FBK PER LA SALUTE

Un nuovo modo di fare medicina: esercizi di alta formazione

SABATO 24 SETTEMBRE 2016

SALA STRINGA - FONDAZIONE BRUNO KESSLER
VIA SOMMARIVE 18 - LOC. POVO (TRENTO)

IL RUOLO DEI LABORATORI CLINICI E DI RICERCA IN TRENTINO. PER UN'ARMONIZZAZIONE DELLA PRATICA E DELLA RICERCA NELLA QUOTIDIANITÀ.

3° INCONTRO DEL SECONDO CICLO FORMATIVO: UN NUOVO MODO DI FARE MEDICINA, ESERCIZI DI ALTA FORMAZIONE PARTENDO DAI LUOGHI E DALLE ATTIVITÀ LEGATE AL TERRITORIO.

IL RUOLO DEI LABORATORI CLINICI E DI RICERCA IN TRENTINO. PER UN'ARMONIZZAZIONE DELLA PRATICA E DELLA RICERCA NELLA QUOTIDIANITÀ.

Problemi e bisogni nell'ottica della sostenibilità: il ruolo del Laboratorio clinico

Stato dell'arte e trend futuri: dalla diagnostica classica alla Medicina di precisione

GF Gensini

Key tools of non-evidence based medicine before 1990

- **Ex cathedra pronouncements** by prestigious opinion leader
- **Editorials**
- **Non - systematic** reviews
- **Professional society guidelines** done for the **glory** of the profession
- **Pamphlet** from drug reps
- Other **marketing material** disseminated in medical "scientific" meetings

1992: Evidence Based Medicine

Evidence-Based Medicine

A New Approach to Teaching the Practice of Medicine

Evidence-Based Medicine Working Group

2420 JAMA, November 4, 1992—Vol 268, No. 17

centre for Evidence-Based Medicine TORONTO

http://ktclearinghouse.ca/cebm/

EBM is the integration of

- best research **evidence** with
- clinical expertise and
- patient values.

BMJ

Evidence based medicine: a movement in crisis?

Trisha Greenhalgh *dean for research impact*[1], Jeremy Howick *senior research fellow*[2], Neal Maskrey *professor of evidence informed decision making*[3], for the Evidence Based Medicine Renaissance Group

- The evidence based "quality mark" has been **misappropriated** by **vested interests**
- The **volume** of evidence, especially clinical guidelines, has become **unmanageable**
- **Statistically** significant benefits may be marginal in **clinical practice**
- Inflexible rules and **technology driven prompts** may produce care that is management driven **rather than patient centred**
- **Evidence based guidelines often map poorly to complex multimorbidity**

Greenhalgh T, BMJ 2014

Key tools of non-evidence based medicine in 2016

- Too much **low-quality "evidence**"
- "**Single-disease** medicine"
- **Relying on statistical** significance
- **Overdiagnosis/overtreatment**
- **Care management-(non patient)-driven**

Florence EBM Renaissance

- **Re-assessment** of inspirational principles of EBM
- EBM: **limits of application** (ie "vested interests", too much informations, statistical vs clinical significance, multimorbidity).
- **Technological advancements** deeply **bonded** with medical science and even with **patient management**
- Acknowledgment of the need for a **critical assessment of any application of technology** to the diagnosis and treatment process (eg . Big Data)
- **Enhancement of patient preferences and values (religious too)**

thebmj

FORUM
Academy of Medical Sciences

Stratified, personalised or P4 medicine: a new direction for placing the patient at the centre of healthcare and health education (May 2015)

Summary of a joint FORUM meeting held on 12 May 2015.

Supported by the Academy of Medical Sciences, the University of Southampton, Science Europe and the Medical Research Council.

THE PRECISION MEDICINE INITIATIVE

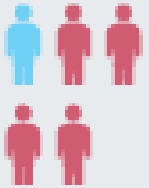
“Tonight, I'm launching **a new Precision Medicine Initiative** to bring us closer to curing diseases like **cancer and diabetes** — and to give all of us access to the **personalized information** we need to keep ourselves and our families **healthier**.”

President Barack Obama, State of the Union Address, January 20, 2015

IMPRECISION MEDICINE

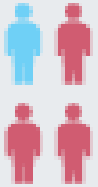
For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

1. ABILIFY (aripiprazole)
Schizophrenia



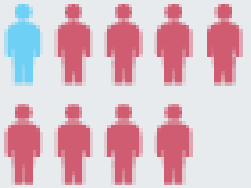
2. NEXIUM (esomeprazole)
Heartburn

3. HUMIRA (adalimumab)
Arthritis



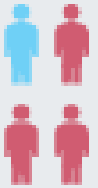
4. CRESTOR (rosuvastatin)
High cholesterol

5. CYMBALTA (duloxetine)
Depression

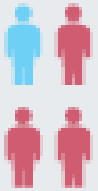


6. ADVAIR DISKUS (fluticasone propionate)
Asthma

7. ENBREL (etanercept)
Psoriasis



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/4dd7ff.

COMMENT

ILLUSTRATION BY GREG CLARKE

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.

WHY NOW?

The **time is right** because of:

Sequencing of the human genome

Improved technologies for biomedical analysis

New tools for using large datasets

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Precision Medicine — Personalized, Problematic, and Promising

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

This article was published on May 27, 2015, at NEJM.org.

Precision medicine
should be viewed as a means of providing the best available health care for a population by

- **identifying the needs** and
- **improving the outcomes** of individual patients.

May 27, 2015, at NEJM

Technological Advances as Drivers of Precision Medicine

The **convergence** of
- genetics,
- informatics, and
- imaging,

along with ***other technologies*** such as:
- cell sorting,
- epigenetics,
- proteomics, and
- metabolomics,

Allow to **refine the classification of disease**, often with important prognostic and treatment implications.

May 27, 2015, at NEJM

Table 1. Examples of Conditions in Which Precision Medicine Has Been Used.*

Medical Field	Disease	Biomarker	Intervention
Cancer	Chronic myeloid leukemia	BCR-ABL	Imatinib[4]
	Lung cancer	EML4-ALK	Crizotinib[3]
Hematology	Thrombosis	Factor V Leiden	Avoid prothrombotic drugs[5]
Infectious disease	HIV/AIDS	CD4+ T cells, HIV viral load	Highly active antiretroviral therapy[6]
Cardiovascular disease	Coronary artery disease	*CYP2C19*	Clopidogrel[7]
Pulmonary disease	Cystic fibrosis	*G551D*	Ivacaftor[8]
Renal disease	Transplant rejection	Urinary gene signature	Antirejection drugs[9]
Hepatology	Hepatitis C	Hepatitis C viral load	Direct-acting antiviral agents[10]
Endocrine disease	Multiple endocrine neoplasia type 2	*RET*	Prophylactic thyroidectomy[11]
Metabolic disease	Hyperlipidemia	LDL cholesterol	Statins[12]
Neurology	Autoimmune encephalitis	CXCL13	Immunotherapy[13]
Psychiatry	Alcohol-use disorder	*GRIK1*	Topiramate[14]
Pharmacogenomics	Smoking cessation	*CYP2A6*	Varenicline[15]
Ophthalmology	Leber's congenital amaurosis	*RPE65*	Gene therapy[16]

* 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.

EBM RENAISSANCE – RIVOLUZIONE DIGITALE E **MEDICINA NARRATIVA**

Cristina Cenci, antropologa, Center for Digital Health Humanities, OMNI-Osservatorio

Medicina Narrativa Italia, DNM-Digital Narrative Medicine

Digital revolution, precision medicine, “new patients”

are the basis of the “EBM Renaissance” through the **systematic personalization** of disease and care trajectories.
In this process **narrative medicine** may support the **integration** of
- **Biomedical and biographic** elements,
- **type** and **subject**,
- **Evidence and clinical intuition**.

Digitali technologies may enhance **the integration of quantitative and narrative data**.

ICT as enabler of personalized medicine

Notes from and remarks inspired by the EU Horizon 2020 Advisory Group for Societal Challenge 1,

"Health, Demographic Change and Well-being" (AGSC1)

by Federico Cabitza federico.cabitza@unimib.it 29/06/2016

Many terms, same concept

Stratified medicine (mainly used in the UK) is more treatment-dependent, while precision medicine (mostly used in US) has a relatively broad meaning as it refers to 4P (Predictive, Preventive, Personalised and Participatory) medicine.

The AGSC 1 recommends the term personalised medicine, because it best reflects the ultimate goal of effectively tailoring treatment based on an individual's 'personal profile', as determined by the individual's genotype and phenotype data.

Based on individuals' profiles, PM aims to identify the optimal treatment regime by avoiding the treatment-failure approach commonly used in current evidence-based medicine

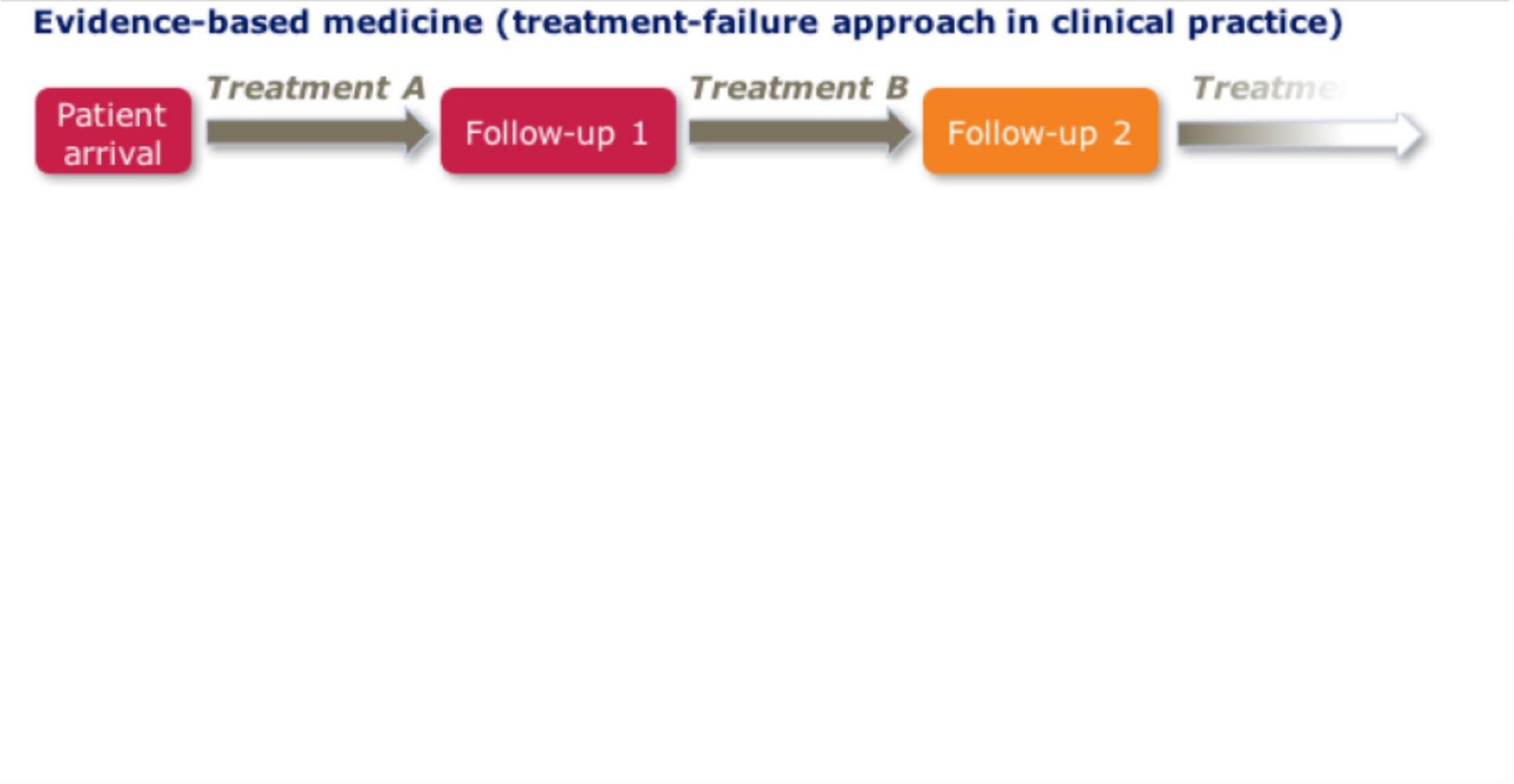


Figure 1. PM approach as compared to treatment-failure evidence-based medicine (EBM) approach in medical practice. A similar PM approach applies to the prevention of disease, where at-risk individuals are identified by their 'personalised profiles'.

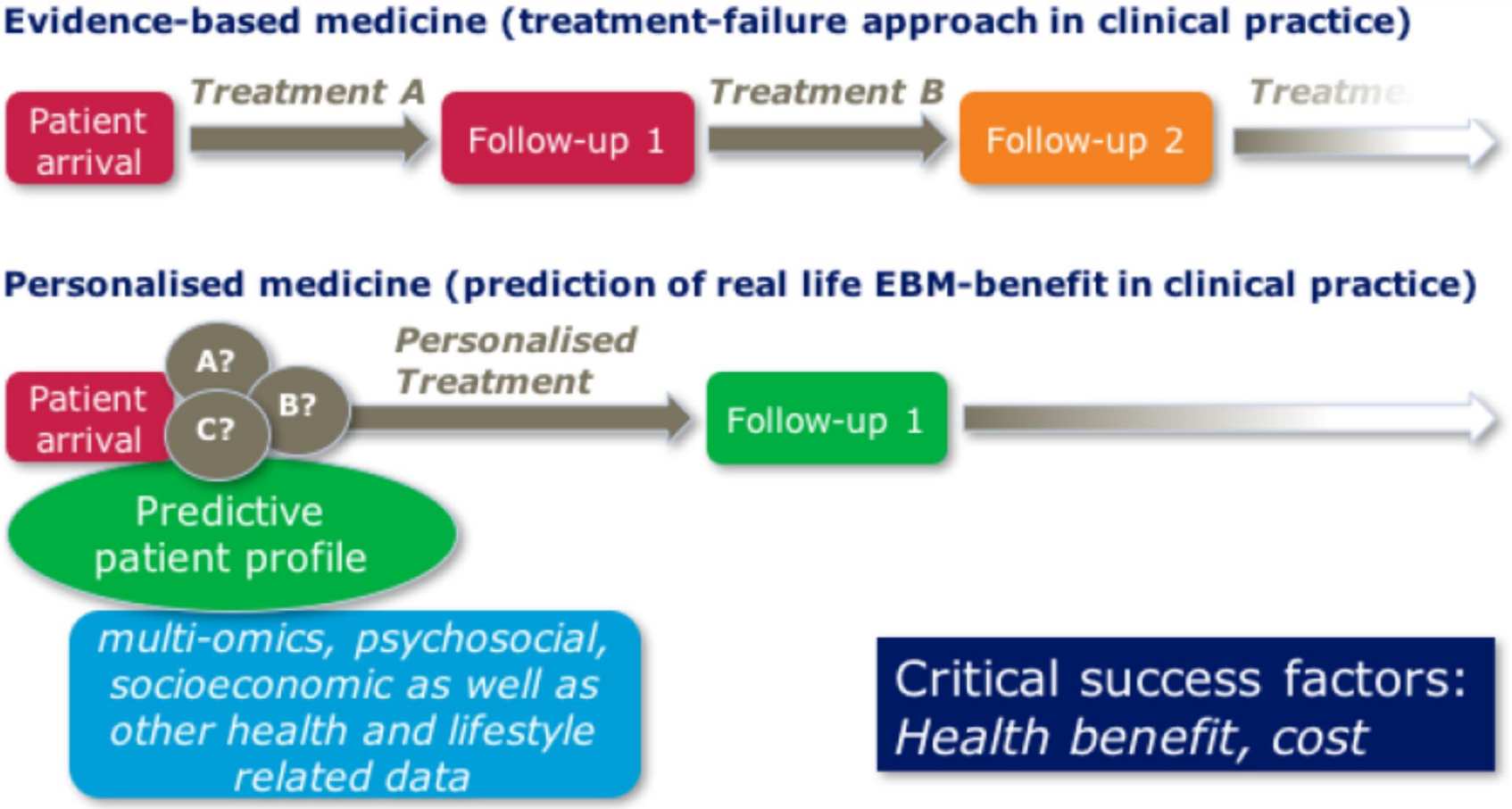


Figure 1. PM approach as compared to treatment-failure evidence-based medicine (EBM) approach in medical practice. A similar PM approach applies to the prevention of disease, where at-risk individuals are identified by their 'personalised profiles'.

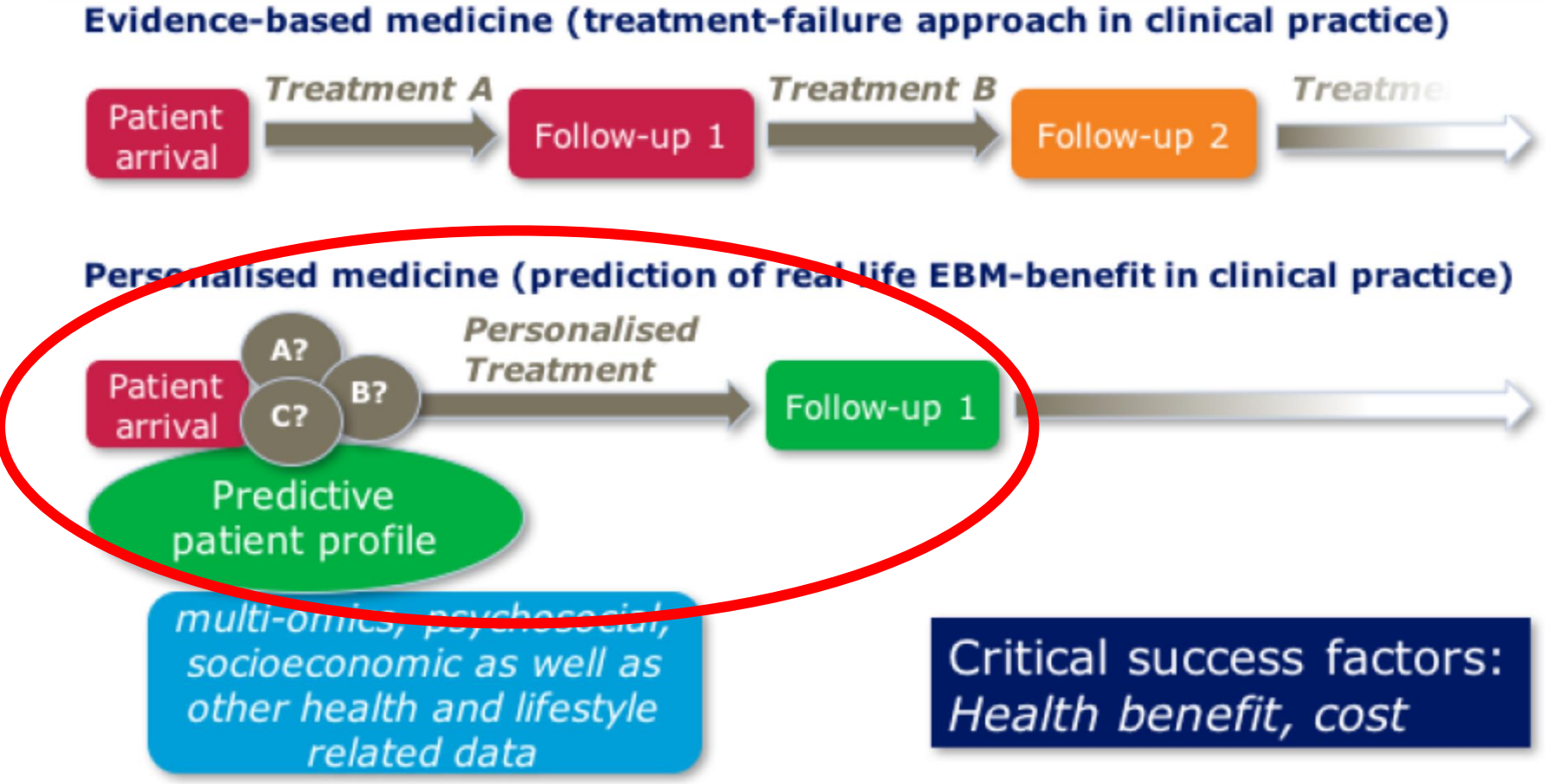


Figure 1. PM approach as compared to treatment-failure evidence-based medicine (EBM) approach in medical practice. A similar PM approach applies to the prevention of disease, where at-risk individuals are identified by their 'personalised profiles'.

Eur. J. Nanomed. 2012;4(1):5–6 © 2012 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/ejnm-2012-0005

Vision Paper by the Editor-in-Chief

"Knowledge-based (personalized) medicine" instead of "evidence-based (cohort) medicine"

Applying nanoscience and computational science to create an effective, safe, curative and affordable medicine of the future

Patrick Hunziker

…a **seemingly clear disease entity** like **myocardial infarction** is a **continuum** in:

- **space** (location of infarct related artery),
- **time** (critical relevance of timing of reopening of occluded artery),
- **severity**,
- **individual factors:**
  - degree of subclinical atherosclerosis not related to the event,
  - variability of coagulation system and platelet response to drugs.

Hunziker: Knowledge-based (personalized) medicine Eur. J. Nanomed. 2012;4(1):5–6

A Framework for Crafting Clinical Practice Guidelines that are Relevant to the Care and Management of People with Multimorbidity

Katrin Uhlig, MS, MD[1], Bruce Leff, MD[2,4], David Kent, MD, Cm, MSc[3], Sydney Dy, MD, MSc[4], Klara Brunnhuber, MD[5], Jako S. Burgers, MD, PhD[6], Sheldon Greenfield, MD[7], Gordon Guyatt, MD, MSc[8], Kevin High, MD[9], Rosanne Leipzig, MD, PhD[10], Cynthia Mulrow, MD, MSc[11], Kenneth Schmader, MD[12], Holger Schunemann, MD, MSc, PhD[8], Louise C. Walter, MD[13], James Woodcock, PhD, MSc, BA(Hons)[14], and Cynthia M. Boyd, MD, MPH[2,4]

The Ariadne principles: how to handle multimorbidity in primary care consultations

Christiane Muth[1*†], Marjan van den Akker[1,2,3†], Jeanet W Blom[4], Christian D Mallen[5], Justine Rochon[6], François G Schellevis[7,8], Annette Becker[9], Martin Beyer[1], Jochen Gensichen[10], Hanna Kirchner[1], Rafael Perera[11], Alexandra Prados-Torres[12], Martin Scherer[13], Ulrich Thiem[14,15], Hendrik van den Bussche[13] and Paul P Glasziou[16]

Multimorbidity: clinical assessment and management

Anticipated publication date: September 2016

A Framework for Crafting Clinical Practice Guidelines that are Relevant to the Care and Management of People with Multimorbidity

Katrin Uhlig, MS, MD[1], Bruce Leff, MD[2,4], David Kent, MD, Cm, MSc[3], Sydney Dy, MD, MSc[4], Klara Brunnhuber, MD[5], Jako S. Burgers, MD, PhD[6], Sheldon Greenfield, MD[7], Gordon Guyatt, MD, MSc[8], Kevin High, MD[9], Rosanne Leipzig, MD, PhD[10], Cynthia Mulrow, MD, MSc[11], Kenneth Schmader, MD[12], Holger Schunemann, MD, MSc, PhD[8], Louise C. Walter, MD[13], James Woodcock, PhD, MSc, BA(Hons)[14], and Cynthia M. Boyd, MD, MPH[2,4]

Table 1. Important Interactions to Consider Regarding Multimorbidity

1. Condition A x Condition B
   Example: Depression is more common in diabetes.[13] Depression may affect self-management, while the burden of long-term self-management may worsen depressive symptoms.
2. Treatment A x Condition B
   Example: use of non-steroidal anti-inflammatory drugs for osteoarthritis may lead to acute renal failure in individuals with chronic kidney disease (CKD).
3. Treatment A x Treatment B
   Example: Many potential drug interactions occur in people on multiple medications, such as the interaction between warfarin and antibiotics.
4. Condition A and Life Expectancy
   Example: The presence of end-stage chronic obstructive pulmonary disease may change the potential benefit of screening for colon cancer.[14,15]

J Gen Intern Med. 2014 Apr;29(4):670-9.

Table 2. Recommendations for Consideration of Multimorbidity in the Development of Clinical Practice Guidelines

Item #	Guideline Development Step	Issue(s) for CPG Developers to Consider in CPG Development	Recommendations
1, 2	Topic nomination and topic scoping	When selecting a topic for guideline development, what may be important interactions between conditions or treatments to address?	a) Consider how disease-disease, disease-treatment, and treatment-treatment interactions, or limitations of life expectancy may result in specific consequences for clinical management. b) Determine whether the guideline should focus on an index condition with consideration of specific coexisting conditions or whether the guideline should focus on a combination of conditions. c) Review or estimate the scope and quality of evidence for the conditions under consideration.
3	Commissioning Work Group: Selection of Members	Who should be included in the guideline panel to provide expertise on relevant conditions?	a) Include experts who have substantial experience managing the relevant patient groups, participate in coordination of care, and regularly engage in shared decision-making. b) Incorporate views or values of patients with relevant coexisting conditions, patient advocates and consumer representatives.
4	Refining the key questions	How should relevant coexisting conditions be considered in the formulation of the guideline's key questions according to PICO criteria: Population, Intervention, Comparator, and Outcomes?	Consider impact of relevant coexisting conditions in the formulation of all components of key questions: a) Determine how coexisting conditions affect the definitions of populations of interest, inclusion and exclusion criteria. b) Determine how coexisting conditions may affect effectiveness and harms of interventions. c) Determine how coexisting conditions affect the choice and range of relevant outcomes, including harms and treatment burden. If surrogates are

Effective Health Care Program

Design and Implementation of N-of-1 Trials: A User's Guide

N of 1

AHRQ
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Design and Implementation of N-of-1 Trials: A User's Guide

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Prepared by:
Brigham and Women's Hospital DEcIDE Methods Center
Boston, MA

Contract No. 290-2005-0016-I

Editors:
Richard L. Kravitz, M.D., M.S.P.H.
Naihua Duan, Ph.D.

ISBN: 978-1-58763-430-7

AHRQ Publication No. 13(14)-EHC122-EF
February 2014

The goal of evidence-based medicine (EBM) is to integrate research evidence, clinical judgment, and patient preferences in a way that maximizes benefits and minimizes harms to the individual patient.
The foundational, gold-standard research design in EBM is the **randomized, parallel group clinical trial**.
However, the majority of patients may be ineligible for or unable to access such trials.
In addition, these clinical experiments generate **average treatment effects,** which may not apply to the individual patient; **some patients may derive greater benefit** than average from a particular treatment, **others less**.

Patients want to know: **which treatment is likely to work better for me?**

To generate **individual treatment effects (ITEs**), clinical investigators have taken several tacks, including:

- subgroup analysis,
- matched pairs designs, and
- n-of-1 trials.

Of these, n-of-1 trials provide the most direct route to estimating the effect of a treatment on the individual.

…n-of-1 trials are situated on the continuum between clinical care and research and hybrids in between.

Heart Failure in the United States (2016)

- About **5.7 million adults in the United States** have heart failure.[1]
- **One in 9 deaths in 2009** included heart failure as contributing cause.[1]
- About **half of people who develop heart failure die within 5 years** of diagnosis.[1]
- Heart failure **costs the nation an estimated $30.7 billion each year**.[3] This total includes the cost of health care services, medications to treat heart failure, and missed days of work.

Heart failure patients are at high risk of repeated hospitalisation

Nº1

CAUSE OF HOSPITALISATION
FOR PATIENTS AGED >65 YEARS
IS HEART FAILURE[1]

Approximately half of heart failure patients over the age of 75 die within a year of hospital admission.[1]

1. Cowie MR, Anker SD, Cleland JGF. Improving Care for Patients With Acute Heart Failure: Before, During and After Hospitalization. Oxford PharmaGenesis; 2014. http://www.oxfordhealthpolicyforum.org/AHFreport. Accessed February 18, 2015.

Heart failure rehospitalisation rates remain high

~44%

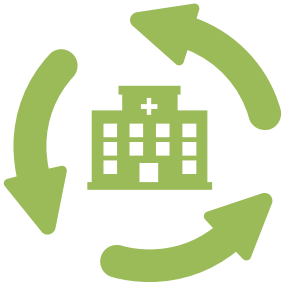
OF HEART FAILURE PATIENTS WHO WERE HOSPITALISED IN EUROPE WILL BE REHOSPITALISED AT LEAST ONCE WITHIN 12 MONTHS OF DISCHARGE[1]

What's even more alarming is that the risk of mortality from heart failure increases with repeat hospitalisations.[2]

1. Cowie MR, Anker SD, Cleland JGF. Improving Care for Patients With Acute Heart Failure: Before, During and After Hospitalization. Oxford PharmaGenesis; 2014. http://www.oxfordhealthpolicyforum.org/AHFreport. Accessed February 18, 2015. 2. Lee DS, Austin PC, Stukel TA, et al. "Dose-dependent" impact of recurrent cardiac events on mortality in patients with heart failure. Am J Med. 2009;122(2):162-169.

Heart failure patients are at high risk of repeated hospitalisation

1 IN 4 HEART FAILURE PATIENTS AGED ≥65 YEARS ARE REHOSPITALISED WITHIN 30 DAYS OF DISCHARGE[1]

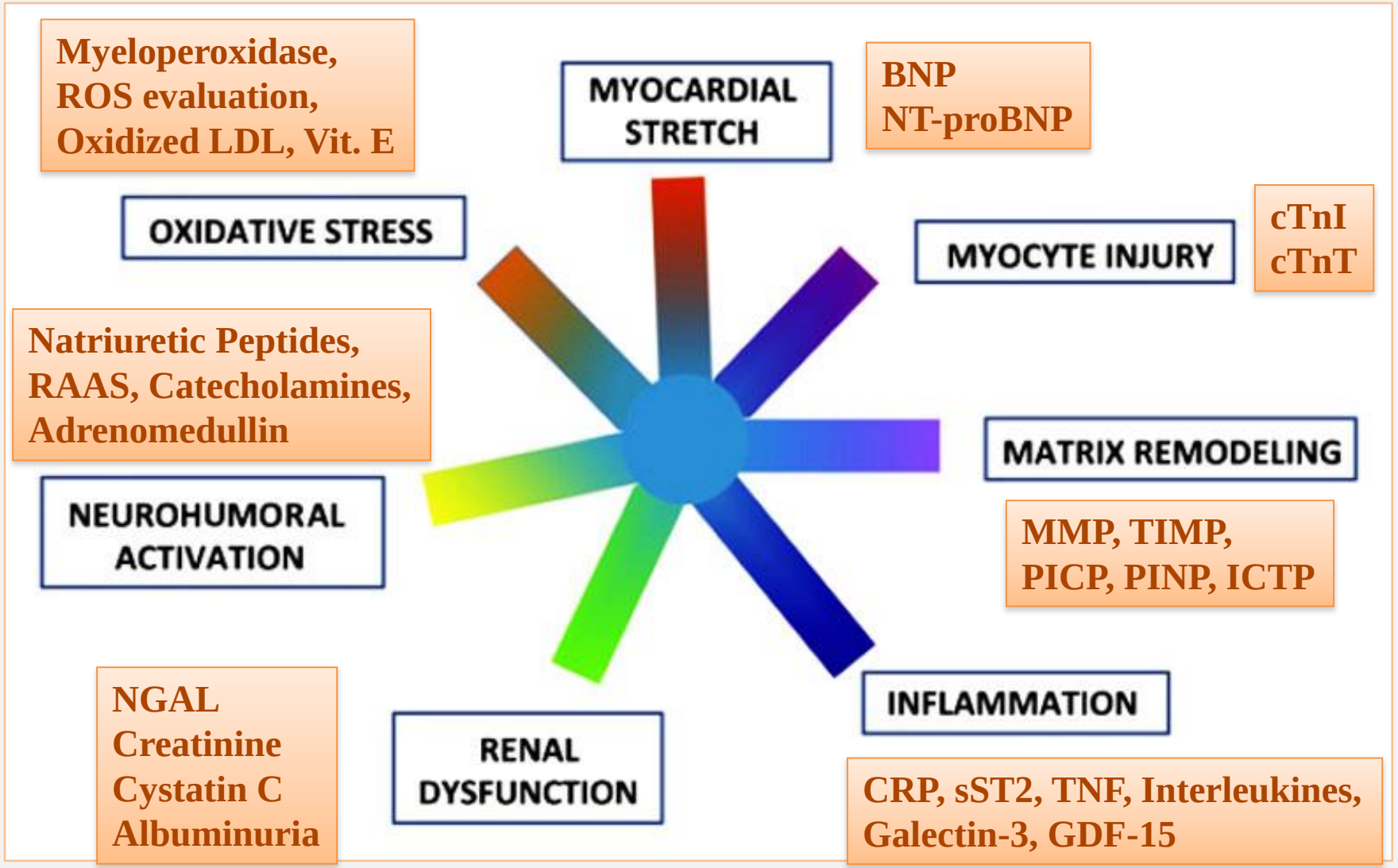


Heart failure is a complex deteriorating condition driven by neurohormonal imbalance, leading to a spiral of worsening disease and punctuated by acute episodes that result in repeated hospitalisations that lead to poor outcomes.[2]

After a hospitalisation, heart failure patients may never regain their previous quality of life.[3]

1. Krumholz HM, Merrill AR, Schone EM, et al. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. Circ Cardiovasc Qual Outcomes. 2009;2(5):407-413. 2. Fauci AS, Braunwald E, Kasper DL, et al, eds. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2008. 3. Cowie MR, Anker SD, Cleland JGF. Improving Care for Patients With Acute Heart Failure: Before, During and After Hospitalization. Oxford PharmaGenesis; 2014. http://www.oxfordhealthpolicyforum.org/AHFreport. Accessed February 18, 2015.

Seven Major Classes of Biomarkers Contributing to the Biomarker Profile in HF



(modified from: Braunwald E. JACC Heart Fail 2013; 1:1-20)

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

3.4 Prognosis

Numerous prognostic markers of death and/or HF hospitalization have been identified in patients with HF (*Web Table 3.5*). However, their clinical applicability is limited and precise risk stratification in HF remains challenging.

European Heart Journal Advance Access published May 20, 2016

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

EUROPEAN SOCIETY OF CARDIOLOGY®

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL.

European Heart Journal Advance Access published May 20, 2016

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Table 9. Recommendations for Biomarkers in HF

Biomarker, Application	Setting	COR	LOE	References
Natriuretic peptides				
Diagnosis or exclusion of HF	Ambulatory, Acute	I	A	212, 217–223, 245–250
Prognosis of HF	Ambulatory, Acute	I	A	222, 224–229, 248, 251–258
Achieve GDMT	Ambulatory	IIa	B	230–237
Guidance for acutely decompensated HF therapy	Acute	IIb	C	259, 260
Biomarkers of myocardial injury				
Additive risk stratification	Acute, Ambulatory	I	A	238–241, 248, 253, 256–267
Biomarkers of myocardial fibrosis				
Additive risk stratification	Ambulatory	IIb	B	242–244
	Acute	IIb	A	248, 253, 256, 258–260, 262, 264–267

COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.

Circulation. 2013;128:e240-e319

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

6.3.3. Other Emerging Biomarkers

Besides natriuretic peptides or troponins, multiple other biomarkers, including those reflecting inflammation, oxidative stress, neurohormonal disarray, and myocardial and matrix remodeling, have been widely examined for their prognostic value in HF. Biomarkers of myocardial fibrosis, soluble ST2 and galectin-3 are not only predictive of hospitalization and death in patients with HF but also additive to natriuretic peptide levels in their prognostic value. Markers of renal injury may also offer additional prognostic value because renal function or injury may be involved in the pathogenesis, progression, decompensation, or complications in chronic or acute decompensated HF.[242–244,264,265,279] Strategies that combine multiple biomarkers may ultimately prove beneficial in guiding HF therapy in the future.

Circulation. 2013;128:e240-e319

Utilizzo dei Biomarcatori nello Scompenso Cronico

- Stratificazione del rischio
- Follow-up ambulatoriale
- Guida alla terapia

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

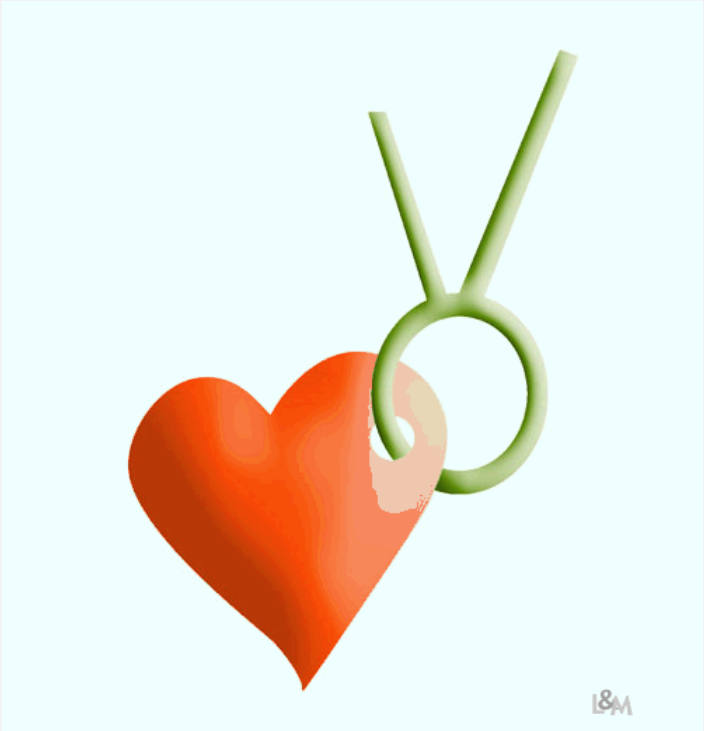
Table 9. Recommendations for Biomarkers in HF

Biomarker, Application	Setting	COR	LOE	References
Natriuretic peptides				
Diagnosis or exclusion of HF	Ambulatory, Acute	I	A	212, 217–223, 245–250
Prognosis of HF	Ambulatory, Acute	I	A	222, 224–229, 248, 251–258
Achieve GDMT	Ambulatory	IIa	B	230–237
Guidance for acutely decompensated HF therapy	Acute	IIb	C	259, 260
Biomarkers of myocardial injury				
Additive risk stratification	Acute, Ambulatory	I	A	238–241, 248, 253, 256–267
Biomarkers of myocardial fibrosis				
Additive risk stratification	Ambulatory	IIb	B	242–244
	Acute	IIb	A	248, 253, 256, 258–260, 262, 264–267

COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; and LOE, Level of Evidence.

Circulation. 2013;128:e240-e319

Quale è il RAZIONALE dell'utilizzo del BNP/NT-proBNP per guidare la terapia nello scompenso cardiaco ?



Which heart failure patients profit from natriuretic peptide guided therapy? A meta-analysis from individual patient data of randomized trials

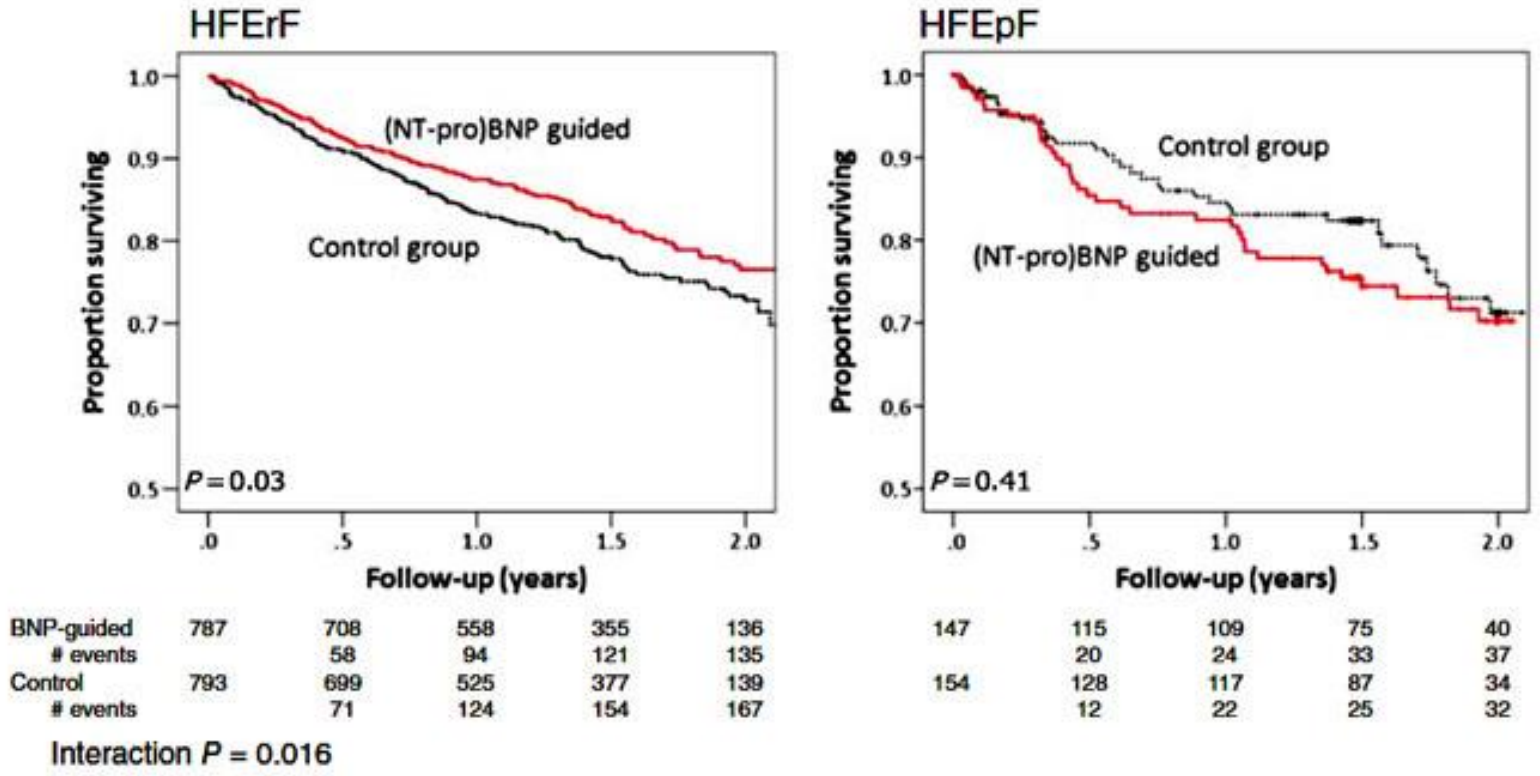


Figure 1 Kaplan–Meier curves of survival comparing patients allocated to (*N*-terminal pro-)brain natriuretic peptide (NT-proBNP)-guided treatment or control group with reduced left ventricular ejection fraction (HFrEF)) and preserved left ventricular ejection fraction (HFpEF).

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2015) **17**, 1252–1261
doi:10.1002/ejhf.401

In quali pazienti risulta efficace ed efficiente effettuare la terapia guidata con BNP/NT-proBNP ?

- **Nei pazienti più giovani e di sesso maschile**
- **Nei pazienti in classe NYHA I-II**
- **Nei pazienti con poche co-morbidità**

Could PRAGMATIC guidelines be hypotesized?

THAT..

- Face complexity (including specific clusters of multimorbidity)
- Clearly identify (absolute) risk/benefit for specific groups of patients
- Underline uncertainty of recommendations
- Include need to evoke patients' values and preferences
- Offer decision aids to help physicians and patients to better understand treatments thresholds
- Declare conflicts among authors on specific issues
- Consider risk of overdiagnosis/overtreatment and deprescribing in specific circumstances
- Are not funded by industry
- Include patients representative and experts in communication

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

Table 1. Nine Dimensions for Assessing the Level of Pragmatism in a Trial, as Proposed in the Pragmatic–Explanatory Continuum Indicator Summary 2 (PRECIS-2) Tool.*

Dimension	Assessment of Pragmatism
Recruitment of investigators and participants	
Eligibility	To what extent are the participants in the trial similar to patients who would receive this intervention if it was part of usual care?
Recruitment	How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
Setting	How different are the settings of the trial from the usual care setting?
The intervention and its delivery within the trial	
Organization	How different are the resources, provider expertise, and organization of care delivery in the intervention group of the trial from those available in usual care?
Flexibility in delivery	How different is the flexibility in how the intervention is delivered from the flexibility anticipated in usual care?
Flexibility in adherence	How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
The nature of follow-up	
Follow-up	How different is the intensity of measurement and the follow-up of participants in the trial from the typical follow-up in usual care?
The nature, determination, and analysis of outcomes	
Primary outcome	To what extent is the primary outcome of the trial directly relevant to participants?
Primary analysis	To what extent are all data included in the analysis of the primary outcome?

* Information in the table is adapted from Loudon et al.[22]

A pragmatic approach to pragmatism would be to adopt the features of pragmatic trials whenever feasible and sensible and when such features do not compromise trial quality and the ability to answer the clinical question of interest.

Stato dell’arte e trend futuri:
dalla diagnostica classica alla Medicina di precisione