Predictive, Personalized, Preventive and Participatory approach to Medicine: “P4” Leroy Hood

Precision Medicine:
Personalized, Problematic, and Promising
J. Larry Jameson, M.D., Ph.D., and Dan L. Longo, M.D.
NEJM 4 June 2015
For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

1. ABILIFY (aripiprazole)  
   Schizophrenia

2. NEXIUM (esomeprazole)  
   Heartburn

3. HUMIRA (adalimumab)  
   Arthritis

4. CRESTOR (rosuvastatin)  
   High cholesterol

5. CYMBALTA (duloxetine)  
   Depression

6. ENBREL (etanercept)  
   Psoriasis

7. ADVAIR DISKUS (fluticasone propionate)  
   Asthma

8. REMICADE (infliximab)  
   Crohn’s disease

9. COPAXONE (glatiramer acetate)  
   Multiple sclerosis

10. NEULASTA (pegfilgrastim)  
    Neutropenia

Based on published number needed to treat (NNT) figures. For a full list of references, see Supplementary Information at go.nature.com/4dr78f.
Increasing failures in drug development
Success rates of clinical proof-of-concept have dropped from 28% to 18%
Insufficient efficacy as the most frequent reason

Reason for failure
- Efficacy: 29%
- Pharmacokinetics/bioavailability: 19%
- Safety: 51%

Therapeutic area
- Other (35)
- Alimentary/metabolism (23)
- Cancer (21)
- Neuroscience (17)
- Cardiovascular (12)

Technical and scientific advances are currently transforming biomedical research, turning an important part of the field into a new modelling and computational science.

High throughput life science data are today affordable and drives important parts of biomedical research. The exploitation of big data is starting to make direct impact in clinical practice.

Example: During 2014 the sequencing company Illumina announced the so called 1000 dollar genome.
MICROFLUIDIC TECHNOLOGIES TO IDENTIFY PATIENT’S PATHOGENIC ANTIBODIES

Isolate Ab-producing B cells at high-throughput from patients

Water

Oil

One cell every 3 droplets
Huge efforts to establish national and international baselines, outlining the global biological variation in populations are ongoing or are being initiated. These studies will provide bases for further developments of personalized/precision medicine. Examples include e.g. Genomics England and the Precision Medicine Initiative in the US as well as targeted projects like The Resilience project.
Global companies like Google, IBM, Amazon and Microsoft are currently positioning themselves to provide services around storage, management and analyses of the new big life science data.
SEARCHING FOR STANDARDIZED PIPELINES FOR HUMAN GENOMICS

Broad Institute, Google Genomics combine bioinformatics and computing expertise to expand access to research tools

**Cambridge, Mass.** June 23rd, 2015 — Broad Institute of MIT and Harvard is teaming up with Google Genomics to explore how to break down major technical barriers that increasingly hinder biomedical research by addressing the need for computing infrastructure to store and process enormous datasets, and by creating tools to analyze such data and unravel long-standing mysteries about human health.
BIOPHARMACEUTICAL COMPANIES ARE COMMITTED TO ADVANCING PERSONALIZED MEDICINES

- **42%** of new medicines in the pipeline have the potential to be personalized medicines.
- **73%** of cancer medicines in the pipeline have the potential to be personalized medicines.
- **33%** expected increase in investment in personalized medicines over the next five years.
- **69%** Expected increase in the number of personalized medicines in development over the next 5 years.

Prospective Validation of a 21-Gene Expression Assay in Breast Cancer

The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study

Figure 1: The paradigm shift of genetic testing
Schematic representation of the steps involved in genetic testing before and after the introduction of next-generation sequencing. The red boxes indicate the role of genetic testing.
MULTIPLEX TESTING IS ALREADY AVAILABLE

OncoType DX
Analyzes by qPCR, mRNA expression of a panel of 21 genes within a tumor to determine a Recurrence Score

MammaPrint
Microarray-based prognostic breast cancer mRNA expression profiling test of 70 genes

AlloMap
qPCR-based expression profile of 11 genes to assist physicians in managing heart transplant patients for potential organ rejection

Tissue of Origin
Microarray technology considers 15 common malignant tumor types, including bladder, breast, and colorectal tumors based on mRNA expression on 1,550 genes
**SINM PhyZioType™ System: Statin-Induced Neuro-Myopathy**

**DIABETES + CVD, Reduction of Cardio-metabolic Risk by Lipid-lowering: Statins**

The SINM PhyZioType System provides the physician with DNA-guided efficacy predictions for aggressive lipid lowering and risk profiles for neuromuscular side effects of atorvastatin, simvastatin, and rosuvastatin. The information can be employed prognostically before prescribing statin therapy or diagnostically to categorize neuro-myopathy in those statin patients already evidencing neurological or muscular symptoms and seeking remedial treatment. The SINM PhyZioType System consists of 4 tests predicting LDL lowering and HDL raising efficacy, and innate side-effect risk for myalgia and CK activity elevation (mopathy), in response to statins on a class-wide and drug-specific basis. A patent on the SINM PhyZioType product is pending as an application.

**Statin Induction + Neuro-Myopathy (SINM), the balance of potency and safety, is the main clinical management challenge of these drugs, particularly in diabetes where treatment targets are aggressive requiring LDL cholesterol levels below 100 mg/dl. In medical practice, Neuro-myopathy presents as a constellation of neuromuscular side effects. Clinical symptoms include myalgia (muscle aches, cramps, weakness) and myopathy (muscular injury monitored by serum elevation of muscle enzymes). Neuro-myopathy is more frequent at the higher doses required for treating advanced cardiovascular disease and varies in extent between individual statins and from patient to patient. Therefore, prescribing the most potent statin on an individual basis is critical as well to avoid maximal doses. Statin usage is ultimately limited by toxicity. Neuro-myopathy is disabling to 10-20% of patients on statins, requires alteration of therapy, burdens healthcare with management costs, and reduces compliance. Only 50% of patients remain on statins 6 months after initiation of therapy.**

Statins are the most prescribed drugs in the world. Statins are the most effective
A real increase in the impact of precision medicine in drug development

138

Total number of FDA-approved drugs with biomarker information provided on their drug label*

20%

1 in 5 FDA approvals in 2014 were for targeted therapies*


*As of March 27, 2015
### EXAMPLES OF CONDITIONS IN WHICH PRECISION MEDICINE HAS BEEN USED*

<table>
<thead>
<tr>
<th>Medical Field</th>
<th>Disease</th>
<th>Biomarker</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Chronic myeloid leukemia</td>
<td>BCR-ABL</td>
<td>Imatinib</td>
</tr>
<tr>
<td></td>
<td>Lung cancer</td>
<td>EML4-ALK</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>Hematology</td>
<td>Thrombosis</td>
<td>Factor V Leiden</td>
<td>Avoid prothrombotic drugs</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>HIV/AIDS</td>
<td>CD4+ T cells, HIV viral load</td>
<td>Highly active antiretroviral therapy</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Coronary artery disease</td>
<td>CYP2C19</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Cystic fibrosis</td>
<td>G551D</td>
<td>Ivacaftor</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Transplant rejection</td>
<td>Urinary gene signature</td>
<td>Antirejection drugs</td>
</tr>
<tr>
<td>Hepatology</td>
<td>Hepatitis C</td>
<td>Hepatitis C viral load</td>
<td>Direct-acting antiviral agents</td>
</tr>
<tr>
<td>Endocrine disease</td>
<td>Multiple endocrine neo-plasia type 2</td>
<td>RET</td>
<td>Prophylactic thyroidectomy</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>Hyperlipidemia</td>
<td>LDL cholesterol</td>
<td>Statins</td>
</tr>
<tr>
<td>Neurology</td>
<td>Autoimmune encephalitis</td>
<td>CXCL13</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>Alcohol-use disorder</td>
<td>GRIK1</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Pharmacogenomics</td>
<td>Smoking cessation</td>
<td>CYP2A6</td>
<td>Varenicline</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Leber's congenital amaurosis</td>
<td>RPE65</td>
<td>Gene therapy</td>
</tr>
</tbody>
</table>

* In the biomarker column, proteins or genes that are probed to find the specific variants of interest are shown. AIDS denotes acquired immunodeficiency syndrome, HIV human immunodeficiency virus, and LDL low-density lipoprotein.
ONCOLOGY IS ON THE LEADING EDGE OF PERSONALIZED MEDICINE

In ten years, cancer patients have seen a four-fold increase in their personalized medicine treatment options.

Breakdown of Oncology Treatment Modalities, Global Market share 2003-2013*

Clinical efficacy of Vemurafenib (PLX-4032, Zelboraf) in melanomas

Key biomarkers:

Stratification: BRAFV600E mutation

Mechanism: P-ERK
Cyclin-D1

Efficacy: Ki-67
18FDG-PET, CT

Clinical endpoint: progression-free survival (%)

Chapman et al, NEJM 2011
Clinical efficacy of Vemurafenib

Before Rx

Vemurafenib, 15 weeks

Vemurafenib, 23 weeks

**Strong initial effects vemurafenib**

- Emerging drug resistance
- Recurrence of aggressive tumors

Tumor tissue heterogeneity

- BRAFV600D/E is driving mutation

- However, also no BRAFV600D/E mutation found in regions of a primary melanoma: Molecular heterogeneity in tumor tissue

Wagle et al, 2011, J Clin Oncol 29:3085

- Biomarker levels in tissue vary
- Biomarker levels in body fluids will vary

- Major challenge for (companion) diagnostics
PERSONALIZED MEDICINES ARE BENEFITTING PATIENTS ACROSS MANY DIFFERENT DISEASES

Across a variety of therapeutic areas, an increasing number of treatments are personalized.*

*FDA approvals with biomarker information in the approved labeling

CD4+ T Cell Autoimmunity to Hypocretin/Orexin and Cross-Reactivity to a 2009 H1N1 Influenza A Epitope in Narcolepsy

Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2

HLA-DQB 1*0602

Doses of viral capsid?
(Pandemrix vs Focetria vaccines)
Other genetic determinants?

ScienceTranslational Medecine; 18/12/2013 (1/8/2014); 1/7/2015
Precision medicine

Patient Disease

Biomarker

Risk prediction

Risk prediction

Diagnostic

Diagnosis

Targeted therapies

Theranostic: Efficacy Toxicity

Therapeutic

Treatment
WHAT TYPES OF BIOMARKERS DO WE HAVE?

1. Screening (e.g. mammography, fecal occult blood)
2. Diagnostic (e.g. cardiac troponin)
3. Prognosis (e.g. cytokeratins, estrogen receptors)
4. Prediction of response to treatment (e.g. HER2)
5. Patient follow-up (e.g. PSA)
BIOMARKER RESEARCH AND VALIDATION: A LONG JOURNEY

- Analytical validity
- Clinical validity
- Clinical utility
- Analytical validity
  & Clinical utility
  & Health economics

Target Selection → Lead Identification → Pre-clinical Validation → Regulatory Clinical Trial Phase I, II, III → Product Launch Marketing

Biomarker Discovery → Biomarker Confirmation Assay Development → Biomarker Validation → Clinical Validation and Utility → Regulatory Approval (US/EU) Clinical Adoption

Number of Analytes
Number of Samples
Large cohorts, quality assured samples

- Analytical and clinical validity drive regulatory approval
- Clinical utility and health economics benefits drive reimbursement
PARTNERSHIPS AND COLLABORATIONS ARE TRANSFORMING THE RESEARCH AND DEVELOPMENT OF PERSONALIZED MEDICINES

AMP (Accelerating Medicines Partnership)

Developing new diagnostics and biological targets for treatments in Alzheimer’s disease, type 2 diabetes, rheumatoid arthritis, and lupus.

The Partners: biopharmaceutical companies, NIH, patient and disease organizations

Biomarkers Consortium

Combining expertise and resources to rapidly identify, develop, and qualify biomarkers, which will then advance new therapies and guide improvements in regulatory and clinical decision-making.

The Partners: biopharmaceutical companies, NIH, CMS, FDA, patient and disease organizations

Lung-MAP (Lung Cancer Master Protocol)

Using comprehensive genetic screening to identify mutations in lung cancer patients in order to direct them to a specific investigational treatment, all operating under a single clinical trial protocol.

The Partners: biopharmaceutical companies, NIH, FDA, patient and disease organizations

INTEGRATING INFORMATION ABOUT IMMUNE RESPONSE, GENETIC & ENTEROTYPE VARIABILITY
A population based assessment of the Genetic & Environmental Determinants of Immune Phenotype Variance
1,000 HEALTHY DONORS COHORT

- Clinical data
- Serology
- Whole blood 20ml
- Whole blood 50ml
- Nasal swabs / Stool
- Skin Biopsy

- Microbes
- Adjuvants
- Cytokines
- TCR stim

- Supernatant
- Cell pellets

√ Fully recruited
1000 donors
5 decades of life
2 timepoints

- 1000 eCRF
- 10 Panels
- 1000 Genotypes
- 180,000 Supernatant Tubes
- 60,000 RNA profiles
- 1000 Enterotypes
- 300 fibroblast lines

- ≥ 300 var / p
- ≥ 500 var / p
- 750K var / p
- ≥ 60 var / tube
- ≥ 2000 var / p
- ≥ 600 var / tube
- ≥ 24000 var / d
- 16S rRNA NGS
- iPS
We need functional biomarkers
PROFILING INDUCED IMMUNE RESPONSES

Reliable, reproducible results

Culture Medium + Adjuvant of choice

Screw Cap (easy harvesting)

Rubber Seal (closed system)

Stimulus

<table>
<thead>
<tr>
<th>Null</th>
</tr>
</thead>
<tbody>
<tr>
<td>HK E.coli 0111:B4</td>
</tr>
<tr>
<td>HK S. aureus</td>
</tr>
<tr>
<td>HK L. rhamnosus</td>
</tr>
<tr>
<td>BCG (Immyucyst)</td>
</tr>
<tr>
<td>HK H. pylori</td>
</tr>
<tr>
<td>HK C. Albicans</td>
</tr>
</tbody>
</table>

Influenza A Virus (live)

Sendai virus (live)

C12-iE-DAP
CPPD
FSL-1
Poly I:C
LPS-EB (ultrapure)
Flagellin-ST
Gardiquimod
R848
ODN 2216

Lipoarabinomannan

WGP
IFN (Intron A)
IFN (Betaseron)
IFN (Imukin)

TNF
IL-1
IL-23
-CD3 +
-CD28

Enterotoxin SEB

Partnership with Myriad RBM

Microbe
MAMP
Cytokine
TCR
POINT-OF-CARE FUNCTIONAL IMMUNE ASSAYS PERMITS ON-SITE SAMPLE COLLECTION STANDARDIZATION

A) Prefill tubing with blood

B) Pull, until it “clicks”

C) Break away plunger

D) Mix gently 3x

E) Incubate for 4h (mRNA, miRNA analysis) or 22h (protein and lipidome studies)

380,000 banked samples (1000 donors x 40 TC tubes)
The Center for Translational Science
THE CRT STRUCTURE

Clinical Coordination

Technical Cores

Bioinformatics / Education Communication
Precision Medicine: Personalized, Problematic, and Promising

J. Larry Jameson, M.D., Ph.D., and Dan L. Longo, M.D.

NEJM 4 June 2015
There exist several global coordinated efforts to achieve standardization and sharing of big life science data, notably the Global Alliance for Genomics and Health, but due to heterogeneity, diversity and immaturity of technologies, practices and frameworks the tasks are currently overwhelming.
DISEASES ARE THE RESULT OF PERTURBATIONS IN COMPLEX BIOMOLECULAR NETWORKS
The implementation of personalized medicine requires a confluence of multiple factors. Full implementation of personalized medicine can only be achieved when all sectors converge toward the center.
WE ARE FACING ENORMOUS CHALLENGES AROUND ESTABLISHING REPLICABLE AND REPRODUCIBLE RESEARCH PRACTICES FOR DATA INTENSIVE BIOMEDICAL SCIENCE

- Fast technological developments make it hard to establish stable standards.
- Both techniques and protocols are constantly evolving.
- Holistic and integrative analyses over different platforms and between different datatypes are extremely challenging.
- Storage, management, analysis and sharing of data are subject to legal and ethical considerations.
THE COMMUNITY IS PUSHING FOR REPRODUCIBLE RESEARCH

Announcement: Reducing our irreproducibility
24 April 2013

Over the past year, Nature has published a string of articles that highlight failures in the reproducibility of published research (collected and freely available at go.nature.com/). The problems arise in laboratories, but journals such as this one compound them when they exert sufficient scrutiny over the results that they publish, and when they do not publish enough information for other researchers to assess results properly.

From next month, Nature and the Nature research journals will introduce editorial measures to address the problem by improving the consistency and quality of reporting in life-sciences. To ease the interpretation and improve the reliability of published results we will more systematically ensure that key methodological details are reported, and we will give more weight to methods sections. We will examine statistics more closely and encourage authors to be transparent, for example by including their raw data.

Rebooting review
Nature Biotechnology 33, 319 (2015) | doi:10.1038/nbt.3202
Published online 07 April 2015

Nature Biotechnology is reevaluating editorial oversight of papers centered on computational analyses in anticipation of the 'big data' world.

Computational biology papers pose particular challenges to the peer review process. Often, a computational approach or its software implementation may be insufficiently documented or missing. The version of the software may not match the algorithm described in a paper or reproduce the published results. And source code associated with software central to the main claims of a paper may not be made available. These issues have prompted Nature
THE CANCER TEST

A nonprofit’s effort to replicate 50 top cancer papers is shaking up labs

Science 26 juin 2015
Cancer papers that Amgen could reproduce on a published study that Bayer completely reproduced. 14 of 67. 55%
Novel methodologies for clinical trials?

Time for one-person trials
Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy,
Personal profile-based healthcare

Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

Institut Pasteur
THE INSTITUT PASTEUR IN 2015

- 55,000 square meter campus in the heart of Paris
- 2,500 persons
- 14 National Reference centers
- 8 WHO collaborating centers
- 10 Nobel laureates
- More than 60 nationalities
- 46% «non-french» scientists
- 1,100 scientists
- 1,300 postdocs
- 500/year students
- Master, PhD, postdoc
- Industrial partnerships (20 biotech, 4 listed)
- 11 Scientific departments
- 130 Research units

Research fields:
- Microbiology
- Infectious diseases
- Immunology
- Neurosciences
- Stem cells
- Cancer
- Genetics
- Genetics
- Microbiology
- Infectious diseases
- Immunology
- Neurosciences
- Stem cells
- Cancer
- Genetics
33 Institutes Pasteur gather about 9,500 people in 26 countries, over 5 continents.

- In agreement with the local health authorities.
- Within the international network, the institutes share their knowledge, their research programs and keep control of the development of infectious diseases.
- A major partner for international institutions, Foundations, Governments and industrials.
The Institut Pasteur is moving to establish a global framework for reproducible research with unified bio-banking, data storage, management and analysis. Resources will be connected and shared through the IP cloud for data analysis.
INSTITUT PASTEUR IS CONNECTED TO THE EUROPEAN INITIATIVE ELIXIR.

The IP network has the ambition to take a globally leading role to secure alignment around our focus on precision medicine for global health.
Sample collection

Sample handling*

*and storage

Technical cores

Data analysis

Data storage & access

Sample collection

Sample handling*

*and storage

Technical cores

Data analysis

Data storage & access

Whole Blood

Fecal Sample

Transcriptomics

Enterotyping

Genetics / Epigenetics

Proteomics

Immunophenotyping

Metabolomics

Whole Blood

Fecal Sample

Transcriptomics

Enterotyping

Genetics / Epigenetics

Proteomics

Immunophenotyping

Metabolomics

VH−1
VH−3
VH−4
VH−5
VH−7
Vk−1
Vk−2
Vk−3
VH−1
VH−3
VH−4
VH−5
VH−7
Vk−1
Vk−2
Vk−3
The Institut Pasteur International Network for Data Analysis (IP-INDA): An aligned global community for data analysis ready for action

Global collaborative dynamism through local adaption

Developing and sharing best practices in bioinformatics globally, performing training and engaging in data intensive biomedical research.

Follow us on https://twitter.com/IGDA_Pasteur