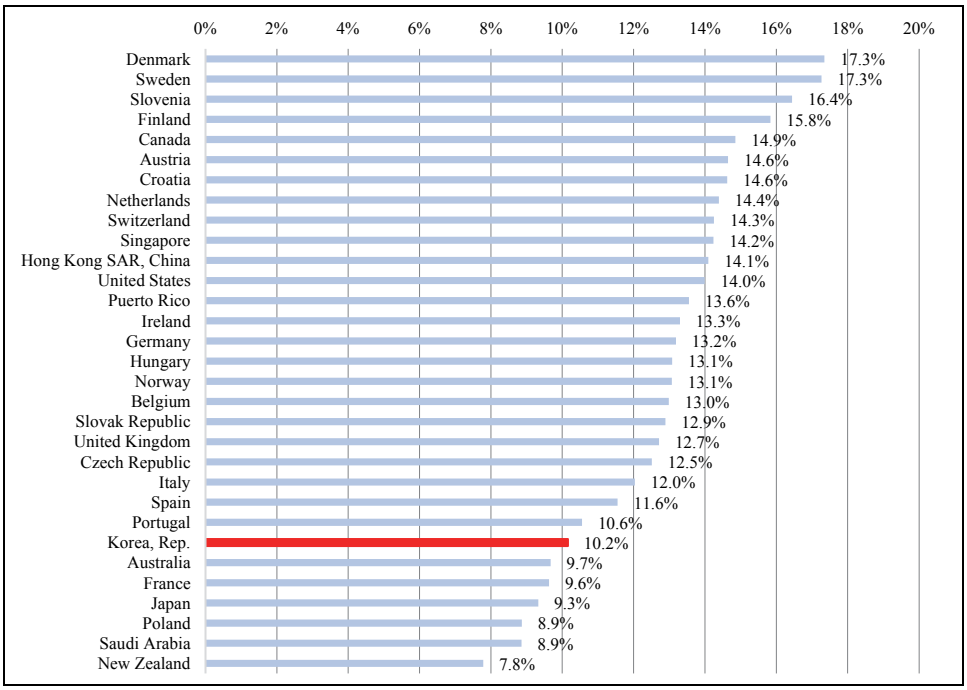
Figure 6. Number of Post-2005 Drugs Sold in 2018: High-income Countries



[28] This estimate is about twice as high as the estimate obtained in a study (Lichtenberg, 2018) based on a different type of 2-way fixed effects research design. That study examined the impact of new drug launches on hospitalization in 2015 for 67 diseases in 15 OECD countries, and found that the reduction in 2015 hospital expenditure that was attributable to post-1981 drug launches was 5.3 times as large as 2015 expenditure on those drugs.

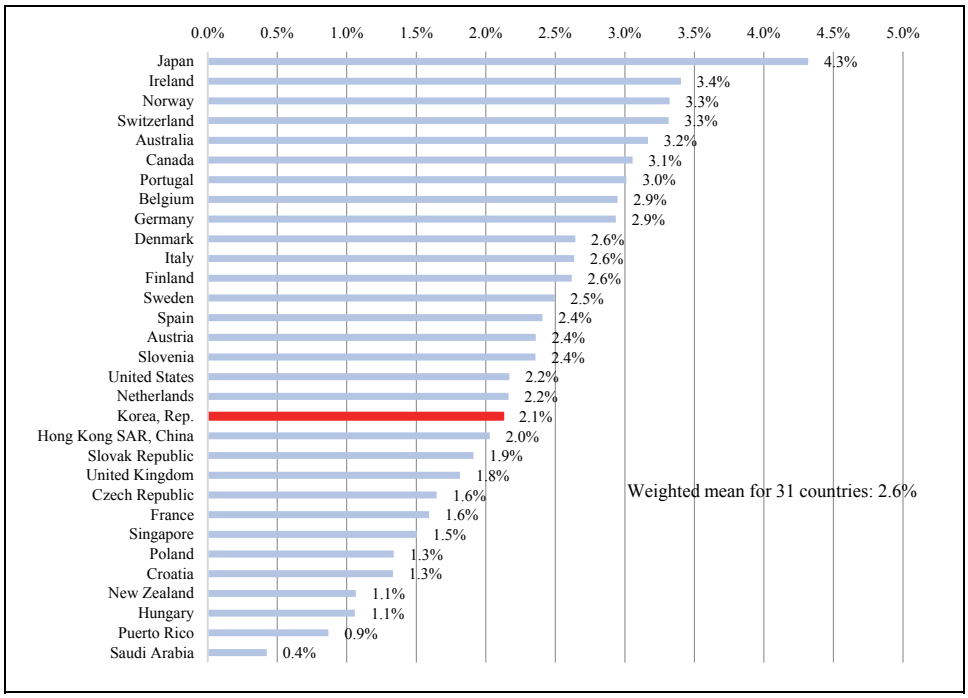
A second measure of access to new drugs is the ratio of the number of post-2005 drugs sold in 2018 to the total number of drugs sold in 2018. The total number of drugs sold in Korea in 2018 (1703) was higher than mean total number of drugs sold in the 31 countries (1455). Consequently, as shown in Figure 7, Korea's rank with respect to this ratio was lower (25 out of 31) than its rank with respect to the number of new (post-2005) drugs sold in 2018.

Figure 7. Number of Post-2005 Drugs Sold in 2018 as % of All Drugs Sold in 2018: High-income Countries



A third, and perhaps most meaningful, measure of access to new drugs is the fraction of standard units (e.g. the fraction of pills) sold that were units of post-2005 drugs. As shown in Figure 8, 2.1% of the standard units sold in Korea in 2018 were units of post-2005 drugs. This figure is lower than the weighted mean figure for 31 high-income countries: 2.6%. Korea ranked 19 out of 31 countries.

Figure 8. Number of Post-2005 Standard Units Sold in 2018 as % of Total Number of Standard Units Sold in 2018: High-income Countries



VI. SUMMARY AND CONCLUSIONS

We have performed an econometric assessment of the role that pharmaceutical innovation—the introduction and use of new drugs—has played in improving the health of Koreans, by investigating whether diseases for which more new drugs were launched had larger subsequent increases in longevity and smaller subsequent increases in hospitalization. The number of new drug launches varied considerably across diseases.

Drugs launched during 1993-2012 are estimated to have increased mean age at death by 1.71 years between 1995 and 2015. Drugs launched during 2003-2012 are estimated to have increased mean age at death by 1.09 years between 2005 and 2015. This is about one fourth of the actual increase in mean age at death during that period. If drugs launched during 2003-2012 did not affect the total number of deaths or their

distribution across diseases, those drug launches reduced the number of life-years lost in 2015 by 300,057. The average effect on mean age at death of a drug approved during the second half of the 1993-2012 period was 45% larger than the average effect of a drug approved during the entire period; a possible explanation for this is that the average quality of drugs launched during 2003-2012 was higher than the average quality of drugs launched during 1993-2002.

Between 1993-1995 and 2011-2015, the five-year relative survival rate from all cancers combined increased by 29.5 percentage points, from 41.2% to 70.7%. We estimated that new drugs launched during 1989-2003 increased the survival rate by 23.2 percentage points—78.5% of the total increase.

The 2014-2017 growth in the number of hospital days is inversely related across diseases to the growth in the number of drugs that had ever been launched 6-9 years earlier. It is most strongly related to the growth in the number of drugs that had ever been launched 7 years earlier. Our estimates implied that, if no new drugs had been launched during 2008-2010, the number of hospital days in 2017 would have been 8.1% higher than it actually was. We estimated that the new drugs that were launched during 2008-2010 reduced the number of hospital days in 2017 by 13.0 million.

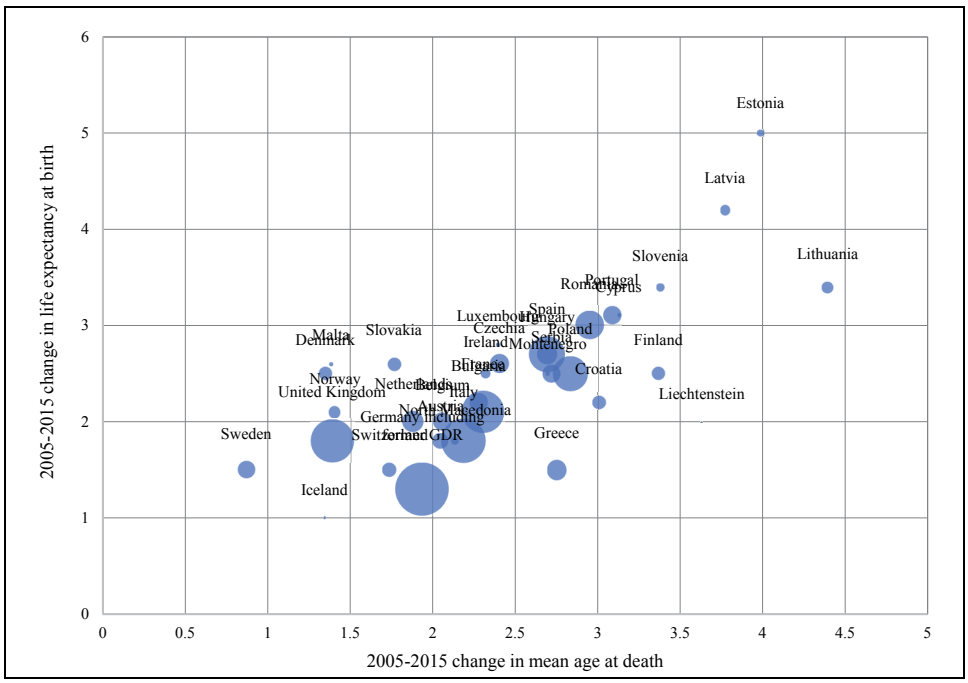
If the drugs launched during 2003-2012 had had no effect on other medical expenditure in 2015, the cost per life-year gained would not have exceeded 6332 USD. These estimates indicate that, even if we ignore the effect of new drugs on hospital utilization, the drugs launched during 2003-2012 were very cost–effective, overall.

When the effect of new drugs on hospital utilization is accounted for, the evidence indicates that, in the long run, pharmaceutical innovation was cost-saving as well as life-year saving. The estimated reduction in 2017 hospital expenditure attributable to new drugs launched during 2008-2010 was 10.5 times as high as 2017 expenditure on those drugs.

Access to new drugs in Korea in 2018 was somewhat lower than access to new drugs in other high-income countries. Korea ranked 19 out of 31 countries with respect to the fraction of standard units (e.g. the fraction of pills) sold that were units of post-2005 drugs.

APPENDIX

Appendix Figure 1. Correlation across 35 European Countries between 2005-2015 Changes in Mean Age at Death and Life Expectancy at Birth



Bubble size is proportional to the number of deaths in 2015.
Source: Author's calculations based on data from Eurostat database.

Appendix Table 1. Data on Mortality and Number of Drugs ever Launched, by ICD-10 Block

ICD-10 subchapter	Mean age at death		Number of deaths		Number of drugs ever launched					
	2005	2015	2005	2015	1990	1995	2000	2005	2010	2015
A00-A09 Intestinal infectious diseases	65.4	80.0	94	670	16	17	17	17	17	17
A15-A19 Tuberculosis	67.5	75.3	2893	2208	11	11	12	12	12	14
A20-A28 Certain zoonotic bacterial diseases	44.2	67.5	3	2	9	10	10	10	10	10
A30-A49 Other bacterial diseases	71.7	78.5	1174	3104	40	45	49	50	50	50
B00-B09 Viral infections characterized by skin and mucous membrane lesions	75.8	79.2	59	36	10	10	14	15	15	15
B15-B19 Viral hepatitis	56.8	66.1	841	667	5	5	7	10	12	13
B20-B24 Human immunodeficiency virus [HIV] disease	46.4	56.2	69	104	0	0	2	2	3	3
B25-B34 Other viral diseases	29.6	61.3	11	13	1	1	4	4	5	5
B35-B49 Mycoses	65.0	71.0	48	86	8	13	16	20	22	23
B50-B64 Protozoal diseases	38.5	68.8	3	15	13	13	14	14	14	14
C00-C14 Malignant neoplasms of lip, oral cavity and pharynx	64.4	67.0	844	1170	1	2	3	3	3	3
C15-C26 Malignant neoplasms of digestive organs	66.3	70.3	36412	39768	7	9	15	17	23	25
C30-C39 Malignant neoplasms of respiratory and intrathoracic organs	69.4	72.5	14633	18131	11	14	18	20	23	27
C43-C44 Melanoma and other malignant neoplasms of skin	68.3	72.9	313	500	2	2	3	5	5	9
C45-C49 Malignant neoplasms of mesothelial and soft tissue	57.6	63.4	401	626	11	13	13	13	16	21
C50-C50 Malignant neoplasm of breast	55.5	59.3	1589	2354	14	19	28	32	36	38
C51-C58 Malignant neoplasms of female genital organs	64.1	65.5	2155	2508	15	18	21	22	23	23
C60-C63 Malignant neoplasms of male genital organs	76.4	78.2	934	1731	10	13	15	16	16	20
C64-C68 Malignant neoplasms of urinary tract	70.8	73.4	1720	2696	11	12	13	14	14	16
C69-C72 Malignant neoplasms of eye, brain and other parts of central nervous system	55.1	60.0	1178	1289	9	9	9	10	10	11
C73-C75 Malignant neoplasms of thyroid and other endocrine glands	65.4	71.0	422	418	4	4	4	4	6	9
C76-C80 Malignant neoplasms of ill-defined, secondary and unspecified sites	68.8	74.6	832	1035	18	21	29	33	38	44
C81-C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	58.0	66.5	3251	4442	31	34	36	41	49	54
D00-D09 In situ neoplasms	72.5	78.8	3	26	10	12	13	14	19	19
D10-D36 Benign neoplasms	64.1	71.7	191	255	12	13	16	16	17	19

ICD-10 subchapter	Mean age at death		Number of deaths		Number of drugs ever launched					
	2005	2015	2005	2015	1990	1995	2000	2005	2010	2015
D37-D48 Neoplasms of uncertain or unknown behaviour	65.6	72.8	546	1145	6	6	8	12	19	20
D50-D53 Nutritional anaemias	75.7	78.1	45	44	7	7	7	8	11	11
D55-D59 Haemolytic anaemias	57.5	72.8	24	17	9	9	9	11	14	15
D60-D64 Aplastic and other anaemias	58.2	75.5	208	393	8	8	8	9	12	12
D65-D69 Coagulation defects, purpura and other haemorrhagic conditions	60.6	72.4	100	122	16	16	17	19	20	21
D70-D77 Other diseases of blood and blood-forming organs	50.5	60.8	55	123	1	6	10	13	14	17
D80-D89 Certain disorders involving the immune mechanism	24.1	64.9	10	25	8	8	8	10	10	10
E10-E14 Diabetes mellitus	70.1	75.7	11776	10556	6	9	18	25	32	35
E15-E16 Other disorders of glucose regulation and pancreatic internal secretion	73.3	73.8	33	67	6	6	9	10	10	10
E20-E35 Disorders of other endocrine glands	70.1	76.7	96	72	21	22	24	24	24	27
E70-E90 Metabolic disorders	58.9	70.4	273	675	44	46	54	63	68	76
F00-F09 Organic, including symptomatic, mental disorders	82.9	85.3	3205	4451	0	0	1	1	1	1
F10-F19 Mental and behavioural disorders due to psychoactive substance use	54.6	57.0	1040	787	15	15	15	16	17	17
F20-F29 Schizophrenia, schizotypal and delusional disorders	56.6	59.7	148	65	9	9	12	15	16	16
F30-F39 Mood [affective] disorders	55.6	76.2	32	19	17	21	30	33	34	35
F40-F48 Neurotic, stress-related and somatoform disorders	77.9	79.5	26	5	19	21	24	25	27	27
F50-F59 Behavioural syndromes associated with physiological disturbances and physical factors	56.0	70.0	10	4	18	20	21	24	25	26
F70-F79 Mental retardation	40.4	40.4	21	14	0	0	1	1	1	1
G00-G09 Inflammatory diseases of the central nervous system	49.6	64.4	199	219	17	18	19	19	19	20
G10-G14 Systemic atrophies primarily affecting the central nervous system	60.0	64.1	252	530	2	3	4	4	4	4
G20-G26 Extrapyramidal and movement disorders	74.9	78.9	1189	3472	14	15	18	20	20	22
G30-G32 Other degenerative diseases of the nervous system	80.6	86.0	1193	5092	1	1	4	5	5	5
G35-G37 Demyelinating diseases of the central nervous system	57.2	62.2	43	31	6	8	10	12	13	17
G40-G47 Episodic and paroxysmal disorders	43.1	56.0	508	452	31	34	39	44	51	55
G50-G59 Nerve, nerve root and plexus disorders	72.5	81.3	7	4	10	10	12	12	12	12

ICD-10 subchapter	Mean age at death		Number of deaths		Number of drugs ever launched					
	2005	2015	2005	2015	1990	1995	2000	2005	2010	2015
G70-G73 Diseases of myoneural junction and muscle	36.7	43.7	123	163	12	12	12	12	12	12
H65-H75 Diseases of middle ear and mastoid	47.5	55.0	3	2	15	17	17	17	17	17
I10-I15 Hypertensive diseases	77.5	83.8	4520	5050	22	34	45	51	51	52
I20-I25 Ischaemic heart diseases	72.4	76.2	13358	14723	22	30	37	38	39	43
I26-I28 Pulmonary heart disease and diseases of pulmonary circulation	66.0	73.1	215	486	7	7	9	11	13	16
I30-I52 Other forms of heart disease	69.2	76.9	5536	13114	49	60	66	67	70	72
I60-I69 Cerebrovascular diseases	73.2	76.7	31195	24453	13	14	16	17	18	19
I70-I79 Diseases of arteries, arterioles and capillaries	72.5	76.5	1064	1399	21	23	24	27	29	32
I80-I89 Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	66.6	72.5	69	125	26	26	28	28	31	32
J00-J06 Acute upper respiratory infections	63.0	73.2	21	22	35	41	44	47	47	47
J09-J18 Influenza and pneumonia	78.2	81.7	4136	14956	27	33	38	45	45	46
J20-J22 Other acute lower respiratory infections	52.8	79.1	21	68	24	29	32	36	36	36
J30-J39 Other diseases of upper respiratory tract	62.4	78.1	18	27	33	42	43	47	49	49
J40-J47 Chronic lower respiratory diseases	76.9	81.2	7548	7538	40	46	48	53	56	57
J80-J84 Other respiratory diseases principally affecting the interstitium	70.5	75.7	746	1786	7	8	8	8	8	9
J95-J99 Other diseases of the respiratory system	73.7	81.3	481	819	8	9	9	9	9	9
K00-K14 Diseases of oral cavity, salivary glands and jaws	64.5	77.5	5	14	12	12	13	13	13	13
K20-K31 Diseases of oesophagus, stomach and duodenum	73.9	78.1	529	648	12	13	17	18	18	18
K50-K52 Noninfective enteritis and colitis	74.9	75.0	127	64	9	9	10	11	12	14
K65-K67 Diseases of peritoneum	75.2	76.3	170	348	5	6	6	6	6	6
K70-K77 Diseases of liver	58.0	61.3	8392	6847	14	14	16	19	22	23
K80-K87 Disorders of gallbladder, biliary tract and pancreas	72.3	77.8	857	1367	8	8	8	8	8	8
K90-K93 Other diseases of the digestive system	73.2	77.0	356	800	16	16	20	21	21	21
L00-L08 Infections of the skin and subcutaneous tissue	74.7	73.5	39	83	19	25	26	31	32	32
L10-L14 Bullous disorders	80.0	80.7	4	37	9	9	9	10	10	10
L20-L30 Dermatitis and eczema	70.5	87.5	5	1	24	24	26	26	26	27
L50-L54 Urticaria and erythema	64.5	75.9	15	31	8	12	13	15	16	17

ICD-10 subchapter	Mean age at death		Number of deaths		Number of drugs ever launched					
	2005	2015	2005	2015	1990	1995	2000	2005	2010	2015
L80-L99 Other disorders of the skin and subcutaneous tissue	81.8	82.8	340	318	29	30	30	31	31	31
M00-M03 Infectious arthropathies	76.9	77.4	31	78	21	23	23	23	23	23
M05-M14 Inflammatory polyarthropathies	73.9	76.0	274	192	26	28	32	36	37	43
M15-M19 Arthrosis	80.5	86.7	70	55	21	23	26	26	26	27
M30-M36 Systemic connective tissue disorders	46.9	60.0	183	258	12	12	12	15	15	16
M45-M49 Spondylopathies	75.6	78.9	90	132	10	11	13	15	16	17
M50-M54 Other dorsopathies	74.1	82.0	55	22	23	23	23	23	23	23
M70-M79 Other soft tissue disorders	69.2	73.4	51	88	25	26	26	26	26	26
M80-M85 Disorders of bone density and structure	81.2	85.4	639	462	9	9	10	13	15	15
M86-M90 Other osteopathies	71.0	76.4	65	70	16	18	18	20	20	20
N00-N08 Glomerular diseases	69.4	75.6	55	90	11	13	15	15	15	15
N10-N16 Renal tubulo-interstitial diseases	77.2	80.2	86	375	19	22	23	23	23	24
N17-N19 Renal failure	69.3	76.0	2615	5009	10	11	14	17	20	22
N25-N29 Other disorders of kidney and ureter	75.1	79.0	25	24	8	8	8	8	8	9
N30-N39 Other diseases of urinary system	80.7	82.5	189	891	29	36	42	46	48	50
N40-N51 Diseases of male genital organs	78.3	81.0	58	75	17	24	27	32	33	33
N70-N77 Inflammatory diseases of female pelvic organs	73.0	82.3	10	24	14	17	19	21	21	21
N80-N98 Noninflammatory disorders of female genital tract	72.5	78.0	8	10	32	35	38	40	40	40
O60-O75 Complications of labour and delivery	33.4	33.3	17	12	10	10	10	11	12	12
Q20-Q28 Congenital malformations of the circulatory system	12.8	15.1	327	199	1	1	2	2	2	2
Q60-Q64 Congenital malformations of the urinary system	50.1	56.6	33	28	0	0	0	0	0	1
Q65-Q79 Congenital malformations and deformations of the musculoskeletal system	2.0	3.2	28	37	1	2	2	2	2	2
Q80-Q89 Other congenital malformations	13.6	15.1	65	49	4	4	4	4	5	5
R10-R19 Symptoms and signs involving the digestive system and abdomen	62.9	76.3	23	26	24	24	28	29	31	31
R40-R46 Symptoms and signs involving cognition, perception, emotional state and behaviour	80.0	78.1	10	9	12	12	14	14	15	15
R50-R69 General symptoms and signs	85.9	87.2	27420	15420	60	63	70	71	72	72

Appendix Table 2. Data on Cancer Survival and Incidence Rates and Number of Drugs ever Launched, by Cancer Site

	5-year relative survival rate		Age-standardized incidence rate		Number of drugs ever launched					
Site	1996-2000	2011-2015	1999	2015	1990	1995	2000	2005	2010	2015
C00-C14 Lip, oral cavity, and pharynx	46.7%	64.5%	3.6	4.1	1	2	3	3	3	3
C15 Esophagus	15.2%	36.0%	4.1	2.7	2	3	4	4	5	5
C16 Stomach	46.6%	75.4%	43.6	33.8	4	5	7	8	8	8
C18-C20 Colon and rectum	58.0%	76.3%	20.4	30.4	3	3	7	8	9	11
C22 Liver	13.2%	33.6%	27.9	18.2	0	1	2	2	3	3
C23 Gallbladder	19.7%	29.1%	6.5	6.6	0	0	0	0	0	0
C25 Pancreas	7.6%	10.8%	5.6	7.0	1	3	4	4	7	7
C32 Larynx	62.3%	75.5%	2.3	1.3	0	0	0	0	0	0
C34 Lung	12.7%	26.7%	28.5	26.4	8	11	15	17	20	24
C50 Breast	83.2%	92.3%	10.7	24.8	15	20	29	33	37	39
C53 Cervix uteri	80.0%	79.9%	8.5	4.6	6	6	7	8	8	8
C54 Corpus uteri	81.8%	87.8%	1.4	3.1	2	2	2	2	2	2
C56 Ovary	58.9%	64.1%	2.7	3.2	8	11	14	15	16	16
C61 Prostate	67.2%	94.1%	3.1	11.2	4	7	9	10	10	14
C62 Testis	90.4%	95.6%	0.3	0.6	7	7	7	7	7	7
C64 Kidney	66.1%	82.2%	3.0	5.7	4	4	4	5	5	7
C67 Bladder	73.1%	75.8%	4.6	4.3	8	9	10	10	10	10
C69-C72 Brain and CNS	39.0%	40.7%	2.9	2.8	9	9	9	10	10	11
C73 Thyroid	94.9%	100.3%	6.3	35.2	1	1	1	1	2	3
C81 Hodgkin lymphoma	71.2%	82.2%	0.2	0.5	12	13	13	13	13	15
C82-C86 Non-Hodgkin lymphoma	50.8%	62.9%	4.3	5.9	17	18	19	23	25	26
C90 Multiple myeloma	19.8%	40.9%	1.0	1.6	14	14	15	16	17	18
C91-C95 Leukemia	33.3%	51.0%	4.7	5.3	24	26	28	31	37	38

Appendix Table 3. Data on Number of Hospital Days and Number of Drugs ever Launched, by Disease

	Number of hospital days		Number of drugs ever launched					
Cause	2014	2017	1992	1997	2002	2007	2012	2017
0101 Intestinal infectious diseases except diarrhoea	219,150	312,439	10	10	10	10	11	11
0102 Diarrhoea and gastroenteritis of presumed infectious origin	964,994	1,037,242	4	4	4	4	4	4
0103 Tuberculosis	568,019	534,240	12	13	13	13	13	14
0104 Septicaemia	1,221,795	2,024,374	24	26	27	28	28	28
0105 Human immunodeficiency virus (HIV) disease	25,898	22,766	0	4	14	16	20	21
0106 Other infectious and parasitic diseases	783,655	815,668	96	110	120	133	138	138
0201 Malignant neoplasm of colon, rectum and anus	1,396,433	1,584,697	6	6	10	12	12	14
0202 Malignant neoplasm of trachea, bronchus and lung	1,295,765	1,428,924	13	15	18	22	24	26
0203 Malignant neoplasm of skin	95,774	152,839	5	5	8	8	8	11
0204 Malignant neoplasm of breast	1,010,542	1,292,265	16	21	30	36	37	39
0205 Malignant neoplasm of uterus	295,612	341,585	7	7	8	9	9	9
0206 Malignant neoplasm of ovary	257,118	320,517	10	11	14	15	16	16
0207 Malignant neoplasm of prostate	254,129	322,692	5	9	10	11	14	15
0208 Malignant neoplasm of bladder	187,709	227,579	9	9	10	10	10	10
0209 Other Malignant neoplasms	5,441,436	5,927,499	54	56	69	86	98	106
0210 Carcinoma in situ	86,969	124,628	12	13	15	19	20	20
0211 Benign neoplasm of colon, rectum and anus	67,873	70,539	0	0	0	0	0	0
0213 Other Benign neoplasms and neoplasms of uncertain or unknown behaviour	877,941	1,007,287	20	21	28	34	38	39
0301 Anaemias	133,429	166,042	17	17	18	20	22	22
0302 Other diseases of the blood and bloodforming organs	86,702	109,383	22	26	33	36	38	40
0401 Diabetes mellitus	2,656,886	2,638,998	7	11	21	28	33	35
0402 Other endocrine, nutritional and metabolic diseases	394,112	451,901	93	99	112	122	131	133
0501 Dementia	15,004,602	22,166,362	0	0	1	1	1	1
0503 Mental and behavioural disorders due to use of Other psychoactive substance	24,137	24,453	3	3	4	5	5	5

	Number of hospital days		Number of drugs ever launched					
Cause	2014	2017	1992	1997	2002	2007	2012	2017
0504 Schizophrenia, schizotypal and delusional disorders	9,723,989	11,690,961	9	10	13	15	16	16
0505 Mood (affective) disorders	1,803,234	2,035,603	16	22	30	32	33	34
0506 Other Mental and behavioural disorders	2,296,552	2,725,240	47	51	56	63	67	68
0601 Alzheimer's disease	200,824	360,560	1	2	4	5	5	5
0602 Multiple sclerosis	38,565	37,248	11	12	15	17	18	21
0603 Epilepsy	354,512	421,323	18	21	23	26	29	29
0604 Transient cerebral ischaemic attacks and related syndromes	141,079	121,605	7	7	9	9	12	12
0605 Other diseases of the nervous system	9,643,761	15,206,795	55	59	69	72	77	79
0702 Other diseases of the eye and adnexa	181,598	178,520	45	50	60	66	68	69
0901 Hypertensive diseases	2,163,044	1,928,588	29	37	47	49	51	51
0902 Angina pectoris	440,502	476,246	23	24	26	27	30	30
0903 Acute myocardial infarction	276,266	334,723	17	20	23	25	28	28
0904 Other ischaemic heart disease	216,018	231,671	14	16	19	21	22	22
0905 Pulmonary heart disease and diseases of Pulmonary circulation	103,279	128,808	9	9	11	14	18	18
0906 Conduction disorders and cardiac arrhythmias	400,444	480,392	18	20	21	22	25	25
0907 Heart failure	539,476	612,565	17	23	26	27	29	29
0908 Cerebrovascular diseases	14,185,037	14,072,000	13	13	16	16	19	19
0909 Atherosclerosis	116,635	122,407	2	2	3	3	5	5
0911 Other diseases of the circulatory system	730,803	806,058	62	64	68	71	73	73
1001 Acute upper respiratory infections and influenza	954,022	916,338	35	42	46	48	48	48
1002 Pneumonia	5,222,912	6,867,790	28	33	38	42	43	43
1003 Other acute lower respiratory infections	724,314	641,427	22	29	31	34	34	34
1005 Other diseases of upper respiratory tract	254,315	235,087	38	42	45	47	50	50
1006 Chronic obstructive Pulmonary disease and bronchiectasis	1,140,919	1,156,270	36	42	44	47	48	48
1007 Asthma	557,302	503,913	20	21	22	24	26	26
1008 Other diseases of the respiratory system	1,832,517	1,878,269	17	18	18	18	19	19
1103 Diseases of oesophagus	180,968	163,590	6	7	10	10	10	10

	Number of hospital days		Number of drugs ever launched					
Cause	2014	2017	1992	1997	2002	2007	2012	2017
1104 Peptic ulcer	289,656	240,729	7	9	13	13	13	13
1105 Dyspepsia and Other diseases of stomach and duodenum	173,635	146,861	5	5	5	5	5	5
1109 Crohn's disease and ulcerative colitis	76,195	74,948	10	10	12	13	14	15
1110 Other noninfective gastroenteritis and colitis	71,282	65,111	1	1	2	2	2	2
1114 Other diseases of intestine	262,724	284,333	19	19	20	20	21	22
1116 Other diseases of liver	616,774	610,290	15	16	18	22	24	24
1119 Diseases of pancreas	250,487	258,434	2	2	2	2	2	2
1120 Other diseases of the digestive system	547,122	464,275	39	42	45	45	45	45
1201 Infections of the skin and subcutaneous tissue	380,962	438,235	22	25	28	31	32	32
1202 Dermatitis, eczema and papulosquamous disorders	42,993	34,666	31	33	36	39	40	41
1203 Other diseases of the skin and subcutaneous tissue	506,607	763,428	53	58	65	68	71	72
1301 Coxarthrosis (arthrosis of hip)	82,337	88,717	5	5	5	5	5	5
1302 Gonarthrosis (arthrosis of knee)	2,036,467	2,550,484	8	8	8	8	8	8
1304 Other arthropathies	1,381,700	1,383,400	50	51	57	60	63	67
1305 Systemic connective tissue disorders	154,224	171,107	14	14	16	17	17	18
1306 Deforming dorsopathies and spondylopathies	2,112,244	2,357,328	12	13	16	18	19	20
1308 Dorsalgia	699,000	804,097	22	22	22	22	22	22
1309 Soft tissue disorders	1,433,152	1,589,334	27	27	27	27	27	27
1310 Other disorders of the musculoskeletal system and connective tissue	803,879	866,283	32	32	35	38	38	38
1401 Glomerular and renal tubulo-interstitial diseases	545,815	704,823	26	31	32	32	33	33
1402 Renal failure	1,830,819	2,330,361	11	14	16	18	21	21
1404 Other diseases of the urinary system	514,658	689,149	38	44	48	52	56	57
1405 Hyperplasia of prostate	125,203	128,172	3	5	6	8	9	9
1406 Other diseases of Male genital organs	63,850	73,154	17	19	21	23	23	23
1407 Disorders of breast	23,230	22,940	4	4	6	6	6	6
1408 Inflammatory diseases of Female pelvic organs	99,728	82,348	15	18	19	20	20	20

Cause	Number of hospital days		Number of drugs ever launched					
	2014	2017	1992	1997	2002	2007	2012	2017
1409 Menstrual, menopausal and Other Female genital conditions	15,652	16,579	23	23	25	25	25	25
1410 Other disorders of the genitourinary system	193,187	192,074	17	19	21	22	22	22
1501 Medical abortion	936	624	2	2	3	3	3	3
1502 Other pregnancy with abortive outcome	35,814	26,830	3	3	4	4	4	4
1504 Complications of pregnancy predominantly during labour and delivery	260,152	295,620	11	11	11	13	13	13
1505 Single spontaneous delivery	262,745	185,002	0	0	0	1	1	1
1601 Disorders related to short gestation and low birthweight	234,491	216,544	4	4	4	4	4	4
1804 Other symptoms, signs and abnormal clinical and laboratory findings	1,242,236	1,619,036	107	116	125	131	134	135
1901 Intracranial injury	2,089,808	2,238,670	4	4	4	4	5	5
1904 Fracture of femur	2,016,902	2,318,057	0	0	2	3	3	3
1906 Other injuries	11,317,131	11,642,486	12	12	12	12	13	13
1908 Poisonings by drugs, medicaments, and biological substances and toxic effects	101,404	93,922	17	17	17	18	18	18
1909 Complications of Surgical and medical care, n.e.c.	294,865	336,941	25	28	36	41	41	41
1911 Other and unspecified effects of external causes	41,427	47,997	13	14	15	15	15	15
2102 Contraceptive management	131	135	3	3	4	4	5	5
2105 Other factors influencing Health status and contact with Health services	569,158	686,042	19	20	22	23	25	25

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