

**CONGRESSO
NAZIONALE SIGG**

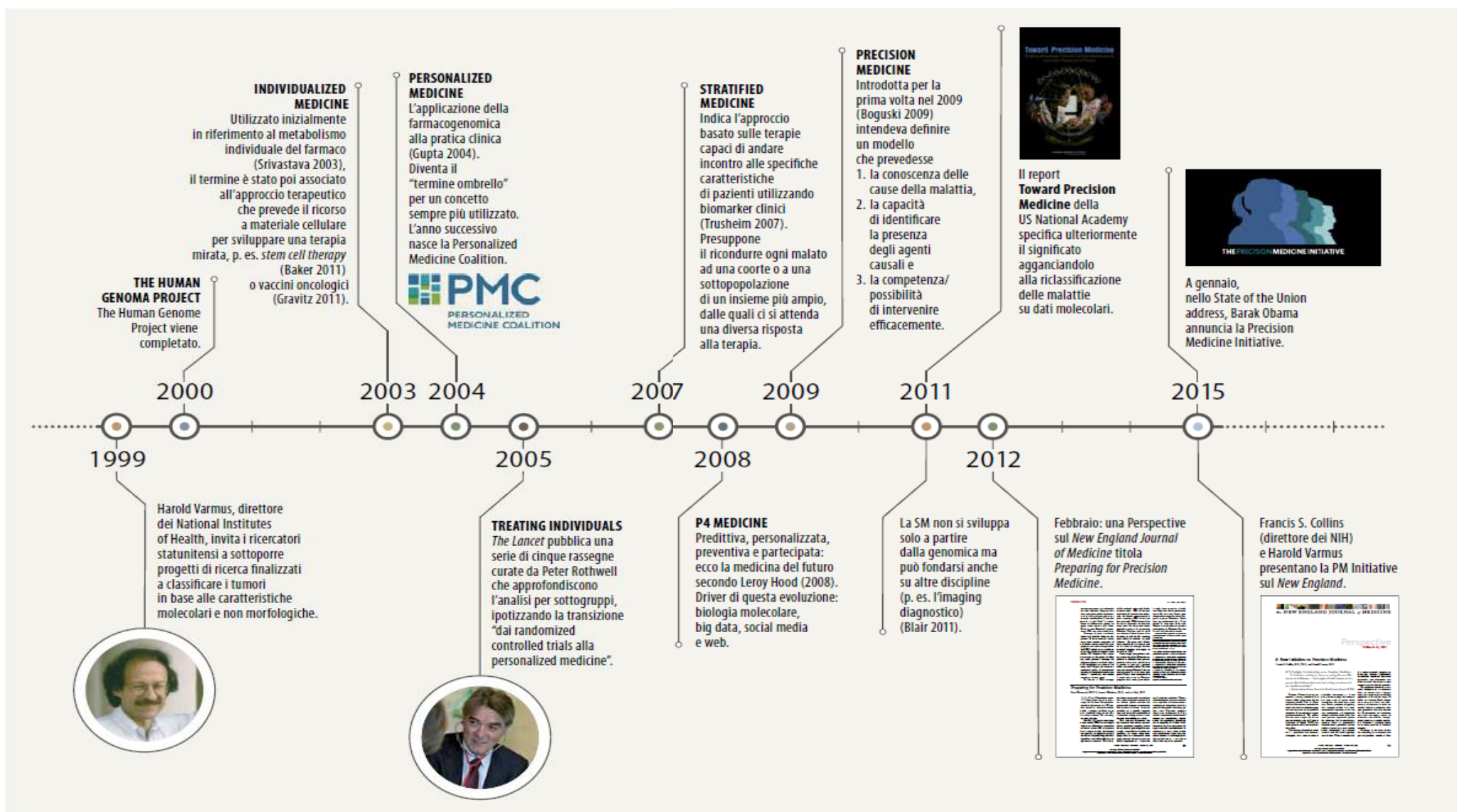
**GLI ANZIANI:
LE RADICI DA PRESERVARE**
ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

Medicina Personalizzata in Geriatria: una vera innovazione?

Fabrizia Lattanzio
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Roadmap temporale



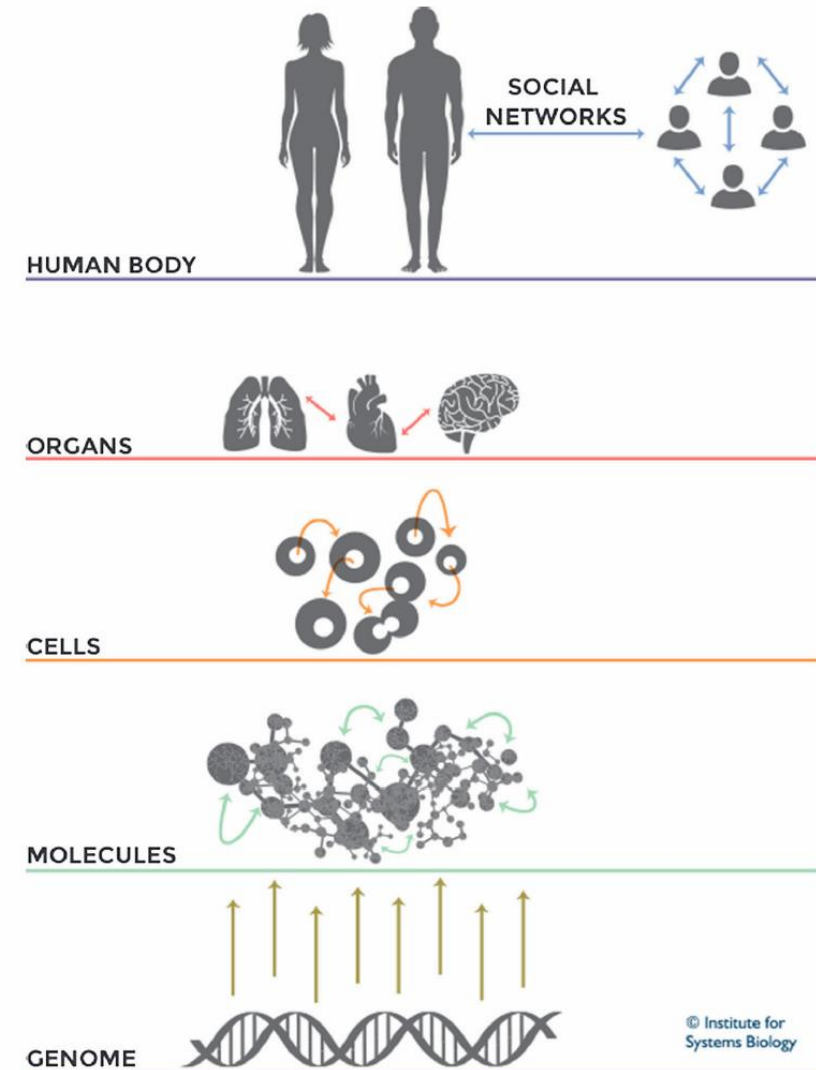
Forward Medicina di Precisione. Recenti progressi in medicina. 2016

System medicine

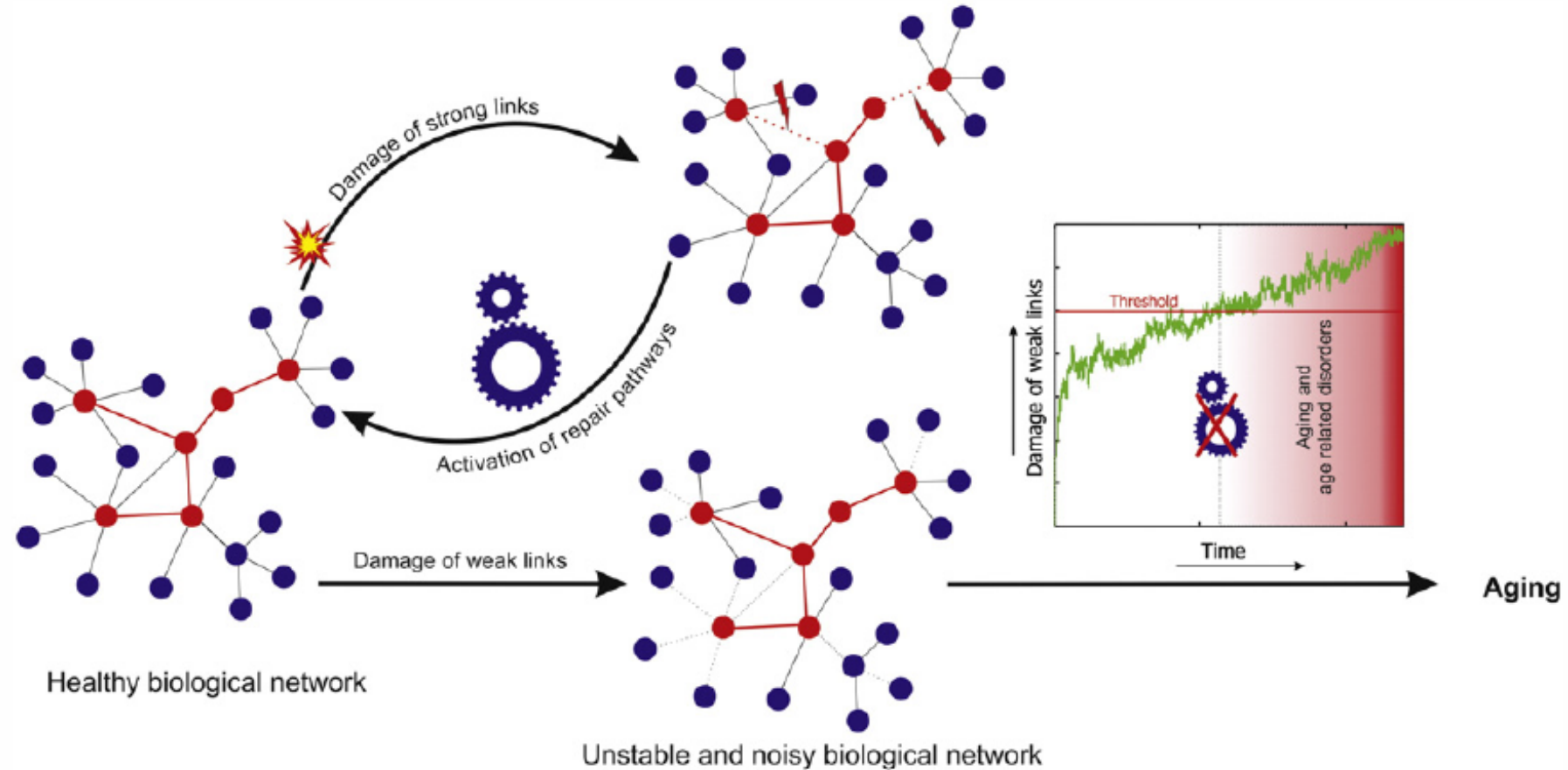
Systems medicine is an interdisciplinary field of study that looks at the systems of the human body as part of an integrated whole, incorporating biochemical, physiological, and environment interactions. Systems medicine draws on systems science and systems biology, and considers **complex interactions** within the human body in light of a patient's **genomics, behavior and environment**

Federoff, Howard; Gostin, Lawrence O. (2009). "Evolving from Reductionism to Holism: Is There a Future for Systems Medicine?". JAMA 302 (9): 994–996.

The human being is a dynamic network of networks



Transition of biological network from healthier to aging phenotype



Deciphering hallmark processes of aging from interaction networks

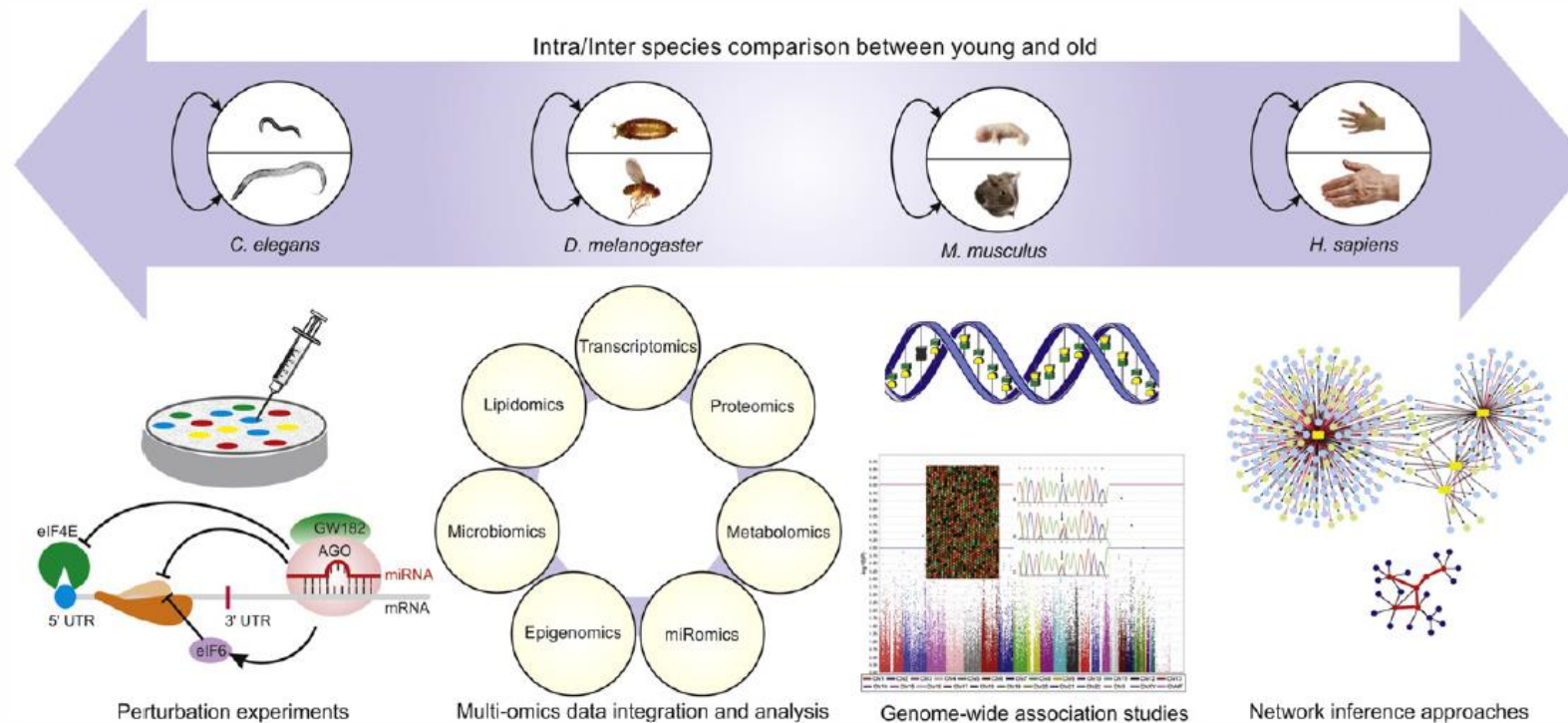


Fig. 2. Commonly used methods and approaches for the identification of aging regulators. Important signatures and processes associated with the aging phenotype can be predicted by comparing molecular profiles from young and aged phenotypes within a species. Many of the process specific molecular signatures are conserved throughout the evolution and can be detected by inter-species comparisons. Targeted perturbation experiments, multi-omics data analysis and integration and genome-wide association studies for the detection of genetic variant are some of the important methods that generate huge amounts of data for intra/inter-species comparison. Finally, systems biology approaches, such as network inference, can be used to prioritize therapeutic targets.

The hallmarks of aging



PERSPECTIVE OPEN

Systems medicine disease maps: community-driven comprehensive representation of disease mechanisms

Alexander Mazein¹, Marek Ostaszewski², Inna Kuperstein^{3,4,5,6}, Steven Watterson⁷, Nicolas Le Novère⁸, Diane Lefaudeux¹, Bertrand De Meulder¹, Johann Pellet¹, Irina Balaur¹, Mansoor Saqi¹, Maria Manuela Nogueira¹, Feng He⁹, Andrew Parton¹⁰, Nathanaël Lemonnier¹⁰, Piotr Gawron², Stephan Gebel², Pierre Hainaut¹⁰, Markus Ollert^{9,11}, Ugur Dogrusoz¹², Emmanuel Barillot^{3,4,5,6}, Andrei Zinovyev^{3,4,5,6}, Reinhard Schneider², Rudi Balling² and Charles Auffray¹

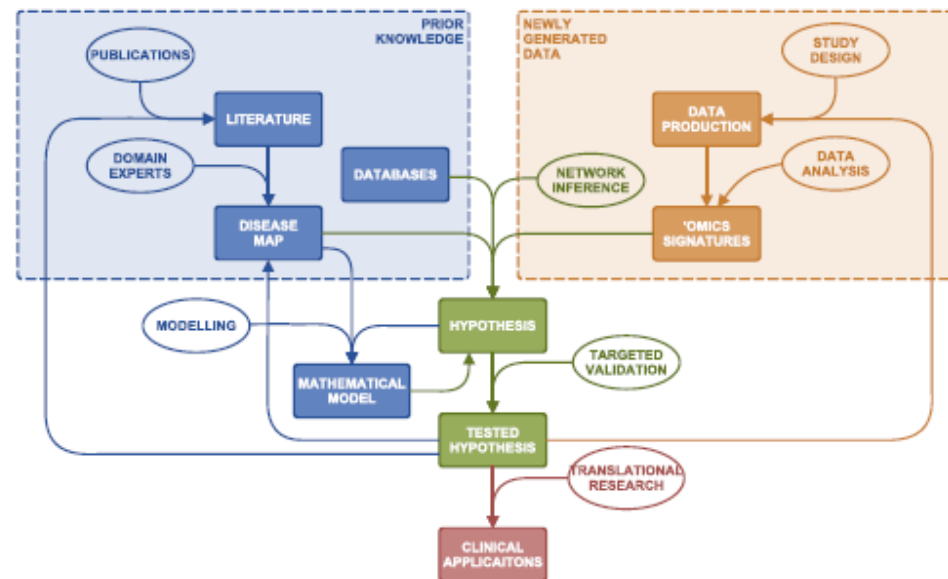


Fig. 1 Outline of the systems medicine rationale. The diagram represents the transformation of diverse prior knowledge and newly generated data into hypotheses using computational and mathematical methods, tools and approaches appropriate for each step

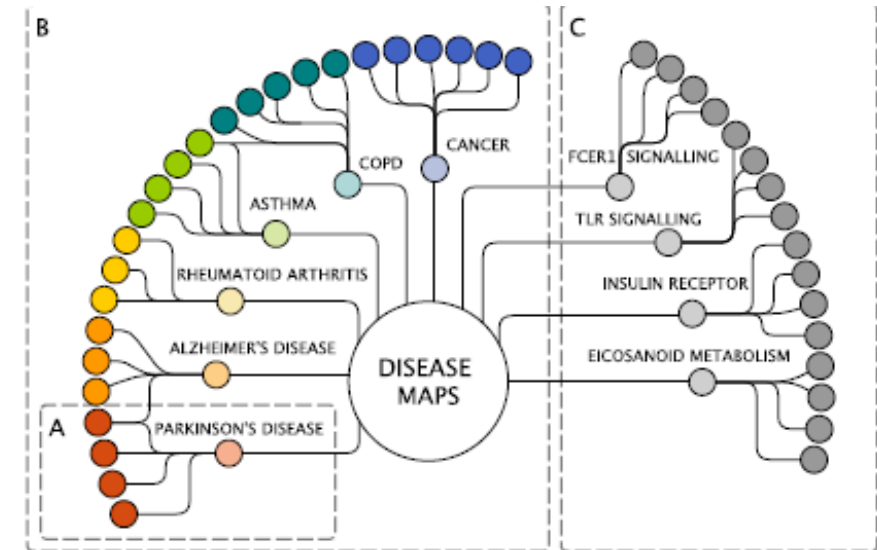


Fig. 3 The Disease Maps Project as a community of communities. **a** A collaboration for building one disease map. **b** Disease expert groups. **c** Pathway expert groups. Light colours: computational biology groups. Solid colours: domain experts. The Disease Maps hub is to be used for sharing experience, improving best practices and agreed-upon protocols, exchanging reusable biological processes and pathway modules. It is also an effort to create an infrastructure and set of tools to help each project to progress faster

Precision medicine

- According to the Precision Medicine Initiative, precision medicine is "an emerging approach for disease **treatment and prevention** that takes into account individual variability in genes, environment, and lifestyle for each person." This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. It is **in contrast to a one-size-fits-all approach**, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals.
- <https://ghr.nlm.nih.gov/primer/precisionmedicine/definition>

SOUNDING BOARD

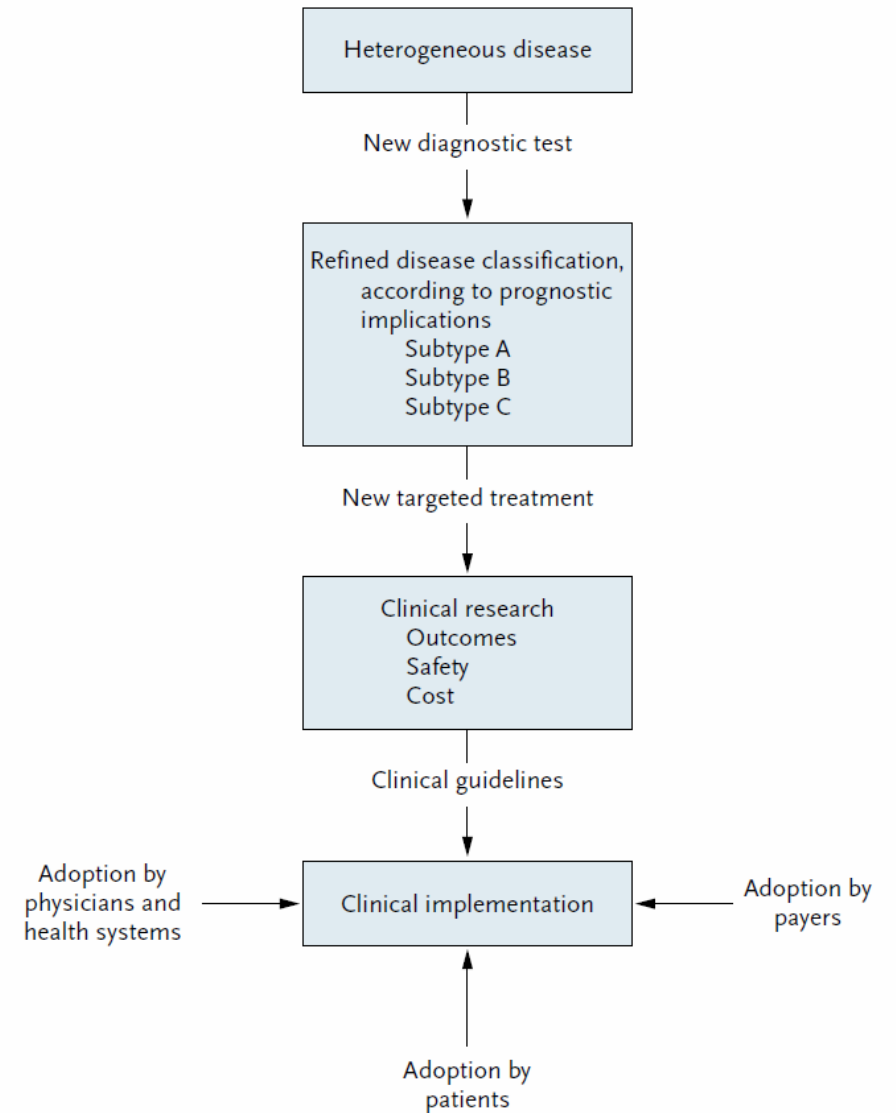
Precision Medicine — Personalized, Problematic, and Promising

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

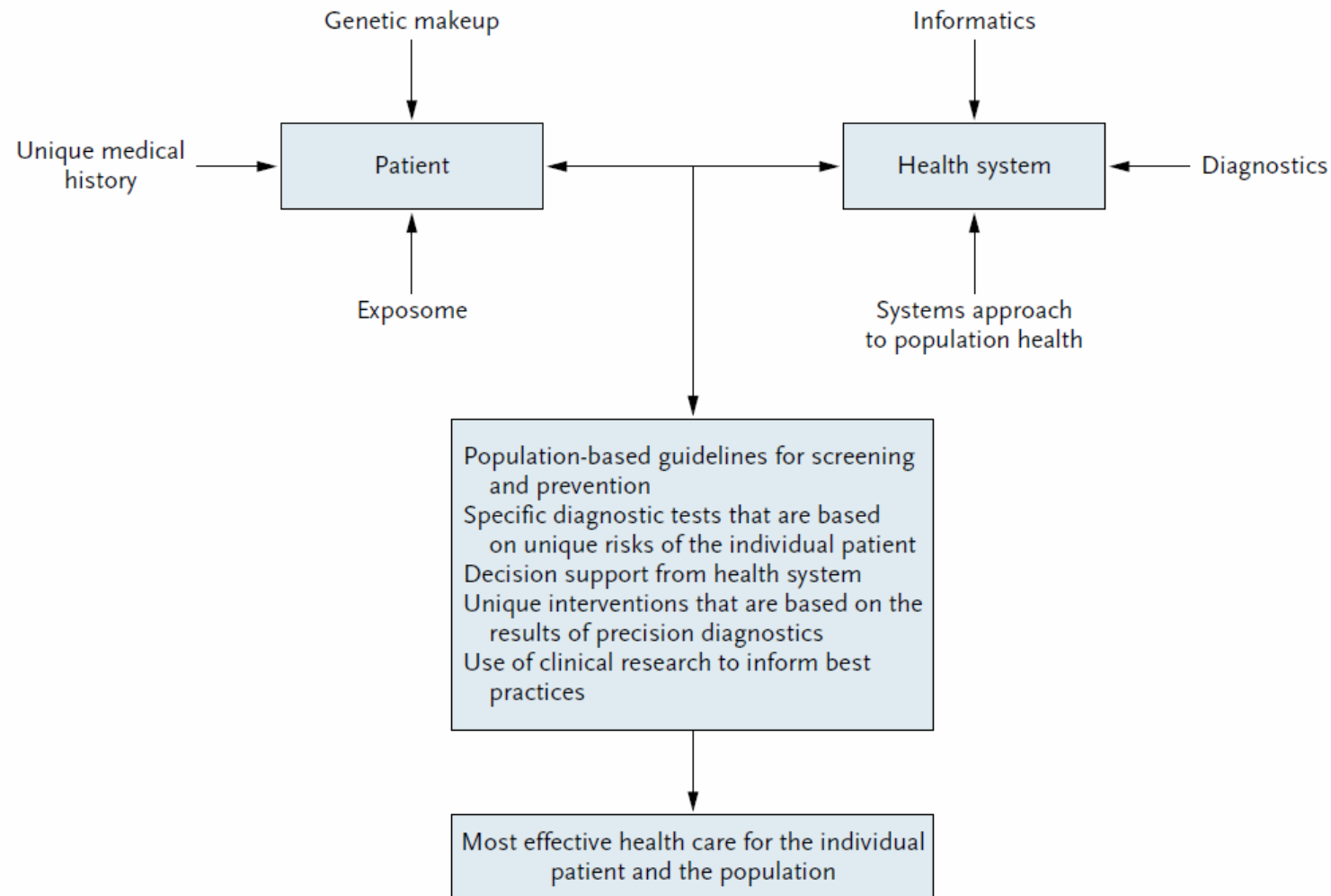
Table 1. Examples of Conditions in Which Precision Medicine Has Been Used.*

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.



Precision medicine needs precision healthcare systems



Precision medicine in age-specific non-small-cell-lung-cancer patients: Integrating biomolecular results into clinical practice—A new approach to improve personalized translational research

T. Vavalà et al. / Lung Cancer 107 (2017) 84–90

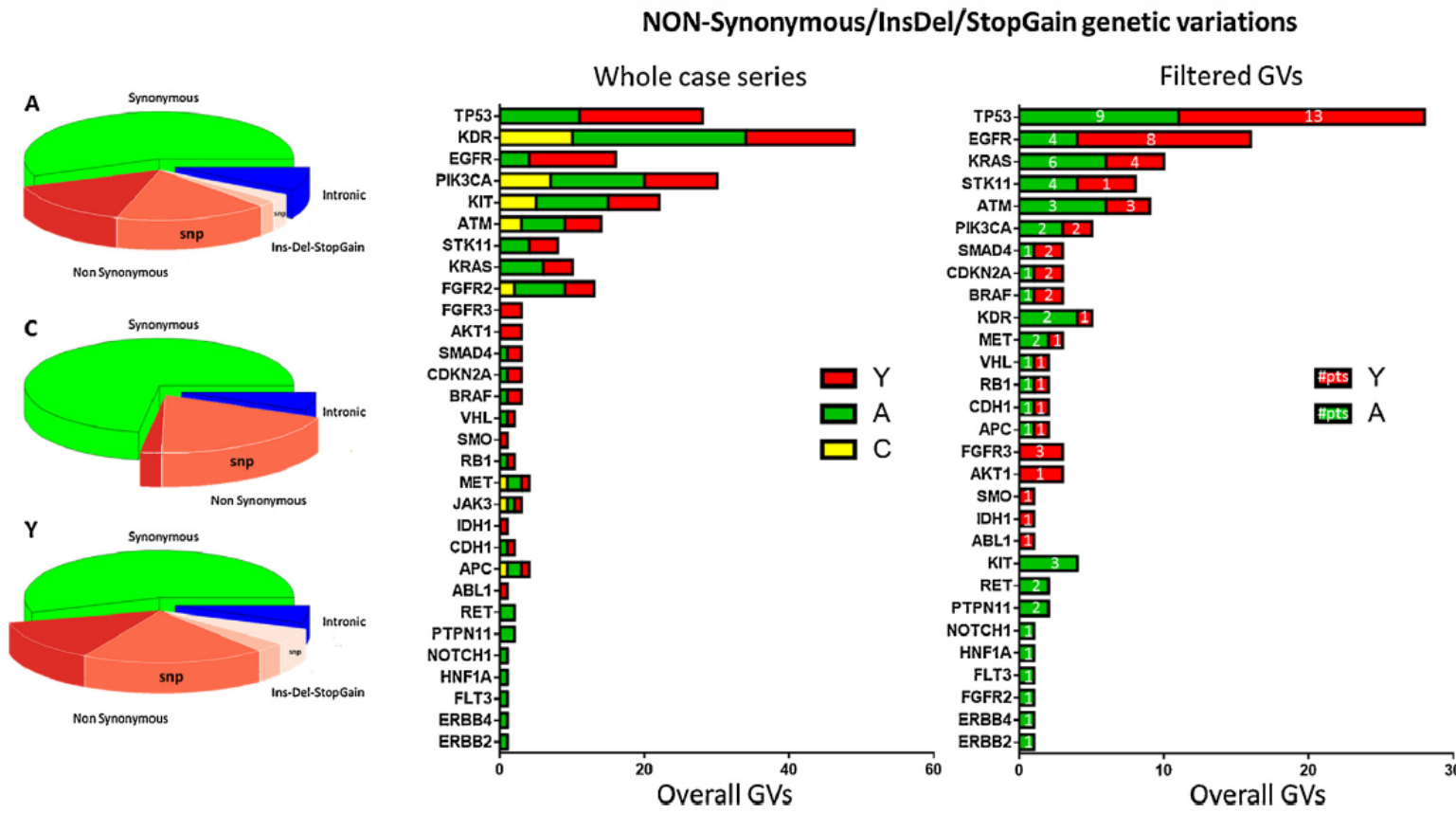
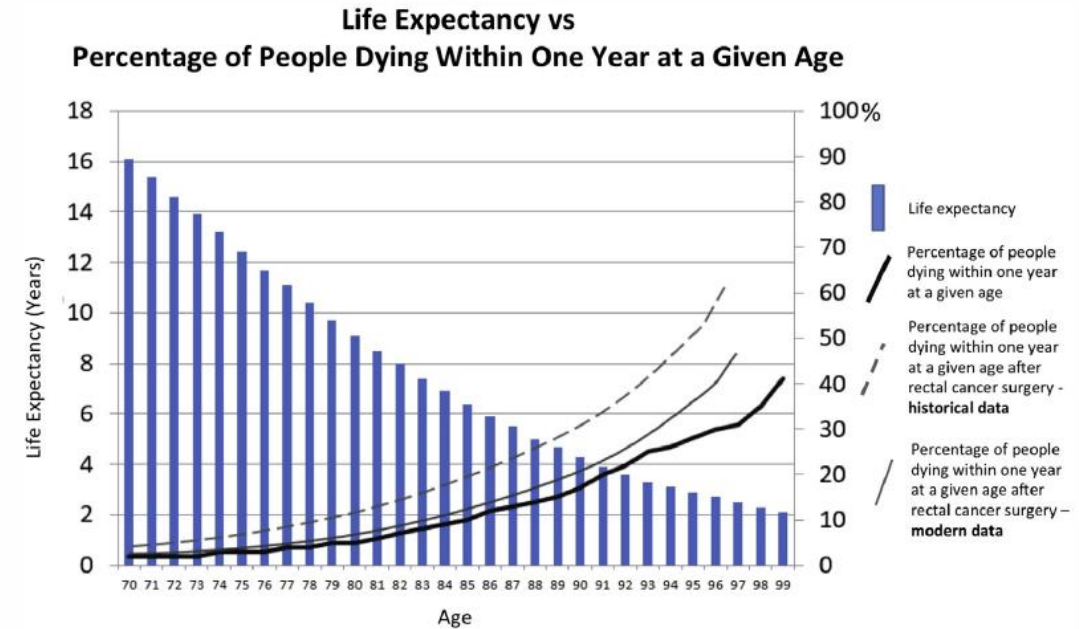
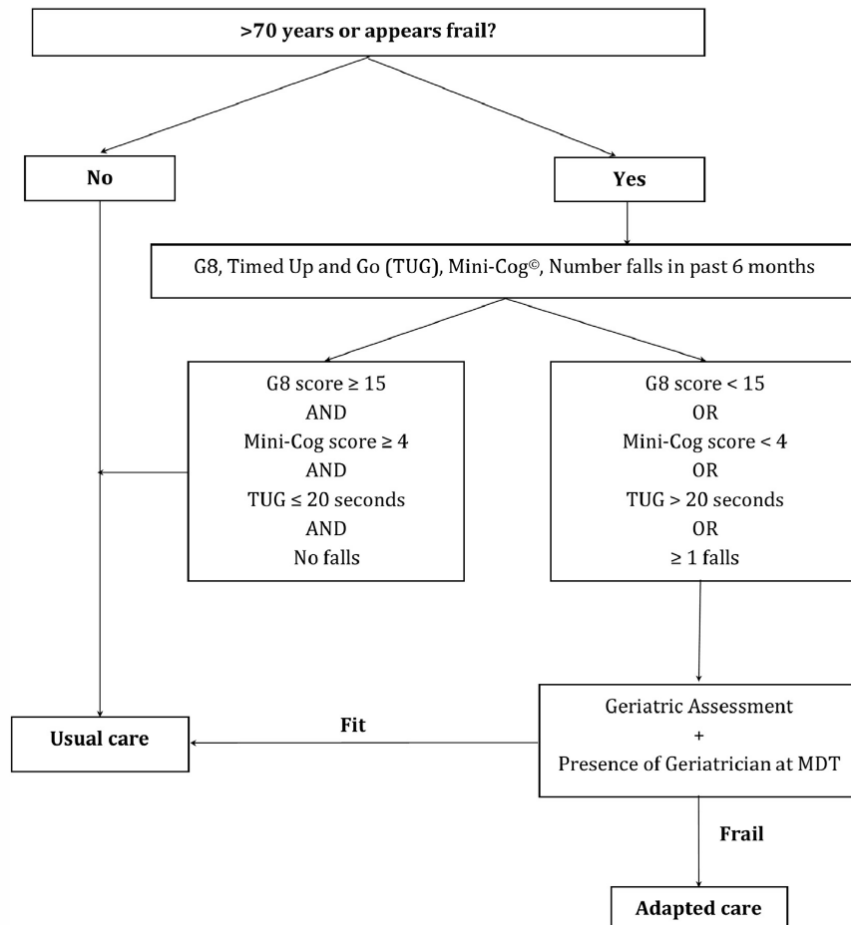


Fig. 1. Summary of genetic variations identified by NGS. Left Panel: The pie charts showed the GV's clustering in the three different population in study (A = Aged, C = Control, Y = Young Adults). In green and in blue were indicated the GV's not changing the affected genes, synonymous and intronic, respectively, while in red shades GV's altering protein coding/regulation: non-synonymous single nucleotide variation and Insertion/Deletion/StopGain (Ins-Del-StopGain). In the latter group the presence of single-nucleotide polymorphism (snp) was also evidenced. Right panel: Non synonymous/regulative variations identified in the cancer-associated genes with at least 10% of allelic frequency are summarized in the left graph, while the right one showed the GV's obtained by the exclusion of those identified in control population ("tolerated polymorphism"). The blocks indicate GV's amount in each population, while the white number counts patients affected.

Personalized management of elderly patients with rectal cancer: Expert recommendations of the European Society of Surgical Oncology, European Society of Coloproctology, International Society of Geriatric Oncology, and American College of Surgeons Commission on Cancer

European Journal of Surgical Oncology 44 (2018) 1685–1702

Proposed Algorithm for Office-Based Frailty Screening

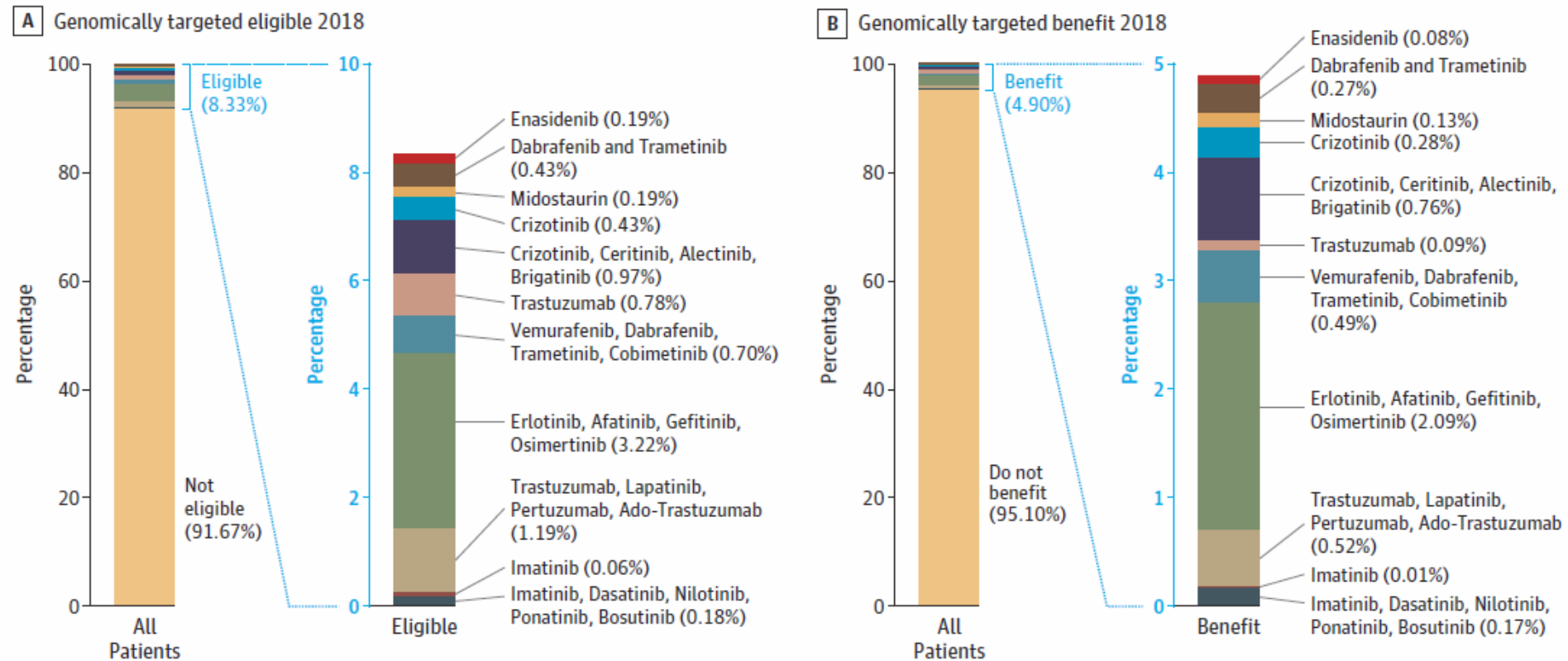


Data in the figure were obtained from 3 separate publications
 1 <https://opendata.cbs.nl/statline/#/CBS/en/> (central bureau of statistics, Dutch life expectancy per year and chance of dying within one year in the Dutch population 2015)
 2 Kankerzorg in beeld- de oudere patient, chapter darmkanker by van Erning FN, Lemmens VEPP, Dekker JWT, Maas Haam, Rutten, HJT, pages 101-116, 2016 published by IKNL the Dutch Cancer Registry
 3 Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol. 2008 May;9(5):494-501

Fig. 3. The Impact of Rectal Cancer Surgery on Life Expectancy in Elderly Patients. The graph demonstrates life expectancy in the elderly, which is generally higher, at a given age, than previously believed. Using historical data, total mesorectal excision was associated with an increased mortality and was, therefore, not advised. Modern surgical data suggest that elderly patients undergoing surgery today have a similar life expectancy to their peers without rectal cancer. Therefore, in properly selected patients, rectal cancer surgery is advised.

Estimation of the Percentage of US Patients With Cancer Who Benefit From Genome-Driven Oncology

Figure 1. Estimated US Patient Eligibility and Benefit From Genomically Targeted Benefit, 2018



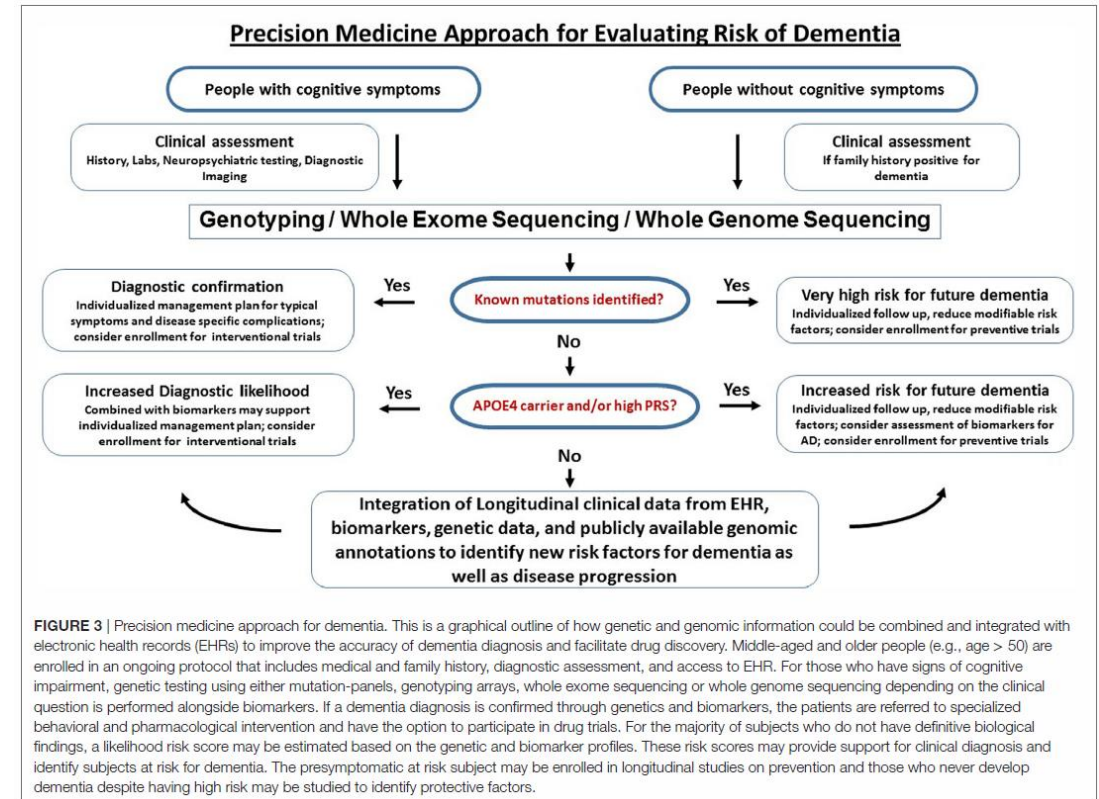
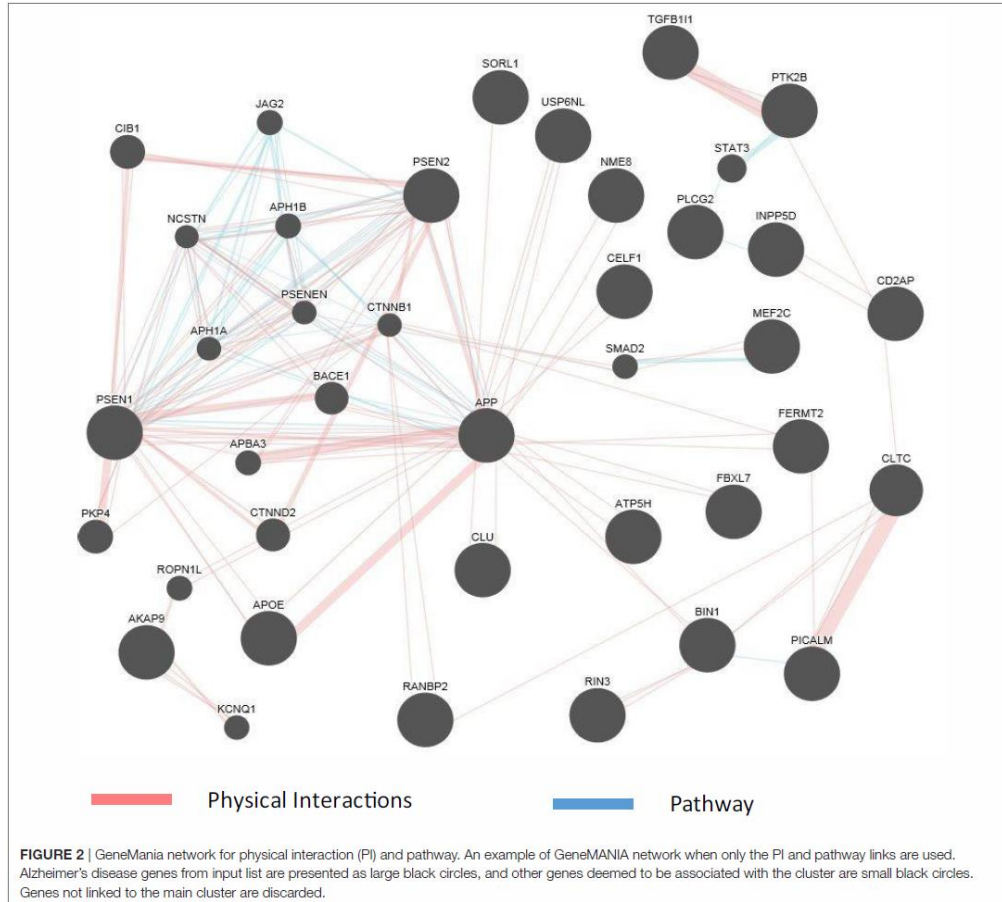
CONCLUSIONS AND RELEVANCE Although the number of patients eligible for genome-driven treatment has increased over time, these drugs have helped a minority of patients with advanced cancer. To accelerate progress in precision oncology, novel trial designs of genomic therapies should be developed, and broad portfolios of drug development, including immunotherapeutic and cytotoxic approaches, should be pursued.

The Role of Genetics in Advancing Precision Medicine for Alzheimer's Disease—A Narrative Review

Yun Freudenberg-Hua^{1,2*}, Wentian Li³ and Peter Davies¹

frontiers
in Medicine

REVIEW
published: 24 April 2018
doi: 10.3389/fmed.2018.00108



Systems Biology and P4 Medicine: Past, Present, and Future

Leroy Hood, M.D., Ph.D.*

President, Institute for Systems Biology, Seattle, WA, USA

- **Personalizzata:** Utilizzo di informazioni cliniche, genetiche, proteomiche, e ambientali di ogni individuo, per la diagnosi e la cura del paziente
- **Predittiva:** Utilizzo di strumenti diagnostici molecolari per predire con precisione i fattori di rischio individuali per lo sviluppo delle malattie e la risposta agli interventi terapeutici
- **Preventiva:** Utilizzo delle conoscenze del rischio per sviluppare piani di prevenzione primaria e secondaria personalizzati.
- **Partecipativa:** Coinvolgimento attivo e consapevole del paziente alla propria prevenzione e cura, con conseguente miglioramento della compliance.

P4 medicine stems from three main trends:

- 1) systems biology and system medicine providing means to unravel the complexity of diseases,
- 2) new capabilities in collecting and analyzing digitalized health data and
- 3) consumers increasing interest in managing their own health.

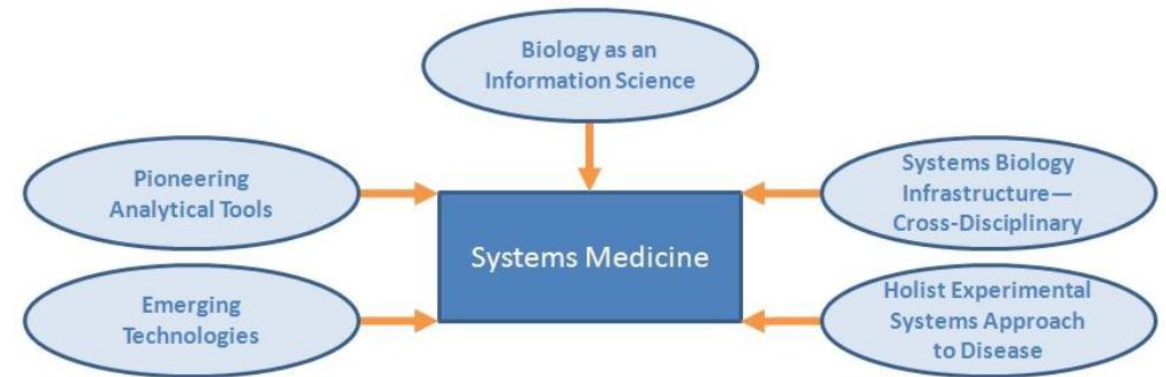


Figure 2. The elements that will allow systems medicine to tackle deciphering biological complexity.

These represent the strategies, technologies, and analytical tools that will enable the implementation of systems biology and P4 medicine.

Systems Biology and P4 Medicine: Past, Present, and Future

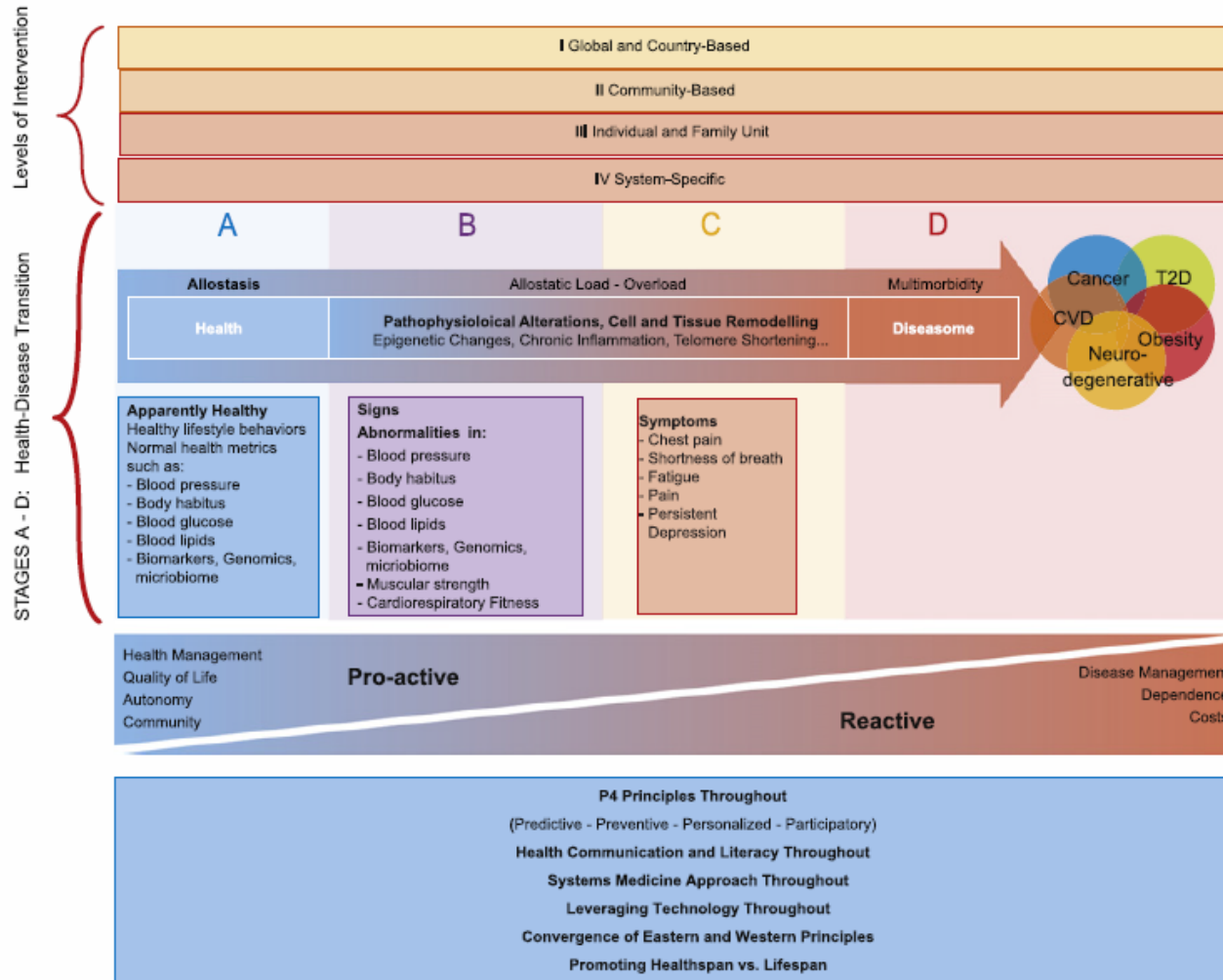
Leroy Hood, M.D., Ph.D.*

President, Institute for Systems Biology, Seattle, WA, USA

Table 1. A comparison between evidence-based medicine and P4 medicine.

Reactive Medicine—Evidence-Based Medicine	Proactive P4 Medicine
Reactive—respond after a patient is sick (symptoms-based)	Proactive—responds before a patient is sick (based on pre-symptomatic markers)
Disease treatment system	Wellness maintenance system
Few measurements	Many measurements, including complete genome sequencing, high-parameter blood diagnostics, many longitudinal omics measurements
Disease-centric, with standard of care associated with population-based disease diagnosis	Individual-centric, with standard of care tailored more fully to multiple measurements on the individual
Records not highly linked nor data integrated	Deeply integrated data that can be mined for continued improvement of health care strategies
Large-scale diffusion of medical information mediated mostly through physicians alone	Social networking of patients to enhanced shared experiences and diffusion of knowledge in consultation with their physicians
Drugs tested against large populations—tens of thousands to develop statistics for FDA	Stratification of disease populations into small groups, 50 or so, that can be effectively treated to achieve FDA approval

The P4H continuum model



P4H Continuum Stakeholders

- Educational systems
- Employers
- Food industry
- Government - Policy Makers
- Health and fitness industry
- Health care organizations and professionals
- Individual and families - People
- Insurance industry and Payers
- Media outlets
- Mobile health and technology companies
- Nonprofit and community organizations
- Professional organizations

Table 2 – The five pillars of P4 medicine.

Pillar 1

- Cutting-edge technologies for generating data regarding multiple dimensions of each person's experience of health and disease.

Pillar 2

- A digital infrastructure linking participating discovery science and clinical institutions, as well as patients/consumers.

Pillar 3

- Personalized data clouds providing information about multiple dimensions of each individual's unique dynamic experience of health and disease ranging from the molecular to the social. These data will include genetic and phenotypic characteristics, medical history, demographics and other sociometrics.

Pillar 4

- New analytic techniques and technologies from deriving actionable knowledge from the data.

Pillar 5

- Systems biology models for understanding the unique health status of each individual in terms of dynamic network states that can be manipulated by cost-effective strategies

The future of precision medicine

Enabling proactive and precise treatments

Sample Use Cases



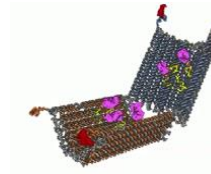
Preventive Measures

Human Longevity Inc. – building the world's most comprehensive database on human genotypes, integrating advanced gene sequencing, digital imaging and innovative machine learning along with personal care information to detect early signals of major diseases in their earlier stages



New Research / Treatment Methods

LiverChip – Dynamic 3-D cell culture platform can exactly mimic the architecture and physiology of the human liver



Increased Precision

Wyss Institute – Harvard scientists built a nano-robot from designer DNA to deliver drug dosages to specific cell types

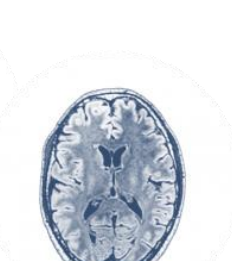
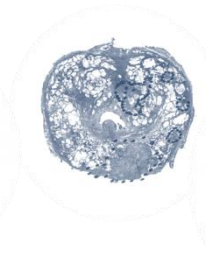
Modificato da: Rajeev Ronanki, Cognitive Computing and Healthcare Innovation Leader, Deloitte Consulting LLP, June 9, 2016



WHOLE GENOME SEQUENCING: Clinical, Disease, Personal, Physical Insights



MAGNETIC RESONANCE IMAGING (MRI): screening for risk factors and early signals of the most critical diseases



The future of precision medicine and Ethics

Trends in Pharmacological Sciences

Implementing Precision Medicine: The Ethical Challenges

Diane M. Korngiebel,¹ Kenneth E. Thummel,² and Wylie Burke^{3,*}

Trends in Pharmacological Sciences, January 2017, Vol. 38, No. 1 <http://dx.doi.org/10.1016/j.tips.2016.11.007>
© 2016 Elsevier Ltd. All rights reserved.

- The concept of precision medicine, defined as the use of genomics, lifestyle, and environmental data to individualize healthcare, offers an unprecedented opportunity to improve clinical care
- Before this approach can be implemented however, evidence is needed to establish the **benefit and the potential risks of specific intervention**, and strategies must be developed to ensure effective **uptake in healthcare settings**
- The steps taken to accomplish these goals involve choices with **ethical implications**

The ethical keywords for precision medicine

Acta Med Iran 2017;55(3):209-217. REVIEW ARTICLE

Ethical Issues Surrounding Personalized Medicine: A Literature Review

Pooneh Salari¹ and Bagher Larijani²

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS OF PERSONALIZED GENOMIC MEDICINE RESEARCH: CURRENT LITERATURE AND SUGGESTIONS FOR THE FUTURE

SHAWNEEQUA L. CALLIER, RACHEL ABUDU, MAXWELL J. MEHLMAN, MENDEL E. SINGER, DUNCAN NEUHAUSER, CHARLISSE CAGA-ANAN AND GEORGIA L. WIESNER

Bioethics ISSN 0269-9702 (print); 1467-8519 (online)
Volume 30 Number 9 2016 pp 698-705

Ethical, legal and social implications of incorporating personalized medicine into healthcare

Personalized
Medicine



Kyle B Brothers^{*,1,2,3}
& Mark A Rothstein^{3,4}

Per. Med. (2015) 12(1), 43-51

ELSI

Potential risks	Positive aspects	Ethical considerations
High cost	Improving quality of healthcare	Increase personal responsibility
Inequality in health care	(accessibility, effectiveness, affordability, public trust)	Individual vs. societal rights in access to information
Violation of privacy		Informed consent
Discrimination		Incidental findings
Negative effect on physician-patient relationship	Fair subject selection	Genetic counseling
Stigmatization		
Exploitation		

Patient-Centered (P4) Medicine and the Older Person

John E. Morley MB, BCh ^{a,*}, Bruno Vellas MD ^b

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Although this original concept was based on the molecular basis of the complexity of diseases (genomic, metabolomics, transcriptomic, and proteomic) and their environmental interactions, it has been enlarged to focus on the clinical characteristics and lifestyle of the individual as well as the availability of disruptive technological advances. Personalized medicine not only allows individuals and their physicians to have a focused approach to their health but also improves efficiency and effectiveness of health care organizations and provides guidelines for national health care systems to develop cost-effective population outcomes.² In many ways, geriatric medicine has been at the forefront of patient-centered medicines by moving away from disease-focused medicine and placing the focus on patient-centered medicine.³ This editorial will focus on some disease-specific

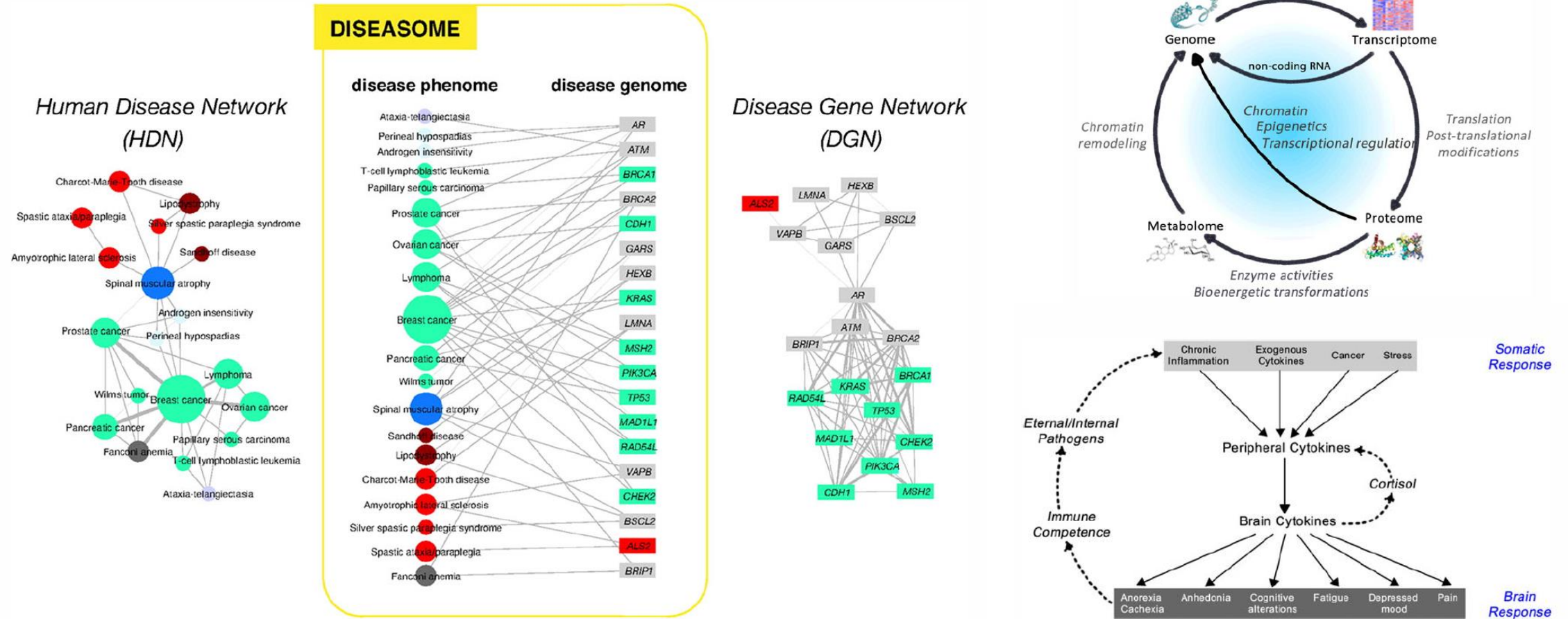
esterase inhibitor trial could be instituted.³⁰ Recognizing that some of these approaches are experimental, all data are put into a mega database to allow recognition of the effectiveness of these approaches.

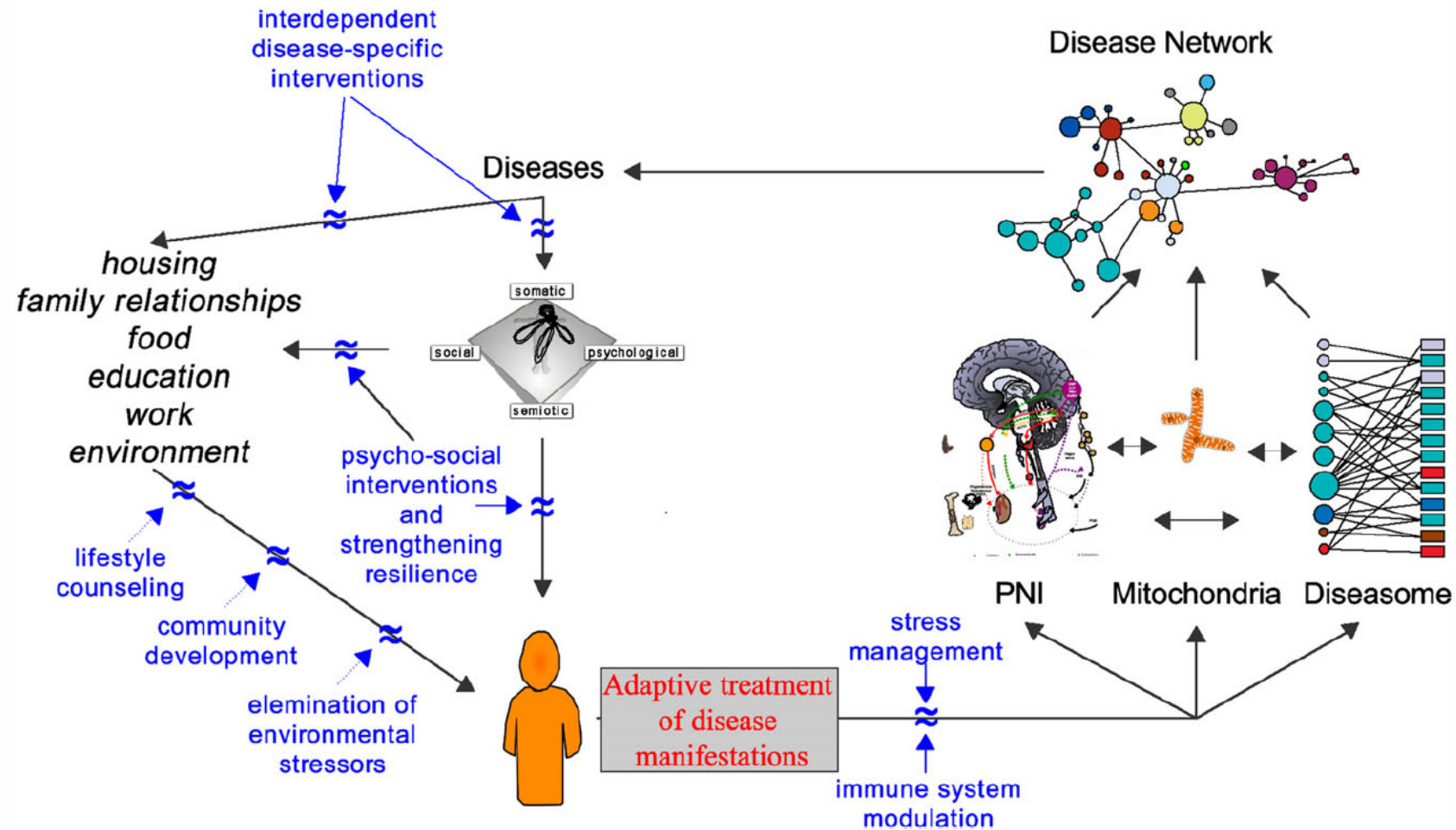
skilled nursing facility.⁹² In the future, we can expect to see more focus on genomics and proteomics in dementia, as pointed out in this article, and in the nutriomic area for nutrition and sarcopenia.^{93,94} An area in which P4 approaches will be essential to have successful outcomes will be in life extension.⁹⁵ Unfortunately, at present, experts in this area are looking at large, nontargeted trials.⁹⁶ It is essential that antiaging approaches are targeted, for example, at the clinical level using metformin for persons with prediabetes where metformin reduces cognitive dysfunction and possibly sarcopenia.^{63,97,98} However, more importantly, antiaging strategies need to be based on treating specific genomic and proteomic profiles.

Middle Age	65+ Years Screening	Positive for Dementia
<ul style="list-style-type: none"> i. Family history of dementia ii. Consider genetic screening (Apo E4, etc) iii. High risk of cardiovascular disease (statin, control blood pressure) iv. Diabetes/Prediabetes (metformin) v. General prevention (Mediterranean diet, extra virgin olive oil, exercise, brain activity exercises) vi. Actively monitor and treat persons with total brain injury (consider measuring CSF GSK-beta and tau) vii. Discuss risks (if any) with patient. Use epidemiological statistics. 	<p>Screen for MCI yearly with MOCA, SLUMS or RCS.</p> <p>If positive:</p> <ul style="list-style-type: none"> i. Check hearing and vision ii. Check treatable causes, e.g., Drugs Depression Metabolic causes Normal pressure hydrocephalus Neurological conditions Infections Sleep apnea Atrial Fibrillation iii. Advise general prevention at middle age iv. Prediabetes → metformin v. Check anticholinergic load → decrease medications and consider cholinesterase inhibitors vi. Advise patient to develop advance directive vii. Check for markers of increased inflammation and consider alpha-lipoic acid if elevated viii. Discuss findings with patient and risks based on epidemiology and genetics 	<ul style="list-style-type: none"> i. Manage hearing and visual deficits and treatable causes ii. Are there symptoms of Lewy Body → SPECT for dopamine receptors? iii. Symptoms, e.g., essential tremor (Fragile X) suggestive of rare dementia → genetic testing iv. MRI or CT for evidence (leukoariosis) of vascular dementia. If so, treat with extra virgin olive oil and alpha lipoic acid. Treat vascular risk factors. Low dose aspirin v. PET scanning: a. glucose b. amyloid-beta c. tau vi. Consider genetic screening and CSF amyloid-beta and tau vii. High anticholinergic burden with early Alzheimers → donepezil trial (3 to 12 months) viii. Consider antisense to APP when available ix. Diabetes → metformin x. Check inflammatory load and consider alpha-lipoic acid xi. Moderate dementia → cognitive stimulation therapy xii. Discuss disease, treatment benefits, costs, advance directive, driving, removing guns, incontinence, caregiver stress

'Multimorbidity' as the manifestation of network disturbances

Joachim P. Sturmberg MD PhD,¹ Jeanette M. Bennett PhD,² Carmel M. Martin MD PhD³ and Martin Picard PhD⁴





... should form the basis for designing much more comprehensive and sophisticated biomedical, social and environmental interventions for people affected by «multimorbidity»

... The rapid developments in ‘multimorbidity’ ‘omics’ technologies aim to provide sensitive assays to quantify people’s personalized health status reflecting whole person immune and bioenergetics states far more sensitively and specifically than currently available biomarkers of specific diseases

Journal of Evaluation in Clinical Practice **23** (2017)

Breaking news from the JAMA

Published online September 17, 2018

SCIENTIFIC DISCOVERY AND THE FUTURE OF MEDICINE

Aging as a Biological Target for Prevention and Therapy

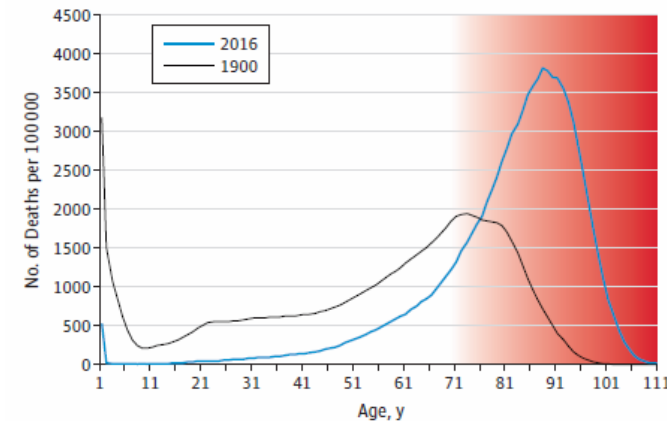
SCIENTIFIC DISCOVERY AND THE FUTURE OF MEDICINE

Aging, Cell Senescence, and Chronic Disease Emerging Therapeutic Strategies

SCIENTIFIC DISCOVERY AND THE FUTURE OF MEDICINE

From Lifespan to Healthspan

Figure. Age Distribution of Life Table Deaths for Women in the United States, per 100 000 People, 1900 and 2016



The red zone represents a period in life when the risk of frailty and disability begins to increase rapidly. The goal of aging science is to delay and compress the red zone, which may extend healthy life. Sources: 1900 data from Bell and Miller¹; 2016 data from Human Mortality Database.²

Precision medicine to precision care: managing multimorbidity

... much attention has been paid to the promise of precision medicine, a term usually used to describe the approach for disease treatment and prevention that takes into account individual variability in their genes, environment and lifestyle.

In the context of multimorbidity, however, precision medicine entails carefully considering the applicability of each recommendation to an individual's profile of conditions, health and functional status, goals and preferences.

... will require changes in clinical practice, medical education, performance and quality measurement, research and policy.

Geriatricians: The Super Specialists

John E. Morley, MB, BCh

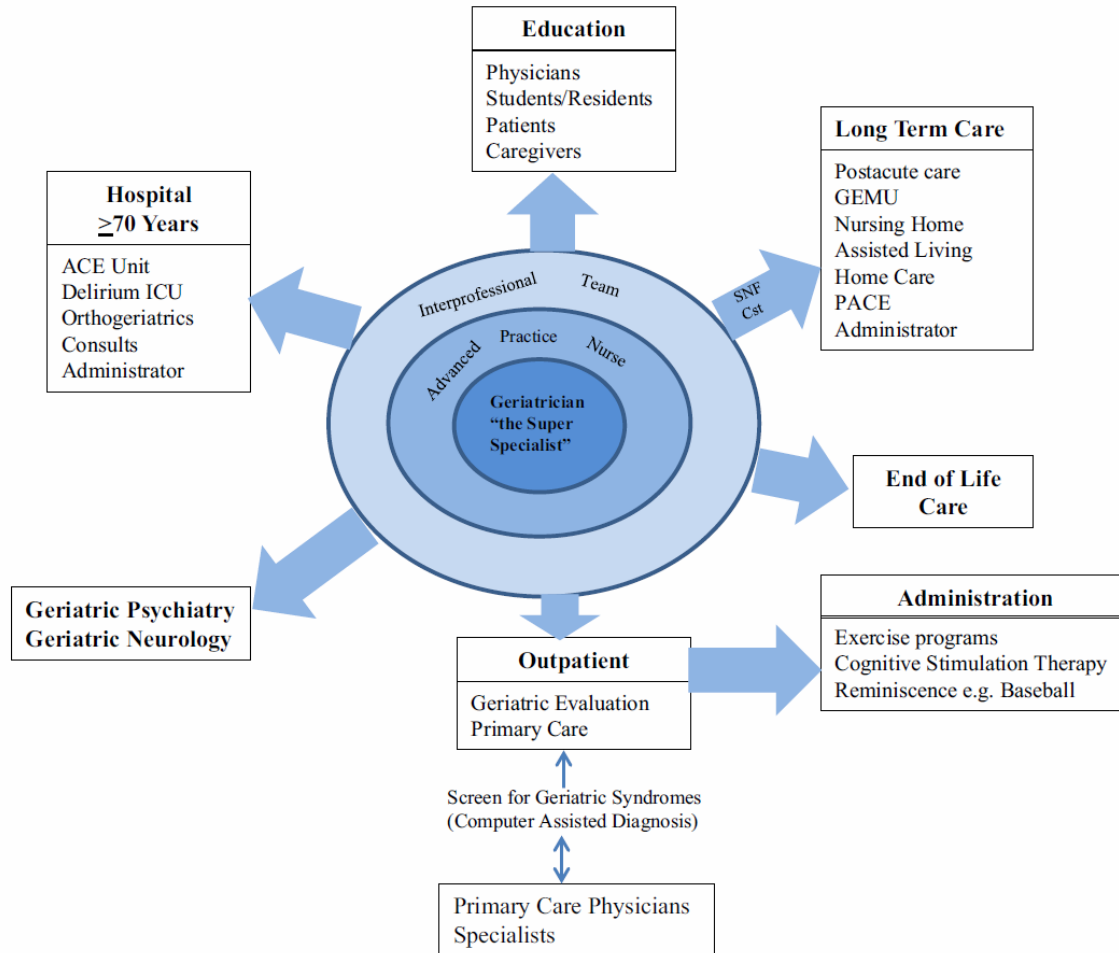


Table 1. The Modern Giants of Geriatrics

1. Frailty
2. Sarcopenia
3. Anorexia of aging
4. Mild cognitive impairment
5. Delirium
6. Falls
7. Depression
8. Dementia
9. Polypharmacy
10. Fatigue

JAGS 65:866–868, 2017
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The 2025 Big “G” Geriatrician: Defining Job Roles to Guide Fellowship Training

Deborah Simpson, PhD,[†] Rosanne M. Leipzig, MD, PhD,[‡] Karen Sauvigné, MA,[‡] and Donald W. Reynolds Geriatrics Education Collaborative*

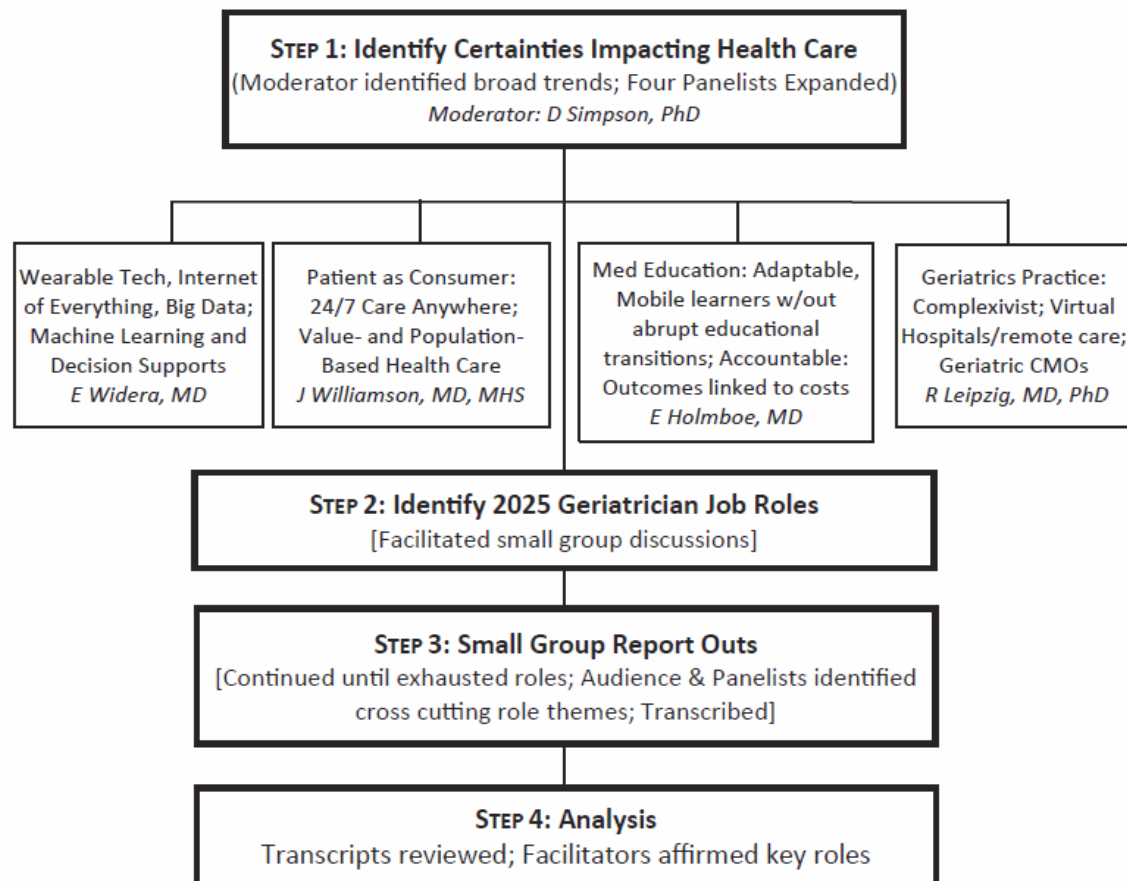


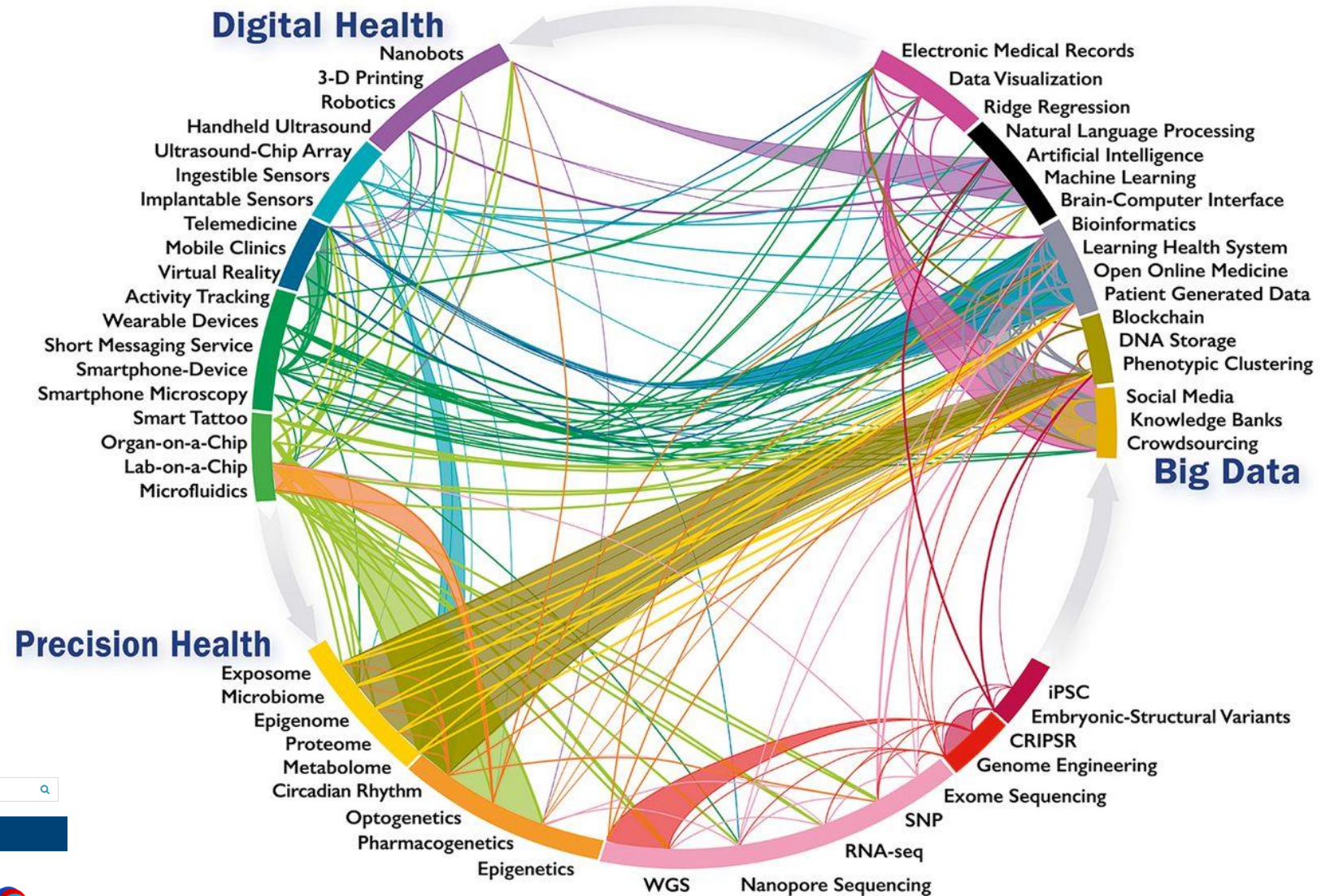
Table 1. 2025 Geriatrician job roles for geriatric patients/populations through direct patient care and/or system level roles

2025 Geriatrician Job Roles	Description	Direct Patient Care	System Roles
Complexivist	Adaptable, continuous learners who optimally apply latest discoveries, analytics, and tools to inform care of medically complex individuals with emphasis on function, patient values, care preferences	✓	✓
Consultant	Support primary and specialist clinical care (little “g”) for older adults using dashboard analytics, prognostic and diagnostic tools, and skillful communication to optimize patient health and function.	✓	✓
Health system leader and innovator	Lead interprofessional teams caring for geriatric populations; lead hospitals and systems; serve as medical director for large population-based health systems; partner in design of clinical and home environments, new technologies, and care models		✓
Functional preventionist	Use data and prognostics to create preventive care models and plans for older and complex populations and monitor performance with clear metrics		✓
Educator for big “G” and little “g” providers	Design medical education curriculum to ensure that all geriatrics principles are core elements in care provided; coach clinicians with subpar geriatrics quality metrics; prepare adaptable learners	✓	✓

Open issues in geriatric care?

- Che cosa è proprio della cultura geriatrica
- Siamo scettici rispetto all'innovazione tecnologica?
- Medicina personalizzata vs epidemiologia clinica

Le innovazioni emergenti e le loro interconnessioni



The Italian IRCCS Network on Aging roadmap

