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The impact of pharmaceutical innovation on longevity and medical expenditure in France, 2000–2009

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ABSTRACT

Longitudinal, disease-level data are used to analyze the impact of pharmaceutical innovation on longevity (mean age at death) and medical expenditure in France during the period 2000–2009. The estimates imply that pharmaceutical innovation increased mean age at death by 0.29 years (3.43 months) during this period—about one-fifth of the total increase in longevity. This estimate is smaller than those obtained in previous studies of Germany and the U.S., but the rate of adoption of new drugs was lower in France. Longevity is much more strongly related to the number of drugs than it is to the number of drug classes.

Pharmaceutical innovation during 2000–2009 is estimated to have increased per capita pharmaceutical expenditure by $125 (26%) in 2009, but most (87%) of this increase was offset by a reduction in hospital expenditure. The baseline estimate of the cost per life-year gained from pharmaceutical innovation in France during 2000–2009 is about $8100. This estimate is fairly close to the mean of estimates obtained ($10,800) from U.S., German, and Australian studies.

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1. Introduction

Longevity increase is increasingly recognized by economists to be an important part of economic growth and development (Nordhaus, 2003; Murphy and Topel, 2006). Economists have also come to recognize that, in the long run, the rate of economic "growth...is driven by technological change that arises from intentional [research and development (R&D)] investment decisions made by profit-maximizing agents" (Romer, 1990) and by public organizations such as the National Institutes of Health. In principle, technological change could be either disembodied or embodied in new goods. Solow (1960) hypothesized that most technological change is embodied: to benefit from technological progress, one must use newer, or later vintage, goods and services. Bresnahan and Gordon (1996) argued that "new goods are at the heart of economic progress." Grossman and Helpman (1991) argued that "almost every product exists on a *quality ladder*, with variants below that may already have become obsolete and others above that have yet to be discovered," and that "each new product enjoys a limited run at the technological frontier, only to fade when still better products come along." Hercowitz (1998: p. 223) also reached the "conclusion...that 'embodiment' is the main transmission mechanism of technological progress to economic growth."

This paper will analyze the impact of pharmaceutical innovation (i.e. the utilization of new drugs) on longevity and medical expenditure in France during the period 2000–2009.[1] The medical substances and devices industries are the most research intensive industries in the

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[1] Only a small fraction of the new drugs used in France were developed in France.

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economy (National Science Foundation, 2013). Pharmaceuticals are also more research-intensive than other types of medical care: in 2007, prescription drugs accounted for 10% of U.S. health expenditure (Center for Medicare and Medicaid Services, 2013: Table 2), but more than half of U.S. funding for biomedical research came from pharmaceutical and biotechnology firms (Dorsey et al., 2010). Moreover, new drugs often build on upstream government research (Sampat and Lichtenberg, 2011).

The overall impact of pharmaceutical innovation on longevity and health can be assessed in a variety of ways.[2] Each approach has advantages and disadvantages. One approach is to survey (as Garthwaite and Duggan, forthcoming did) a large number of case studies of specific drugs or classes of drugs. Two problems with this approach are (1) the specific drugs examined may not constitute a representative sample and (2) different methods and metrics are used in each study, making it difficult to draw general conclusions.

A second approach is to conduct econometric studies of drugs in general.[3] Several types of econometric studies of drugs in general can be performed. One can perform studies using patient-level data, to investigate the following question: do patients using newer drugs live longer than patients using older drugs, controlling for their demographic characteristics (age, sex, race, income, education, etc.), medical conditions, behavioral risk factors, and other variables?[4] Alternatively, one can perform studies using aggregate data, preferably longitudinal (panel) data.[5] There are two main types of studies based on aggregate panel data. One can analyze longitudinal *region*-level data, to investigate the following question: has life expectancy increased more rapidly in regions (e.g. states or countries) experiencing more pharmaceutical innovation, controlling for changes in income, education, and other variables?[6]

One can also analyze longitudinal *disease*-level data, to determine whether life expectancy has increased more rapidly for people with diseases experiencing more pharmaceutical innovation. A potential advantage of this approach is that variation across diseases in the pace of pharmaceutical innovation may be "more exogenous" (e.g. due to heterogeneous scientific opportunity) than variation across individuals or regions. This approach has been applied to U.S. data (Lichtenberg, 2007b, 2009). It has also been applied to some French data (Lichtenberg, 2012a, 2013b), but these were studies of specific diseases (cancer and orphan diseases), and they did not provide estimates of the overall impact of pharmaceutical innovation on longevity and medical expenditure in France. Since the French health care system is quite different from the U.S. system,[7] obtaining these estimates for France is worthwhile.

Several recent studies have shown that prescription drug cost-sharing, which affects the *quantity* of pharmaceutical consumption, has a "spillover effect" on hospital utilization. One study (Chandra et al., 2010) found a "rather modest offsetting rise in hospital care when physician and prescription drug copayments are raised, but. . .substantial offsets for the sickest populations with chronic diseases" (p. 211). Another study (Karaca-Mandic et al., 2012) found that "greater cost sharing for asthma medications was associated with a slight reduction in medication use and higher rates of asthma hospitalization among children aged 5 years or older" (p. 1284). Pharmaceutical innovation may have a spillover effect on hospital utilization, because it tends to increase the *quality* (and perhaps also the quantity) of pharmaceutical consumption. Even though pharmaceutical innovation is very likely to increase pharmaceutical expenditure, if it reduces hospital expenditure, it may not increase (and could even reduce) total medical expenditure.[8]

For this study, longitudinal, disease-level data were obtained from several rich databases (Thériaque, the WHO Mortality Database, Eurostat, and the IMS Health MIDAS database) to examine the impact of pharmaceutical innovation on longevity, pharmaceutical expenditure, and hospital utilization in France during the period 2000–2009.[9] By combining the estimates of the effect of pharmaceutical innovation on longevity, pharmaceutical expenditure, and hospital utilization, the incremental cost-effectiveness (cost per life-year gained) of pharmaceutical innovation in France during the period 2000–2009 can be estimated.

[2] For a review of the literature on the impact of medical innovation in general, see the 604-page report prepared by the Australian Productivity Commission (2005).

[3] Garthwaite and Duggan (forthcoming) are skeptical about the feasibility of the second approach. They argue that "the sheer number of treatments often makes it difficult to estimate the effect of pharmaceuticals on overall health. The number of conditions for which there are now treatments, and the ways in which these conditions are inter-related, generates a large number of confounding factors that can hamper attempts to estimate the causal effects of these drugs on overall health. Overcoming this difficulty often requires researchers to focus on the effect of only one medication, or one class of medications." However, they provide very little evidence to support their position. They say that a reexamination of data from one study of drugs in general showed that the results were "very sensitive to particular modeling decisions." They did not cite a subsequent article (Lichtenberg, 2007a) that demonstrated that the results were much less sensitive than had been claimed. Moreover, many other studies of the overall impact of pharmaceutical innovation have not been challenged.

[4] Lichtenberg et al. (2009) studied the impact of pharmaceutical innovation on longevity using patient-level data on elderly residents of Quebec, and Lichtenberg (2013a,b) studied this issue using patient-level data on elderly Americans.

[5] Grunfeld and Griliches (1960: p. 1) showed that "aggregation of economic variables can, and in fact frequently does, reduce. . .specification errors. Hence, aggregation does not only produce an aggregation error, but may also produce an aggregation gain." In particular, patient-level data are surely more subject to selection effects (the sickest patients might get the newest—or oldest—treatments) than aggregate data.

[6] Lichtenberg (2011) studied the impact of pharmaceutical innovation on longevity using longitudinal state-level U.S. data, and Lichtenberg (2012a) studied this issue using longitudinal state-level German data.

[7] The French health care system is one of universal health care largely financed by government national health insurance. In its 2000 assessment of world health care systems, the World Health Organization (2013) found that France provided the "close to best overall health care" in the world.

[8] Newhouse (1992) observed that "technological change is not necessarily expenditure-increasing" (p. 11), and that "hospital expenditure is the single largest component of the overall expenditure increase" (p. 12).

[9] Patient-level and longitudinal region-level data for France are not available.

In the next section, equations to estimate the impact of pharmaceutical innovation on longevity, hospital utilization, and pharmaceutical expenditure will be presented. Data sources are described and descriptive statistics are presented in Section 3. Estimates of econometric models are presented in Section 4. The cost-effectiveness of pharmaceutical innovation in France is assessed in Section 5. The final section contains a summary and conclusions.

2. Econometric models for estimating the impact of pharmaceutical innovation on longevity, hospital utilization, and pharmaceutical expenditure

2.1. Longevity model

In his model of endogenous technological change, Romer (1990) hypothesized an aggregate production function such that an economy's output depends on the "stock of ideas" that have previously been developed, as well as on the economy's endowments of labor and capital. The longevity model that will be estimated below may be considered a health production function, in which longevity (age at death) is an indicator of health output or outcomes, and the cumulative number of drugs approved is analogous to the stock of ideas. The model will be of the following form:

$$\text{AGE\_DEATH}_{it} = \beta_k \ln(\text{N\_CHEM\_SUBSTANCES}_{i,t-k}) + \alpha_i + \delta_t + \varepsilon_{it} \quad (1)$$

where

AGE_DEATH_{it}	= mean age at death from disease i in year t (t = 2000,. . .,2009)
$\text{N\_CHEM\_SUBSTANCES}_{i,t-k}$	= $\sum_d \text{IND}_{di}\,\text{APP}_{d,t-k}$ = the number of chemical substances (drugs) to treat disease i commercialized by the end of year $t-k$
IND_{di}	= 1 if drug d is used to treat (indicated for) disease i = 0 if drug d is not used to treat (indicated for) disease i
$\text{APP}_{d,t-k}$	= 1 if drug d was commercialized by the end of year $t-k$ = 0 if drug d was not commercialized by the end of year $t-k$
α_i	= a fixed effect for disease i
δ_t	= a fixed effect for year t

Inclusion of year and disease fixed effects controls for the overall increase in French longevity and for stable between-disease differences in longevity. A positive and significant estimate of β_k in Eq. (1) would signify that diseases for which there was more pharmaceutical innovation had larger increases in longevity. Eq. (1) will be estimated by weighted least-squares, weighting by the number of deaths caused by disease i in year t. Standard errors will be clustered within diseases.

If this model is correctly specified, it will enable determination of how much of the increase in mean age at death during the sample period (2000–2009) can be attributed to the introduction of new drugs. The expression $(\delta_{2009} - \delta_{2000})$ indicates the 2000–2009 increase in longevity, controlling for (holding constant) the number of drugs, i.e. in the absence of pharmaceutical innovation. Suppose Eq. (1) is estimated, excluding $\ln(\text{N\_CHEM\_SUBSTANCES}_{i,t-k})$, and that the year fixed effects from that equation are denoted by δ'_t. Then $(\delta'_{2009} - \delta'_{2000})$ indicates the 2000–2009 increase in longevity, not holding constant the number of drugs, i.e. in the presence of pharmaceutical innovation, and $(\delta'_{2009} - \delta'_{2000}) - (\delta_{2009} - \delta_{2000})$ is an estimate of the 2000–2009 increase in longevity attributable to pharmaceutical innovation.

There is a potential pitfall in analyzing the relationship between pharmaceutical innovation related to a disease and the mean age of deaths caused by the disease. Suppose that the introduction of a new drug for a disease reduces the number of people who die from the disease; people who would have died from the disease, absent the new drug, die from other diseases instead. The estimates will not capture between-disease spillover effects. In principle, such between-disease spillover effects could be substantial. However, they appear to be quite modest in practice. Between 2000 and 2009, mean age at death in France increased by 1.39 years, from 75.53 to 76.92 years. Calculations indicate that if the number of deaths, by cause, in 2000 had prevailed during the entire 2000–2009 period, mean age at death would have increased by 1.11 years. Hence 80% of the actual increase in mean age at death was due to within-disease increases; only 20% was due to a shift in the distribution of causes of death.

Life expectancy at birth is probably the most commonly cited measure of longevity, but the measure of life expectancy to be analyzed is mean age at death.[10] The main reason is that life expectancy at birth (or at higher ages) cannot be measured for specific diseases. A more minor "disadvantage" of this indicator is that it is "hypothetical," rather than "actual": it is based on the period life table, which describes what *would* happen to a hypothetical (or synthetic) cohort if it experienced throughout its entire life the mortality conditions of a particular time period (Arias, 2010).

Mean age at death and life expectancy at birth (LE_BIRTH) are both probability-weighted averages of age at death:

$$\text{AGE\_DEATH} = \sum_a p_{1a}\, a$$

$$\text{LE\_BIRTH} = \sum_a p_{2a}\, a$$

where a denotes age at death, and p_{1a} and p_{2a} are probabilities of dying at age a. In the case of AGE_DEATH, the probabilities depend only on the number of deaths at each age: $p_{1a} = \text{N\_DEATHS}_a / \sum_a \text{N\_DEATHS}_a$. In the case of LE_BIRTH, the probabilities depend on the population at each age (POP_a) as well as the number of deaths: $p_{2a} = d_{a-1}[(1-d_0)\,(1-d_1)\,\ldots\,(1-d_{a-2})]$, where $d_a = \text{N\_DEATHS}_a / \text{POP}_a$. Since the AGE_DEATH calculation is based only on people who have died, whereas the LE_BIRTH calculation is based on the entire population, AGE_DEATH might be considered a censored measure. Although LE_BIRTH

[10] Government agencies such as the Australian Institute of Health and Welfare (2013), Statistics Canada (http://www.cbc.ca/news/canada/story/2008/01/14/death-stats.html), and the Arizona Department of Health Services (http://www.azdhs.gov/plan/report/ahs/ahs2010/pdf/2d1.pdf) publish data on mean age at death.

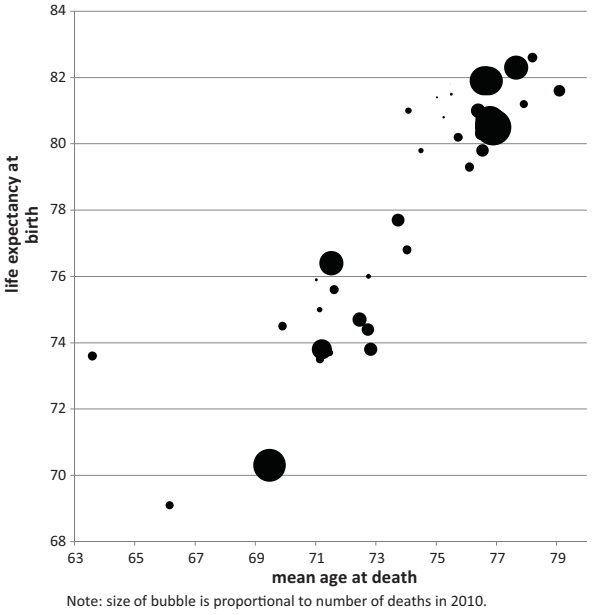

Fig. 1. Correlation across countries between mean age at death and life expectancy at birth in 2010.

cannot be measured by disease, both measures (and the correlation between them) can be calculated by country and year. Both measures were calculated for 39 European countries during the period 1960–2010. As shown in Fig. 1, there is a very strong positive correlation across countries between LE_BIRTH in 2010 and AGE_DEATH in 2010. The weighted (by total number of deaths) least-squares coefficient from the regression of LE_BIRTH on AGE_DEATH is 1.21 (t-value = 16.6, R^2 = 0.88). There is also a strong positive correlation across countries between the *growth rates* of AGE_DEATH and LE_BIRTH.[11]

The measure of pharmaceutical innovation in Eq. (1)—the number of chemical substances previously commercialized to treat a disease—is not the theoretically ideal measure. Longevity is presumably more strongly related to the drugs *actually* used to treat a disease than it is to the drugs that *could be* used to treat the disease. A preferable measure is the mean *vintage* of drugs used to treat a disease, defined as $\text{VINTAGE}_{it} = \sum_d Q_{dit}\ \text{LAUNCH\_YEAR}_d / \sum_d Q_{dit}$, where Q_{dit} = the quantity of drug d used to treat disease i in year t, and LAUNCH_YEAR_d = the world launch year of drug d.[12] Unfortunately, measurement of VINTAGE_{it} is infeasible: although data on the total quantity of each drug in each year ($Q_{d \cdot t} = \sum_i Q_{dit}$) are available, many drugs are used to treat multiple diseases, and there is no way to determine the quantity of drug d *used to treat disease* i in year t.[13] However, it is shown in Appendix 1 that there is a highly significant positive correlation across *drug classes* between changes in the (quantity-weighted) vintage of drugs and changes in the number of chemical substances previously commercialized within the drug class.

Pharmaceutical innovation is not the only type of medical innovation that is likely to contribute to longevity growth. Other medical innovation, such as innovation in diagnostic imaging, surgical procedures, and medical devices, is also likely to affect longevity growth. Therefore, measures of these other types of medical innovation should be included in the longevity model (Eq. (1)).[14] Unfortunately, longitudinal disease-level measures of non-pharmaceutical medical innovation are not available for France. However, longitudinal disease-level measures of non-pharmaceutical and pharmaceutical medical innovation are available for the U.S. during the period 1997–2007. In Appendix 2, it is shown that, in the U.S., the rate of pharmaceutical innovation is not positively correlated with the rate of medical procedure innovation and may be *negatively* correlated with the rate of diagnostic imaging innovation. This suggests that failure to control for other medical innovation is unlikely to result in overestimation of the effect of pharmaceutical innovation on longevity growth.

In Eq. (1), mean age at death from disease i in year t depends on the number of chemical substances (drugs) to treat disease i commercialized by the end of year $t-k$, i.e. there is a lag of k years. One would expect there to be a substantial lag because (1) new drugs diffuse gradually—they won't be used widely until years after commercialization and (2) drugs for chronic conditions (which account for most drug use) may have to be consumed for several years for their full health benefits to be realized. Eq. (1) will be estimated for different values of k: k = 1,3,5,. . .,25.[15] The mean lag between the stock of drugs commercialized for a disease and mean age at death from the disease can be computed as follows, including only the values of k for which β_k is statistically significant: $\text{LAG\_MEAN} = \sum_k \beta_k\, k / \sum_k \beta_k$.

[11] In a weighted (by total number of deaths) least-squares regression of the form $\text{LE\_BIRTH}_{ct} = \beta\ \text{AGE\_DEATH}_{ct} + \alpha_c + \delta_t + \varepsilon_{ct}$, where $\text{LE\_BIRTH}_{c \cdot t}$ = LE_BIRTH in country c in year t, the estimate of β is 0.523 (Z = 5.39, p-value <.0001).

[12] According to the Merriam Webster dictionary, one definition of vintage is "a period of origin or manufacture (e.g. a piano of 1845 vintage)". http://www.merriam-webster.com/dictionary/vintage. Robert Solow (1960) introduced the concept of vintage into economic analysis. Solow's basic idea was that technical progress is "built into" machines and other goods and that this must be taken into account when making empirical measurements of their roles in production. This was one of the contributions to the theory of economic growth that the Royal Swedish Academy of Sciences cited when it awarded Solow the 1987 Alfred Nobel Memorial Prize in Economic Sciences.

[13] Outpatient prescription drug claims usually don't show the indication of the drug prescribed. Claims for drugs administered by doctors and nurses (e.g. chemotherapy) often show the indication of the drug, but these account for just 15% of drug expenditure. These data are not available for France.

[14] However, the number of people exposed to pharmaceutical innovation tends to be much larger than the number of people exposed to other types of medical innovation. In 2007, 62% of Americans consumed prescription drugs, while only 8% of Americans were admitted to hospitals (Source: Medical Expenditure Panel Survey, 2007 Full Year Consolidated Data File).

[15] A separate model is estimated for each value of k, rather than including multiple values ($\text{N\_CHEM\_SUBSTANCES}_{i,t-1}$, $\text{N\_CHEM\_SUBSTANCES}_{i,t-3}$, $\text{N\_CHEM\_SUBSTANCES}_{i,t-5}$,. . .) in a single model because N_CHEM_SUBSTANCES is highly serially correlated (by construction), which would result in extremely high multicollinearity if multiple values were included.

The measure of pharmaceutical innovation, N_CHEM_SUBSTANCES$_{i,t-k}$ = $\sum_d$ IND$_{di}$ APP$_{d,t-k}$, is based on whether drug d had an indication for disease i *at the end of 2011*. One would prefer to base the measure on whether drug d had an indication for disease i *at the end of year* $t-k$. However, FDA data suggest that changes in drug indications are relatively infrequent: only 83 out of 3882 (2% of) FDA drug applications have been for new indications.[16]

In Eq. (1), longevity is assumed to depend on the *log* of the stock of drugs. Although this functional form is probably appropriate, because pharmaceutical innovation, like most economic activities, is probably subject to diminishing marginal productivity, it does require exclusion of observations in which the lagged stock of drugs was zero. Hence, the longevity effect of the introduction of the *first* new drug for a disease is not captured in this model. This effect may not be insignificant: the first drug for HIV/AIDS was launched in 1987, which falls within our sample period when $k \geq 13$.[17] We will therefore also estimate an alternative specification, in which ln(N_CHEM_SUBSTANCES$_{i,t-k}$) is replaced by (N_CHEM_SUBSTANCES$_{i,t-k}$/N_CHEM_SUBSTANCES$_{i,2009}$): the ratio of the number of drugs in year $t-k$ to the number of drugs at the end of the sample period (2009). With this specification, an observation can be included even if the stock of drugs was zero in that year, as long as the stock of drugs was positive in 2009.

Chemical substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. In the Anatomical Therapeutic Chemical (ATC) classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology, drugs are classified in groups at five different levels. The highest (1st) level is the "anatomical main group" level; there are 14 anatomical main groups. The 2nd, 3rd, 4th, and 5th levels are "therapeutic subgroup," "pharmacological subgroup," "chemical subgroup," and "chemical substance," respectively.[18] Age at death from a disease may depend on the number of chemical (or pharmacological) *subgroups* that have previously been developed to treat the disease rather than, or in addition to, the number of chemical *substances* (drugs) that have previously been developed to treat the disease. This will be investigated by estimating versions of Eq. (1) in which N_CHEM_SUBSTANCES$_{i,t-k}$ is replaced by N_CHEM_SUBGROUP$_{i,t-k}$

where

N_CHEM_SUBGROUP$_{it}$	= $\sum_g$ IND$_{gi}$ APP$_{gt}$
IND$_{gi}$	= 1 if any drugs in chemical subgroup g are used to treat (indicated for) disease i = 0 if no drugs in chemical subgroup g are used to treat (indicated for) disease i
APP$_{gt}$	= 1 if any drugs in chemical subgroup g had been commercialized by the beginning of year t = 0 if no drugs in chemical subgroup g had been commercialized by the beginning of year t

2.2. Hospital utilization model

To assess the impact of pharmaceutical innovation on hospital utilization, models of the following form will be estimated:

$$\ln(\text{HOSP\_UTIL}_{it}) = \beta_k \ln(\text{N\_CHEM\_SUBSTANCES}_{i,t-k}) + \alpha_i + \delta_t + \varepsilon_{it} \quad (2)$$

where HOSP_UTIL$_{it}$ = an (age-adjusted) measure of hospital utilization associated with disease i in year t. Eq. (2) will be estimated by weighted least-squares, weighting by Σ_t HOSP_UTIL$_{it}$. Standard errors will be clustered within diseases. Two different measures of hospital utilization will be analyzed: the age-adjusted rate of hospital *discharges* per 100,000 population, and the age-adjusted rate of hospital *days* per 100,000 population. The ratio of hospital days to hospital discharges is the average length of stay in the hospital.

2.3. Pharmaceutical expenditure model

Data on pharmaceutical expenditure, by disease and year, are not available for France. To assess the impact of pharmaceutical innovation on pharmaceutical expenditure, data on pharmaceutical innovation and expenditure, by *drug class* (i.e. the 3-digit EphMRA Anatomical Therapy Class (ATC3)) and year will be analyzed. Models of the following form will be estimated:

$$\ln(\text{DRUG\_EXPEND}_{ct}) = \beta_k \ln(\text{N\_MOLECULE}_{c,t-k}) + \alpha_c + \delta_t + \varepsilon_{ct} \quad (c = 1, \ldots, 303; t = 2005, \ldots, 2010; k = 0, \ldots, 5) \quad (3)$$

where

DRUG_EXPEND$_{ct}$	= the ex-manufacturer value (expressed in U.S. dollars) of products in ATC3 sold during year t
N_MOLECULE$_{c,t-k}$	the number of molecules in ATC3 at the end of year $t-k$ = $\sum_m$ IN_CLASS$_{mc}$ ON_MARKET$_{m,t-k}$
IN_CLASS$_{mc}$	= 1 if any product in ATC class 3 sold during 2000–2010 contains molecule m = 0 if no product in ATC class 3 sold during 2000–2010 contains molecule m

[16] Source: Drugs@FDA Data Files.

[17] Lichtenberg (2003) analyzed the effect of new drugs on HIV mortality in the U.S. during the period 1987–1998.

[18] The complete classification of metformin illustrates the structure of the code:

A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Blood glucose lowering drugs, excl. insulins (3rd level, pharmacological subgroup)
A10BA	Biguanides (4th level, chemical subgroup)
A10BA02	Metformin (5th level, chemical substance)

ON_MARKET_{mt} = 1 if any product containing molecule m is sold by the end of year t
= 0 if no product containing molecule m is sold by the end of year t

Eq. (3) will be estimated by weighted least squares, weighting by expenditure on the drug class during the entire 2005–2010 period ($DRUG\_EXPEND_c = (1/6) \Sigma_t DRUG\_EXPEND_{ct}$).

3. Data sources, disease classification, and descriptive statistics

Data sources. The data necessary to construct the number of chemical substances and subgroups, by disease and year, were obtained from Thériaque (http://www.theriaque.org/) a database of official, regulatory and bibliographic information on all drugs available in France, intended for health professionals, and funded by the *Centre National Hospitalier d'Information sur le Médicament*. The data necessary to construct mean age at death and the number of deaths, by disease and year, were obtained from the WHO Mortality Database (http://www.who.int/healthinfo/morttables/en/), which covers deaths registered in national civil registration systems, with underlying cause of death as coded by the relevant national authority. Underlying cause of death is defined as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" in accordance with the rules of the International Classification of Diseases. The data necessary to construct age-adjusted measures of hospital utilization, by disease and year, were obtained from Eurostat.[19] The data necessary to measure pharmaceutical innovation and expenditure, by drug class and year, were obtained from the IMS Health MIDAS database.[20]

Disease classification. In the Thériaque database, drug indications are coded using the International Classification of Diseases, Tenth Revision (ICD-10; http://www.who.int/classifications/icd/en/). France began using the ICD-10 system to classify its mortality data in 2000.[21] The most recent year for which mortality data are available for France in the WHO Mortality Database is 2009. The analysis will therefore cover the period 2000–9 The ICD-10 contains 12,131 distinct disease codes. These are grouped into 263 "blocks," such as "A00–A09 Intestinal infectious diseases," and "C30–C39 Malignant neoplasms of respiratory and intrathoracic organs."[22] The analysis will be performed using data at the ICD-10 block level.

Descriptive statistics. Summary statistics on longevity and pharmaceutical innovation in France are shown in Appendix Table 1. The average annual number of deaths during 2000–2009 was about 529 thousand. Mean age at death increased by 1.39 years, from 75.53 to 76.92 years. As of the end of 1995, 240 pharmacological subgroups, 644 chemical subgroups, and 1822 chemical substances had been commercialized in France. By the end of 2010, the number of pharmacological subgroups, chemical subgroups, and chemical substances had increased by 5%, 14%, and 32%, respectively. The average annual number of chemical substances commercialized was 39.

To illustrate the nature of the disease-specific data on pharmaceutical innovation, Appendix Table 2 lists in chronological order the chemical substances and chemical subgroups with an indication for a particular disease, melanoma and other malignant neoplasms of skin (ICD-10 codes C43–C44). According to the Theriaque database, there are currently 21 substances indicated for this disease; seven of these have been commercialized since 1999. These substances fall into 14 chemical subgroups; four of these subgroups have been established (commercialized) since 1997.

Fig. 2 illustrates the heterogeneity of diseases with respect to their rates of pharmaceutical innovation. In 2000, there were six diseases for which the number of chemical substances previously commercialized in France was between 64 and 69. For three of these diseases, five or fewer new chemical substances were commercialized during the period 2001–2011. For the other three, at least eleven new chemical substances were commercialized during that period. Appendix Table 3 shows data on mortality and the number of chemical substances that had been commercialized in 2000 and 2009 for each of the 105 diseases (ICD-10 Blocks) for which there was at least one chemical substance in 2009.

Data on the number of hospital days and discharges and average length of stay, for all causes of diseases (ICD-10 codes A00-Z99) excluding external causes of morbidity and mortality (V00–Y98) and liveborn infants (Z38), are shown in Appendix Table 4. Eurostat hospital data, like WHO mortality data, are classified by ICD-10, but the hospital classification is somewhat different from the ICD-10 block classification shown in Appendix Table 3. Appendix Table 5 shows data on the number of hospital discharges, days, and average length of stay, in 2000 and 2010, by diagnosis as defined in the Eurostat classification.

4. Empirical results

4.1. Longevity equation estimates

Estimates of parameters from longevity (mean age at death) models are presented in Table 1. All models were estimated by weighted least squares, weighting by

[19] See http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database.

[20] IMS (2011) describes MIDAS as "a unique data platform for assessing worldwide healthcare markets. It integrates IMS national audits into a globally consistent view of the pharmaceutical market, tracking virtually every product in hundreds of therapeutic classes and providing estimated product volumes, trends and market share through retail and non-retail channels. MIDAS data is updated monthly and retains 12 years of history."

[21] France used the ICD-9 classification from 1979 to 1999. The U.S. Centers for Medicare & Medicaid Services has produced Diagnosis Code Set General Equivalence Mappings for translating ICD-10 codes to ICD-9 codes, and vice versa, but in many cases there is not a one-to-one correspondence between ICD-10 and ICD-9 codes. See http://www.cms.gov/Medicare/Coding/ICD10/2012-ICD-10-CM-and-GEMs.html.

[22] See http://en.wikipedia.org/wiki/ICD-10 and http://apps.who.int/classifications/apps/icd/ClassificationDownload/DLArea/icd102010en-Meta.zip.

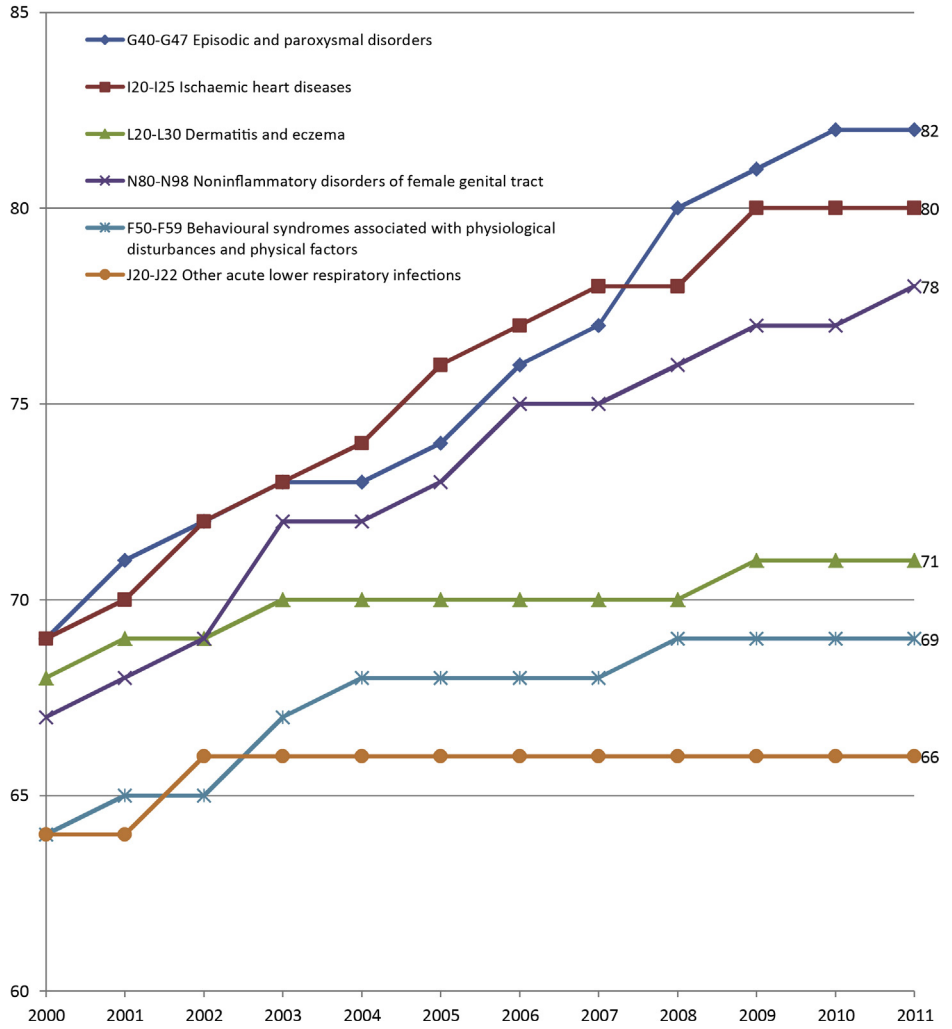

Fig. 2. Number of chemical substances previously commercialized in France for selected diseases, 2000–2011.

N_DEATHS_{it}, the number of deaths from disease i in year t. This is appropriate because, due to the inclusion of fixed disease effects, we are in essence analyzing within-disease *changes* in age at death, and as shown in Appendix Fig. 1, the variance of these changes is much larger for diseases causing few deaths than it is for diseases causing many deaths.

Panel A shows estimates of β_k ($k = 1, 3, \ldots, 25$) from Eq. (1). Each estimate is from a separate model. The estimate of β_1 is not statistically significant, but the estimates of β_k are positive and significant for $3 \leq k \leq 17$. This indicates that an increase in the number of chemical substances for a disease has a positive effect on mean age at death from the disease 3–17 years later. The estimated 2000–2009 longevity increase attributable to pharmaceutical innovation (Δ) ranges between 0.15 years (for $k = 9$) and 0.42 years (for $k = 15$); the mean of the estimates of Δ for $3 \leq k \leq 17$ is 0.29 years. The mean lag between the number of chemical substances commercialized for a disease and mean age at death from the disease ($LAG\_MEAN = \sum_k \beta_k k / \sum_k \beta_k$ for $3 \leq k \leq 17$) is 9.94 years.

To assess the importance of newly added drugs, a version of Eq. (1) including an additional explanatory variable—$\ln(N\_CHEM\_SUBSTANCES_{i,t-1} - N\_CHEM\_SUBSTANCES_{i,t-k})$—was also estimated.[23] In the 9-year lag model, the coefficients on $\ln(N\_CHEM\_SUBSTANCES_{i,t-9})$ and $\ln(N\_CHEM\_SUBSTANCES_{i,t-1} - N\_CHEM\_SUBSTANCES_{i,t-9})$ were both positive and significant: the estimates (p-values) were 0.74 (.0063) and 0.24 (.0178), respectively. In the 15-year lag model, the coefficient on $\ln(N\_CHEM\_SUBSTANCES_{i,t-1} - N\_CHEM\_SUBSTANCES_{i,t-15})$ was not significant: the estimates (p-values) were 1.25 (.0038) and 0.10 (.6154), respectively. In both the 9-year and 15-year lag models, including the additional explanatory variable had virtually no effect on the estimate of Δ, i.e. the estimate of the 2000–2009 longevity increase attributable to pharmaceutical innovation.

Panel B of Table 1 shows estimates of an alternative functional form of the relationship, which permits inclusion of observations with zero chemical substances (but does not impose diminishing marginal productivity): $\ln(N\_CHEM\_SUBSTANCES_{i,t-k})$ is replaced by ($N\_CHEM\_$

[23] $N\_CHEM\_SUBSTANCES_{i,t-1} - N\_CHEM\_SUBSTANCES_{i,t-k}$ = the number of drugs introduced between year $t-k$ and year $t-1$.

Table 1
Estimates of longevity (mean age at death) models.

Lag (k)	A. $AGE\_DEATH_{it} = \beta_k$ **ln(N_CHEM_SUBSTANCES$_{i,t-k}$)** $+ \alpha_i + \delta_t + \varepsilon_{it}$				B. $AGE\_DEATH_{it} = \beta_k$ **(N_CHEM_SUBSTANCES$_{i,t-k}$/ N_CHEM_SUBSTANCES$_{i,2009}$)** $+ \alpha_i + \delta_t + \varepsilon_{it}$				C. $AGE\_DEATH_{it} = \beta_k$ **ln(N_CHEM_SUBGROUPS$_{i,t-k}$)** $+ \alpha_i + \delta_t + \varepsilon_{it}$			
	Estimate	**Z**	**Pr > |Z|**	**Δ**	**Estimate**	**Z**	**Pr > |Z|**	**Δ**	**Estimate**	**Z**	**Pr > |Z|**	**Δ**
1	1.745	1.67	0.095	0.31	1.684	1.95	0.052	0.26	**1.851**	**2.96**	**0.003**	**0.26**
3	**1.463**	**2.67**	**0.008**	**0.31**	**1.700**	**2.28**	**0.022**	**0.30**	1.241	1.95	0.051	0.18
5	**0.958**	**3.38**	**0.001**	**0.27**	**1.414**	**2.17**	**0.030**	**0.30**	0.689	1.08	0.280	0.13
7	**0.753**	**3.21**	**0.001**	**0.20**	**1.402**	**2.15**	**0.031**	**0.28**	0.341	0.60	0.550	0.06
9	**0.582**	**2.57**	**0.010**	**0.15**	**1.313**	**2.00**	**0.046**	**0.25**	−0.036	−0.08	0.940	−0.01
11	**0.699**	**2.22**	**0.027**	**0.18**	**1.723**	**3.07**	**0.002**	**0.30**	0.200	0.53	0.595	0.03
13	**1.153**	**2.67**	**0.008**	**0.40**	**2.446**	**3.89**	**<.000**	**0.50**	0.438	1.24	0.214	0.12
15	**1.212**	**2.99**	**0.003**	**0.42**	1.53	0.127	0.32	0.25	0.676	1.70	0.090	0.18
17	**1.029**	**2.38**	**0.017**	**0.36**	0.61	0.545	0.15	0.30	0.696	1.75	0.079	0.20
19	0.815	1.92	0.055	0.31	0.13	0.896	0.03	0.50	0.479	1.32	0.185	0.15
21	0.674	1.54	0.124	0.25	−0.769	−0.51	0.613	−0.13	0.066	0.17	0.864	0.02
23	0.176	0.33	0.743	0.07	−1.743	−1.18	0.239	−0.27	−0.250	−0.65	0.514	−0.09
25	0.213	0.38	0.702	0.08	−1.722	−1.16	0.246	−0.25	0.139	0.38	0.707	0.05

Note: Estimates in bold are statistically significant (p-value <.05)
All models were estimated by weighted least squares, weighting by N_DEATHS_{it}. Standard errors are clustered within diseases. $\Delta = (\delta'_{2009} - \delta'_{2000}) - (\delta_{2009} - \delta_{2000})$ is an estimate of the 2000–2009 increase in longevity attributable to pharmaceutical innovation.

$SUBSTANCES_{i,t-k}$/$N\_CHEM\_SUBSTANCES_{i,2009}$). In this case, the estimates of β_k are positive and significant for $3 \leq k \leq 13$. The estimates of Δ range between 0.25 years (for $k = 9$) and 0.50 years (for $k = 13$); the mean of the estimates of Δ for $3 \leq k \leq 13$ is 0.32 years. The mean lag between the number of chemical substances commercialized and mean age at death ($LAG\_MEAN = \sum_k \beta_k k / \sum_k \beta_k$ for $3 \leq k \leq 13$) is 8.45 years.

Panel C of Table 1 shows estimates of the logarithmic model (Eq. (1)) in which the number of chemical substances is replaced by the number of chemical subgroups. Only one of the estimates (β_1) is statistically significant, which indicates that longevity is much more strongly related to the number of substances than it is to the number of subgroups. The estimate of Δ for $k = 1$ is slightly smaller than the mean of the estimates in Panels A and B. The fact that β_1 is the only significant coefficient in Panel C suggests that new chemical subgroups increase longevity much sooner (but not more) than new chemical substances.

If there were a significant correlation between age at death from disease i and pharmaceutical innovation for disease j, where i and j are different, unrelated diseases, one might doubt that the significant correlations reported in Table 1 were indicative of a positive impact of pharmaceutical innovation on longevity. This possibility was investigated by estimating the equation $AGE\_DEATH_{it} = \beta_5 \ln(N\_CHEM\_SUBSTANCES_{j,t-5}) + \alpha_i + \delta_t + \varepsilon_{it}$, where $j \neq i$, i.e. by randomly mismatching the innovation data to the longevity data. $k = 5$ was chosen, because β_5 is the most significant coefficient in Panel A of Table 1. This procedure was performed 50 times, randomly mismatching the innovation data to the longevity data each time. The mean of the estimates of β_5 was .028, less than 3% of the estimate of β_5 in Panel A of Table 1. Only two of the fifty estimates were positive and significant, and neither of these was as significant as the estimate of β_5 in Panel A of Table 1; five estimates were *negative* and significant. The results of this "falsification analysis" indicate that it is reasonable to interpret the significant correlations reported in Table 1 as indicative of a positive impact of pharmaceutical innovation on longevity.

4.2. Hospital utilization equation estimates

Estimates of parameters from hospital utilization models are presented in Table 2. Panel A shows estimates of Eq. (2), in which HOSP_UTIL is defined as the age-adjusted rate of hospital discharges per 100,000 population. None of the estimates are statistically significant, although the estimates of β_5 and β_7 are nearly significant (p-value <.06).

Panel B shows estimates of Eq. (2), in which HOSP_UTIL is defined as the age-adjusted rate of hospital days per 100,000 population. Four of the estimates (for $5 \leq k \leq 11$) are negative and significant (p-value <.02). The mean of the estimates of Δ for $5 \leq k \leq 11$ is −.093, indicating that pharmaceutical innovation during 2000–2010 reduced the number of hospital days in 2010 by about 9.3%. The mean lag between the number of chemical substances and hospitalization is 7.74 years.

Panel C shows estimates of the alternative functional form of the hospital days model, in which $\ln(N\_CHEM\_SUBSTANCES_{i,t-k})$ is replaced by $(N\_CHEM\_SUBSTANCES_{i,t-k}/N\_CHEM\_SUBSTANCES_{i,2009})$. This functional form does not fit the data as well as the logarithmic model does, but the estimates of β_9 and β_{11} are significant; they imply a slight lower estimate of Δ (−.086), and a longer lag (10.0 years).

Panel D of Table 2 shows estimates of the logarithmic version of the hospital days model, in which the number of chemical substances is replaced by the number of chemical subgroups. Three of the estimates are statistically significant, but comparison of Panels B and D reveals that the age-adjusted rate of hospital days (like longevity) is much

Table 2
Estimates of hospital utilization models.

k (lag)	Estimate	Z	Pr > |Z|	Δ	Estimate	Z	Pr > |Z|	Δ
	A. $\ln(\mathbf{DISCHARGES}_{it}) = \beta_k \ln(\mathbf{N\_CHEM\_SUBSTANCES}_{\mathbf{i,t-k}}) + \alpha_i + \delta_t + \varepsilon_{it}$				B. $\ln(\mathbf{DAYS}_{it}) = \beta_k \ln(\mathbf{N\_CHEM\_SUBSTANCES}_{\mathbf{i,t-k}}) + \alpha_i + \delta_t + \varepsilon_{it}$			
1	−0.420	−1.16	0.248	−0.040	−0.347	−1.16	0.247	−0.041
3	−0.634	−1.60	0.109	−0.069	−0.490	−1.57	0.117	−0.065
5	−0.732	−1.92	0.055	−0.096	**−0.674**	**−2.56**	**0.011**	**−0.107**
7	−0.662	−1.95	0.052	−0.085	**−0.760**	**−2.78**	**0.005**	**−0.099**
9	−0.327	−1.09	0.275	−0.043	**−0.641**	**−2.93**	**0.003**	**−0.084**
11	−0.341	−1.14	0.254	−0.043	**−0.658**	**−2.97**	**0.003**	**−0.082**
13	−0.140	−0.52	0.603	−0.031	−0.098	−0.44	0.660	−0.027
15	−0.084	−0.31	0.754	−0.021	0.027	0.12	0.905	0.008
	C. $\ln(\mathbf{DAYS}_{it}) = \beta_k \ln(\mathbf{N\_CHEM\_SUBGROUPS}_{\mathbf{i,t-k}}) + \alpha_i + \delta_t + \varepsilon_{it}$				D. $\ln(\mathbf{DAYS}_{it}) = \beta_k \ln(\mathbf{N\_CHEM\_SUBGROUPS}_{\mathbf{i,t-k}}) + \alpha_i + \delta_t + \varepsilon_{it}$			
1	−0.153	−0.97	0.334	−0.024	−0.384	−1.12	0.262	−0.039
3	−0.209	−1.22	0.222	−0.034	−0.465	−1.28	0.200	−0.051
5	−0.287	−1.36	0.174	−0.051	**−0.570**	**−1.97**	**0.049**	**−0.076**
7	−0.405	−1.51	0.131	−0.059	**−0.682**	**−2.10**	**0.036**	**−0.066**
9	**−0.882**	**−2.70**	**0.007**	**−0.086**	−0.331	−1.39	0.165	−0.033
11	**−0.963**	**−2.65**	**0.008**	**−0.085**	**−0.428**	**−2.13**	**0.034**	**−0.039**
13	−0.121	−0.32	0.747	−0.021	0.070	0.44	0.661	0.017
15	0.119	0.33	0.742	0.021	0.098	0.56	0.578	0.024

Note: Estimates in bold are statistically significant (p-value <.05)
DISCHARGES, the age-adjusted rate of hospital discharges per 100,000 population; DAYS, the age-adjusted rate of hospital days per 100,000 population; $\Delta = (\delta'_{2010} - \delta'_{2000}) - (\delta_{2010} - \delta_{2000})$ is an estimate of the 2000–2010 log change in the age-adjusted hospitalization rate attributable to pharmaceutical innovation.
All models were estimated by weighted least-squares. Weight for estimates in Panel A is Σ_t DISCHARGES$_{it}$; weight for estimates in Panel B, C, and D is Σ_t DAYS$_{it}$. Standard errors are clustered within diseases.

Table 3
Estimates of models of the effect of pharmaceutical innovation on pharmaceutical expenditure (Eq. (3)).

Model	Parameter	Estimate	Std. Err.	Z	Pr > |Z|
1	β_0	0.768	0.473	1.62	0.104
2	β_1	**0.952**	**0.434**	**2.19**	**0.028**
3	β_2	**1.157**	**0.325**	**3.56**	**0.000**
4	β_3	**1.354**	**0.232**	**5.83**	**<.0001**
5	β_4	**1.078**	**0.211**	**5.11**	**<.0001**
6	β_5	**0.811**	**0.237**	**3.42**	**0.001**

more strongly related to the number of substances than it is to the number of subgroups.

A falsification analysis of the hospital utilization results similar to the falsification analysis of the longevity results was performed. The equation $\ln(\text{DAYS}_{it}) = \beta_{11} \ln(\text{N\_CHEM\_SUBSTANCES}_{j,t-5}) + \alpha_i + \delta_t + \varepsilon_{it}$, where $j \neq i$, was estimated, i.e. the innovation data were randomly mismatched to the hospital utilization data. $k = 11$ was chosen, because β_{11} is the most significant coefficient in Panel B of Table 2. This procedure was performed 50 times, randomly mismatching the innovation data to the hospital utilization data each time. The mean of the estimates of β_5 was −.063, less than 10% of the estimate of β_{11} in Panel B of Table 2. Only three of the fifty estimates were negative and significant, and none of these was as significant as the estimate of β_{11} in Panel B of Table 2; two estimates were *positive* and significant. The results of this "falsification analysis" indicate that it is reasonable to interpret the significant correlations reported in Table 2 as indicative of a negative impact of pharmaceutical innovation on hospital utilization.

4.3. Pharmaceutical expenditure equation estimates

Estimates of Eq. (3) are shown in Table 3. The estimate of β_0 indicates that the relationship across drug classes between the growth in expenditure (ex-manufacturer value) and the contemporaneous growth in number of molecules is not statistically significant. However, the estimates of β_1–β_5 indicate that the relationship between the growth in expenditure and the growth in the number of molecules 1–5 years earlier is statistically significant. Growth in the number of molecules 3 years earlier has the largest and most significant effect. A 10% increase in the number of molecules in a drug class is associated with a 13.5% increase in expenditure on that class 3 years later.

The estimates in Table 3 indicate that the increase in pharmaceutical expenditure is most closely related to the increase in the number of molecules 3 years earlier. Hence, to calculate the increase in 2009 pharmaceutical expenditure attributable to lagged pharmaceutical innovation during 2000–2009, one would like to know the number of molecules sold in France during the period 1997–2006.

Table 4
Estimation of incremental cost effectiveness of pharmaceutical innovation: baseline case.

Line	Variable	Actual values, 2009 (Y_{actual})	Estimated values in 2009 in the absence of 9 prior years of pharmaceutical innovation ($Y_{no\_innovation}$)	Difference ($Y_{no\_innovation} - Y_{actual}$)	Basis for $Y_{no\_innovation}$ estimate
1	**Life expectancy (mean age at death)**	76.92	76.63	−0.29	Table 1, Panel A
	Per capita medical expenditure in 2009, USD PPP				
2	Prescription drug expenditure	$608	$483	−$125	Table 3
3	Hospital expenditure	$1462	$1571	$109	Table 2, Panel B
4	Other medical expenditure	$1739	$1739	$0	Assumption that pharma. innovation has no effect on other medical expenditure
5	Total medical expenditure	$3809	$3793	−$16	Sum of Rx, hospital, and other medical expenditure
6	**Lifetime medical expenditure (= life expectancy * total medical expenditure in 2009)**	$292,990	$290,681	−$2309	

Source for data on actual medical expenditure in 2009: http://stats.oecd.org/.

Unfortunately, data on the number of molecules (as defined by IMS) sold in France prior to 2000 are not available. Theriaque data on the number of chemical substances in 1997 and 2006 will therefore be used instead. As shown in Appendix Table 1, the number of chemical substances increased from 1922 in 1997 to 2278 in 2006. The estimate of β_3 in Table 3 implies that the 1997–2006 increase in the number of chemical substances increased pharmaceutical expenditure in 2009 by 25.9% (= exp [1.354 * ln(2278/1922)] − 1). However, the increase in 2009 pharmaceutical expenditure attributable to pharmaceutical innovation during 1997–2006 may have been smaller than that—about 18.0%—because during the period 2000–2010, the growth rate of the number of IMS molecules was 28% lower than the growth rate of Theriaque chemical substances.

5. The cost-effectiveness of pharmaceutical innovation in France

Estimates of the effect of pharmaceutical innovation on mean age at death (Table 1), hospital utilization (Table 2), and pharmaceutical expenditure (Table 3) were presented above. Now these estimates will be used to calculate the incremental cost-effectiveness of pharmaceutical innovation, i.e. the cost per life year gained from the introduction of new drugs. The incremental cost-effectiveness ratio (ICER) is defined as follows[24]:

$$\mathrm{ICER} = \frac{(\mathrm{LE}_{actual} * \mathrm{MedExpend}_{actual}) - (\mathrm{LE}_{no\_innovation} * \mathrm{MedExpend}_{no\_innovation})}{\mathrm{LE}_{actual} - \mathrm{LE}_{no\_innovation}}$$

where

$\mathrm{MedExpend}_{actual}$	= actual per capita medical expenditure in 2009
$\mathrm{MedExpend}_{no\_innovation}$	= estimated per capita medical expenditure in 2009 in the absence of 9 prior years of pharmaceutical innovation
LE_{actual}	= actual life expectancy in 2009
$\mathrm{LE}_{no\_innovation}$	= estimated life expectancy in 2009 in the absence of 9 prior years of pharmaceutical innovation

Table 4 shows a "baseline" calculation of the ICER. After this calculation is explained, some sensitivity analysis, which will indicate the effect of modifying the assumptions underlying the baseline calculation, will be performed. Line 1 shows the actual value of life expectancy (mean age at death) in 2009 (76.92 years), and the estimated value (76.63 years, derived from the estimates in Panel A of Table 1) in the absence of (lagged) pharmaceutical innovation during the period 2000–2009. The estimates indicate that life expectancy would have been 0.29 years (3.44 months) lower in 2009 in the absence of pharmaceutical innovation.

Lines 2–4 show three components of medical expenditure, and line 5 shows their sum, total medical expenditure. The 2009 actual values (expressed in USD PPP) were obtained from http://stats.oecd.org/. Pharmaceutical expenditure is considered first, in line 2. The estimate of β_3 in Table 3 implied that, if no new chemical substances had been commercialized during 1997–2006, per capita pharmaceutical expenditure in 2009 would have been $125 lower ($483 instead of $608[25]). Hospital expenditure is considered next, in line 3. The estimates in Panel B of Table 2 implied that, in the absence of lagged pharmaceutical innovation during 2000–2009, the number of hospital days would have been 9.3% higher in 2009.

[24] $\mathrm{LE}_{actual} * \mathrm{MedExpend}_{actual}$ = actual (undiscounted) lifetime medical expenditure; $\mathrm{LE}_{no\_innovation} * \mathrm{MedExpend}_{no\_innovation}$ = estimated (undiscounted) lifetime medical expenditure in the absence of 9 prior years of pharmaceutical innovation.

[25] $608 is the sum of prescription drug expenditure ($520) and over-the-counter drug expenditure ($88).

Evidence based on U.S. data indicates that the elasticity of hospital expenditure with respect to the number of hospital days is about 0.81. If it is assumed that this also applies to France, then hospital expenditure would have been 7.4% (= 0.81 * 9.3%) higher in 2009 in the absence of lagged pharmaceutical innovation during 2000–2009. Hence, per capita hospital pharmaceutical expenditure in 2009 would have been $109 higher ($1571 instead of $1462). Longitudinal disease-level data on expenditure on or utilization of other medical services are not available, so it is assumed (in line 4) that pharmaceutical innovation had no effect on other medical expenditure. As shown in line 5, under these assumptions per capita medical expenditure in 2009 would have been slightly ($16) lower in the absence of prior pharmaceutical innovation, because the estimated increase in hospital expenditure would have been slightly smaller than the estimated reduction in pharmaceutical expenditure. Lifetime medical expenditure would have been $2309 lower in the absence of prior pharmaceutical innovation, due to the reductions in life expectancy and annual medical expenditure. The calculations in Table 4 imply that the cost per life-year gained from the introduction of new drugs was $8065 (= −$2309/−0.29 years), which is a very small fraction of leading economists' estimates of the value of (or consumers' willingness to pay for) a one-year increase in life expectancy. Aldy and Viscusi (2008) estimate that the average value of (willingness to pay for) an American life-year is $300,000.

Changes in any of the estimates or assumptions documented in Table 4 will, of course, change one's estimate of the ICER. A change that can substantially increase the ICER is reducing the estimate of the hospital cost reduction attributable to pharmaceutical innovation. If it is assumed that the hospital cost reduction is half as large as that implied by the estimates in Panel B in Table 2—about 3.7% instead of 7.4%—the ICER is about $23,000. If it is assumed that there is *no* hospital cost reduction, the ICER is $37,000. Even this figure is well below the consensus value of a statistical life-year.

Moreover, there are several good reasons to think that the calculations in Table 4 lead to an *overestimate* of the ICER. First, the increase in life expectancy attributable to pharmaceutical innovation may be underestimated. The increase in life expectancy at birth during 2000–2009 was 59% larger than the increase in mean age at death (2.22 years vs. 1.39 years). Second, the increase in pharmaceutical expenditure attributable to pharmaceutical innovation may be overestimated (by about 42%), because the growth rate of the number of IMS molecules was lower than the growth rate of Theriaque chemical substances. And third, in Table 4 it is assumed that pharmaceutical innovation had no effect on other medical expenditure, but it may have reduced other medical expenditure—especially nursing home expenditure—as it appears to have reduced hospital expenditure. If it is assumed that the hospital cost reduction is half as large as that implied by the estimates in Panel B of Table 2—about 3.7% instead of 7.4%—and that pharmaceutical innovation also reduced other medical expenditure by 3.7%, the ICER would be below $6000.

This study is subject to several limitations. One limitation is that the estimates do not capture between-disease spillover effects, because the relationship analyzed is between pharmaceutical innovation related to a disease and the mean age of deaths caused by the disease. These effects appear to be fairly modest in practice—80% of the actual increase in mean age at death was due to within-disease increases; only 20% was due to a shift in the distribution of causes of death—but accounting for these spillover effects would certainly be desirable.

A second limitation is that the outcome measure analyzed is the number of life-years, not the number of *quality-adjusted* life-years (QALYs). As argued in Lichtenberg (2009), even though quality of life is generally far from perfect towards the end of life, the increase in QALYs attributable to innovation could be either greater than or less than the increase in life-years.

A third limitation is that controlling for other types of medical innovation, such as innovation in diagnostic imaging, surgical procedures, and medical devices, was infeasible, since longitudinal disease-level measures of non-pharmaceutical medical innovation are not available for France. Such data are available for the U.S. during the period 1998–2007, and they suggest that failure to control for other medical innovation is unlikely to result in overestimation of the effect of pharmaceutical innovation on longevity growth, but further research on this issue is clearly warranted.

6. Summary and conclusions

In this paper, longitudinal, disease-level data were used to analyze the impact of pharmaceutical innovation on longevity (mean age at death) and medical expenditure in France during the period 2000–2009. The estimates imply that pharmaceutical innovation increased mean age at death by 0.29 years (3.43 months) during this period—about one-fifth of the total increase in longevity. This estimate is smaller than those obtained in some previous studies: Lichtenberg (2012a) estimated that pharmaceutical innovation increased life expectancy at birth by 0.45 years in Germany during the period 2000–2007, and Lichtenberg (2013a) estimated that it increased the life expectancy (mean time till death) of elderly Americans by 0.44 years during the period 1996–2003.[26] But Lichtenberg (2012b: Appendix Table A2) found that the 2000–2009 increase in the mean vintage of drugs was much lower in France (3.9 years) than it was in Germany (9.0 years) and the U.S. (7.8 years), so one would expect the contribution of pharmaceutical innovation to longevity increase to be smaller in France.

Pharmaceutical innovation during 2000–2009 is estimated to have increased per capita pharmaceutical expenditure by $125 (26%) in 2009, but most (87%) of this increase was offset by a reduction in hospital expenditure. The baseline estimate of the cost per life-year gained from pharmaceutical innovation in France during 2000–2009 is about $8100. This estimate is fairly close to the mean of estimates obtained ($10,800) from the U.S. and German studies just cited and from two other

[26] The first study was based on longitudinal state-level data, and the second study was based on cross-sectional patient-level data.

studies of Australia and the U.S. (Lichtenberg and Duflos, 2008; Lichtenberg, 2011), which ranged between $3600 and $16,200. French drug prices are about 17% lower than U.S. drug prices, slightly lower than German drug prices, and about the same as Australian drug prices (Lichtenberg, 2010: Fig. 1).

Longevity and hospital utilization are much more strongly related to the number of drugs than they are to the number of drug classes. One possible explanation for this is that the number of drugs in a class may reflect how important or valuable that class is. A new class (or mechanism of action) that represents a major breakthrough is likely to attract more entry than a new class that is of minor therapeutic significance. Also, the first drug in a class is not necessarily, and may not usually be, the most important drug in the class (DiMasi and Faden, 2011). For example, lovastatin was the first statin marketed in the U.S. (in 1987), but this drug was clearly superseded by later statins such as simvastatin and atorvastatin.

In recent years, several emerging economies, including India, Argentina and the Philippines, have passed laws placing strict limits on pharmaceutical patents, and Brazil and Thailand have been issuing compulsory licenses for AIDS drugs for years under multilateral agreements that allow such actions on public health grounds (Harris and Thomas, 2013). While such policies may benefit patients in those countries in the short run, in the long run, they are likely to diminish incentives for new drug development, particularly because sales in emerging markets like Brazil and China are expected to account for 30 percent of global pharmaceutical spending by 2016, up from 20 percent in 2011, according to IMS Health. The evidence presented in this paper indicates that reduced investment in pharmaceutical innovation would have adverse long-term effects on longevity and other aspects of health.

Appendix 1. The effect of pharmaceutical innovation on prescription drug vintage

In the text it was hypothesized that there is a significant positive correlation across drug classes between the growth in the number of molecules and the subsequent growth in the mean vintage of drugs. The IMS MIDAS data may be used to test this hypothesis. The data enable identification of: (1) all products within a class; (2) all molecules within each product; and (3) the vintage (initial world launch year) of each molecule. Hence, the weighted mean vintage of products in drug class c in year t can be measured:

Rx_VINTAGE_{ct}	= the weighted mean vintage of products in drug class c in year t = $\Sigma_p\ Q_{pct}\ \text{VINT}_p / \Sigma_p\ Q_{pct}$
Q_{pct}	= the quantity (number of standard units) of product p in drug class c in year t
VINT_p	= the mean vintage (initial commercialization year) of the molecules contained in product p

The following relationship between the number of molecules and the mean vintage of drugs was estimated:

$$\text{Rx\_VINTAGE}_{ct} = \pi \ln(\text{N\_MOLECULE}_{c,t-k}) + \alpha_c + \delta_t + \varepsilon_{it}$$
$$(c = 1, \ldots, C; t = 2005, \ldots, 2010; k = 0, \ldots, 5) \qquad \text{(A1)}$$

Table A1
Summary statistics on longevity and pharmaceutical innovation in France.

Year	Number of deaths	Mean age at death
2000	530,850	75.53
2001	531,072	75.53
2002	535,140	75.75
2003	552,335	76.18
2004	509,419	75.80
2005	527,516	76.26
2006	515,952	76.21
2007	520,535	76.50
2008	532,474	76.77
2009	537,197	76.92

Year	Number of (3rd level ATC) pharmacological subgroups	Number of (4th level ATC) chemical subgroups	Number of (5th level ATC) chemical substances
1995	240	644	1822
1996	242	653	1873
1997	243	664	1922
1998	243	674	1976
1999	244	680	2027
2000	245	686	2062
2001	245	688	2095
2002	247	692	2140
2003	248	695	2176
2004	249	702	2214
2005	250	706	2246
2006	251	711	2278
2007	251	716	2305
2008	252	724	2345
2009	253	727	2379
2010	253	731	2411

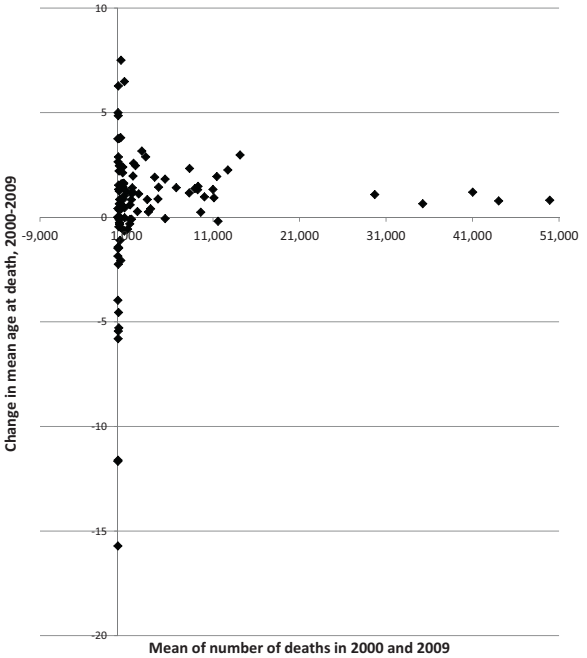

Fig. A1. Relationship across diseases between average number of deaths and change in mean age at death, 2000–2009.

Table A2
Chemical substances (drugs) and chemical subgroups used to treat C43–C44 Melanoma and other malignant neoplasms of skin.

Chemical substance (WHO ATC 5th level)	Year first commercialized in France
H02AB02 Dexamethasone	1959
H02AB04 Methylprednisolone	1959
H02AB01 Betamethasone	1963
V03AF03 Calcium folinate	1973
L01AD02 Lomustine	1976
L01AX04 Dacarbazine	1976
L01AD01 Carmustine	1983
L03AB05 Interferon alfa-2b	1987
B01AB04 Dalteparin	1988
J02AC01 Fluconazole	1988
B03XA01 Erythropoietin	1989
L01AD05 Fotemustine	1989
L03AB04 Interferon alfa-2a	1989
V03AF04 Calcium levofolinate	1993
D06BB10 Imiquimod	1999
B03XA02 Darbepoetin alfa	2001
L01XE01 Imatinib	2001
M05BA08 Zoledronic acid	2002
L01XD03 Methyl aminolevulinate	2007
V09DB06 Technetium Tc-99M rheniumsulfide colloid	2008
L01XC11 Ipilimumab	2011
B01AB Heparin group	1945
H02AB Glucocorticoids	1953
M05BA Bisphosphonates	1962
L01AX Other alkylating agents	1970
V03AF Detoxifying agents for antineoplastic treatment	1973
D06BB Antivirals	1974
L01AD Nitrosoureas	1976
L03AB Interferons	1987
J02AC Triazole derivatives	1988
B03XA Other antianemic preparations	1989
L01XD Sensitizers used in photodynamic/radiation therapy	1997
L01XC Monoclonal antibodies	1998
L01XE Protein kinase inhibitors	2001
V09DB Technetium Tc-99M, particles and colloids	2008

Source: Author's calculations based on Theriaque data.

Table A3
Data on mortality and number of drugs, by ICD-10 Block, 2000 and 2009.

ICD-10 Block	Number of deaths		Mean age at death		DRUG_STOCK	
	2000	2009	2000	2009	2000	2009
A15–A19 Tuberculosis	633	358	76.9	77.5	16	16
A30–A49 Other bacterial diseases	4441	4974	77.2	78.7	95	101
A50–A64 Infections with a predominantly sexual mode of transmission	7	5	70.4	68.5	39	40
B00–B09 Viral infections characterized by skin and mucous membrane lesions	116	127	78.5	78.1	28	29
B15–B19 Viral hepatitis	900	672	67.0	67.0	11	18
B20–B24 Human immunodeficiency virus [HIV] disease	1012	511	44.0	50.5	19	35
B25–B34 Other viral diseases	133	85	72.2	66.9	9	10
B50–B64 Protozoal diseases	45	60	56.4	62.7	29	31
B65–B83 Helminthiases	8	7	72.5	56.8	17	18
B99–B99 Other infectious diseases	1310	1885	81.8	82.9	24	25
C00–C14 Malignant neoplasms of lip, oral cavity and pharynx	4643	3870	63.8	65.7	13	15
C15–C26 Malignant neoplasms of digestive organs	42,338	45,697	73.5	74.3	24	35
C30–C39 Malignant neoplasms of respiratory and intrathoracic organs	27,575	31,825	67.4	68.5	31	36
C40–C41 Malignant neoplasms of bone and articular cartilage	649	525	60.9	62.4	12	14
C43–C44 Melanoma and other malignant neoplasms of skin	1772	2289	69.4	71.8	15	20
C45–C49 Malignant neoplasms of mesothelial and soft tissue	1627	2005	67.3	69.9	21	30
C50–C50 Malignant neoplasm of breast	11,068	11,818	68.9	70.8	39	46
C51–C58 Malignant neoplasms of female genital organs	6500	6985	71.2	72.6	28	35
C60–C63 Malignant neoplasms of male genital organs	9284	9164	79.0	80.4	27	31
C64–C68 Malignant neoplasms of urinary tract	7713	8799	74.4	75.5	19	23
C69–C72 Malignant neoplasms of eye, brain and other parts of central nervous system	3012	3422	60.2	63.1	18	21
C73–C75 Malignant neoplasms of thyroid and other endocrine glands	529	576	69.4	71.5	11	17
C76–C80 Malignant neoplasms of ill-defined, secondary and unspecified sites	11,637	10,579	71.5	72.4	42	53
C81–C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	12,458	12,974	72.6	74.9	57	73
C97–C97 Malignant neoplasms of independent (primary) multiple sites	2841	2692	72.2	75.3	6	8
D50–D53 Nutritional anaemias	151	171	86.0	88.4	14	17
D55–D59 Haemolytic anaemias	119	86	71.2	69.7	14	18
D60–D64 Aplastic and other anaemias	947	1018	81.2	82.5	16	19
D65–D69 Coagulation defects, purpura and other hemorrhagic conditions	539	411	72.7	74.1	31	32
D70–D77 Other diseases of blood and blood-forming organs	235	305	72.4	71.9	15	22
D80–D89 Certain disorders involving the immune mechanism	285	249	66.7	69.2	11	12
E00–E07 Disorders of thyroid gland	823	655	84.1	85.1	17	19
E10–E14 Diabetes mellitus	10,816	11,168	78.5	79.8	37	58
E20–E35 Disorders of other endocrine glands	182	137	77.0	77.6	37	40

Table A3 (*Continued*)

ICD-10 Block	Number of deaths		Mean age at death		DRUG_STOCK	
	2000	2009	2000	2009	2000	2009
E50–E64 Other nutritional deficiencies	42	24	75.6	69.8	56	60
E70–E90 Metabolic disorders	3889	3681	79.2	79.6	98	123
F10–F19 Mental and behavioral disorders due to psychoactive substance use	3480	3592	56.9	57.1	37	41
F20–F29 Schizophrenia, schizotypal and delusional disorders	387	402	72.0	72.4	32	33
F30–F39 Mood [affective] disorders	1144	1097	79.4	78.9	54	57
F40–F48 Neurotic, stress-related and somatoform disorders	376	322	82.7	80.6	55	59
F50–F59 Behavioral syndromes associated with physiological disturbances and physical factors	63	86	74.1	69.5	64	69
F60–F69 Disorders of adult personality and behavior	.	13	.	85.2	.	22
F70–F79 Mental retardation	144	121	61.0	61.1	13	14
F80–F89 Disorders of psychological development	20	25	43.3	45.9	14	15
F99–F99 Unspecified mental disorder	45	48	69.6	64.2	13	14
G00–G09 Inflammatory diseases of the central nervous system	353	376	54.9	62.4	34	38
G10–G14 Systemic atrophies primarily affecting the central nervous system	1387	1731	66.5	67.3	2	2
G20–G26 Extrapyramidal and movement disorders	4189	5089	81.8	82.7	32	35
G30–G32 Other degenerative diseases of the nervous system	9008	19,235	83.1	86.0	4	6
G35–G37 Demyelinating diseases of the central nervous system	532	614	61.4	63.8	10	12
G40–G47 Episodic and paroxysmal disorders	1612	1880	66.7	68.7	69	81
G50–G59 Nerve, nerve root and plexus disorders	7	9	75.4	71.4	12	13
G60–G64 Polyneuropathies and other disorders of the peripheral nervous system	132	142	73.6	75.8	8	8
G70–G73 Diseases of myoneural junction and muscle	306	346	50.9	54.7	16	16
H80–H83 Diseases of inner ear	1	4	77.5	81.3	18	18
H90–H95 Other disorders of ear		1		77.5		8
I00–I02 Acute rheumatic fever	6	4	78.3	78.8	16	17
I05–I09 Chronic rheumatic heart diseases	1780	1548	78.1	79.5	0	1
I10–I15 Hypertensive diseases	7626	8952	82.6	84.9	104	123
I20–I25 Ischemic heart diseases	45,330	36,700	78.8	80.0	69	80
I26–I28 Pulmonary heart disease and diseases of pulmonary circulation	5719	5213	78.9	78.8	18	25
I30–I52 Other forms of heart disease	49,798	50,044	83.1	83.9	125	132
I60–I69 Cerebrovascular diseases	38,404	32,076	81.3	82.0	22	24
I70–I79 Diseases of arteries, arterioles and capillaries	11,093	8909	79.9	80.8	53	57
I80–I89 Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	1942	1213	80.2	80.1	73	81
I95–I99 Other and unspecified disorders of the circulatory system	215	183	80.3	81.2	13	14
J00–J06 Acute upper respiratory infections	26	22	65.9	54.3	106	108
J20–J22 Other acute lower respiratory infections	3778	3006	86.2	87.1	64	66
J40–J47 Chronic lower respiratory diseases	9494	9043	78.9	80.4	96	103
J80–J84 Other respiratory diseases principally affecting the interstitium	1562	1844	77.2	78.4	16	16
K20–K31 Diseases of esophagus, stomach and duodenum	1509	1303	79.6	79.5	40	42
K50–K52 Noninfective enteritis and colitis	767	766	80.8	81.3	14	15
K65–K67 Diseases of peritoneum	574	679	77.1	77.9	12	12
K70–K77 Diseases of liver	9438	8388	62.5	63.8	17	24
K80–K87 Disorders of gallbladder, biliary tract and pancreas	2220	2586	77.8	79.0	15	16
K90–K93 Other diseases of the digestive system	2222	2297	79.1	79.4	32	33
L10–L14 Bullous disorders	148	146	86.8	87.2	10	10
L40–L45 Papulosquamous disorders	3	1	74.2	62.5	44	51
L50–L54 Urticaria and erythema	27	22	73.0	71.6	30	34
M00–M03 Infectious arthropathies	61	114	80.6	82.1	58	58
M05–M14 Inflammatory polyarthropathies	620	530	78.7	80.3	58	68
M15–M19 Arthrosis	212	193	86.6	86.2	39	42
M20–M25 Other joint disorders	.	2	.	70.0	.	22
M30–M36 Systemic connective tissue disorders	918	592	76.5	75.9	21	25
M40–M43 Deforming dorsopathies	197	144	76.5	80.3	4	4
M45–M49 Spondylopathies	198	200	81.5	81.2	25	28
M50–M54 Other dorsopathies	21	21	70.8	75.8	35	36
M80–M85 Disorders of bone density and structure	201	152	86.4	86.2	31	41
M86–M90 Other osteopathies	1219	1535	84.3	84.0	39	41
N00–N08 Glomerular diseases	106	80	75.2	76.5	18	18
N10–N16 Renal tubulo–interstitial diseases	572	805	82.5	84.1	37	38
N17–N19 Renal failure	4669	6239	81.6	83.4	19	23
N25–N29 Other disorders of kidney and ureter	54	65	75.9	78.8	8	10
N30–N39 Other diseases of urinary system	1268	1559	84.6	85.2	89	93
N40–N51 Diseases of male genital organs	419	361	82.6	84.2	54	56
N70–N77 Inflammatory diseases of female pelvic organs	44	28	79.4	84.3	42	43
N80–N98 Noninflammatory disorders of female genital tract	52	42	81.1	78.8	67	77
O60–O75 Complications of labor and delivery	11	15	34.3	32.8	16	17
P05–P08 Disorders related to length of gestation and fetal growth	167	115	0.6	0.5	4	5
P35–P39 Infections specific to the perinatal period	108	99	0.5	0.5	1	1
Q20–Q28 Congenital malformations of the circulatory system	711	574	22.6	24.2	1	2

Table A3 (*Continued*)

ICD-10 Block	Number of deaths		Mean age at death		DRUG_STOCK	
	2000	2009	2000	2009	2000	2009
R00–R09 Symptoms and signs involving the circulatory and respiratory systems	9758	13,393	80.1	79.9	53	54
R10–R19 Symptoms and signs involving the digestive system and abdomen	141	156	80.0	81.3	61	63
R40–R46 Symptoms and signs involving cognition, perception, emotional state and behavior	239	251	83.3	82.2	37	38
R50–R69 General symptoms and signs	9668	9502	88.5	88.7	126	134

Table A4
Age-adjusted rates of hospital discharges hospital days and average length of stay, France, 2000–2010.

Year	Hospital discharges per 100,000 population	Hospital days per 100,000 population	Average length of stay
2000	17,090	100,248	5.9
2001	16,612	97,440	5.9
2002	16,138	95,283	5.9
2003	15,831	92,252	5.8
2004	15,696	90,319	5.8
2005	15,458	87,526	5.7
2006	15,199	84,312	5.5
2007	14,882	81,959	5.5
2008	14,687	78,493	5.3
2009	14,561	77,179	5.3
2010	14,286	75,799	5.3

All causes of diseases (A00–Z99) excluding external causes of morbidity and mortality (V00–Y98) and liveborn infants according to place of birth (Z38).

Table A5
Data on age-adjusted hospitalization rates and number of drugs, by ICD-10 Block, 2000 and 2010.

ICD10	Hospital discharges per 100,000 population		Hospital days per 100,000 population		Average length of stay		Number of drugs	
	2000	2010	2000	2010	2000	2010	2000	2010
A00–A08 – Intestinal infectious diseases except diarrhea	49	59	179	193	3.6	3.3	37	40
A09 – Diarrhea and gastroenteritis of presumed infectious origin	72	64	234	188	3.3	2.9	18	18
A15–A19_B90 – Tuberculosis	14	10	208	149	15.0	15.4	16	16
A40_A41 – Septicaemia	45	38	646	529	14.4	13.8	52	55
ABORT_OTH – Other pregnancy with abortive outcome (O00–O03, O05–O08)	148	90	293	166	2.0	1.8	6	7
ARTHROPAT_OTH – Other arthropathies (M00–M15, M18–M22, M24–M25)	237	256	1300	1187	5.5	4.6	102	114
A_B_OTH – Other infectious and parasitic diseases (remainder of A00–B99)	138	104	748	637	5.4	6.1	279	306
B20–B24 – Human immunodeficiency virus [HIV] disease	9	4	117	51	13.0	14.5	19	35
C18–C21 – Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal	53	69	708	854	13.4	12.4	14	22
C33_C34 – Malignant neoplasm of trachea, bronchus and lung	72	56	788	613	10.9	10.9	27	34
C43_C44 – Malignant neoplasms of skin	32	26	136	86	4.2	3.3	15	20
C50 – Malignant neoplasm of breast	106	109	745	496	7.1	4.6	39	48
C53–C55 – Malignant neoplasm of uterus	25	21	197	156	8.0	7.3	13	17
C56 – Malignant neoplasm of ovary	13	10	153	107	12.2	10.5	23	26
C61 – Malignant neoplasm of prostate	62	67	536	494	8.6	7.4	21	27
C67 – Malignant neoplasm of bladder	55	55	412	367	7.5	6.6	17	19
C_OTH – Other malignant neoplasms (remainder of C00–C97)	451	319	4902	3238	10.9	10.1	85	127
D00–D09 – In situ neoplasms	25	23	108	92	4.3	4.0	15	23
D00–D48_OTH – Other in situ neoplasms, benign neoplasms and neoplasms of uncertain or unknown behavior (remainder of D00–D48)	236	185	1151	835	4.9	4.5	28	38
D12 – Benign neoplasm of colon, rectum, anus and anal canal	80	52	200	122	2.5	2.4	0	1
D50–D64 – Anaemias	89	120	644	777	7.2	6.5	31	35
D65–D89 – Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	35	36	224	209	6.4	5.8	48	57
E10–E14 – Diabetes mellitus	209	168	1656	1109	7.9	6.6	37	60

Table A5 (*Continued*)

ICD10	Hospital discharges per 100,000 population		Hospital days per 100,000 population		Average length of stay		Number of drugs	
	2000	2010	2000	2010	2000	2010	2000	2010
E_OTH – Other endocrine, nutritional and metabolic diseases (remainder of E00–E90)	232	232	1373	1253	5.9	5.4	202	240
F00–F03 – Dementia	28	26	363	329	12.9	12.5	14	15
F10 – Mental and behavioral disorders due to use of alcohol	135	155	724	485	5.4	3.1	32	34
F11–F19 – Mental and behavioral disorders due to psychoactive substance use	8	10	36	43	4.2	4.4	18	21
F20–F29 – Schizophrenia, schizotypal and delusional disorders	14	14	73	53	5.4	3.8	32	33
F30–F39 – Mood [affective] disorders	95	60	643	321	6.8	5.4	54	58
F_OTH – Other mental and behavioral disorders (remainder of F00–F99)	90	83	573	511	6.4	6.1	120	130
G30 – Alzheimer's disease	12	7	137	77	11.2	11.2	4	6
G35 – Multiple sclerosis	111	17	618	83	5.6	4.9	10	12
G40_G41 – Epilepsy, status epilepticus	52	89	384	456	7.4	5.1	29	35
G45 – Transient cerebral ischemic attacks and related syndromes	17	40	198	205	11.7	5.1	15	16
G_OTH – Other diseases of the nervous system (remainder of G00–G99)	344	252	2022	1596	5.9	6.3	123	141
H00–H59_OTH – Other diseases of the eye and adnexa (remainder of H00–H59)	152	126	514	327	3.4	2.6	129	137
H25_H26_H28 – Cataract	434	139	800	194	1.8	1.4	3	3
H60–H95 – Diseases of the ear and mastoid process	126	96	455	285	3.6	3.0	59	60
I10–I15 – Hypertensive diseases	62	37	386	193	6.2	5.2	104	126
I20 – Angina pectoris	201	153	1036	608	5.1	4.0	48	54
I21_I22 – Acute myocardial infarction including subsequent myocardial infarction	121	88	882	511	7.3	5.8	36	44
I23–I25 – Other ischemic heart disease	137	143	715	571	5.2	4.0	33	40
I26–I28 – Pulmonary heart disease and diseases of pulmonary circulation	52	52	578	450	11.2	8.7	18	26
I44–I49 – Conduction disorders and cardiac arrhythmias	224	207	1259	952	5.6	4.6	38	42
I50 – Heart failure	210	163	2115	1541	10.1	9.5	51	55
I60–I69 – Cerebrovascular diseases	182	157	2078	1617	11.4	10.3	22	24
I70 – Atherosclerosis	96	70	894	488	9.3	7.0	6	8
I83 – Varicose veins of lower extremities	236	69	677	162	2.9	2.4	8	10
INJ_OTH – Other injuries (S10–S51, S53–S71, S73–S81, S83–T14, T79)	562	416	2678	1835	4.8	4.4	11	11
INTESTINE_OTH – Other diseases of intestine (K55, K58–K59, K63)	119	92	512	396	4.3	4.3	86	87
I_OTH – Other diseases of the circulatory system (remainder of I00–I99)	390	339	3002	2323	7.7	6.8	154	164
J00–J11 – Acute upper respiratory infections and influenza	69	45	190	119	2.8	2.7	111	114
J12–J18 – Pneumonia	157	160	1508	1304	9.6	8.2	76	83
J20–J22 – Other acute lower respiratory infections	115	90	680	408	5.9	4.5	64	66
J40–J44_J47 – Chronic obstructive pulmonary disease and bronchiectasis	76	72	688	655	9.0	9.0	85	92
J45_J46 – Asthma and status asthmaticus	85	68	388	227	4.6	3.4	44	47
J60–J99 – Other diseases of the respiratory system	238	191	2700	2002	11.3	10.5	35	35
K00–K08 – Disorders of teeth and supporting structures	233	72	367	135	1.6	1.9	29	31
K09–K14 – Other diseases of oral cavity, salivary glands and jaws	22	19	88	74	4.0	3.8	31	32
K20–K23 – Diseases of esophagus	69	46	335	212	4.8	4.6	12	14
K25–K28 – Ulcer of stomach, duodenum and jejunum	36	22	270	158	7.5	7.2	17	18
K29–K31 – Dyspepsia and other diseases of stomach and duodenum	39	35	174	132	4.5	3.8	21	21
K50_K51 – Crohn's disease and ulcerative colitis	26	28	200	194	7.6	6.9	14	15
K52 – Other noninfective gastroenteritis and colitis	28	23	136	108	4.9	4.6	1	1
K56 – Paralytic ileus and intestinal obstruction without hernia	90	77	785	594	8.7	7.7	4	4
K60–K62 – Diseases of anus and rectum	100	91	380	290	3.8	3.2	4	5
K70 – Alcoholic liver disease	56	35	589	382	10.6	10.8	6	11
K71–K77 – Other diseases of liver	37	31	312	260	8.5	8.4	17	24
K80 – Cholelithiasis	179	182	1149	811	6.4	4.4	6	6
K81–K83 – Other diseases of gallbladder and biliary tract	38	53	303	314	8.0	6.0	11	12
K85–K87 – Diseases of pancreas	41	53	434	438	10.6	8.2	3	3
K_OTH – Other diseases of the digestive system (remainder of K00–K93)	59	54	533	467	9.0	8.6	44	45
L00–L08 – Infections of the skin and subcutaneous tissue	111	112	482	424	4.3	3.8	59	65
L20–L45 – Dermatitis, eczema and papulosquamous disorders	19	14	129	82	6.8	5.8	84	93
L_OTH – Other diseases of the skin and subcutaneous tissue (remainder of L00–L99)	82	61	666	465	8.1	7.6	128	139
M16 – Coxarthrosis [arthrosis of hip]	117	133	1526	1181	13.0	8.9	39	41
M17 – Gonarthrosis [arthrosis of knee]	92	133	1077	1188	11.7	8.9	39	43
M23 – Internal derangement of knee	151	84	438	280	2.9	3.3	11	11
M30–M36 – Systemic connective tissue disorders	26	22	208	154	8.0	7.0	21	26
M40–M49 – Deforming dorsopathies and spondylopathies	62	68	520	523	8.5	7.7	26	29
M50_M51 – Cervical disc disorders, other intervertebral disc disorders	108	70	663	372	6.1	5.3	6	7
M53_M80–M99 – Other disorders of the musculoskeletal system and connective tissue	107	88	912	680	8.5	7.8	70	80
M54 – Dorsalgia	109	72	659	371	6.1	5.1	33	33

Table A5 (*Continued*)

ICD10	Hospital discharges per 100,000 population		Hospital days per 100,000 population		Average length of stay		Number of drugs	
	2000	2010	2000	2010	2000	2010	2000	2010
M60–M79 – Soft tissue disorders	167	176	657	610	3.9	3.5	46	47
N00–N16 – Glomerular and renal tubulo–interstitial diseases	126	137	711	676	5.6	4.9	50	51
N17–N19 – Renal failure	57	56	580	555	10.3	9.9	19	23
N20–N23 – Urolithiasis	162	143	484	345	3.0	2.4	13	13
N25–N39 – Other diseases of the urinary system	122	101	625	418	5.1	4.1	97	103
N40 – Hyperplasia of prostate	98	92	732	541	7.5	5.9	9	12
N41–N51 – Other diseases of male genital organs	87	65	280	223	3.2	3.4	45	45
N60–N64 – Disorders of breast	63	43	201	120	3.2	2.8	13	13
N70–N77 – Inflammatory diseases of female pelvic organs	45	36	169	116	3.8	3.3	42	43
N91–N95 – Menstrual, menopausal and other female genital conditions	56	24	166	65	3.0	2.7	54	61
N_OTH – Other diseases of the genitourinary system (remainder of N00–N99)	234	177	1024	640	4.4	3.6	31	34
O04 – Medical abortion	53	38	89	65	1.7	1.7	4	5
O10–O48 – Complications of pregnancy predominantly in the antenatal period	421	584	2403	3083	5.7	5.3	35	35
O60–O75 – Complications of labor and delivery	272	702	1658	3760	6.1	5.4	16	17
O80 – Single spontaneous delivery	1033	1027	5073	4372	4.9	4.3	0	1
O85–O92 – Complications predominantly related to the puerperium	8	13	38	51	4.6	4.0	21	21
P07 – Disorders related to short gestation and low birth weight, not elsewhere classified	846	1017	16,925	17,999	20.0	17.7	4	5
P_OTH – Other conditions originating in the perinatal period (remainder of P00–P96)	2935	4017	21,474	25,894	7.3	6.4	25	25
Q – Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	130	103	689	516	5.3	5.0	12	14
R07 – Pain in throat and chest	108	109	361	229	3.3	2.1	14	15
R10 – Abdominal and pelvic pain	249	140	687	318	2.8	2.3	14	14
R_OTH – Other symptoms, signs and abnormal clinical and laboratory findings (remainder of R00–R99)	748	627	3974	2837	5.3	4.5	281	295
S06 – Intracranial injury	175	112	644	497	3.7	4.4	5	5
S72 – Fracture of femur	124	77	1872	906	15.1	11.8	0	4
S82 – Fracture of lower leg, including ankle	108	91	818	532	7.6	5.8	0	2
S_T_OTH – Other and unspecified effects of external causes (remainder of S00–T98)	35	29	108	75	3.1	2.6	61	62
T20–T32 – Burns and corrosions	19	14	187	144	9.8	10.0	26	26
T36–T65 – Poisonings by drugs, medicaments and biological substances and toxic effects	178	172	428	372	2.4	2.2	30	31
T80–T88 – Complications of surgical and medical care, not elsewhere classified	168	90	1591	679	9.4	7.6	57	61
UPRESPIR_OTH – Other diseases of upper respiratory tract (J30–J34, J36–J39)	160	119	420	274	2.6	2.3	97	104
Z30 – Contraceptive management	17	15	39	25	2.2	1.7	23	29
Z51 – Other medical care	478	481	2186	2925	4.6	6.1	5	5
Z_OTH – Other factors influencing health status and contact with health services (remainder of Z00–Z99)	761	801	3284	2662	4.3	3.3	21	25

Table A6
Estimates of the relationship between the number of molecules and the mean vintage of drugs (Eq. (A1)).

Parameter	Estimate	SE	Z	$\Pr > \lvert Z \rvert$
A. Weighted by quantity (standard units)				
$\ln(\text{N\_MOLECULE}_{c,t})$	3.114	3.662	0.85	0.395
$\ln(\text{N\_MOLECULE}_{c,t-1})$	7.202	5.440	1.32	0.186
$\ln(\text{N\_MOLECULE}_{c,t-2})$	**12.218**	**5.789**	**2.11**	**0.035**
$\ln(\text{N\_MOLECULE}_{c,t-3})$	**13.780**	**4.257**	**3.24**	**0.001**
$\ln(\text{N\_MOLECULE}_{c,t-4})$	**8.779**	**3.977**	**2.21**	**0.027**
$\ln(\text{N\_MOLECULE}_{c,t-5})$	5.095	3.484	1.46	0.144
B. Weighted by expenditure (ex-manufacturer value)				
$\ln(\text{N\_MOLECULE}_{c,t})$	3.533	2.177	1.62	0.105
$\ln(\text{N\_MOLECULE}_{c,t-1})$	**4.971**	**2.403**	**2.07**	**0.039**
$\ln(\text{N\_MOLECULE}_{c,t-2})$	**6.111**	**2.372**	**2.58**	**0.010**
$\ln(\text{N\_MOLECULE}_{c,t-3})$	**7.207**	**2.601**	**2.77**	**0.006**
$\ln(\text{N\_MOLECULE}_{c,t-4})$	**5.849**	**2.032**	**2.88**	**0.004**
$\ln(\text{N\_MOLECULE}_{c,t-5})$	**4.445**	**1.965**	**2.26**	**0.024**

Estimates of Eq. (A1) are shown in Appendix Table 6. The models were estimated by weighted least squares. The weight used in the models in Panel A is the *quantity* (number of standard units) of products sold in class c in year t ($\sum_p Q_{pct}$). The first two models indicate that mean vintage is not related to the number of molecules in the current or previous year, but the next three models indicate that there is a significant relationship between mean vintage and the number of molecules 2–4 years earlier. The number of molecules 3 years earlier has the largest (and most significant) effect on mean vintage.

The weight used in the models in Panel B is the ex-manufacturer *value* of products sold in class c in year t. Once again, the coefficient on the contemporaneous number of molecules is not significant. There is a significant positive relationship between mean vintage and the number of molecules 1–5 years earlier, and the number of molecules 3 years earlier has the largest effect on mean vintage.

Appendix 2. The correlation between pharmaceutical innovation and other medical innovation

As discussed earlier, pharmaceutical innovation is not the only type of medical innovation that is likely to contribute to longevity growth. Other medical innovation, such as innovation in diagnostic imaging, surgical procedures, and medical devices, is also likely to affect longevity growth. Therefore, measures of these other types of medical innovation should be included in the longevity model (Eq. (1)). Unfortunately, longitudinal disease-level measures of non-pharmaceutical medical innovation are not available for France. However, longitudinal disease-level measures of non-pharmaceutical and pharmaceutical medical innovation are available for the U.S. during the period 1997–2007. Now these data will be described, and used to assess whether the rates of pharmaceutical and non-pharmaceutical medical innovation are correlated across diseases.

Four different measures of medical innovation were constructed: innovation in self-administered drugs, provider-administered drugs (e.g. chemotherapy), diagnostic imaging procedures, and other outpatient and inpatient medical procedures.

Self-administered drugs. The mean vintage of self-administered prescription drugs consumed, by disease (diagnosis) and year, was computed:

$\text{SELF\_Rx\_VINTAGE}_{it}$ = the weighted mean vintage of self-administered prescriptions for disease i in year t (t = 1997,. . ., 2007)
= $\sum_m \text{N\_SELF\_Rx}_{mit}\ \text{FDA\_YEAR}_m / \sum_m \text{N\_SELF\_Rx}_{mit}$

N_SELF_Rx_{mit} = the number of self-administered prescriptions for disease i in year t that contained molecule m

FDA_YEAR_m = the initial FDA approval year of molecule m

Data on the number of self-administered outpatient prescriptions, by molecule, diagnosis, and year (N_Rx_{mit}) were obtained from the Prescribed Medicines Files of the 1998–2007 Medical Expenditure Panel Survey (http://meps.ahrq.gov/mepsweb/index.jsp), the most complete source of U.S. data on the cost and use of health care and health insurance coverage. Data on the vintage (initial FDA approval year) of each molecule (FDA_YEAR_m) were obtained from the Drugs@FDA data files (http://www.fda.gov/Drugs/InformationOnDrugs/ucm079750.htm).

Provider-administered drugs. A similar methodology was used to calculate the mean vintage of provider-administered drugs, by disease (diagnosis) and year:

$\text{PROV\_Rx\_VINTAGE}_{it}$ = the weighted mean vintage of provider-administered drugs for disease i in year t (t = 1998,. . ., 2007)
= $\sum_m \text{N\_DRUG\_PROC}_{mit}\ \text{FDA\_YEAR}_m / \sum_m \text{N\_DRUG\_PROC}_{mit}$

N_DRUG_PROC_{mit} = the number of outpatient and inpatient drug procedures for disease i in year t that contained molecule m

Data on the number of outpatient and inpatient drug procedures, by molecule(s) administered, principal diagnosis (ICD9) code, and year (N_PROC_{mit}) were obtained from MEDSTAT MarketScan Commercial Claims and Encounters Database produced by Thomson Medstat (Ann Arbor, MI).[27] Each claim in this database includes information about the procedure performed, the patient's diagnosis (ICD9 code), and the date of service.

Diagnostic imaging procedures. The fraction of diagnostic imaging procedures performed that were "advanced" procedures (as defined by the Centers for Medicare and Medicaid Services (CMS)), by disease and year, was calculated:

$$\text{ADV\_IMAG\%}_{it} = \frac{\sum_p \text{N\_IMAGE\_PROC}_{pit}\text{ADV}_p}{\sum_p \text{N\_IMAGE\_PROC}_{pit}}$$

where

$\text{N\_IMAGE\_PROC}_{pit}$ = the number of times diagnostic imaging procedure p was performed in connection with diagnosis i in year t

ADV_p = 1 if procedure p is an advanced imaging procedure
= 0 if procedure p is a standard imaging procedure

Advanced imaging procedures involve either a computed tomography (CT) scan or magnetic resonance imaging (MRI). For example, code 71010 (Radiologic examination, chest; single view, frontal) is a standard imaging procedure, and code 70450 (Computed tomography, head or brain; without contrast material) is an advanced imaging procedure.

Data on $\text{N\_IMAGE\_PROC}_{pit}$ were obtained from the MEDSTAT MarketScan Commercial Claims and Encounters Database. Data on ADV_p were obtained from the CMS

[27] The MarketScan Databases capture person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services from a selection of large employers, health plans, and government and public organizations. The MarketScan Databases link paid claims and encounter data to detailed patient information across sites and types of providers, and over time. The annual medical databases include private sector health data from approximately 100 payers. Historically, more than 500 million claim records are available in the MarketScan Databases. The Commercial Claims and Encounters Database provides data on the medical experience of active employees, early retirees, COBRA continues, and their dependents insured by employer-sponsored plans (i.e. non-Medicare eligibles). I am grateful to the National Bureau of Economic Research for making these data available to me.

Table A7
Statistics about four measures of pharmaceutical and non-pharmaceutical innovation in the U.S., 1998–2007.

Year	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Number of self-administered prescriptions (N_SELF_Rx)	172,031	173,950	182,677	277,866	339,308	304,324	317,065	317,587	341,994	300,099
Mean vintage of self-administerd drugs (SELF_Rx_VINTAGE)	1976.0	1976.8	1978.1	1979.2	1980.3	1981.6	1981.5	1982.1	1982.5	1982.8
Number of provider-administered drug procedures (N_DRUG_PROC)	23,575	28,397	21,654	20,540	17,767	14,346	28,720	53,427	49,160	45,707
Mean vintage of provider-administerd drugs (PROV_Rx_VINTAGE)	1964.8	1966.4	1966.9	1967.1	1968.1	1968.1	1969.8	1972.1	1971.0	1971.5
Number of imaging procedures (N_IMAGE_PROC)	392,742	374,890	360,341	358,001	348,815	337,305	357,686	362,767	347,069	434,870
Fraction of diagnostic imaging procedures performed that were "advanced" procedures (ADV_IMAG%)	16%	18%	20%	21%	22%	23%	25%	27%	27%	27%
Number of other (non-drug and non-imaging) outpatient and inpatient medical procedures performed (N_OTHER_PROC)	566,173	595,376	628,149	645,276	618,415	627,227	676,213	656,161	706,004	730,503
Fraction of other (non-drug and non-imaging) outpatient and inpatient medical procedures performed that were "new" (post-1991) procedures (NEW_OTHER_PROC%)	15%	17%	22%	22%	23%	25%	27%	29%	30%	31%

Berenson-Eggers Type of Service (BETOS) file (http://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/BETOS.html).

Other outpatient and inpatient medical procedures. The fraction of other (non-drug and non-imaging) outpatient and inpatient medical procedures performed that were "new" (post-1991) procedures, by disease and year, was calculated:

$$\text{NEW\_OTHER\_PROC}\%_{it} = \frac{\sum_p \text{N\_OTHER\_PROC}_{pit}\text{NEW}_p}{\sum_p \text{N\_OTHER\_PROC}_{pit}}$$

where

$\text{N\_OTHER\_PROC}_{pit}$ = the number of times procedure p was performed in connection with diagnosis i in year t
NEW_p = 1 if procedure p is a "new" (post-1991) procedure
= 0 if procedure p is an "old" (pre-1992) procedure

A "new" procedure was defined as a procedure whose code did not exist in 1991. Data on $\text{N\_OTHER\_PROC}_{pit}$ were obtained from the MEDSTAT MarketScan Commercial Claims and Encounters Database. Data on NEW_p were obtained from the 1991 CMS Physician/Supplier Procedure Summary Master File (http://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/NonIdentifiableDataFiles/PhysicianSupplierProcedureSummaryMasterFile.html).

Statistics about the four measures of pharmaceutical and non-pharmaceutical innovation in the U.S. during the period 1998–2007 are shown in Appendix Table 7. As one would expect, all four measures increased during this period.

To assess whether rates of pharmaceutical and non-pharmaceutical medical innovation are correlated across diseases, the following equations were estimated:

$$\begin{aligned}\text{SELF\_Rx\_VINTAGE}_{it} &= \beta_1 \text{ADV\_IMAG}\%_{it} \\ &+ \beta_2 \text{NEW\_OTHER\_PROC}\%_{it} \\ &+ \alpha_i + \delta_t + \varepsilon_{it} \end{aligned} \quad \text{(A2)}$$

$$\begin{aligned}\text{PROV\_Rx\_VINTAGE}_{it} &= \beta_1 \text{ADV\_IMAG}\%_{it} \\ &+ \beta_2 \text{NEW\_OTHER\_PROC}\%_{it} \\ &+ \alpha_i + \delta_t + \varepsilon_{it} \quad (t \\ &= 1998, \ldots, 2007) \end{aligned} \quad \text{(A3)}$$

Both equations were estimated by weighted least squares. The weight used for Eq. (A2) was ($\sum_m \text{N\_SELF\_Rx}_{mit}$), and the weight used for Eq. (A3) was ($\sum_m \text{N\_PROV\_Rx}_{mit}$). Both equations were estimated at two different levels of disease aggregation: 2-digit ICD-9 (there were 109 diseases at that

Table A8
Correlation between pharmaceutical innovation and other medical innovation in the U.S., 1998–2007.

Dependent variable	Level of aggregation	Parameter	Estimate	Std. Error	Z	$Pr > \|Z\|$
Mean vintage of self-administered drugs (SELF_Rx_VINTAGE)	2-Digit ICD-9 (109 diseases)	ADV_IMAG%	−1.988	2.245	−0.89	0.3759
		NEW_OTHER_PROC%	−0.159	3.015	−0.05	0.9578
Mean vintage of self-administered drugs (SELF_Rx_VINTAGE)	3-Digit ICD-9 (955 diseases)	ADV_IMAG%	−1.312	0.638	−2.06	0.0398
		NEW_OTHER_PROC%	−0.227	1.030	−0.22	0.8254
Mean vintage of provider-administered drugs (PROV_Rx_VINTAGE)	2-Digit ICD-9 (109 diseases)	ADV_IMAG%	2.356	3.432	0.69	0.4924
		NEW_OTHER_PROC%	1.421	3.886	0.37	0.7147
Mean vintage of provider-administered drugs (PROV_Rx_VINTAGE)	3-Digit ICD-9 (955 diseases)	ADV_IMAG%	−0.255	1.244	−0.21	0.8373
		NEW_OTHER_PROC%	1.312	1.650	0.79	0.4266

level), and 3-digit ICD-9 (there were 955 diseases at that level). Disturbances were clustered within diseases.

Estimates of Eqs. (A2) and (A3) are shown in Appendix Table 8. The first model shows that when Eq. (A2) is estimated at the 2-digit ICD-9 level, neither coefficient is statistically significant. This suggests that the rate of innovation in self-administered drugs is uncorrelated across diseases with rates of innovation in imaging and other procedures, but the standard errors are large. When Eq. (A2) is estimated at the 3-digit ICD-9 level, the coefficient on the imaging innovation measure is *negative* and significant: diseases that had greater imaging innovation had less innovation in self-administered drugs. The last two models indicate that the rate of innovation in provider-administered drugs is uncorrelated across diseases, at both the two-digit and three-digit level, with rates of innovation in imaging and other procedures.

These estimates (based on U.S. data) suggest that failure to control for other medical innovation is very unlikely to result in overestimation of the effect of pharmaceutical innovation on longevity growth.

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