Schweizerische Eidgenossenschaft
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Recherche biomédicale en Suisse: how to stay at the top?

Rencontre organisée par le Conseil suisse de la science et de l'innovation

Recherche biomédicale personnalisée ou plus précise: une nuance aux grandes conséquences

Alfredo Morabia, MD, PhD
(Columbia University & Queens College, NY, USA)

Lundi 22 juin 2015, 17h00 à 18h30
Hôtel Bern, Zeughausgasse 9, 3011 Berne
Salle de conférence au 2ème étage

(National Library of Medicine 1G13LM010884)

My message to you:

Distinguishing personalized medicine from precision medicine helps to:

* Understand what is going on

* Make the appropriate investments to meet the new challenges.

« La médecine personnalisée, parfois désignée sous le terme de «médecine de précision», implique aussi bien la recherche que la pratique médicale et vise à appréhender chaque patient comme un individu biologiquement unique.» (CSSI, III:20)

Precision medicine is "One of the foundations of personalised medicine is the ability to **subdivide groups** of patients with a particular disease into **those** whose condition will respond to a given treatment and **those** who will not." (European Science Foundation, 2012, p. 16)

Precision Medicine Initiative,
Pdt Obama. $ 200 millions
Confusion about what it is about.

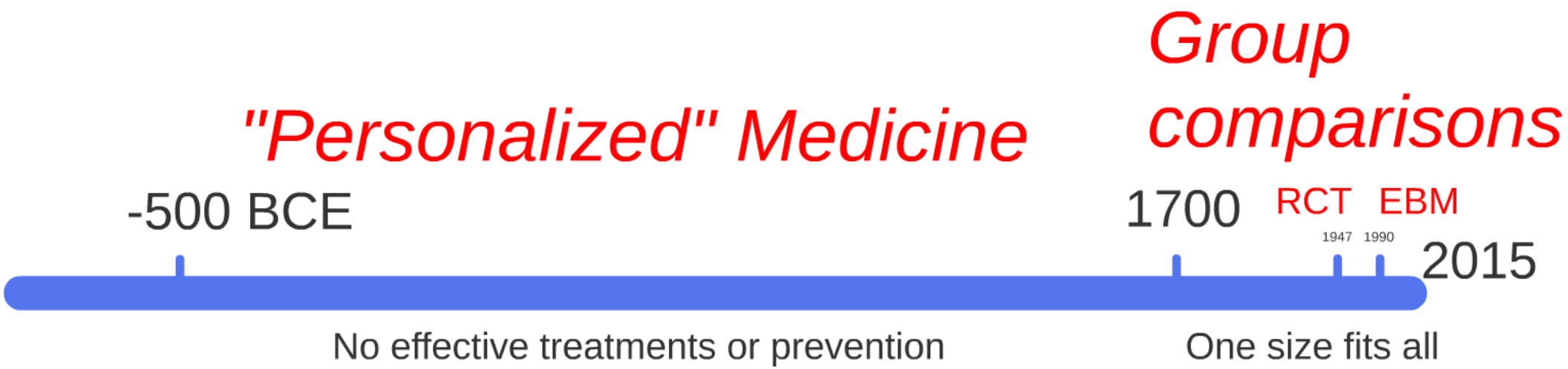
One interpretation

- Obama Initiative = personalized medicine
- Fix discrete mutations that interfere with tumor growth or treatment effect.
- "Simple, soluble questions," NOT complex ones

E.g., Elana Simon, Kareem Abdul-Jabbar, William Elder

Problems with personalized medicine:

- limited (more promises than achievements)
- expensive (personalized therapies cost in 100,000's /person)
- does not address the major health issues


"Personalized" Medicine
Group comparisons
-500 BCE
1700
RCT
EBM
1947
1990
2015
No effective treatments or prevention
One size fits all

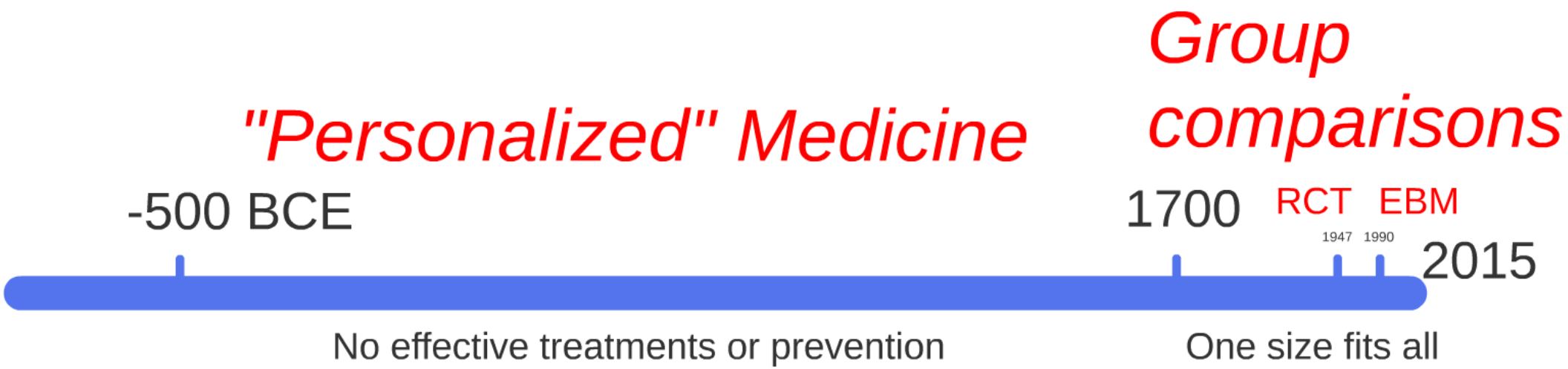
Consider a 45-year-old, white, nonsmoking woman without heart disease or diabetes, elevated serum total cholesterol level (200 mg/dL), decreased high-density lipoprotein level (40 mg/dL), and blood pressure of 130/85 mm Hg who receives lipid-lowering therapy.

=>No major coronary events in the next decade.

100,000 45-year-old, white, nonsmoking woman without heart disease or diabetes, elevated serum total cholesterol level (200 mg/dL), decreased high-density lipoprotein level (40 mg/dL), and blood pressure of 130/85 mm Hg who receives lipid-lowering therapy.

=>1% major coronary events in the next decade.

- Meta-analysis (2006): statin therapy vs. placebo reduces major coronary events by ~ 30%.
- 1.3% => 1% over 10 years
- One case of major coronary even will be prevented for every 333 women treated with statins for 10 years.
- An effect too small to be observed in clinical practice.
- Population data are needed.
- Cohort studies to estimate the expected risk over 10 years and Randomized controlled trials to estimate the treatment effect.


"Personalized" Medicine
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the other interpretation of the Obama Initiative

Evolving from one size fits all to multiple sizes in multiple subgroups

Synergy between:

- Biology/Genetics
- Technology (personal devices, etc)
- Clinical medicine (new "subgroup" nosology)
- Epidemiology/clinical research

Precision medicine is "One of the foundations of personalised medicine is the ability to **subdivide groups** of patients with a particular disease into **those** whose condition will respond to a given treatment and **those** who will not." (European Science Foundation, 2012, p. 16)

ew Initiative on Precision Medicine

S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

> "Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."
>
> — President Barack Obama, State of the Union Address, January 20, 2015

President Obama has long expressed a strong conviction that science offers great potential for improving health. Now, the Presi-

variability into account — is not new[1]; blood typing, for instance, has been used to guide blood transfusions for more than a cen-

VIEWPOINT

SCIENTIFIC DISCOVERY AND THE FUTURE OF MEDICINE

Exceptional Opportunities in Medical Science
A View From the National Institutes of Health

Francis S. Collins, MD, PhD
National Institutes of Health, Bethesda, Maryland.

Editorial page 145

Supplemental content at jama.com

As the world's largest source of biomedical research funding, the US National Institutes of Health (NIH) has been advancing understanding of health and disease for more than a century. Scientific and technological breakthroughs that have arisen from NIH-supported research account for many of the gains that the United States has seen in health and longevity.

For example, an infant born today in the United States can look forward to an average lifespan of about 79 years—nearly 3 decades longer than one born in 1900. Age-adjusted death rates from cardiovascular disease have declined by more than 70% since 1963, with more than half of that decline coming in the last 20 years.[1] Meanwhile, cancer death rates have decreased about 1% annually for the past 15 years.[2] National Institutes of

look forward to a medical landscape in which the pairing of affordable, efficient DNA sequencing and electronic health records could be used to inform a lifetime of health care strategies. Combined with the use of mobile health technology to assist in real-time monitoring of factors such as diet, exercise, blood pressure, heart rate, and blood chemistries, this approach could lead to more precise ways of preventing and managing chronic diseases.

Many would agree that the 86 billion neurons in the human brain represent the most challenging frontier for medical research, and to tackle this in innovative ways, the NIH has just made a major investment in the new Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative.[3] This pioneering, mul-

ise in medical research.

Personalized medicine, also referred to as precision medicine, is a promising area for improving health outcomes. For most of medicine's history, and with notable exceptions like blood transfusion, physicians have been forced to approach prevention and treatment of disease based on the expected response of an average patient because that was the best that could be done. However, a more precise, personalized approach to medicine is becoming possible. One major reason is that the cost of sequencing a human genome has declined substantially and is approaching $1000—an astounding figure considering that it cost about $400 million to

The NEW ENGLAND JOURNAL of MEDICINE 2011

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

ABSTRACT

BACKGROUND

Phase 1 and 2 clinical trials of the BRAF kinase inhibitor vemurafenib (PLX4032) have shown response rates of more than 50% in patients with metastatic melanoma with the BRAF V600E mutation.

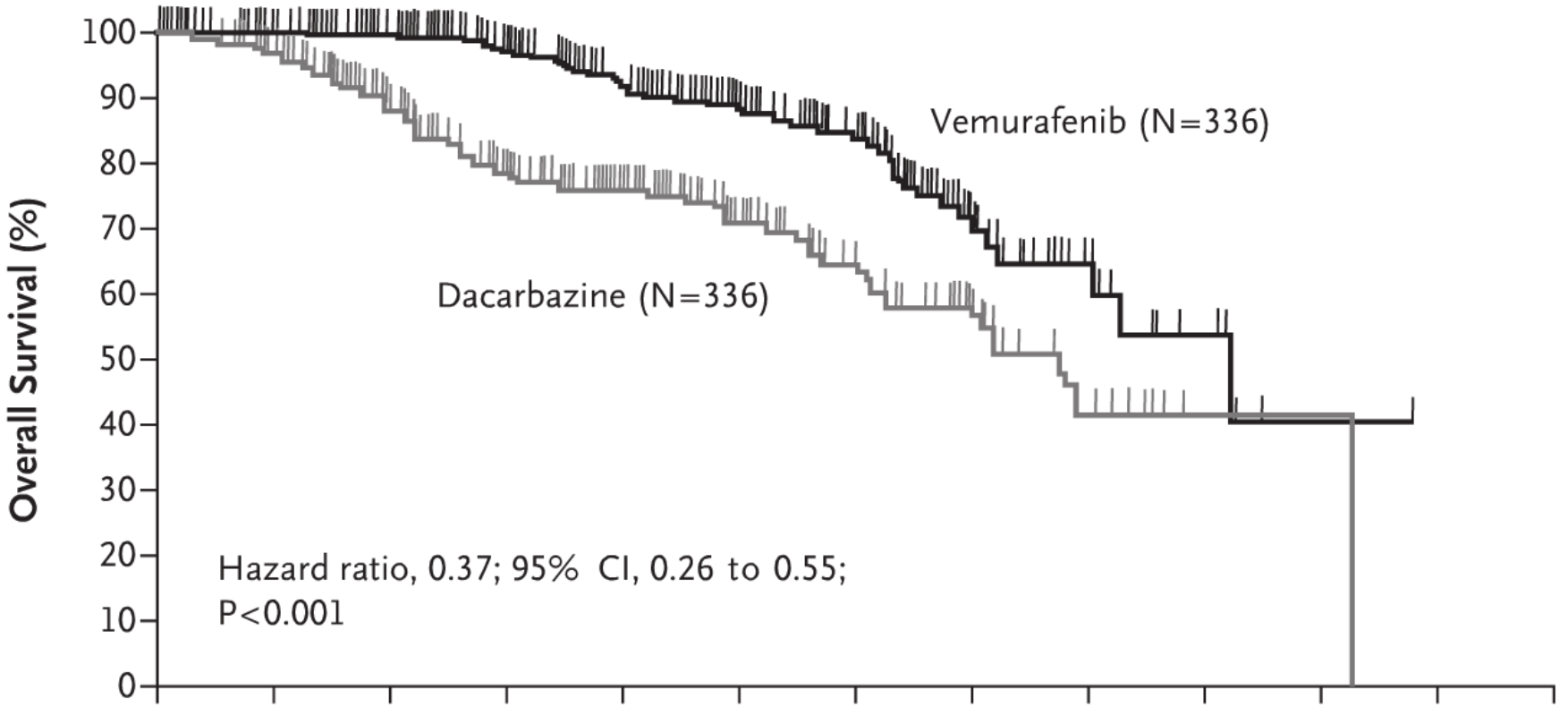
METHODS

We conducted a phase 3 randomized clinical trial comparing vemurafenib with dacarbazine in 675 patients with previously untreated, metastatic melanoma with the BRAF V600E mutation. Patients were randomly assigned to receive either vemurafenib (960 mg orally twice daily) or dacarbazine (1000 mg per square meter of body-surface area intravenously every 3 weeks). Coprimary end points were rates of overall and progression-free survival. Secondary end points included the response rate, response duration, and safety. A final analysis was planned after 196 deaths and an interim analysis after 98 deaths.

RESULTS

At 6 months, overall survival was 84% (95% confidence interval [CI], 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine group. In the interim analysis for overall survival and final analysis for progression-free survival, vemurafenib

A Overall Survival



No. at Risk

Dacarbazine	336	283	192	137	98	64	39	20	9	1	1	0	0
Vemurafenib	336	320	266	210	162	111	80	35	14	6	1	0	0

B Subgroup Analyses of Overall Survival

Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	672	0.37 (0

PERSPECTIVE

30/9/2010

doi:10.1038/nature09339

Translating cancer research into targeted therapeutics

J. S. de Bono[1,2] & Alan Ashworth[3]

The emphasis in cancer drug development has shifted from cytotoxic, non-specific chemotherapies to molecularly targeted, rationally designed drugs promising greater efficacy and less side effects. Nevertheless, despite some successes drug development remains painfully slow. Here, we highlight the issues involved and suggest ways in which this process can be improved and expedited. We envision an increasing shift to integrated cancer research and biomarker-driven adaptive and hypothesis testing clinical trials. The goal is the development of specific cancer medicines to treat the individual patient, with treatment selection being driven by a detailed understanding of the genetics and biology of the patient and their cancer.

Many important advances in cancer medicine, particularly earlier

This traditional population-based trials paradigm pursues the accrual

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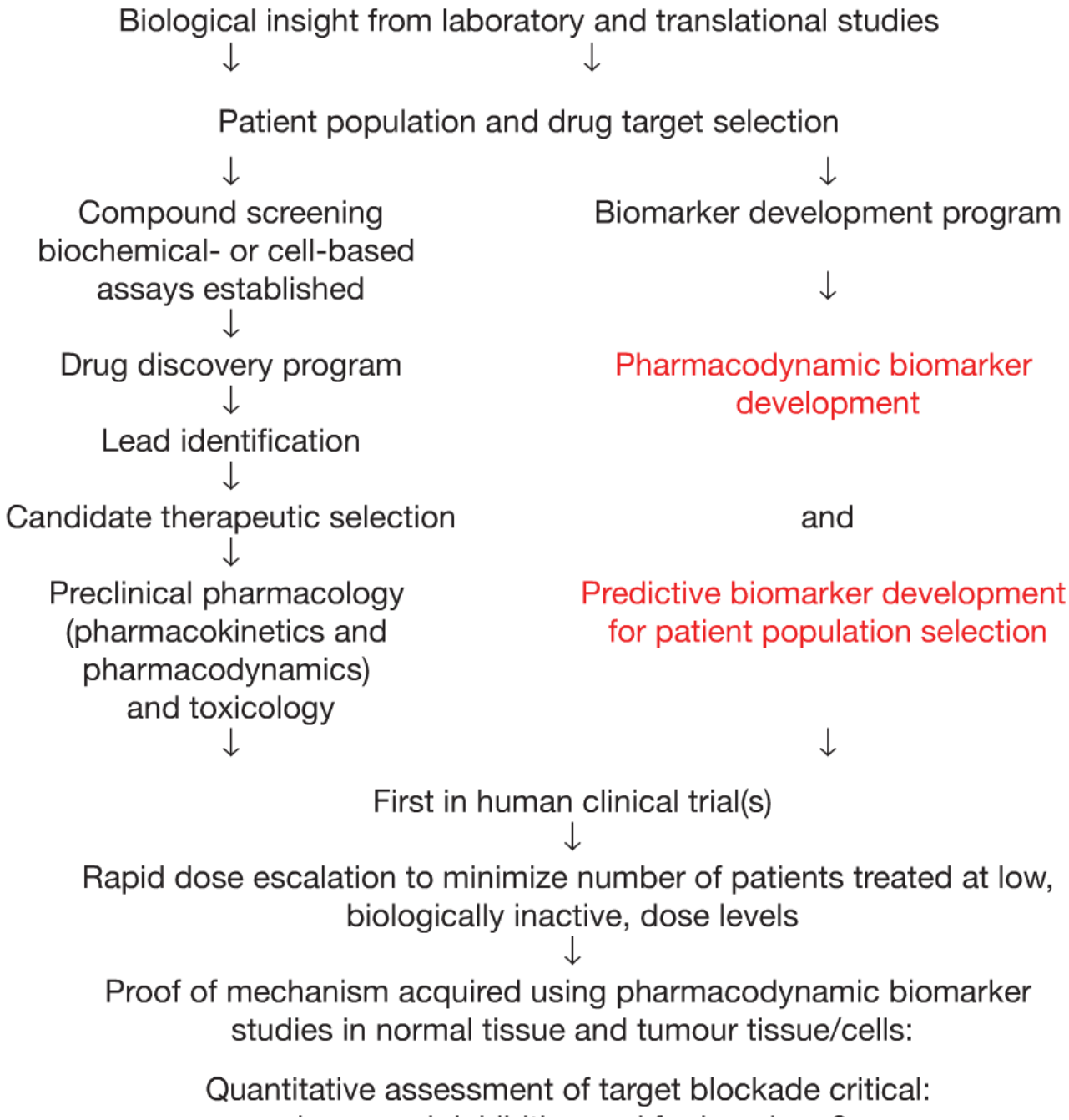
Recommended schema for hypothesis testing anti-cancer drug development



Subgroups => Very large study populations

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Ultimately, we will need to evaluate the most promising approaches in much larger numbers of people over longer periods. Toward this end, we envisage assembling over time a longitudinal "cohort" of 1 million or more Americans who have volunteered to participate in research. Participants will be asked to give consent for extensive characterization of biologic specimens (cell populations, proteins, metabolites, RNA, and DNA — including whole-genome sequencing, when costs permit) and behavioral data, all linked to their electronic health records. Qualified

Collins & Varmus 2015

Precision medicine = using biology, technology, clinical medicine and epidemiology to move from "average" treatments to more "precise" subgroup treatments.
Ambition: Treat main burden of diseases

Synergy (and not necessarily competition) between biology, technology, clinical medicine, and epidemiology.

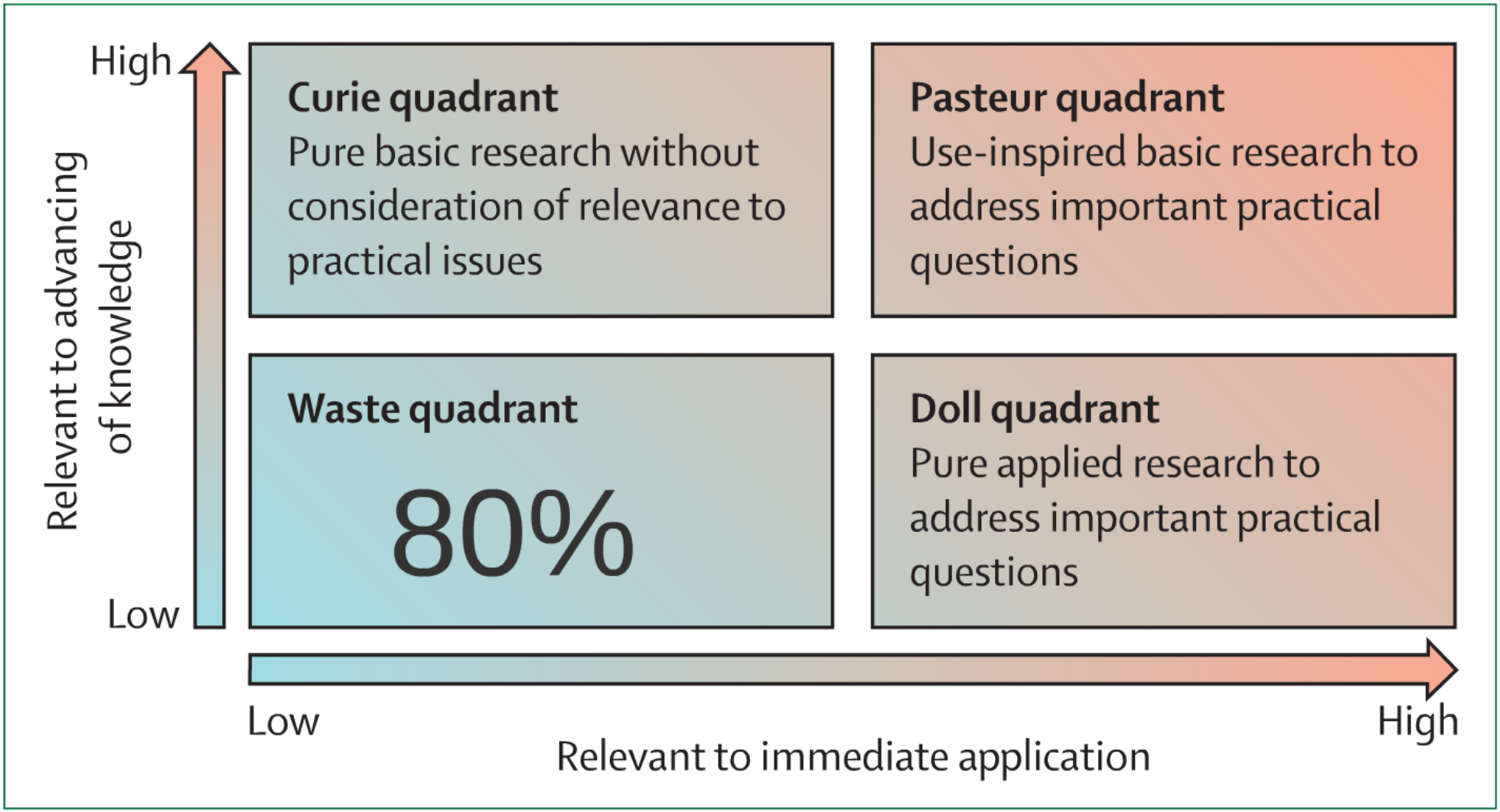

Figure 1: **Classification of different categories of research** Lancet 2009

Switzerland's assets re: precision medicine

« Il faut sans cesse rappeler à quel point l'expérience d'un clinicien peut contribuer au renouvellement des connaissances scientifiques. »(III :25)

Synergy (and not necessarily competition) between biology, technology, clinical medicine, and epidemiology.

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