

## Bayer Lunch and Learn

고혈압, 혈관질환, 그리고 정밀의학



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4 Summary

# Risk factors for Stroke

## Non-modifiable factors

- ① Age
- ② Sex
- ③ Race
- ④ Family history

## Modifiable factors

- ① Hypertension
- ② Diabetes
- ③ Dyslipidemia
- ④ Smoking
- ⑤ Carotid disease
- ⑥ Cardiac disease such as atrial fibrillation
- ⑦ Obesity
- ⑧ Inactivity

WASHINGTON, D.C.  
April 9, 1944

9th	202/102	P.M.	196/96
10th	196/94	"	200/104
11th	192/96	"	204/100
12th	200/102	"	204/98
13th	196/100	"	202/98
14th	206/100	"	200/96
15th	206/102	"	196/100
16th	215/102	"	206/120
17th	216/120	"	206/116 (Dr. Bruen 4th sound)
18th	220/120	(4th sound)	Unicorp 1; KI $\neq$ x t.i.d. ac.
19th	218/120	P.M.	204/104
20th	212/106	Noon	210/96 9:54 p.m. 190/100 (KI discontinued)
21st	9:05 a.m.	234/126	10:05 a.m. (sitting) 210/116; 10:05 a.m. 218/120 (prone, both arms checked) 6:45 p.m. after outing 214/120; 9:50 p.m. 220/114.
22nd	9:30 a.m.	214/120	11:30 a.m. 210/114; 6:30 p.m. (after boat trip) 206/110.
23rd	10:15 a.m.	214/118	( $\frac{1}{2}$ hr drive) 9:45 212/114.
24th	10:05 a.m.	222/128	10:30 p.m. 220/116
25th	10:05	224/116	10 p.m. 214/106 (after luncheon party).
26th	10. a.m.	214/112	10:30 p.m. 222/110
27th	10:15 a.m.	222/118	9:45 p.m. 210/114
28th	224/124	P.M.	230/120 (one additional digit tablet Tuesday and Friday)
29th	9:30 a.m.	(on swamking) 196/118; (sitting after breakfast) 10:10 226/120; (Prone, after E.E.) 220/118; 2:15 (after lunch) 226/112 (Theosodate discontinued) 9:30 p.m. 210/110	
30th	6:45 (Prone, on swamking)	210/110; (after breakfast) 10:00 206/104; ; after lunch 206/114; 9:00 p.m. 224/120	
May 1st.	Prone 9:30 a.m.	220/116; Noon 210/110; 2 p.m. (after lunch 210/ 106; 10:30 p.m. 210/112.	

Franklin D. Roosevelt Library

# IHD vs Stroke and SBP

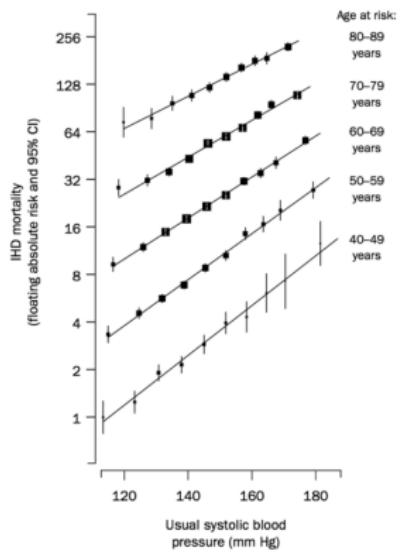


Figure 1. Ischemic heart disease (IHD) mortality

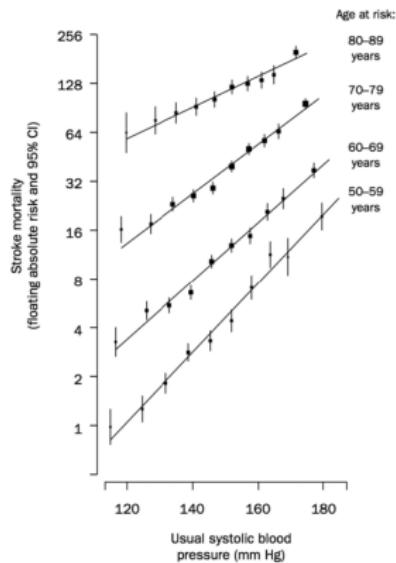
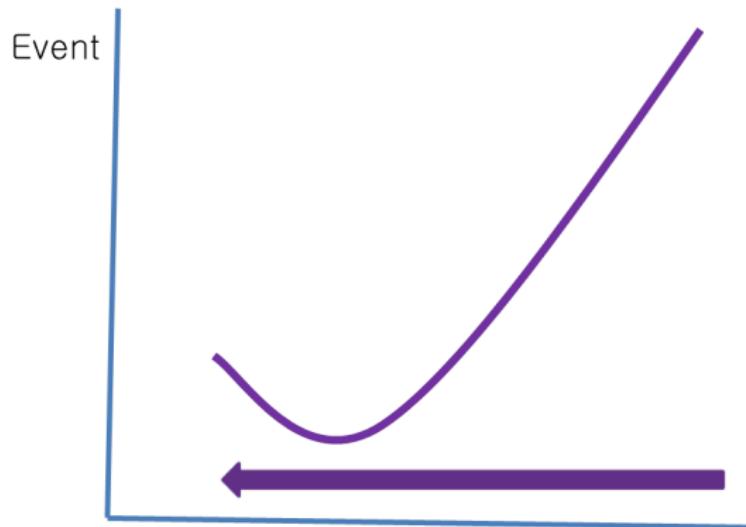
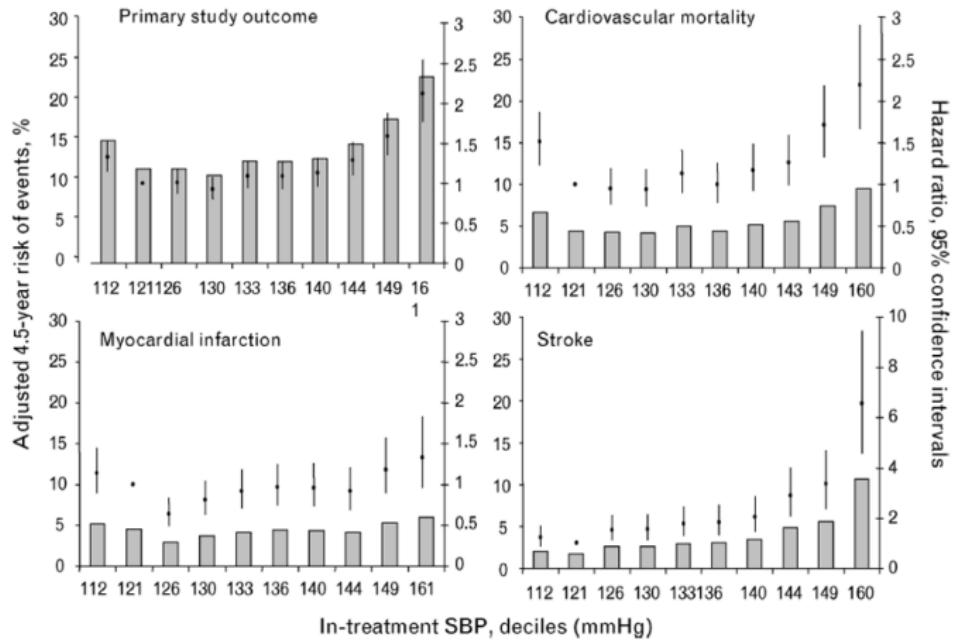


Figure 2. Stroke mortality

# Hypertension: J curve ?



# Ontarget study

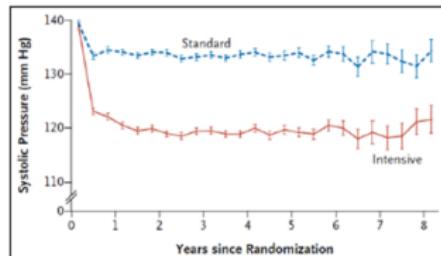


# The lower BP looks beneficial in stroke: ACCORD

- 4733 patients with type 2 DM

- SBP

< 140 mm Hg vs. < 120 mm Hg



Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	%/yr	no. of events	%/yr		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03

N Engl J Med. 2010 362(17):1575-85

*The NEW ENGLAND  
JOURNAL of MEDICINE*

ESTABLISHED IN 1812

NOVEMBER 26, 2015

VOL. 373 NO. 22

A Randomized Trial of Intensive versus  
Standard Blood-Pressure Control

The SPRINT Research Group\*

ABSTRACT

**BACKGROUND**

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

**METHODS**

We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

The members of the writing committee (Jackson T. Wright, Jr., M.D., Ph.D., Jeff D. Williamson, M.D., M.H.S., Paul K. Whelton, M.D., Joni K. Snyder, R.N., B.S.N., M.A., Kaycey M. Sink, M.D., M.A.S., Michael V. Rocco, M.D., M.S.C.E., David M. Reboussin, Ph.D., Mahboob Rahman, M.D., Suzanne Oparil, M.D., Cora E. Lewis, M.D., M.S.P.H., Paul L. Kimmel, M.D., Karen C. Johnson, M.D., M.P.H., David C. Goff, Jr., M.D., Ph.D., Lawrence J. Fine, M.D., Dr.P.H., Jeffrey A. Cutler, M.D., M.P.H., William C. Cush-

# SPRINT: Demographics

	Intensive Tx.	Standard Tx.
Number	4678	4683
Age	$67.9 \pm 9.4$	$67.9 \pm 9.5$
Female	1684 (36.0%)	1648 (35.2%)
CVD	940 (20.1%)	937 (20.0%)
CKD	1330 (28.4%)	1315 (28.1%)
GFR	$71.8 \pm 20.7$	$71.7 \pm 20.5$
Initial BP	139.7/78.2 mm Hg	139.7/78.0 mm Hg
Mean SBP	121.5 mm Hg	134.6 mm Hg

Exclusion: History of stroke (not CE or stenting)

# SPRINT: Primary outcome

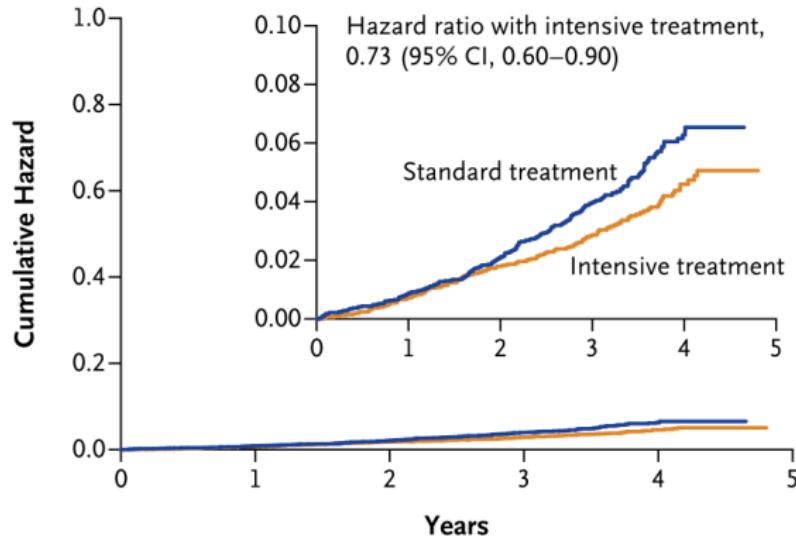
The first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes.

**Table 2.** Primary and Secondary Outcomes and Renal Outcomes.\*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	% per year	no. of patients (%)	% per year		
All participants	(N=4678)		(N=4683)			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005

# SPRINT: All cause mortality

Death from Any Cause



N Engl J Med. 2015 Nov 26;373(22):2103-16

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**ORIGINAL CONTRIBUTION**

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# Association of *BRCA1* and *BRCA2* Mutations With Survival, Chemotherapy Sensitivity, and Gene Mutator Phenotype in Patients With Ovarian Cancer

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Da Yang, PhD

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Sofia Khan, PhD

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Yan Sun, MD, PhD

---

Kenneth Hess, PhD

---

Ilya Shmulevich, PhD

---

Anil K. Sood, MD

---

Wei Zhang, PhD

**Context** Attempts to determine the clinical significance of *BRCA1/2* mutations in ovarian cancer have produced conflicting results.

**Objective** To determine the relationships between *BRCA1/2* deficiency (ie, mutation and promoter hypermethylation) and overall survival (OS), progression-free survival (PFS), chemotherapy response, and whole-exome mutation rate in ovarian cancer.

**Design, Setting, and Patients** Observational study of multidimensional genomics and clinical data on 316 high-grade serous ovarian cancer cases that were made public between 2009 and 2010 via The Cancer Genome Atlas project.

**Main Outcome Measures** OS and PFS rates (primary outcomes) and chemotherapy response (secondary outcome).

INCREASED SURVEILLANCE OF *BRCA1/2* germ line mutation carriers is a non...

Yang, D., et al. (2011). "Association of *BRCA1* and *BRCA2* mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer." *JAMA* 306(14): 1557-1565.

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## Don't Delay News of Medical Breakthroughs

By ERIC J. TOPOL and HARLAN M. KRUMHOLZ    SEPT. 17, 2015

[f](#) [t](#) [g](#) [e](#) [b](#) [101](#)



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Medicine needs to change its approach to releasing new, important information. Throughout science we are seeing more rapid modes of communication. The traditional approach was not to publish until everything was finalized and ready to be chiseled in stone. But these sorts of delays are unnecessary with the Internet.

[http://www.nytimes.com/2015/09/18/opinion/dont-delay-news-of-medical-breakthroughs.html?\\_r=0](http://www.nytimes.com/2015/09/18/opinion/dont-delay-news-of-medical-breakthroughs.html?_r=0)

## EDITORIAL



## A SPRINT to the Finish

Jeffrey M. Drazen, M.D., Stephen Morrissey, Ph.D., Edward W. Campion, M.D.,  
and John A. Jarcho, M.D.

We were therefore surprised by the call from Topol and Krumholz for immediately “placing the data on the NIH website.”<sup>2</sup> We believe that it is critical to give the investigators, on behalf of the study participants, who invested years of their lives in the study, the opportunity to see what led the sponsor to stop the trial and then the opportunity to distill a clinical message from it. There are cogent reasons to follow this approach

Drazen, J. M., et al. "A SPRINT to the Finish." *New England Journal of Medicine* 2015;373:2174-2175

## EDITORIALS



## Data Sharing

Dan L. Longo, M.D., and Jeffrey M. Drazen, M.D.

The aerial view of the concept of data sharing is beautiful. What could be better than having high-quality information easily harvested for the possibility that new nuggets of useful data are lying there, previously unseen? The potential for leveraging existing results for even more benefit pays appropriate increased tribute to the patients who put themselves at risk to generate the data. The moral imperative to honor their collective sacrifice is the trump card that takes us right.

However, many of us have actually conducted clinical research, managed clinical studies and data collection and analysis, and curated data sets have concerns about the details. The first concern is that someone not involved in the generation and collection of the data may not understand the choices made in defining the protocol or specifying what kind of data are to be combined from independent studies and consider comparable. How heterogeneous were the study populations? Were the eligibility criteria the same? Can it be assumed that the differences in study populations, data collection and analysis, and treatments, both protocol-specified and unspecified, can be ignored?

A second concern held by many is that a new class of research people will emerge who had nothing to do with the design and execution of the study but use another group's data for their own ends, possibly stealing from the research productivity planned by the data gatherers, or even use the data to try to disprove what the original investigators had posited. There is concern among some front-line researchers that the system will be taken over by what some researchers have characterized as "research parasites."

This issue of the Journal offers a product of data sharing that can exceed the optimism. The new investigations arrived on the scene with their own ideas and worked symbiotically, rather than parasitically, with the investigators holding the data, moving the field forward in a way that neither group could have done on its own. In this case, Dateba and colleagues<sup>1</sup> had a hypothesis that colon cancers arising from more primitive colonic epithelial precursors might be more aggressive and have a higher risk of relapse and might be more likely to benefit from adjuvant treatment. They found a gene whose expression appeared to correlate with the expression of genes that characterize more mature colon cancers on gene-expression arrays and whose product was reliably measurable in resected colon cancer specimens by immunohistochemistry. To assess the clinical use of this potential biomarker, they needed a sufficiently large group of patients whose archived tissues could be used to assess biomarker expression and who had been treated in relatively homogeneous way.

They proposed a collaboration with the National Surgical Adjuvant Breast and Bowel Project (NSABP) cooperative group, a research consortium funded by the National Cancer Institute that has conducted major trials in the treatment of breast and bowel cancer for the past 50 years. The NSABP provided access to tissue and to clinical trial results on an individual patient basis. This symbiotic collaboration found that a small proportion (4%) of colon cancers did not express the biomarker and that the survival of patients with those tumors was poorer than that of patients whose tumors expressed the biomarker. Furthermore, when the effect of adjuvant chemotherapy was assessed, nearly all

# "Research Parasite"

276

THE NEW ENGLAND JOURNAL OF MEDICINE

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Longo, D. L. and J. M. Drazen (2016). "Data Sharing." *New England Journal of Medicine* 374(3): 276-277.

A second concern held by some is that a new class of research person will emerge — people who had nothing to do with the design and execution of the study but use another group's data for their own ends, possibly stealing from the research productivity planned by the data gatherers, or even use the data to try to disprove what the original investigators had posited. There is concern among some front-line researchers that the system will be taken over by what some researchers have characterized as “research parasites.”

Longo, D. L. and J. M. Drazen (2016). "Data Sharing." *New England Journal of Medicine* 374(3): 276-277.

The screenshot shows the homepage of Science Translational Medicine. At the top, there's a banner for 'Science Signaling' with the tagline 'From Molecules to Man'. Below it, the main title 'Science Translational Medicine' is displayed, along with the AAAS logo. A navigation bar includes links for Home, News, Journals, Topics, and Careers. On the right side, there are buttons for 'Subscribe', 'Renew my subscription', and 'Sign up for alerts'. A search bar and a magnifying glass icon are also present.

The main content area features a large image of a man with a beard, identified as 'Derek Lowe'. The title of the article is 'IN THE PIPELINE' in large, bold letters. Below the title, the subtitle reads: 'Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of Science Translational Medicine.' The article title is 'Attack of the Research Parasites', written by Derek Lowe on January 22, 2016. The text discusses the sharing of clinical data and its impact on science.

On the right side of the article, there are two columns of links:

- MORE FROM SCIENCE TRANSLATIONAL MEDICINE**
  - » [Editorial](#)
  - » [Current Table of Contents](#)
  - » [In the Pipeline](#)
  - » [About Science Translational Medicine](#)
- RECENT COMMENTS**
  - » [Shusterman on A Good Old Fashioned Election](#)
  - » [Kevan on A Good Old Fashioned Election](#)
  - » [Peter S. Shukla on A Good Old Fashioned Election](#)
  - » [Shusterman on A Good Old Fashioned Election](#)
  - » [Kevan on A Good Old Fashioned Election](#)

It's that second paragraph that really sets people off, and it is unfortunately worded. Science actually advances on this sort of thing – calling people who use or build on previous data sets “research parasites” is actually fairly silly. ..... We stand on each other's shoulders in this business; that's how science works. It's not the scientists that worry me here.

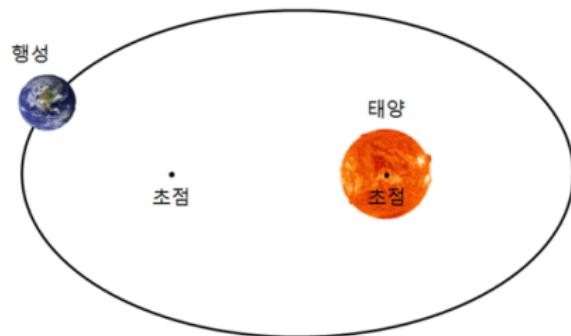
<http://blogs.sciencemag.org/pipeline/archives/2016/01/22/attack-of-the-research-parasites>

If I have seen further than others, it is by standing upon the shoulders of giants.



<https://flowersforsocrates.com/2017/01/04/on-this-day-january-4-2017/isaac-newton-shoulders-of-giants-quote/>

# Tycho Brahe and Johannes Kepler



By Eduard Ender (1822-1883) - <http://cache.eb.com/eb/image?id=83677&rendTypeld=4> Now redirects to <http://media.web.britannica.com/eb-media/77/83677-004-72A98E5A.jpg>. Public Domain, <https://commons.wikimedia.org/w/index.php?curid=822362>

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## Data Scientists = Research Parasites?

**David Shaywitz, CONTRIBUTOR**I write about entrepreneurial innovation in medicine. [FULL BIO](#)

Opinions expressed by forbes contributors are their own.



This Thursday, Dec. 29, 2011 photo shows the entrance to the editorial offices of the New England Journal of Medicine in Boston. (AP Photo/Michael Dwyer)

<http://www.forbes.com/sites/davidshaywitz/2016/01/21/data-scientists-research-parasites/#3c54d7563d1c>

My Twitter TWTR -0.11% feed exploded in response to this editorial:

Michael Eisen, geneticist at UC-Berkeley: “One of the most shockingly anti-science things ever written.”

Sek Kathiresan, cardiologist/geneticist at MGH/Broad: “Shocking to see disparaging term ‘research parasite’ to describe use of data often created w/ public funds.”

Michael Hoffman, computational genomicist at the Princess Margaret Cancer Centre, Toronto: “Fear that others may use data ‘to try to disprove what the original investigators had posited’ is a dangerous misunderstanding of science.”

<http://www.forbes.com/sites/davidshaywitz/2016/01/21/data-scientists-research-parasites/#3c54d7563d1c>

EDITORIAL

#IAmAResearchParasite

In the middle of study progress in policies for data sharing, a new editorial expressed a contentious view. The author describes the concept of "research paradox" who expand data sets that are collected and created by others. Every time, these data sets are used, they are modified. In this case, the conclusions produced are based on the original research source. The editorial raised the point of how anyone could use the data without "misinterpreting it, and the danger of perpetuating the misconception in the literature evolution. The editorial advised instead that data sets should be made available to the public involving the authors of the original study as co-authors.

The research community immediately took to Twitter to express their support for the editor and ResearchParadox to voice opposition to the editorial. This discussion has shown that about the large-scale features of this plan is apparent. It is clear that the data-sharing practices and the early establishment of the policy have been successful. Aspects such as determining the shape of the policy, the scope of the community, the internal structure of Data sharing, the role of the administrator, and many other topics could not have been answered from a single investigator's field grants. One meta-analysis I published on the use of data sharing in the field of medicine and those of others, including the 18th-century British explorer Captain James Cook, illustrating Cook as a coauthor on 13 publications, showed that the data set would have been feasible or desirable to include the details of others, living on land, who had contributed to his success. In this case, the data were not meta-analyzed to determine the best way to implement data sharing, but we learned the big picture.

"There are  
for re-call  
for new

*"There are costs...  
for re-collecting data  
for new uses."*

A black and white portrait of Marvina McFerrin, Editor-in-Chief of Science Journals. She is a woman with blonde hair, smiling, wearing a dark top. The background is slightly blurred.

Marvina McFerrin is  
*Editor-in-Chief*,  
Science Journals

implementation, and it takes more than commercially appropriate software. Agencies requesting support in transitioning to an e-cataloging system have long funded data and sample collection, but the agency must also commit to the process of the transition by making new awards contingent on compliance. Repositories are instrumental in setting forms for the submission of data. The data manager can accept and output data in the standard format. The science community supports data professionals who are responsible for the quality of data submitted to the agency. This is a critical role for the agency, as well as for other major observing programs.

Often overlooked is the importance of having well-established metadata, so that those not involved in the data collection process will know what the data means. As an example, in an oceanographic temperature dataset, the agency probably had to agree on what TIRI meant. What is a temperature at atmospheric pressure? What is a temperature at the sea surface?

An illustration showing a hand wearing a blue glove pointing its index finger towards a second, separate yellow glove.

Communities must discourage low-quality data collection. A well-attended poster presentation at one recent scientific

our present systems meeting some years ago compared the crossover errors (shifts) of non-time-dependent measurements (such as depth soundings, free ship track where they intersected in the world's oceans. Any discrepancy at a crossing could be attributed to poor data quality control or other ship errors with thousands of crossings, initiations with systematically more mistakes than others stand out. The results did not escape the attention of the funding agencies that support ship time.

There are costs to implementing data reuse, but there are also costs for irreproducible research and for reflecting data for new uses. And no amount of funding can reconstruct lost ephemeral or time-dependent phenomena for which the data were not well curated. No more excuses! Let's step up to data sharing.

Marcia McNutt is  
Editor-in-Chief,  
*Science*; *Ames*

[Downloaded from <http://science.scientificmag.org/>] on August 19, 2016

In the midst of steady progress in policies for data sharing, a recent editorial expressed a contrarian view.\* The authors described the concern of some scientists about the rise of an underclass of “research parasites” who exploit data sets that are collected and curated by others. Even worse, these parasites might use such data to try to disprove the conclusions posited in the data’s original source studies. The editorial raised the points of how anyone not involved in the original study could use the data without misrepresenting

McNutt, M. (2016). "#IAmAResearchParasite." *Science* 351(6277): 1005-1005.

gram. One meta-analysis I published on the South Pacific benefited from observations of my own and those of others, including the 18th-century British explorer Captain James Cook. Involving Cook as a coauthor on my paper was clearly not an option, any more than it would have been feasible or desirable to include the dozens of others, living or dead, who had contributed to the data repository. Many fields, including the biomedical sciences, are now benefiting from meta-analyses of data to better understand the big picture.

Effective data sharing is not trivial or inexpensive

but with thousands of crossings, institutions with systematically more misfits than others stand out. The results did not escape the attention of the funding agencies that support ship time.

There are costs to implementing data reuse, but there are also costs for irreproducible research and for re-collecting data for new uses. And no amount of funding can reconstruct lost ephemeral or time-dependent phenomena for which the data were not well curated. No more excuses: Let's step up to data sharing.

- Marcia McNutt

McNutt, M. (2016). "#IAmAResearchParasite." *Science* 351(6277): 1005-1005.

**Iddo Friedberg**

@iddux



Follow

I propose a new science award: "The Research Parasite Award is given to those who used someone else's data to do some really cool sh\*t"

12:54 AM - 23 Jan 2016



51



84

<http://www.greenelab.com/parasite-award/>



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An application requires:

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- Junior Parasite (aka the sporozoite): a PDF of one paper published after peer review on which the application will be judged.
- Sustained Parasitism (aka the merozoite): PDFs of three papers published after peer review on which the application will be judged.

<http://www.greenelab.com/parasite-award/>

## EDITORIAL

Data Sharing and the *Journal*

Jeffrey M. Drazen, M.D.

We want to clarify, given recent concern about our policy, that the *Journal* is committed to data sharing in the setting of clinical trials. As stated in the Institute of Medicine report from the committee<sup>1</sup> on which I served and the recent editorial by the International Committee of Medical Journal Editors (ICMJE),<sup>2</sup> we believe there is a moral obligation to the people who volunteer to participate in these trials to ensure that their data are widely and responsibly used. *Journal* policy will therefore follow that outlined in the ICMJE editorial and the IOM report: when appropriate systems are in place, we will require a commitment from authors to make available the data that underlie the reported results of their work within 6 months after we publish them.

In the process of formulating our policy, we spoke to clinical trialists around the world. Many were concerned that data sharing would require them to commit scarce resources with little direct benefit. Some of them spoke pejoratively in describing data scientists who analyze the data of others.<sup>3</sup> To make data sharing successful, it is important to acknowledge and air those concerns.<sup>3</sup> In our view, however, research-

ers who analyze data collected by others can substantially improve human health.

We need your help to move medicine forward and improve patient care. Our enemy is disease. By working in collaboration, as we have suggested,<sup>4</sup> biologists, data scientists, and clinical trialists can advance the art, and everyone will gain. Clinical trial data are some of the highest quality data in medicine. They should be used responsibly and extensively to help alleviate suffering. We believe that we will all benefit most if this is done collaboratively, but the *Journal's* data sharing policy will apply in all settings.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

This article was published on January 25, 2016, at NEJM.org.

**1.** Committee on Strategies for Responsible Sharing of Clinical Trial Data. Sharing clinical trial data: maximizing benefits while minimizing risk. Washington, DC: National Academies Press; 2015.

**2.** Longo DL, Backus J, Bergeron C, et al. Sharing clinical trial data — a proposal from the International Committee of Medical Journal Editors. *N Engl J Med* 2016;374:384-6.

**3.** Longo DL, Drazen JM. Data sharing. *N Engl J Med* 2016;374:276-7.

DOI: 10.1056/NEJMoa1401087  
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Drazen, J. M. (2016). "Data Sharing and the Journal." *New England Journal of Medicine* 374(19): e24.

Participants in clinical research volunteer in order to support the development of scientific knowledge and help future patients. Inherent in their commitment is the belief that research will lead to new insights that will be disseminated. As clinical researchers, we fully support the concept of data sharing as fundamental to achieving this goal.

*Cardiovascular, T. A. R. O. C. f. C. E. o. S. S. (2016). "Sharing Data from Cardiovascular Clinical Trials — A Proposal." New England Journal of Medicine 375(5): 407-409.*



The NEW ENGLAND JOURNAL of MEDICINE

# Perspective

AUGUST 4, 2016

## Strengthening Research through Data Sharing

Elizabeth Warren, J.D.

Data sharing has incredible potential to strengthen academic research, the practice of medicine, and the integrity of the clinical trial system. Some benefits are obvious: when

to the data underlying trial results can provide an avenue for independent confirmation of results and further analyses of the data set, raising the bar for academic

Warren, E. (2016). "Strengthening Research through Data Sharing." *New England Journal of Medicine* 375(5): 401-403.  
Back to presentation

# 진료: 4차 산업혁명



## 제 1차 산업혁명

18세기

증기기관 기반의  
기계화 혁명

증기기관을 활용하여  
영국의 섬유공업이  
거대산업화



## 제 2차 산업혁명

19세기~20세기 초

전기·에너지 기반의  
대량생산 혁명

공장에 전력이 보급  
되어 벨트 컨베이어를  
사용한 대량 생산보급



## 제 3차 산업혁명

20세기 후반

컴퓨터와 인터넷 기반의  
지식정보 혁명

인터넷과 스마트  
혁명으로 미국주도의  
글로벌 IT기업 부상



## 제 4차 산업혁명

2015년~

IOT/CPS/인공지능  
기반의  
만물초지능 혁명

사람, 사물, 공간을  
초연결, 초지능화  
하여 산업구조  
사회 시스템 혁신

### 원격진료

AI for practice

IoT + Big Data

Genomic data into clinic

# We want something like this in genetics

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 ORIGINAL CONTRIBUTION

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## Association of *BRCA1* and *BRCA2* Mutations With Survival, Chemotherapy Sensitivity, and Gene Mutator Phenotype in Patients With Ovarian Cancer

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Da Yang, PhD

Sofia Khan, PhD

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Yan Sun, MD, PhD

Kenneth Hess, PhD

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Ilya Shmulevich, PhD

Anil K. Sood, MD

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Wei Zhang, PhD

**Context** Attempts to determine the clinical significance of *BRCA1/2* mutations in ovarian cancer have produced conflicting results.

**Objective** To determine the relationships between *BRCA1/2* deficiency (ie, mutation and promoter hypermethylation) and overall survival (OS), progression-free survival (PFS), chemotherapy response, and whole-exome mutation rate in ovarian cancer.

**Design, Setting, and Patients** Observational study of multidimensional genomics and clinical data on 316 high-grade serous ovarian cancer cases that were made public between 2009 and 2010 via The Cancer Genome Atlas project.

**Main Outcome Measures** OS and PFS rates (primary outcomes) and chemotherapy response (secondary outcome).

 INCREASED SURVEILLANCE OF *BRCA1/2* germline mutation carriers is a non-

Yang, D., et al. (2011). "Association of *BRCA1* and *BRCA2* mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer." *JAMA* 306(14): 1557-1565.

# In the era of precision medicine,



The American College of  
Obstetricians and Gynecologists  
WOMEN'S HEALTH CARE PHYSICIANS

## patient education Fact Sheet

PFS007: BRCA1 and BRCA2 Mutations MARCH 2015

### **BRCA1 and BRCA2 Mutations**

Cancer is a complex disease thought to be caused by several different factors. A few types of cancer run in families. These types, called "hereditary" or "familial" cancer, have been linked to changes in genes that can be passed from parents to children. Changes in genes are called **mutations**.

**Hereditary breast and ovarian cancer syndrome** is a type of familial cancer. It most commonly is linked to mutations in two genes called **BRCA1** and **BRCA2**. Inheriting one of these mutations increases the risk of getting breast cancer, ovarian cancer, and other types of cancer. About 10% of cases of ovarian cancer and 3–5% of cases of breast cancer are due to mutations in **BRCA1** and **BRCA2**.

**Table 1.** Breast Cancer and Ovarian Cancer Risk for Women With *BRCA* Mutations

Type of Cancer	Risk for the General Population	Risk With <i>BRCA1</i> Mutation	Risk With <i>BRCA2</i> Mutation
Breast	12%	55–65%	45%
Ovary	1.4%	39%	11–17%

# In stroke,

Table 3. Selected Genetic Causes of Stroke

Disease	Mode of Inheritance	Gene/Protein	Mechanism of Stroke	Common Clinical Manifestations
Single gene disorders that primarily cause stroke				
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy	Autosomal dominant	NOTCH3/MOTD3	Small vessel disease	Ichemic stroke, leukoencephalopathy, migraine, psychiatric manifestations, and dementia
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy	Autosomal recessive	HTXB1/H3A3 serine peptidase-1	Small vessel disease	Ichemic stroke, leukoencephalopathy, premature baldness, and spasticity
Familial amyloid angiopathy	Autosomal dominant	APP/alpha-secretase precursor protein	Rupture of small cortical vessels	Lobar hemorrhage, intracranial, leukoencephalopathy, dementia, and amputated spells
Collagen 1 (COL4A1) mutations	Autosomal dominant	COL4A1/col4a1 chain of collagen type 4	Rupture of cortical and subcortical vessels	Superficial and deep hemorrhages, intracranial aneurysms, hematuria, and cystic kidney disease
Genetic disorders that include stroke as manifestations				
Ehlers-Danlos type 4	Autosomal dominant	COL3A1/type II procollagen	Arterial dissection	Ankle, nose, spine, liss dissolution/hypertrophy; aneurysms/pseudaneurysms; visceral and hepatic failure, and uterine rupture during pregnancy
Fabry disease	X-linked	GAL $\alpha$ -galactosidase A	Large and small artery disease	Ichemic stroke and renal, hepatic, angiokeratoma, corneal opacities and calcifications, neuropathy (intermittent), hypertension, and renal failure
Martor syndrome	Autosomal dominant	FBXW7/Arbiter 1	Arterial dissection and carotid emboles	Ichemic stroke, arterial dissection, carotid, posterior circulation, and vertebral arteries, venous dysfunction/heart failure, and edema/leg cramps
Mitochondrial encephalopathy with lactic acid and stroke-like episodes	Maternal	Mitochondrial DNA (mt)-12 (mitochondrially encoded RNA loci) tRNA leucine 1 (LMTN1) mtDNA variants	Energy failure and metabolic stroke	Ichemic stroke that does not observe vascular boundaries, short stature, developmental delay, seizures, vision loss, hypoglycemia, and diabetes mellitus
Sickle cell disease	Autosomal recessive	HBB $\beta$ -globin (hemoglobin subunit)	Large and small vessel disease and moyamoya syndrome	Ichemic stroke, painful crises, vascular crises, and bacterial infections
Smooth muscle $\alpha$ -actin mutation-associated disorders	Autosomal dominant	ACTA2/smooth muscle $\alpha$ -actin	Moyamoya syndrome	Ichemic stroke, coronary artery disease, thoracic aortic aneurysms, and moyamoya syndrome
Common genetic variants				
TSPO2	Common variant	TSPO2/treponem-2	Vascular development and atherosclerosis	Large vessel ischemic stroke
F002	Common variant	F002/forkhead transcription factor	Smooth muscle cell differentiation of smooth muscle cell and pericyte coverage of cerebral vessels	All stroke, small vessel stroke, and premature and extensive white matter disease
ABP	Common and rare variants	ABP/leukod group protein	Thrombosis	Thrombosis and ischemic stroke
ASAC9	Common and rare variants	ASAC9/leucine-rich protease	Atherosclerosis	Large vessel ischemic stroke
PTD2	Common and rare variants	PTD2	Skeletal muscle development and regulation of ion channels, modulation of gene expression, and cell proliferation	Cardioembolic ischemic stroke and atrial fibrillation
ZFNA3	Common and rare variants	ZFNA3	Atrial fibrillation	Cardioembolic ischemic stroke and atrial fibrillation

# Terminology

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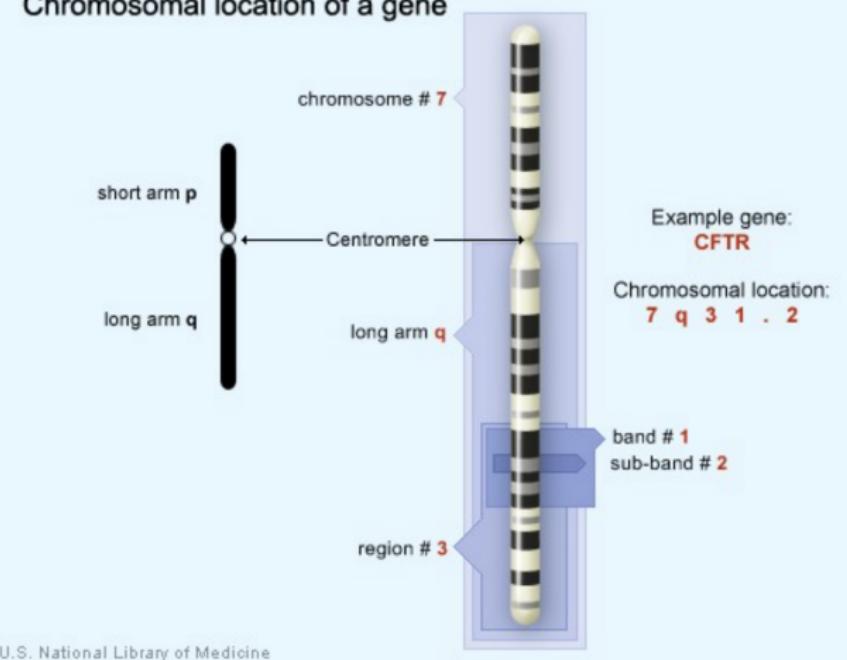
RESEARCH ARTICLE

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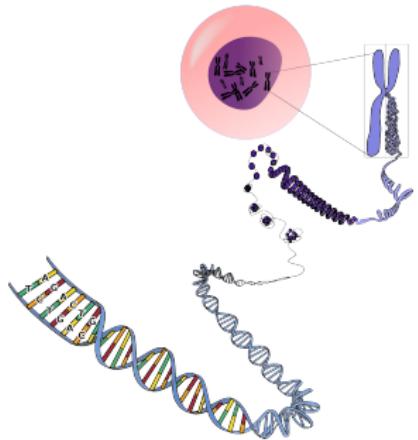
## Genetic Variation at 16q24.2 Is Associated With Small Vessel Stroke

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Jordana T. Bell,<sup>11</sup> Eilis Hannon,<sup>12</sup> Jonathan Mill,<sup>12,13</sup> Ganesh Chauhan,<sup>14,15</sup>

## Chromosomal location of a gene



# Location of DNA variation



- Whole chromosomal and whole genome changes: ~1-6 billion bp
    - Aneuploidy (abnormal number of chromosomes)
    - Aneusomy (fewer or more copies than 2 of a chromosome)
    - Interchromosomal translocations
    - Ring chromosomes
  - Microscopic to submicroscopic
    - Segmental aneusomy
    - Chromosomal deletions
    - Chromosomal insertions
    - Chromosomal inversions
    - Intrachromosomal translocations
    - Chromosomal abnormality
    - Fragile sites
  - 1 kb to submicroscopic
    - Copy number variants (CNVs)
    - Segmental duplications
    - Inversions, translocations
    - CNV regions
    - Microdeletions
    - Microduplications
  - 2 bp to 1,000 bp
    - Microsatellites, minisatellites
    - Insertion-deletions (Indels)
    - Inversions
    - Di-, tri-, tetra-nucleotide repeats
    - Variable number tandem repeats e.g. microsatellites
  - Single nucleotide 1 bp
    - Indels
    - SNPs
- bp indicates base pairs; SNP single nucleotide polymorphisms.

Cytogenetic  
changes

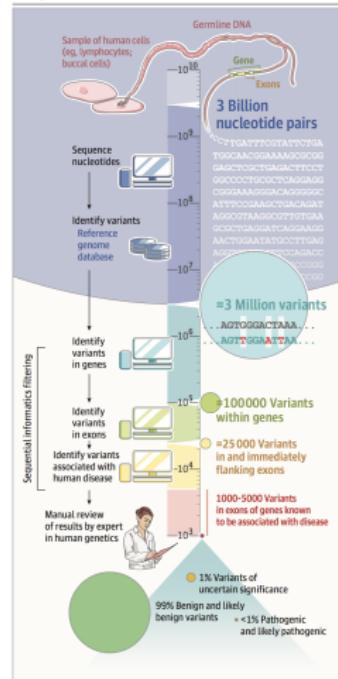


Molecular  
genetic  
changes

# Amount of data

- Interpretation of information
  - 3,000,000,000 base pairs
  - 3,000,000 SNPs
  - 100,000 variants in exon
- significance level in GWAS:  
 $5 * 10^{-8} = 0.05 * 10^{-6}$
- rs\*\*\*\*\*\*(number):  
 Reference SNP cluster ID

Figure. Informatic and Human Analysis Required for Finding Rare Pathogenic Variants in a Human Genome



Evans JP et al. JAMA May 9, 2017 Volume 317, Number 18

# Genetic causes of stroke

- Specific rare single gene disorder:

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

Sickle cell anemia

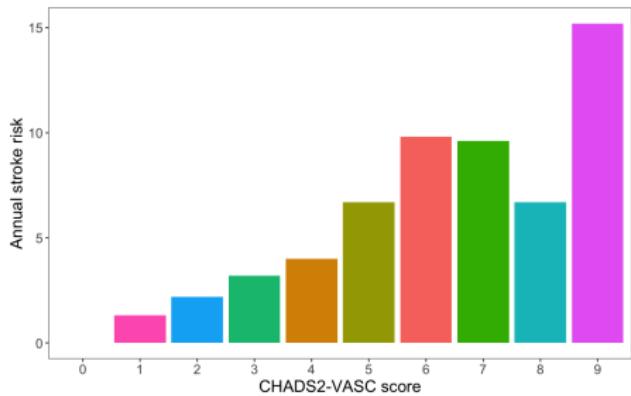
- Common and rare variants of genetic polymorphism:

PITX2 (AF)

ABO (Thrombosis)

# Thromboembolic risk of AF

<i>CHA<sub>2</sub>DS<sub>2</sub>-VASc</i> criteria	Score
CHF	1
Hypertension	1
Age $\geq$ 75 years	2
Diabetes mellitus	1
Stroke or TIA	2
Vascular disease	1
Age 65-74 years	1
Sex category (female)	1



Gage BF et al. JAMA 2001;285:2864-70; Lip G et al. Chest 2010;137:263-72

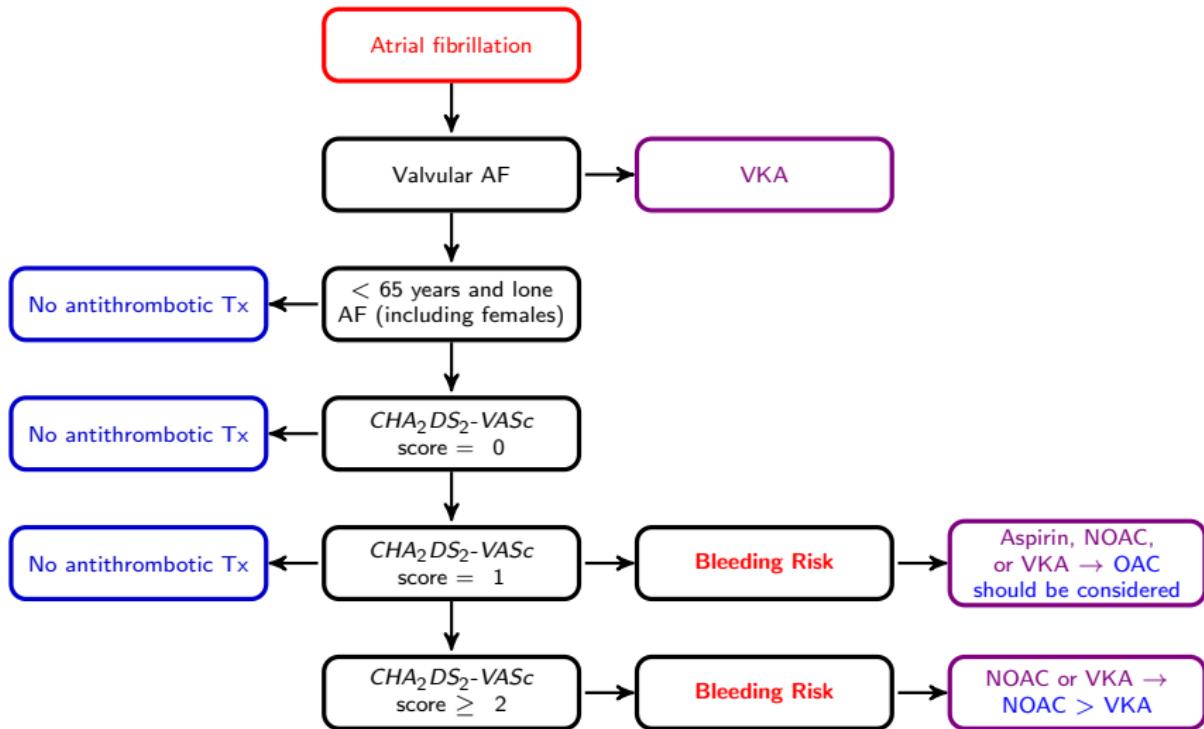
January C, T, et al. Circulation 2014

KY Park (CAU)

고혈압, 뇌졸중, 그리고 정밀의학

April 22, 2019

40 / 45



Frequently,

- AF is diagnosed after the development of large infarction.
- AF is asymptomatic.
- AF is paroxysmal.
- Stroke mechanism can not be determined in some patients.

Genetic marker of AF can be helpful in these situations.

## ORIGINAL RESEARCH ARTICLE

## Genetic Risk Prediction of Atrial Fibrillation

ORIGINAL RESEARCH  
ARTICLE

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Editorial, see p 1321

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**BACKGROUND:** Atrial fibrillation (AF) has a substantial genetic basis. Identification of individuals at greatest AF risk could minimize the incidence of cardioembolic stroke.

**METHODS:** To determine whether genetic data can stratify risk for development of AF, we examined associations between AF genetic risk scores and incident AF in 5 prospective studies comprising 18 919 individuals of European ancestry. We examined associations between AF genetic risk scores and ischemic stroke in a separate study of 509

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## Viewpoints

## A Strategy for Genomic Research on Common Cardiovascular Diseases Aiming at the Realization of Precision Medicine

### Personal Insights and Perspectives

Hiroyuki Morita, Issei Komuro

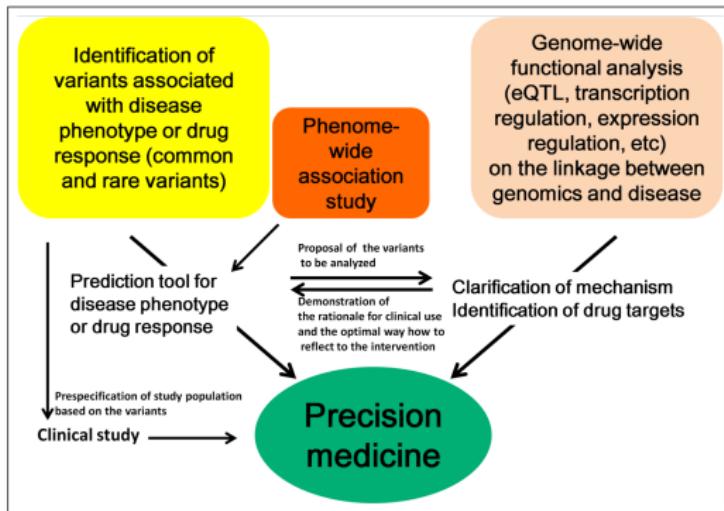


Figure. Schematic representation of genomic research on common diseases toward the realization of precision medicine.

Morita, H. and I. Komuro Circ Res 2016;119(8): 900-903.

## Take-Home Message

- 한국은 급속도로 노령화되는 사회이며, 향후 뇌졸중과 고혈압으로 인한 사회적 부담이 급증할 것입니다.
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