The future of cardiovascular research

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The future of cardiovascular research

- Past
- Present and immediate future: “wake up call”
- The Future
Electrocardiography

Cholesterol and atherosclerosis
This truly seminal paper led ultimately to the cholesterol theory of atherogenesis, which in turn resulted in successful attempts to lower serum cholesterol in order to reverse, prevent, or at least retard the development of atherosclerosis and its complications.

Anitschkow: Zentralbbl Allg Medizinisch Pathol Und Pathol Anat 1913;24:1

Cardiac catheterization
First carried out by Forssmann in 1929, a urologist, won the Nobel Prize

Cardiovascular surgery
The first cardiovascular operation in 1939, ligation of a patent ductus arteriosus in a seven and a half-year old girl

Coronary angiography and percutaneous coronary angioplasty
In 1958, while performing an angiogram of the aortic root, the tip of the catheter accidentally slipped into the ostium of the right coronary artery.

Sones et al: Circulation 20:773, 1959

The coronary care unit
In 1961, Desmond Julian, a registrar (fellow/resident) in cardiology at the Royal Infirmary in Edinburgh, wrote a brief paper describing the coronary care unit that was published in Lancet, in which he stated:

Cardiovascular drugs

Preventive cardiology

Cardiac imaging: Echocardiography
During World War II, ultrasound was widely used to detect submarines and to track torpedoes. The collaboration between two brilliant Norwegians, an emeritus Professor of Cardiology, Inge Edler, and an engineer, Helmut Hertz, led to the development of echocardiography.

Edler and Hertz: Kungl Fysiogr Sallsk Lund Forth24, 1954

Cardiac pacemakers and defibrillation
What Happened Before 2007?

• Facebook didn’t exist yet
• Twitter was still a sound
• Cloud was still in the sky
• 4G was a parking space
• “applications” were what you sent to college
• LinkedIn most people thought it was a prison
• Big Data was a good name for a rap star

The Race Between Human and Technology

Rate of Change

Time

Human Adaptability

We are here
Where are the Future Opportunities in the Cardiovascular Field?

Unmet Patients’ need ➔ Technology

Unmet Patients’ need
Where are the Future Opportunities in the Cardiovascular Field?

Unmet Patients’ need

Technology

Mash up

Military Technology

Academic Centers

a mixture or fusion of disparate elements.
Where are the Future Opportunities in the Cardiovascular Field?

• Precision (Individualized) medicine

• big data analysis

• Remote medicine

• Robotic
Personalized Medicine: Precision medicine

Will provide the link between an individual’s molecular and genetic and clinical profiles

Will effect

Therapy directed to the root cause of the disease will replace treating the symptoms

Pharmaceutical industry
Symptoms

Medical History & Physical examination

Presumptive Diagnosis

Treatment based on large clinical trials

- Wrong diagnosis
- Net effect of beneficial and toxic effects

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Rate of efficacy with standard drug treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (all types)</td>
<td>25</td>
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<tr>
<td>Alzheimer's disease</td>
<td>30</td>
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<tr>
<td>Incontinence</td>
<td>40</td>
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<tr>
<td>Hepatitis C</td>
<td>47</td>
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<tr>
<td>Osteoporosis</td>
<td>48</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>50</td>
</tr>
<tr>
<td>Migraine (prophylaxis)</td>
<td>50</td>
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<tr>
<td>Migraine (acute)</td>
<td>52</td>
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<tr>
<td>Diabetes</td>
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<td>Asthma</td>
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<tr>
<td>Schizophrenia</td>
<td>60</td>
</tr>
<tr>
<td>Depression</td>
<td>62</td>
</tr>
</tbody>
</table>
There are several aspects to personalized medicine:
- Diagnosis
- Personalized treatment

Patient group:
- Drug toxic but beneficial
- Drug toxic but not beneficial
- Same diagnosis, same prescription
- Drug not toxic and not beneficial
- Drug not toxic and beneficial

Drug not toxic and not beneficial
The use of genetic markers to select patients for clinical trials may reduce adverse drug reaction by 10-20%.

Caution: not covered by insurance
No firm data on link to therapy
No firm data from a randomized study on benefit

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release
May 23, 2017

Release

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotheraphy drugs.
The number of patients in clinical trials

Coronary Artery Surgery Study (CASS): a randomized trial of coronary bypass surgery
Survival data

- 1983: 780 patients
- 1997: 1829 patients
- 2004: 4126 patients
- 2007: 780 patients
- 2008: 17,802 patients
- 2012: 1220 patients
Machine Learning

• Used by Amazon, Netflix, Google, Uber to predict consumer behavior

• Capable of analyzing large volumes of data
  • Can identify previously unknown associations
  • Established based on a machine-learning based financial trading company.

• Bring to light “hidden” information within existing medical data. Building decision support tools for personalized risk assessment of life threatening conditions.

Machine Learning vs Regression Modeling

Machine learning is data driven rather than hypothesis driven (used by statisticians) potential link between a feature and outcome.

This graph represents the relationship of 2 parameters but in reality, multiple relationships are tested.
Patient Featurization

Patient

EHR Data

Admin, Demographics
Lab Results (time series)
Vital Signs
Diagnoses & History
Procedures
Medications
Habits

Features Extraction

$X_1$
$X_2$
...
$X_N$

Patient Feature Vector
Predictive Models for Multiple Outcomes

- Address multiple types of outcomes and select those that are actionable

Electronic Health Record

Admin, Demographics, Habits
Lab Results (time series)
Diagnoses, History, …

EarlySign Machine Learning Models

Outcome

- Cancer: Colorectal, Lung, Prostate, Upper GI
- Chronic Diseases: Diabetic Nephropathy, Pre-Diabetes to Diabetes, Acute Kidney Injury
- Dozens More...

No Flag
Follow guidelines and best practice

Red Flag
Expedited treatment, assessment, referral, close monitoring, diagnostic tests, etc.
MeScore – a tool for eScreening

Use the results of a low-cost and readily available blood test to simultaneously calculate risk scores for multiple types of cancers.

Standard CBC results

AGE

GENDER

Smoking

Computational Model

Colorectal Cancer

Lung Cancer

Gastric Cancer

Receiver Operator Curves

Medscape Medical News > Conference News
Watson-Powered Diabetes App Predicts Hypoglycemia

Robert Lowes
January 08, 2016

2 comments

EDITORS’ RECOMMENDATIONS

Real-World Severe Hypoglycemia in Diabetics Exceeds Trial Rates

14 Cancer Centers, IBM Install Supercomputer in Clinic

FDA OKs Insulin Pump With Low-Glucose Suspend Feature

LAS VEGAS — Watson, the IBM supercomputer that won TV’s Jeopardy, will soon be able to help patients with diabetes prevent hypoglycemia, medical device maker Medtronic announced here at the giant Consumer Technology Association Digital Health Summit.

The company expects to introduce a smartphone app this summer that will provide timely hypoglycemic warnings to patients using its insulin-management devices.

The idea for the app arose from an unpublished study that Medtronic conducted using Watson’s “cognitive computing” — buzz words heard commonly at the show. The supercomputer
Death from Cardiovascular Cause ≤180 Days following PCI

![ROC Curve](image)

- **AUC = 0.881**
- **P < 0.001**

**Sensitivity** vs **1-specificity**

- Red line: Machine learning
- Blue line: Logistic regression
Electronic Records Implementation

Advisory - Patient Safety

Readmission Risk

PROBLEM
This patient is at high risk for 30 day congestive heart failure readmission after percutaneous coronary intervention.

Average risk for hospital readmission for congestive heart failure is 0.7%
This patient’s risk is 18.1%

Place order: Heart failure nurse home call in 2 days.
Place order: Social work request for home visiting nurse
Place order: Cardiology follow up appointment in 5 days

Snooze 1 hr
Perspectives

Bone Marrow Mononuclear Cell Therapy for Acute Myocardial Infarction
A Perspective From the Cardiovascular Cell Therapy Research Network


Abstract—To understand the role of bone marrow mononuclear cells in the treatment of acute myocardial infarction, this overview offers a retrospective examination of strengths and limitations of 3 contemporaneous trials with attention to critical design features and provides an analysis of the combined data set and implications for future directions in cell therapy for acute myocardial infarction. (Circ Res. 2014;114:1564-1568.)

Placebo-adjusted Effect Size for Δ in LVEF Over Time as a Function

Relationship Between Change in LVEF Over Time and BL EF in TIME

Mash-up: Between different technologies and cells

Synergy of Device and BioTech

Left Ventricular Assist Device  

Beating Heart Cells Created from Stem Cells

Macrostructure stabilization → Microstructure integration
Building your own aortic valve
Where are the Opportunities in the Medical Field?

• Big data (machine learning)

• Precision (Individualized) medicine

• Remote diagnosis and treatment
Standardization and equalizing Access to care

Physician shortage

![Image of world map showing physician density per 10,000 population with different color coding for regions with varying densities.](image-url)

![Image of road sign indicating Nearest Town 13 km and Health Care 300 km](image-url)
The Wearable Decade

...from watches, patches and tattoo's
Privacy in Healthcare: data security

63% of customers are comfortable with storing their medical records on a cloud.

39% don’t trust internet sites to keep my health information private and secure.

Information customers are willing to share online:

- 25% Exercise/physical activity
- 28% Weight
- 26% Sleep patterns
- 20% Nutritional information (eg, calories consumed, etc)
- 25% Symptoms/general health complaints
- 15% Vital signs (eg, blood pressure, heart rate, etc)
Intracardiac monitoring was performed in 37 patients at high risk for acute coronary syndromes. The implanted monitor continuously evaluated the patients’ ST segments sensed from a conventional pacemaker right ventricle apical lead, and alerted patients to detected ischemic events.
Methods: A cohort of employees in Tennessee was subjected to a health risk assessment at baseline. Those who did not meet all 5 healthy benchmarks – body mass index, blood pressure, glucose, total cholesterol and smoking status – were prospectively assigned to a web-based personal health assistant and had repeat measurements taken at 90 days.

Reductions in Raw FRS (left) and Converted FRS 10-year cardiovascular risk percentage (right)

Percent Change from Baseline in Risk Factors After Completing the Online PHA

- HDL cholesterol
- LDL cholesterol
- SBP
- BMI
- Glucose
- Total cholesterol
- Triglycerides
Patients with New York Heart Association (NYHA) class III heart failure, a previous hospital admission for heart failure were enrolled in 64 centers in the USA. They were randomly assigned by use of a centralized electronic system to management with a wireless implantable hemodynamic monitoring (W-IHM) system (treatment group) or to a control group for at least 6 months. Only
“Listening” to our body

It’s not what we say, It’s HOW we say it

Just Blink: New Device Detects Disease Through Eye Movement

Genetics and epigenetic play a large role in determining face shape,
These figures illustrate representative voice signal characteristics signals from a patient prior and following coronary angiography and intervention as compared to a normal control.

**Average FFT transform of selected voice recording segments**

CAD patient prior to angiography

CAD patient after angiography and intervention

Example of voice signal of a healthy individual
Remote voice recognition of CAD
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Robotic Revolution; across all industries

World-wide industrial robot installations

Automatic Nations
Top 5 markets for industrial robot sales

Source: International Federation of Robots

We now drive cars, have vision & vacuum robotically...we will **not** be manually controlling catheters in the future...
The synchrony of imaging and catheter movement
...practice, plan and perfect...
CorPath 200 System
Control Console
Interventional Cockpit
Cockpit Monitors (Live/Reference Angio, Hemo)
Technology Requirements

Cath lab – at the patient

Immerse IC virtually into the cath lab

Education
Planning the procedure for the future
Particle therapy for noncancer diseases

Christoph Bert
GSI Helmholtzzentrum für Schwerionenforschung, Biophysics Department, Planckstraße 1, 64291 Darmstadt, Germany

Rita Engenhart-Cabillic
Philips-University Marburg, Center for Radiology, Department of Radiation Therapy, Baldinger Strasse, 35043 Marburg, Germany

Future treatment by photon bean therapy for atrial fibrillation

A good use of a drone
Flying ambulance drone to deliver emergency shock

00:29.229
Pigeons (Columba livia) as Trainable Observers of Pathology and Radiology Breast Cancer Images

Pigeons (Columba livia) – share many visual system properties with humans – can serve as promising surrogate observers of medical images.

The pigeons’ training environment

Generalization from training to test image sets.
After training with differential reinforcement, the birds successfully classified previously unseen breast tissue images in the testing sets, at all magnifications, with no statistically significant decrease in accuracy compared to training-set performance.

Results of training and testing with mammograms with or without calcifications

Flock sourcing. Pooling the birds’ decisions led to significantly better discrimination.
Soon you could be competing with a robot for a job.

Economists are sharply divided over the exact timing of the threat from robots and other forms of futuristic technology. Some see an imminent threat, others believe it won't happen until later this century – if at all.

1. **Toll booth operators and cashiers:** People who work in the transactional space shouldn't be big fans of the Apple Watch or Apple Pay.

2. **Marketers:** Powerful advertising tools of the future may allow brands to fashion their messages to customers with precision accuracy.

3. **Interventional cardiologists and radiologists??**
Comparison of Changes in SBP at 6 Months in 3 Trials of Renal Denervation

Mean reduction in SBP (mm Hg)

Pocock and Gersh: JACC, 2014
The Natural History of Evolving Therapies

Excitement/euphoria

Reality check

The initial enthusiasm has been tempered and the number of unanswered questions is not decreasing.

Nonetheless the concept maintains its promise.

In perspective

Progress

Depression
The future is here: *Fantastic Voyage 1966*
Conservative Management
medical therapies

- ↓ LDL
- ↑ HDL
- ↓ Inflammation
- ↓ Angiogenesis
- ↓ Thrombosis

Invasive Management
revascularization

- ↓ Restenosis

PCI

Management of CAD

- Drug Delivery
- Medical therapy

- Synthetic HDL

CABG

- Tissue Engineered Vascular Graft

Heat-induced Ablation

Endothelial Cell Recruitment

↑ Endothelialization

↑ Graft success

Drug Delivery
Investigative Pathways Leading from Gene Discovery to Clinical Application

- **Genomic discovery**
  - GWAS
  - Sequencing

- **Hypothesis-driven research**
  - Molecular and cellular studies
  - Animal models
  - Induced pluripotent stem-cell models

- **Disease-risk prediction**
  - Risk-factor assessment
  - Primary and secondary prevention
  - Prediction analysis and modeling

- **Disease pathophysiology**
  - Clinical trials
  - Biomarker studies

- **Personalized therapy**
  - Patient assessment
  - Clinical intervention

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• Twitter was still a sound

• Cloud was still in the sky

• 4G was a parking space

• “applications” were what you sent to college

• LinkedIn most people thought it was a prison

• Big Data was a good name for a rap star

• Skype, for most people, was a typographical error.
