The impact of pharmaceutical innovation on the longevity and health of elderly Americans

Evidence from Linked Medical Expenditure Panel Survey-National Death Index Data

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Longevity increase is an important part of economic growth and development

- Nordhaus estimated that, “to a first approximation, the economic value of increases in longevity over the twentieth century is about as large as the value of measured growth in non-health goods and services”.
- Murphy and Topel observed that “the historical gains from increased longevity have been enormous. Over the 20th century, cumulative gains in [U.S.] life expectancy were worth over $1.2 million per person for both men and women. Between 1970 and 2000 increased longevity added about $3.2 trillion per year to national wealth, an uncounted value equal to about half of average annual GDP over the period.”
- In its Human Development Reports, the United Nations Development Program ranks countries by their value of the Human Development Index, which is based on life expectancy at birth as well as on the adult literacy rate and per capita GDP.

Technological progress determines the rate of long-run economic growth

- Since the 1950s, economists have recognized that, in the long run, the rate of economic growth is determined by (indeed equal to) the rate of technological progress.
- In neoclassical growth models developed by Nobel laureate Robert Solow and colleagues, an economy will always converge towards a steady state rate of growth, which depends only on the rate of technological progress.

How could Bill Clinton win the 1992 U.S. presidential election?

It's the economy, stupid

- "**It's the economy, stupid**" was a phrase in American politics widely used during Bill Clinton's successful 1992 presidential campaign against George H. W. Bush. For a time, Bush was considered unbeatable because of foreign policy developments such as the end of the Cold War and the Persian Gulf War. The phrase, made popular by Clinton campaign strategist James Carville, refers to the notion that Clinton was a better choice because Bush had not adequately addressed the economy, which had recently undergone a recession.
- http://en.wikipedia.org/wiki/It%27s_the_economy,_stupid

What determines the rate of economic growth (and longevity growth)?

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It’s technological progress, stupid.

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Endogenous growth models

- In early models of economic growth, the rate of technological progress was assumed to be given, or exogenous: technological progress was regarded as “manna from heaven.”
- Economists began to relax this clearly unrealistic assumption in the 1980s, by developing so-called “endogenous growth models.” In Paul Romer’s model, “growth…is driven by technological change that arises from intentional [R&D] investment decisions made by profit-maximizing agents.”
- Jones argues that “technological progress [is] the ultimate driving force behind sustained economic growth”, and that “technological progress is driven by research and development (R&D) in the advanced world”.
- Growth may also be driven by technological change arising from R&D investment by public organizations, e.g. the National Institutes of Health.

Embodied vs. disembodied technological progress

- Suppose firm X invests in R&D, and that this investment results in a valuable discovery.
- If the technological advance is disembodied, consumers and other firms could benefit from the discovery without purchasing firm X’s goods or services; they could benefit just by reading or hearing about the discovery.
- However, if the technological advance is embodied, consumers and other firms must purchase firm X’s goods or services to benefit from its discovery.

Embodied vs. disembodied technological progress

- Solow argued that "many if not most innovations need to be embodied in new kinds of durable equipment before they can be made effective. Improvements in technology affect output only to the extent that they are carried into practice either by net capital formation or by the replacement of old-fashioned equipment by the latest models…"
- Romer also assumes that technological progress is embodied in new goods: "new knowledge is translated into goods with practical value," and "a firm incurs fixed design or research and development costs when it creates a new good. It recovers those costs by selling the new good for a price that is higher than its constant cost of production."
- Grossman and Helpman argued that "innovative goods are better than older products simply because they provide more 'product services' in relation to their cost of production."
- Bresnahan and Gordon stated simply that "new goods are at the heart of economic progress," and Bils said that "much of economic growth occurs through growth in quality as new models of consumer goods replace older, sometimes inferior, models."
- We hypothesize that innovations may be embodied in nondurable goods (e.g. drugs) and services as well as in durable equipment.

- "The conclusion is that 'embodiment' is the main transmission mechanism of technological progress to economic growth." (p. 223)
- Zvi Hercowitz, "The 'embodiment' controversy: A review essay", *Journal of Monetary Economics* 41 (1998) 217-224.

Product vintage

- When technological progress is embodied in new goods, the welfare of consumers (and the productivity of producers) depends on the *vintage* of the goods (or inputs) they purchase.
- In this context, “vintage” refers to the year in which the good was first produced or sold. For example, the vintage of the drug simvastatin is 1993: that is the year it was approved by the FDA, and first sold.
- Solow was the first economist to develop a growth model that distinguished between vintages of (capital) goods. In Solow's model, new capital is more valuable than old capital because--since capital is produced based on known technology, and technology improves with time--new capital will be more productive than old capital.
- A number of econometric studies (Bahk and Gort, Hulten, Sakellaris and Wilson) have shown that manufacturing firms using later-vintage equipment have higher productivity.

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Effect of vintage depends on R&D intensity

- The extent to which the welfare of consumers or the productivity of producers depends on the vintage of the goods they purchase should depend on the research intensity of those goods. The greater the research intensity of the goods, the greater the impact of their vintage on consumer welfare and producer productivity.
- According to the National Science Foundation, the pharmaceutical and medical devices industries are the most research intensive industries in the economy.
- In 1997, “medical substances and devices firms had by far the highest combined R&D intensity at 11.8 percent,…well above the 4.2-percent average for all 500 top 1997 R&D spenders combined. The information and electronics sector ranked second in intensity at 7.0 percent.” The pattern of 1997 R&D spending per employee is similar to that for R&D intensity, with medical substances and devices again the highest at $29,095 per employee. Information and electronics is second at $16,381. Combined, the top 500 1997 R&D firms spent $10,457 per employee.

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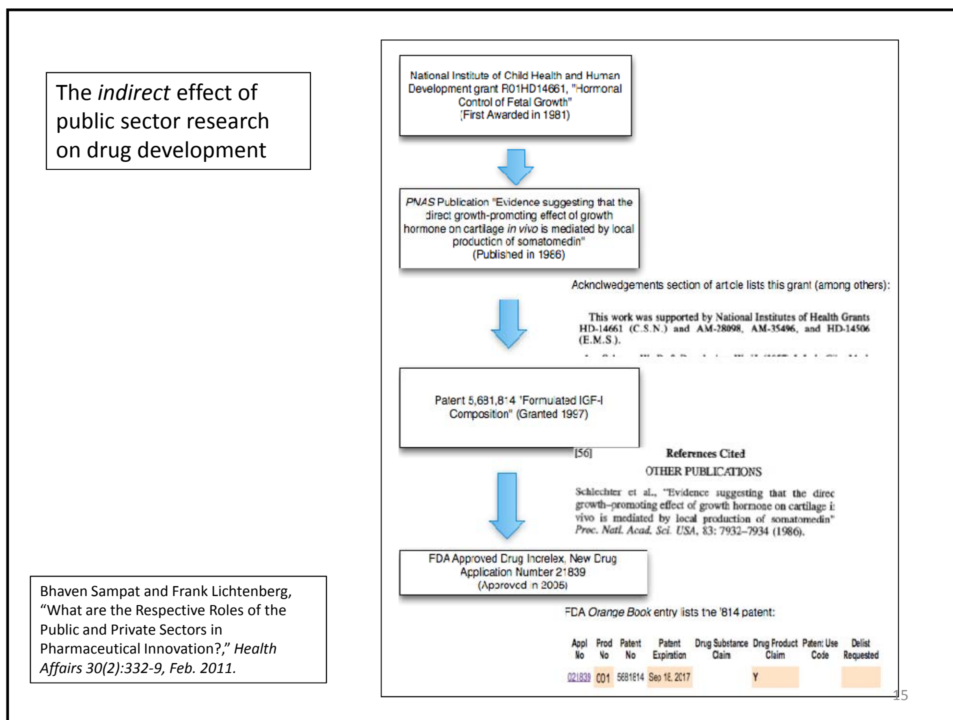

Fractions of New Molecular Entities Approved between 1988 and 2005 with Direct or Indirect Links to Public Sector Funding

	Standard NMES	*Priority NMEs*	*All NMEs*
N	224	155	379
Share covered by a government funded patent	3.1 %	17.4 %	9.0 %
Share citing at least one government funded patent	15.6 %	39.4%	25.3%
Share citing at least one government funded publication	31.3%	56.1%	41.4%
Share citing either a government funded patent or publication	36.2%	64.5%	47.8%

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Role of government in pharmaceutical innovation

- The direct role of the public sector has been modest: only 9% of drugs are covered by a government-funded patent.
- The government has played an indirect role in almost half of the NMEs approved, and in almost 2/3 of priority-review NMEs.
- However, only ¼ of pharmaceutical expenditure in 2006 was on drugs whose patents cited either a government-funded patent or a government-funded publication.
- Also, only ¼ of the scientific publications cited in drug patents were supported by the government.
- HIV drugs have relied on public-sector investment to a far greater extent than other new drugs.

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Key hypothesis

- Patients using newer drugs at time t_0 are less likely to die between time t_0 and time t_1, controlling for an extensive set of patient characteristics
- Pharmaceutical innovation, which causes the mean vintage of prescription drugs consumed to increase over time, accounts for a significant amount of longevity growth

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Previous research

- In two recently published studies, I have examined the effect of pharmaceutical innovation on longevity using patient-level data. The basic approach was to investigate whether patients using newer drugs at time t_0 were less likely to die between time t_0 and time t_1, controlling for other characteristics of the patient at time t_0.
  - Lichtenberg, Frank R., Paul Grootendorst, Marc Van Audenrode, Dominick Latremouille-Viau, and Patrick Lefebvre,"The impact of drug vintage on patient survival: a patient-level analysis using Quebec's provincial health plan data," *Value in Health 12 (6), 847–856.*
  - Lichtenberg, Frank R., "The effect of drug vintage on survival: Micro evidence from Puerto Rico's Medicaid program," in M. Grossman, B. Lindgren, R. Kaestner, and Kristian (eds.), *Pharmaceutical Markets and Insurance Worldwide (Advances in Health Economics and Health Services Research, Volume 22), pp. 273-292.*
- Both of these studies were based entirely on administrative data. One study was based on medical and pharmacy claims data from Quebec's provincial health plan (Régie de l'assurance maladie du Québec), during the period 1997-2006. A second study was based on medical and pharmacy claims data from Puerto Rico's Medicaid program during the period 2000-2002.
- Both studies controlled for some basic demographic characteristics (age, sex, and region), overall utilization of medical services, and patient diagnoses as reflected in claims data. However, due to data limitations, neither study controlled for other potentially important determinants of survival—such as race, educational attainment, income, marital status, and behavioral risk factors (body mass index and smoking)—that may be correlated with the vintage of drugs used by the patient.
- In the Puerto Rico study, the patient's vital status could only be tracked for 2.5 years after the period of prescription drug use.
- Neither study was based on nationally representative samples of individuals.

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Current study

- The current study supersedes some important limitations of the two previous studies.
- I will reexamine whether patients using newer drugs at time t_0 were less likely to die between time t_0 and time t_1, controlling for a much more extensive set of patient characteristics than has been used in previous studies.
- I am able to track the patient's vital status for up to 10 years after the period of prescription drug use, and the study is based on a nationally representative sample of Americans.

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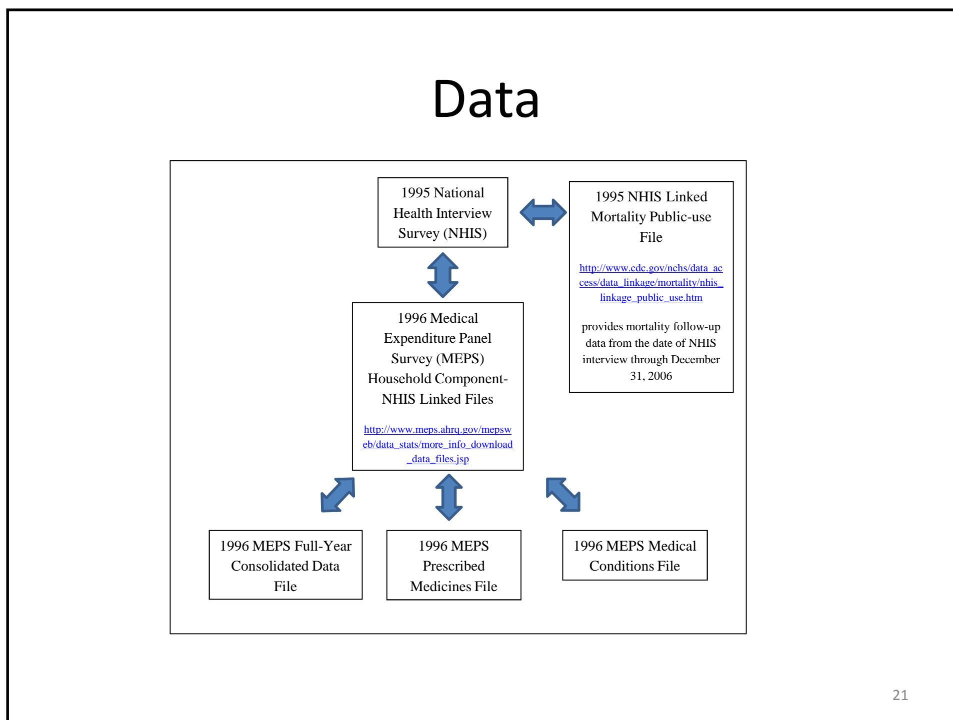
Data
1995 National Health Interview Survey (NHIS)
1995 NHIS Linked Mortality Public-use File
http://www.cdc.gov/nchs/data_access/data_linkage/mortality/nhis_linkage_public_use.htm
provides mortality follow-up data from the date of NHIS interview through December 31, 2006
1996 Medical Expenditure Panel Survey (MEPS) Household Component-NHIS Linked Files
http://www.meps.ahrq.gov/mepsweb/data_stats/more_info_download_data_files.jsp
1996 MEPS Full-Year Consolidated Data File
1996 MEPS Prescribed Medicines File
1996 MEPS Medical Conditions File
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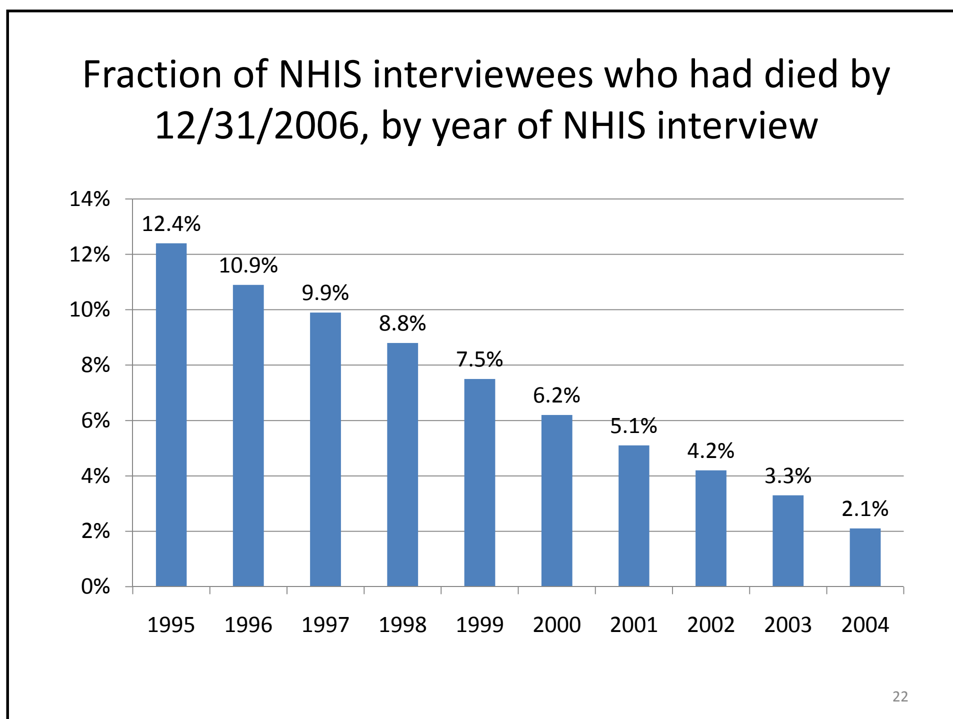
Fraction of NHIS interviewees who had died by 12/31/2006, by year of NHIS interview
14%
12%
10%
8%
6%
4%
2%
0%
12.4%
10.9%
9.9%
8.8%
7.5%
6.2%
5.1%
4.2%
3.3%
2.1%
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
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Exclusions

- Provider-administered drugs (e.g. chemotherapy)
  - These may account for about 15% of total drug expenditure
- Nursing home residents
  - 43.3 nursing home residents per 1000 population 65 and over in 1999 http://www.cdc.gov/nchs/data/hus/hus09.pdf#105

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Reduced form model

$survival_time_i = \beta\ rx_vintage_i + age_dummies + sex_dummies + race_dummies + medical_condition_dummies\ educational_attainment_dummies + income_dummies + + region_dummies + insurance_coverage_dummies + marital_status_dummies + \varepsilon_i$

where

$survival_time_i$ = the number of years patient i lived after being interviewed = $death_date_i - interview_date_i$

$rx_vintage_i$ = the mean vintage of prescription drugs used by patient i

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Medical conditions

MEPS Medical Conditions files contain variables describing medical conditions reported by respondents in several sections of the MEPS questionnaire, including the Condition Enumeration section, all questionnaire sections collecting information about health provider visits, prescription medications, and disability days.

Conditions can be added to the MEPS conditions roster in several ways:

- A condition can be reported in the Priority Condition Enumeration section in which persons are asked if they have ever been diagnosed with specific conditions.
- The condition can be identified as the reason reported by the household respondent for a particular medical event (hospital stay, outpatient visit, emergency room visit, home health episode, prescribed medication purchase, or medical provider visit).
- The condition may be reported as the reason for one or more episodes of disability days.
- Finally, the condition may be reported by the household level respondent as a condition "bothering" the person during the reference period.

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Right censoring

- Since most NHIS respondents were still alive on 12/31/2006, most observations are right censored.
- I will account for this by using a statistical procedure (the SAS LIFEREG procedure) that fits parametric models to failure time data that can be uncensored, right censored, left censored, or interval censored.
- To reduce the degree of censoring, I will analyze people who were 65 and over when interviewed during 1996-1999. (Drawback: data on BMI and smoking are not available before 2001. However, these variables are not correlated with rx_vintage.)

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Weibull distribution

The Weibull distribution is one of the most commonly used distributions in reliability. It is commonly used to model time to fail.

The probability density function of a Weibull random variable *X* is:

$$f(x;\lambda,k) = \begin{cases} \frac{k}{\lambda}\left(\frac{x}{\lambda}\right)^{k-1} e^{-(x/\lambda)^k} & x \geq 0, \\ 0 & x < 0, \end{cases}$$

where $k > 0$ is the *shape parameter* and $\lambda > 0$ is the *scale parameter* of the distribution.

- The shape parameter is what gives the Weibull distribution its flexibility. By changing the value of the shape parameter, the Weibull distribution can model a wide variety of data. If k = 1 the Weibull distribution is identical to the exponential distribution, if k = 2, the Weibull distribution is identical to the Rayleigh distribution; if k is between 3 and 4 the Weibull distribution approximates the normal distribution. The Weibull distribution approximates the lognormal distribution for several values of k.
- If the quantity *X* is a "time-to-failure", the Weibull distribution gives a distribution for which the failure rate is proportional to a power of time. The *shape* parameter, *k*, is that power plus one, and so this parameter can be interpreted directly as follows:
  - A value of $k<1$ indicates that the failure rate decreases over time. This happens if there is significant "infant mortality", or defective items failing early and the failure rate decreasing over time as the defective items are weeded out of the population.
  - A value of $k=1$ indicates that the failure rate is constant over time. This might suggest random external events are causing mortality, or failure.
  - A value of $k>1$ indicates that the failure rate increases with time. This happens if there is an "aging" process, or parts that are more likely to fail as time goes on.

The mean of a Weibull random variable can be expressed as:

$$\lambda\Gamma\left(1+\frac{1}{k}\right)$$

where $\Gamma(z)$ is the Gamma function:

$$\Gamma(z)=\int_0^\infty t^{z-1}e^{-t}\,dt\,.$$

http://en.wikipedia.org/wiki/Weibull_distribution
http://www.engineeredsoftware.com/nasa/weibull.htm

mean = exp(β X)* Γ(1+(1/k))

since ln λ = β X.

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Measuring vintage

I will analyze a number of alternative measures of vintage. One measure is based on the mean vintage of the ingredients contained in a patient's prescriptions:

$$rx_vintage_i = \frac{\Sigma_a\, n_rx_{ai}\, fda_ingredient_year_a}{\Sigma_a\, n_rx_{ai}}$$

where

n_rx_{ai} = the number of prescriptions for patient i that contained active ingredient a

$fda_ingredient_year_a$ = the year in which the FDA first approved active ingredient a

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Alternative measure of vintage

The fraction of prescriptions containing "new" (e.g. post-1990) active ingredients

$$rx_post1990\%_i = \frac{\Sigma_a n_rx_{ai}\, post1990_a}{\Sigma_a n_rx_{ai}}$$

where

$post1990_a = 1$ if $fda_ingredient_year_a > 1990$

$= 0$ if $fda_ingredient_year_a \leq 1990$

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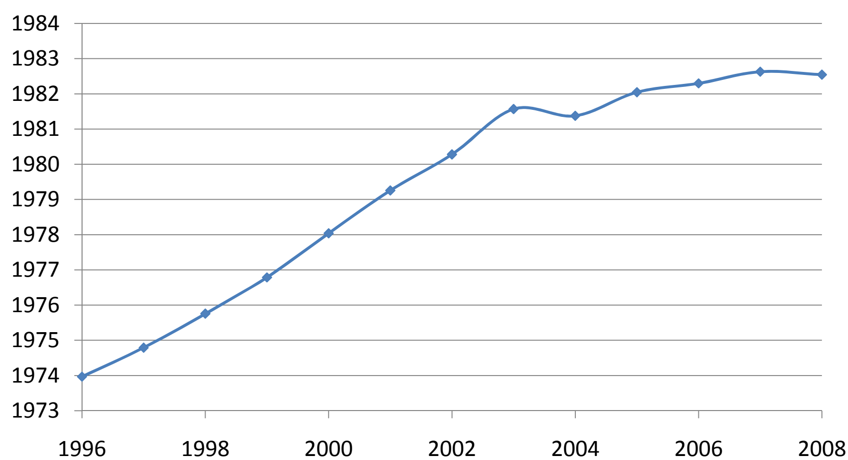
rx_vintage



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year	fda_year	post1990	n_rx
1996	1974.0	16%	122,436
1997	1974.8	20%	197,795
1998	1975.8	24%	144,039
1999	1976.8	28%	143,729
2000	1978.0	33%	146,989
2001	1979.3	37%	213,830
2002	1980.3	40%	254,411
2003	1981.6	44%	207,673
2004	1981.4	43%	241,603
2005	1982.0	44%	279,824
2006	1982.3	44%	303,009
2007	1982.6	45%	255,473
2008	1982.5	45%	253,902
1996-2003	7.6	27%	
2003-2008	1.0	2%	

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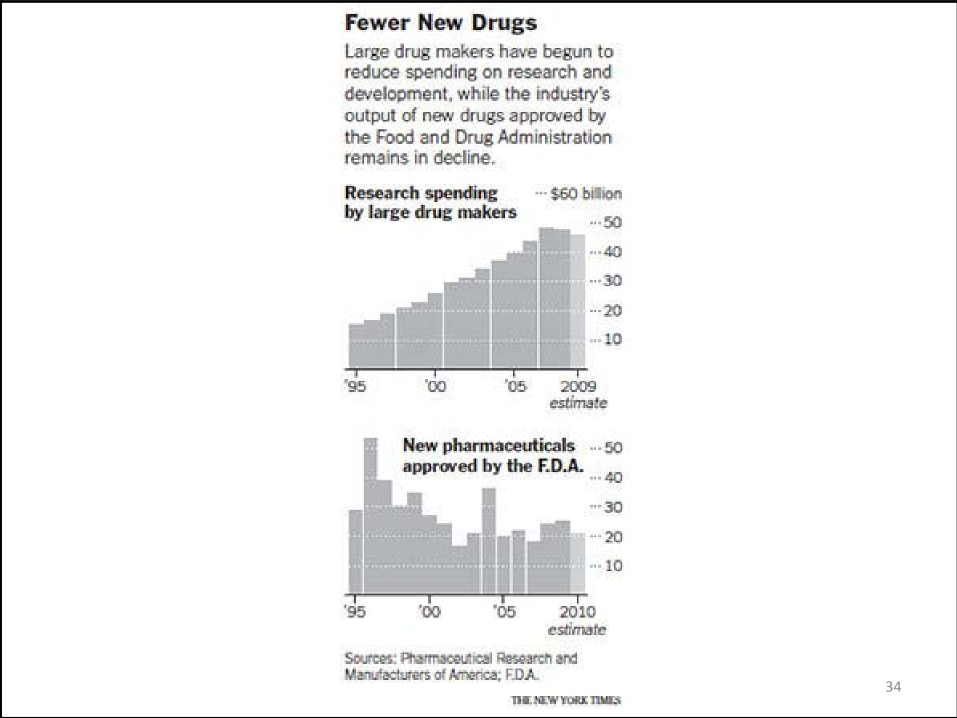

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Practice variation

- I believe that heterogeneous pharmaceutical treatment of patients, controlling for their diagnoses, demographic characteristics, insurance coverage, and other factors, is primarily due to physician practice variation.
- Wennberg (2004) argues that “unwarranted [treatment] variation—variation not explained by illness, patient preference, or the dictates of evidence-based medicine—is a ubiquitous feature of U.S. health care.”
- A large number of studies have documented the importance of unexplained variation in medical care in general and prescribing behavior in particular.

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Practice variation

- Lee et al (2008) showed that “pediatric and adult transplant physicians differed significantly in their management strategies for chronic myeloid leukemia, acute and chronic graft-versus-host disease, and choice of graft source for patients with aplastic anemia. Among adult transplant physicians, there was little agreement on the patient factors favoring reduced intensity conditioning or myeloablative conditioning.”
- DeSalvo et al (2000) reported “wide variation…in assignment of reappointment interval with mean return intervals…ranging from 2.2 to 20.5 weeks. Sex was a significant provider independent variable…Female providers assigned earlier reappointment intervals for their patients.”
- Solomon et al (2003) found that “established risk factors for NSAID-associated gastrointestinal toxicity were poor predictors of who was prescribed a selective COX-2 inhibitor; in contrast, physician prescribing preference was an important determinant.”
- De Las Cuevas et al (2002) showed that “there is a remarkable degree of variation in antidepressant prescribing by psychiatrists and general practitioners; this is due to economic and social factors as much as to morbidity differences.”
- Rochon et al (2007) found that “residents in facilities with high antipsychotic prescribing rates were about 3 times more likely than those in facilities with low prescribing rates to be dispensed an antipsychotic agent, irrespective of their clinical indication.”

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[Dartmouth Atlas of Health Care]

- “Studies that have looked carefully at the additional services provided in high-spending regions have shown that the higher volume of care does not produce better outcomes for patients. Medicare beneficiaries in high-spending regions do not receive more “effective care” (services shown by randomized trials to result in better health outcomes, such as making sure that heart attack patients get proper medication).”
- http://www.dartmouthatlas.org/downloads/reports/Spending_Brief_022709.pdf

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Conventional wisdom

- There is considerable regional variation in medical expenditure
- Medical expenditure is uncorrelated across regions with health outcomes
- Therefore, “money doesn’t matter”
- Moreover, much of the growth and variation in medical expenditure is due to medical technology
- Therefore, “technology doesn’t matter”

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Only one tenth of individual variation in drug vintage is explained

Explanatory variables:

- Sex
- Age
- Year
- Educational attainment
- Race
- Region
- Marital status
- Poverty category
- Insurance coverage
- BMI
- Smoking
- 110 medical condition dummy variables

Estimates with no explanatory variables for population age 65+

(whose mean age is 74.3)

λ	14.61
k	1.24
mean = $\lambda\ \Gamma(1+(1/k))$	12.99

As expected, k > 1: the mortality rate increases with time.
Estimated life expectancy of this population is 12.99 years.
When I include sex and age dummy variables, coefficient on female = .26, implying that mean life expectancy of females is about 26% higher than mean life expectancy of males.
Comparison with published estimates from National Vital Statistics Reports, Vol. 58, No. 21, June 28, 2010 :

Average number of years of life remaining at age 75 in 2000, both sexes	11.1
Average number of years of life remaining at age 75 in 2000, males	9.9
Average number of years of life remaining at age 75 in 2000, females	12.0

Published estimates of life expectancy, and of female-male differential (19%), are somewhat smaller than estimates implied by my model.
Period vs. cohort life table.

Dependent Variable	Log(surv_time)
Censoring Variable	MORTSTAT
Censoring Value(s)	0
Number of Observations	5093
Noncensored Values	2054
Right Censored Values	3039
Left Censored Values	0
Interval Censored Values	0
Name of Distribution	Weibull
Log Likelihood	-4526.52068

Selected estimates from survival model

(model also includes 100+ medical condition dummy variables)

Parameter	Level1	Estimate	StdErr	ChiSq	ProbChiSq
fda_year		0.005751	0.001841	9.757118	0.001786
age	65-69	1.410315	0.095705	217.1539	3.78E-49
age	70-74	1.119716	0.091164	150.8568	1.13E-34
age	75-79	0.798467	0.087746	82.80492	9.06E-20
age	80-84	0.477265	0.086717	30.2911	3.72E-08
age	85-89	0.299828	0.092506	10.50525	0.00119
age	90+	0			
SEX	Female	0.35397	0.040451	76.5739	2.12E-18
year	1996	-0.16854	0.048472	12.08982	0.000507
year	1997	-0.12759	0.052521	5.901103	0.015131
year	1998	0.003216	0.058061	0.003067	0.955832
year	1999	0			
race2	ASIAN OR PACIFIC ISLANDER	0.352128	0.162779	4.679572	0.030523
race2	BLACK	-0.10803	0.049858	4.694412	0.030261
race2	WHITE	0			
POVCAT	1	-0.11144	0.055403	4.046054	0.044275
POVCAT	2	-0.15482	0.066244	5.461927	0.019435
POVCAT	3	-0.08299	0.05122	2.625103	0.105186
POVCAT	4	-0.00395	0.047386	0.00695	0.933559
POVCAT	5	0			
inscov	ANY PRIVATE	-0.43498	0.51335	0.717988	0.396805
inscov	PUBLIC ONLY	-0.4881	0.512997	0.905308	0.341362
educyr	00 - 08 ELEMENTARY GRADES 1 - 8	-0.16692	0.093448	3.190755	0.074056
educyr	09 - 11 HIGH SCHOOL GRADES 9 - 11	-0.27049	0.094643	8.167902	0.004264
educyr	12 GRADE 12	-0.19545	0.091087	4.60409	0.031896
educyr	13-15 1-3 YEARS COLLEGE	-0.0824	0.098066	0.7061	0.400742
educyr	16 4 YEARS COLLEGE	-0.09733	0.106128	0.841051	0.359096
educyr	17 5+ YEARS COLLEGE	0			
region	MIDWEST	0.067647	0.05099	1.760055	0.184618
region	NORTHEAST	0.042646	0.053109	0.644799	0.421978
region	SOUTH	0.034806	0.047306	0.541361	0.461869
region	WEST	0			

Calculation of incremental cost-effectiveness ratio

	Life expectancy at age 75 (years)	Annual medical expend	Lifetime medical expend	Incremental cost effectiveness ratio
Baseline	11.10	$6,817	$75,666	
Baseline + effect of 7.6-year increase in rx vintage	11.59	$7,121	$82,498	
Effect of 7.6-year increase in rx vintage	0.49	$304	$6,832	$14,080

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Calculation of incremental cost-effectiveness ratio

with adjustment for possible 33% overestimation of effect of rx vintage on LE

	LE	annual medical expend	lifetime medical expend	incremental cost effectiveness ratio
Baseline	11.10	$6,817	$75,666	
Baseline + effect of 7.6-year increase in rx vintage	11.45	$7,121	$81,568	
Effect of 7.6-year increase in rx vintage	0.35	$304	$5,902	$16,643

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Consistency with study based on longitudinal German state-level data

- In that study, I estimated that the increase in drug vintage increased life expectancy by 0.45 years between 2001 and 2007.
- The implied ICER is € 11,597 (= € 5,187 / 0.45 years), or $16,173 (at the current exchange rate of 1.39 $/€) per life-year.
- Lichtenberg, Frank, “The contribution of pharmaceutical innovation to longevity growth in Germany and France, 2001-2007,” *PharmacoEconomics*, forthcoming.

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“Negative findings”

- Priority-review vs. standard-review drugs
- Life expectancy trend

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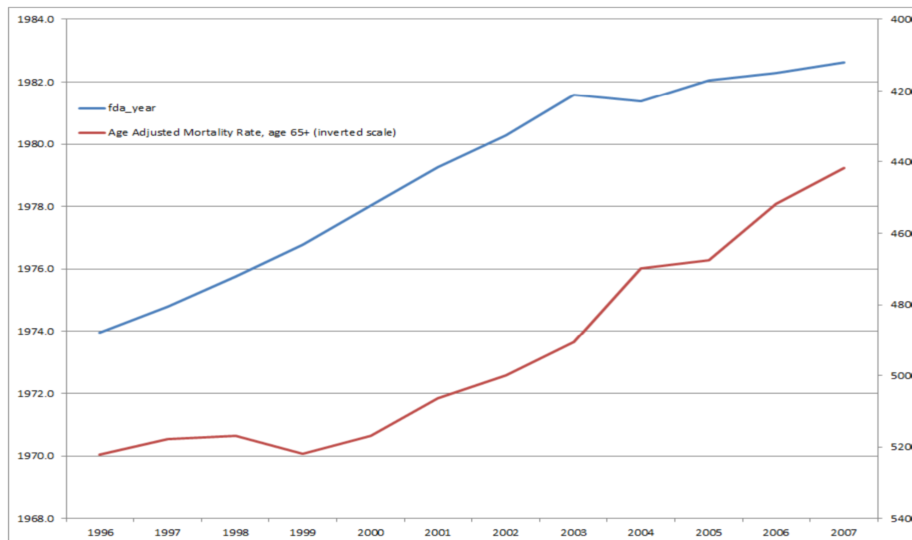
Although vintage has increased much more slowly since 2003, life expectancy has not



Activity limitations

- People who use newer drugs are less likely to have (contemporaneous) activity limitations than people using older drugs, controlling for all of the variables described above.
- Controlling for activity limitations reduces the magnitude of the rx_vintage coefficient in the survival equation by a small amount (about 10-15%)
- This is also true among nursing-home residents, even when we control for facility fixed effects.

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Table 1

Percent distribution of nursing home residents, according to extent of assistance required with activities of daily living

	Activity				
Extent of assistance required	transfer	dress	eat	toilet	bath
Independent	22%	11%	44%	18%	2%
Supervision	7%	7%	23%	6%	6%
Limited assistance	20%	22%	10%	17%	9%
Extensive assistance	28%	35%	9%	28%	46%
Total dependence	22%	25%	15%	31%	37%
	100%	100%	100%	100%	100%

Number of ADL dependencies (number of activities for which the resident is not independent)	Percentage of nursing home residents
0	2%
1	7%
2	7%
3	6%
4	28%
5	50%
	100%

N = 12,357.

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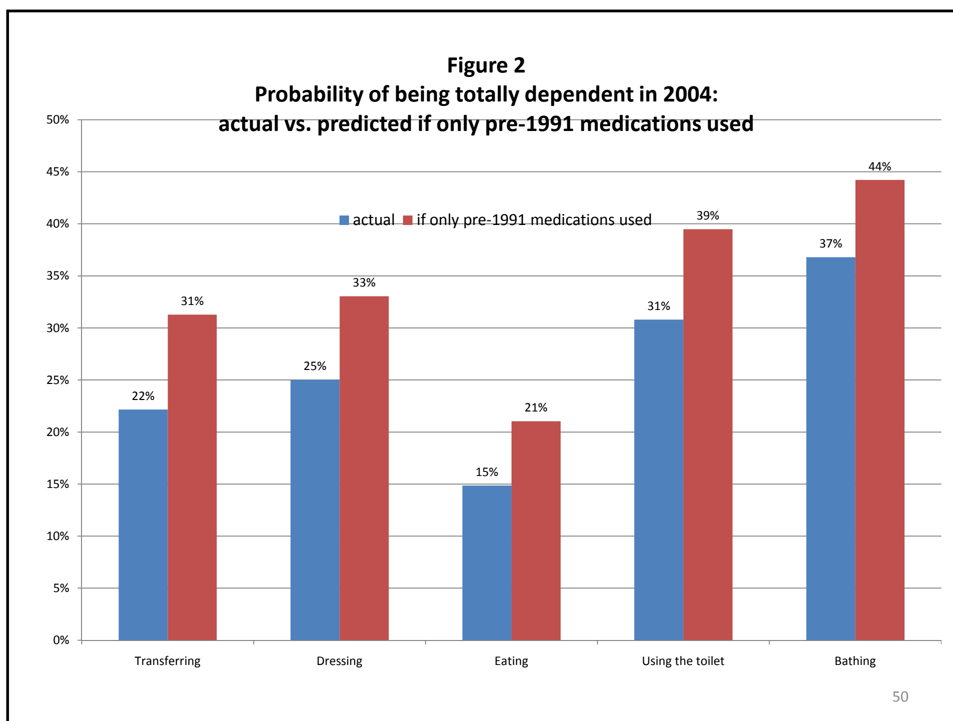

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Summary

- Between 1996 and 2003, the mean vintage of prescription drugs used by seniors increased by 7.6 years.
- I estimate that this increased the life expectancy of seniors by 4-6 months.
- The cost per life-year gained did not exceed $17,000, far below estimates of the value of a statistical life-year.
- Evidence indicates that use of newer drugs also reduced activity limitations of elderly community and nursing-home residents.