ASU Complex Adaptive Systems Initiative
Arizona State University

From Prediction to Prevention
The Annual Burrill Personalized Medicine Meeting

Burrill & Company
Life Sciences: Venture Capital, Private Equity, Merchant Banking, Media

Health Technology Acceleration and Convergence: Implications for Personalized Medicine

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Keynote Address at 5th Annual Burrill Personalized Medicine Meeting
San Francisco, CA, 9 November 2009

Reasonable Expectations for Rational Healthcare

- what works
- why it works
- who it works for
- what works best
- when should it be used optimally

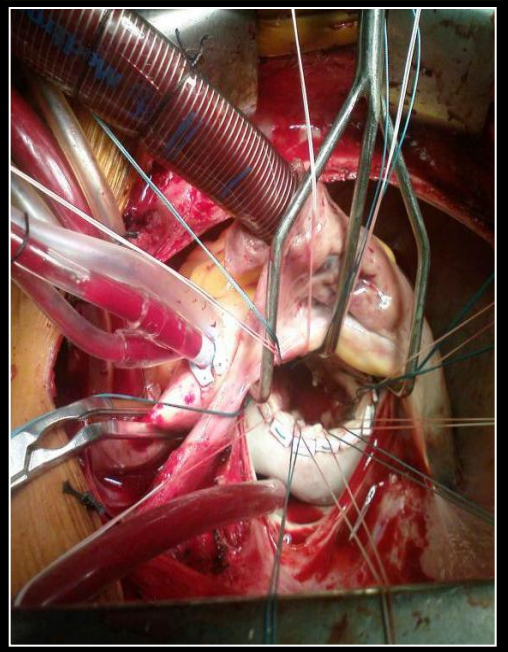
- validated evidence
- mechanism of action
- personalized medicine
- comparative effectiveness
- best practice guidelines, standard-of-care and malpractice

VALUE

Reforming health care
This is going to hurt

AFFORDABLE HEALTH CARE
FOR AMERICA ACT

Major Challenges in Healthcare

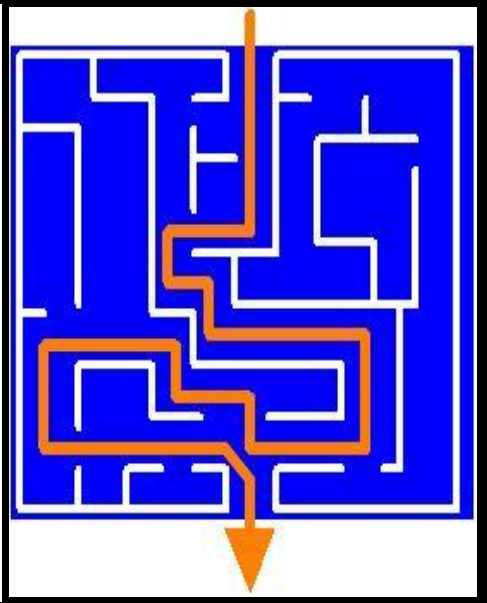
Cost	Demographics	Access	Variation in Clinical Practice
			

Major Challenges in Healthcare

Inefficient Use of Information

Fragmented Care Versus Integrated Care

Duplication, Defensive Medicine & Waste



Protracted Adoption of Innovation

New Value Propositions in Healthcare

- social and economic value of reducing disease burden will rise
  - earlier disease detection and mitigation
  - rational Rx and guaranteed outcomes
  - integrated care management of complex chronic diseases
  - extension of working life
- progressive shift from ‘reactive’ medicine to ‘proactive’ care and ‘integrated’ delivery
  - prospering in an era of increasing constraints
  - managing the limit(s) of society’s willingness and ability to pay for innovation

Dominant Themes in Biomedical R&D

- technology acceleration
- technology convergence
- new cross-disciplinary, cross sector partnerships
- data standards
- data volume
- data diversity and integration
- information infrastructure

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scale **complexity** **networks**

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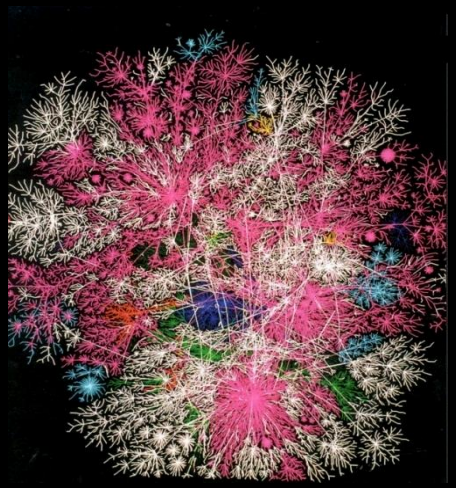
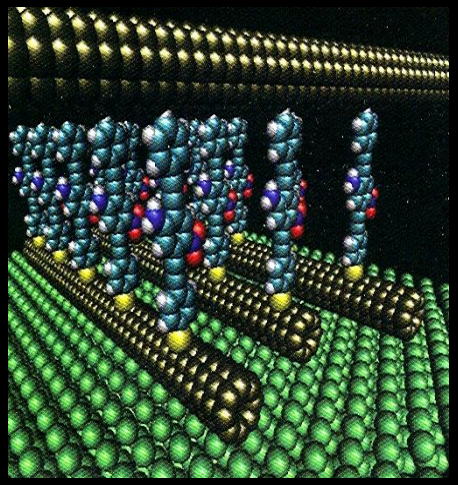
scale **complexity** **networks**

The Strategic Triad:
- **diagnostics (Dx), therapeutics (Rx) and informatics (Ix)**

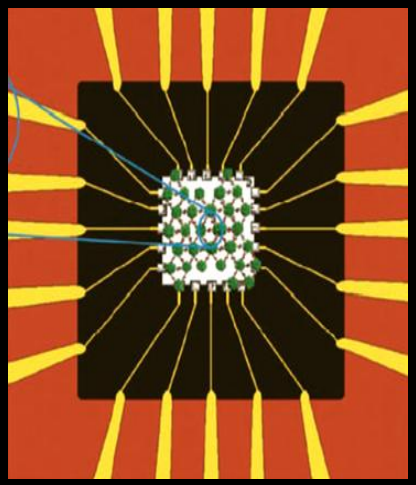
Technology Convergence



Biotechnology,
Systems Biology and
Synthetic Biology



Nanotechnology
Materials Science
and
Miniaturization
Engineering

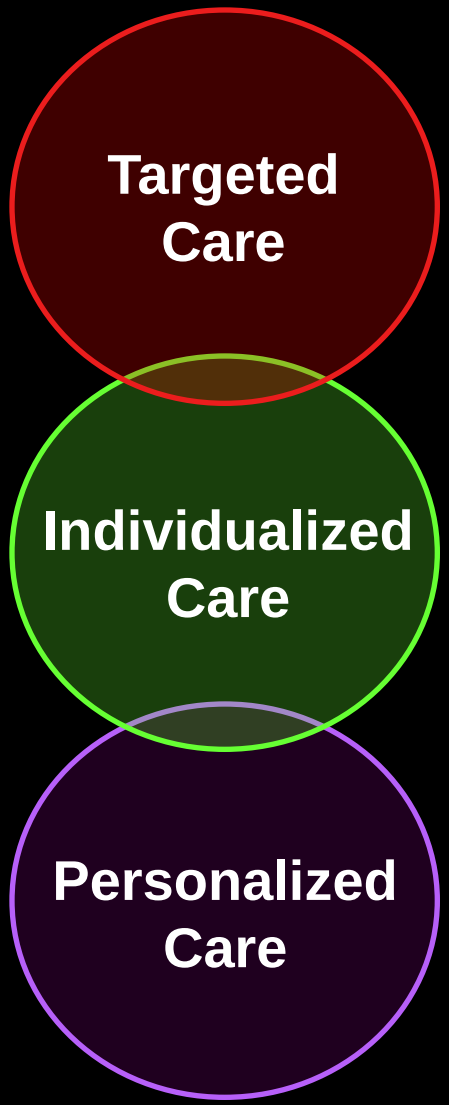


Advanced
Computing
and
Knowledge
Management

• technologies with radical, pervasive and enduring impact

Integration of Dx, Rx and HIx

Personalized Medicine: Progressive Evolution Based on Increasingly Comprehensive Profiling of Disease Risk and Health Status

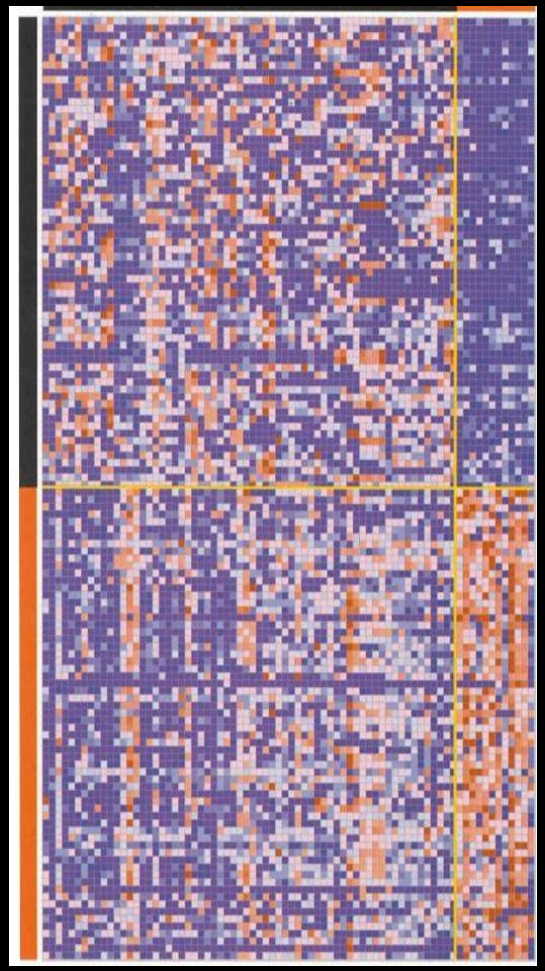


- rational Rx based on profiling of underlying molecular pathology
- MDx and disease subtyping

- rational Rx based on comprehensive molecular profiling of individuals
  - disease subtypes and optimum Rx
  - Rx AE risk
  - disease predisposition risk and mitigation

- integrated framework of care and longitudinal data on individual health status
- real time remote health status monitoring
- transition to disease prediction and preemption

Personalized medicine: Key Drivers



May 2008

Realizing the Potential of Pharmacogenomics: Opportunities and Challenges

Report of the
Secretary's Advisory Committee on Genetics, Health, and Society

President's Council of Advisors on Science and Technology
Executive Office of the President

AVASTIN (bevacizumab)

Rituxan Rituximab

Tarceva erlotinib tablets

gleevec (imatinib mesylate) tablets

ERBITUX CETUXIMAB INJECTION

Tykerb (lapatinib)

Nexavar (sorafenib) tablets

Herceptin trastuzumab

Revlimid (lenalidomide) capsules

SUTENT capsules

Science **Policy** **Cost and Outcomes**

K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy

Vectibix (panitumumab) AMGEN

ERBITUX CETUXIMAB ImClone Systems Incorporated

NCCN

ASCO

clinical guidelines

- higher response in patients with K-RAS versus mutant-K-RAS
- estimated $604 million/year savings (ASCO)

European Medicines Agency emea

FDA

- regulatory endorsement in product labeling

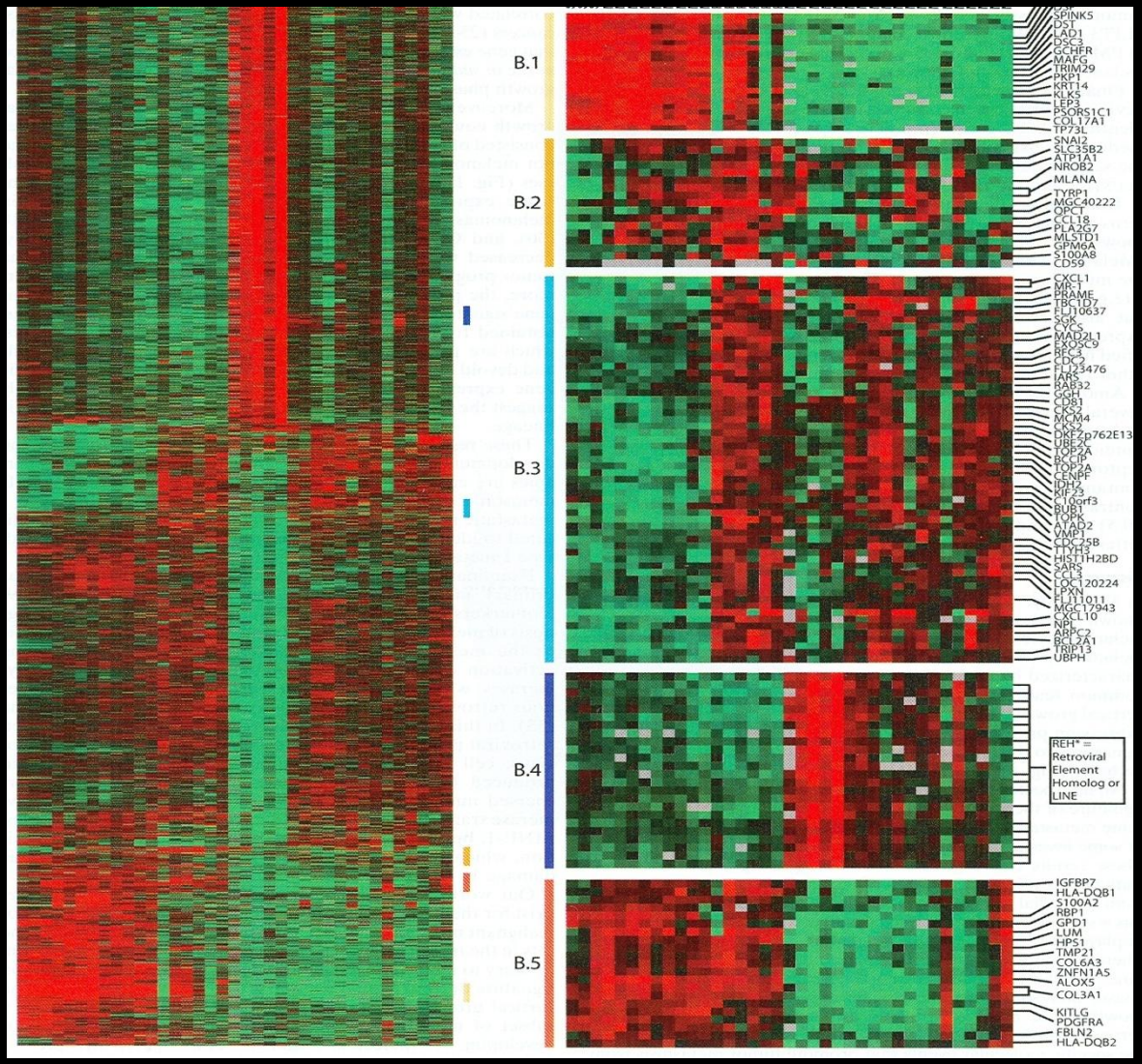
CMS

BlueCross BlueShield

UnitedHealthcare Healing health care. Together.

- payor adoption

Disease Subtyping: Next-Generation Molecular Diagnostics (MDx) And a New Molecular Taxonomy of Disease

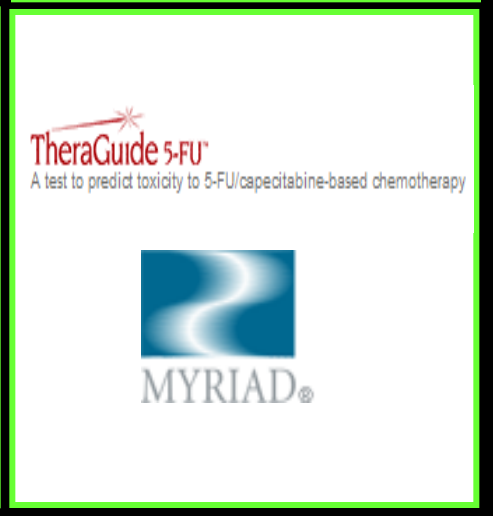


Dx Platforms

- massive parallelism
- miniaturization
- automation
- rapid
- POC

RIGHT Rx for RIGHT DISEASE SUBTYPE

The Emergence of Drug: Diagnostic Combinations



Molecular Medicine and Rational Therapeutics: Targeted Rx and Rise of Molecular Diagnostics and Patient Profiling

- opening era in linking disease molecular pathology to rational Rx
- increasing payor, regulatory and public pressures for reliable ID of Rx-responsive patients
- demand for Dx-Rx combinations will intensify
- Dx-Rx combination will become an obligate element of NDA/BLA submission and product labeling
- development of Dx-Rx combinations as intrinsic components of R&D programs for investigational Rx

Outcomes-Based Risk-Sharing Agreements (OBRAs)

UK: National Health Service

- full or partial refund for non-responders

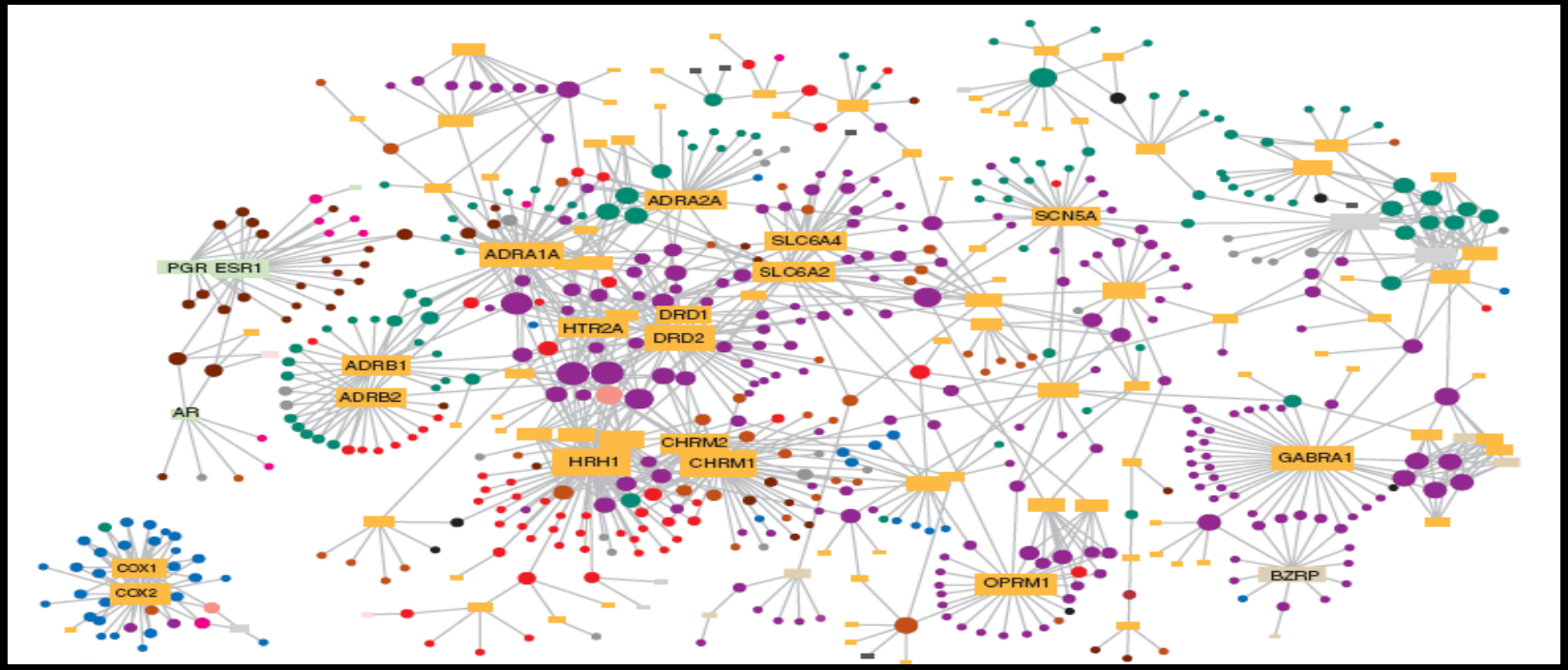
- four Rx cycles
- 50% reduction in serum M protein
- NHS continues to fund
- <50% response company refunds cost of Rx

Outcomes-Based Risk-Sharing Agreements (ORBAs) Come to the USA

- reimburse average treatment cost (not just Rx) for fractures incurred after 6 months therapy
- improved Hb1Ac levels in diabetics over one year increases Rx discount to Cigna

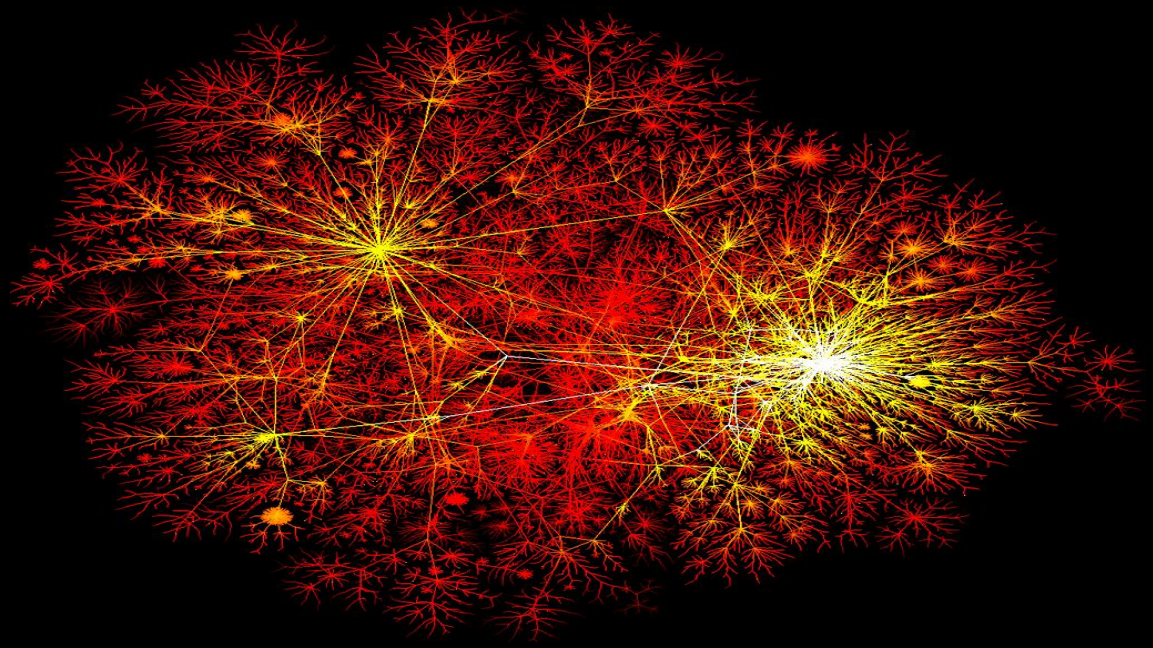
The Conceptual Foundations of Drug Discovery

- from empiricism to rational therapeutics
- from ambiguity to predictability
  - mechanism(s) of action
  - clinical efficacy and safety
  - healthcare outcomes and value

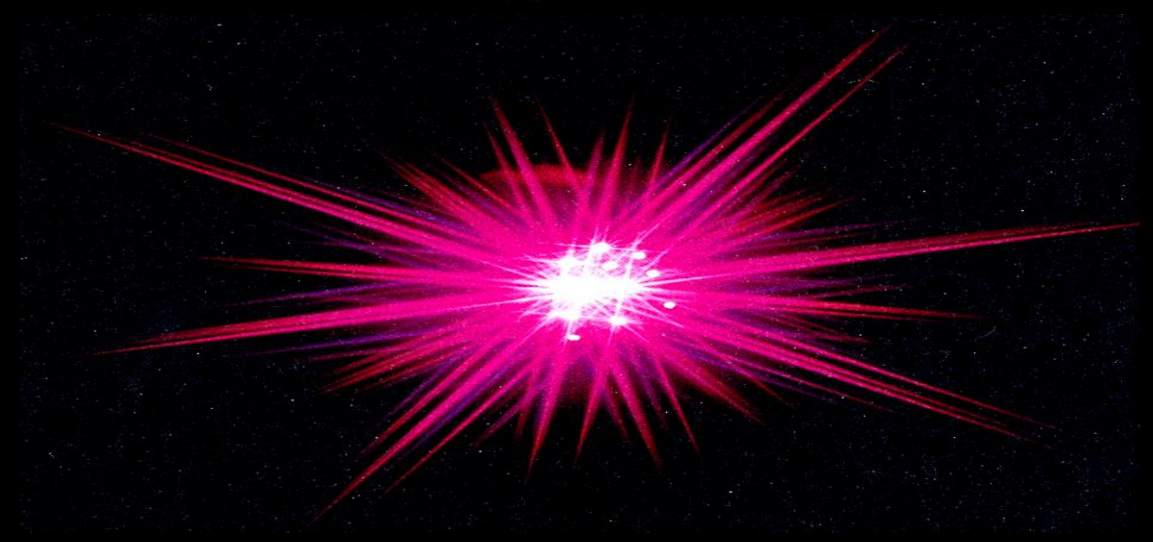


Drug-Target Networks for FDA Approved Rx

Molecular Pathways and Network Analysis: Systems Pharmacology



Deconvolution of Signaling Networks in Disease

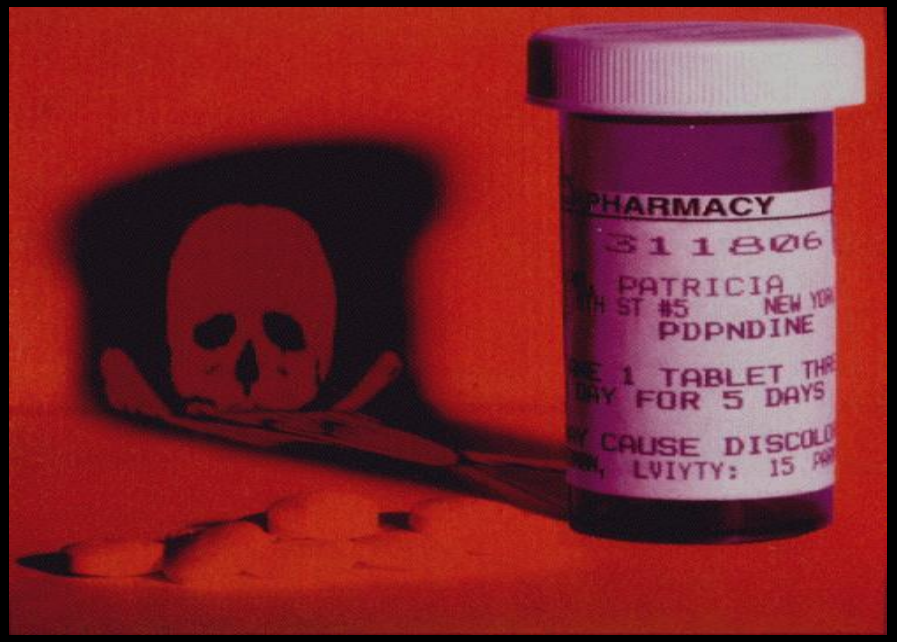


Identification of ‘Fragile’ Nodes/Pathways for Targeted Rx

Molecular Pathways Network Analysis and Systems Pharmacology

- ‘connectivity’ maps
  - correlations between genomic signatures and sets of proteins involved in Rx action
- Rx ‘promiscuity’
  - spectrum of ‘target’ effects required for optimum efficacy
- Rx ‘pleiotropy’
  - undesirable off-target effects and adverse event risk
- ‘synthetic lethal’ screening
  - ID new Rx oncology targets in co-dependent genes required for cell survival
- ‘minimum knockout’ modeling
  - ID/predict smallest number of drug targets to fully block a cellular process

Pharmacogenetic Predisposition to Adverse Drug Reactions



- 1.5 to 3 million annual hospitalizations (US)
- 80 to 140 thousand annual deaths (US)
- est. cost of $30-50 billion

Alert
7/24/08

- update labeling for Abacavir (Ziagen) to require pre-therapy screening for HLA-B*5701 allele to avoid fatal hypersensitivity

Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

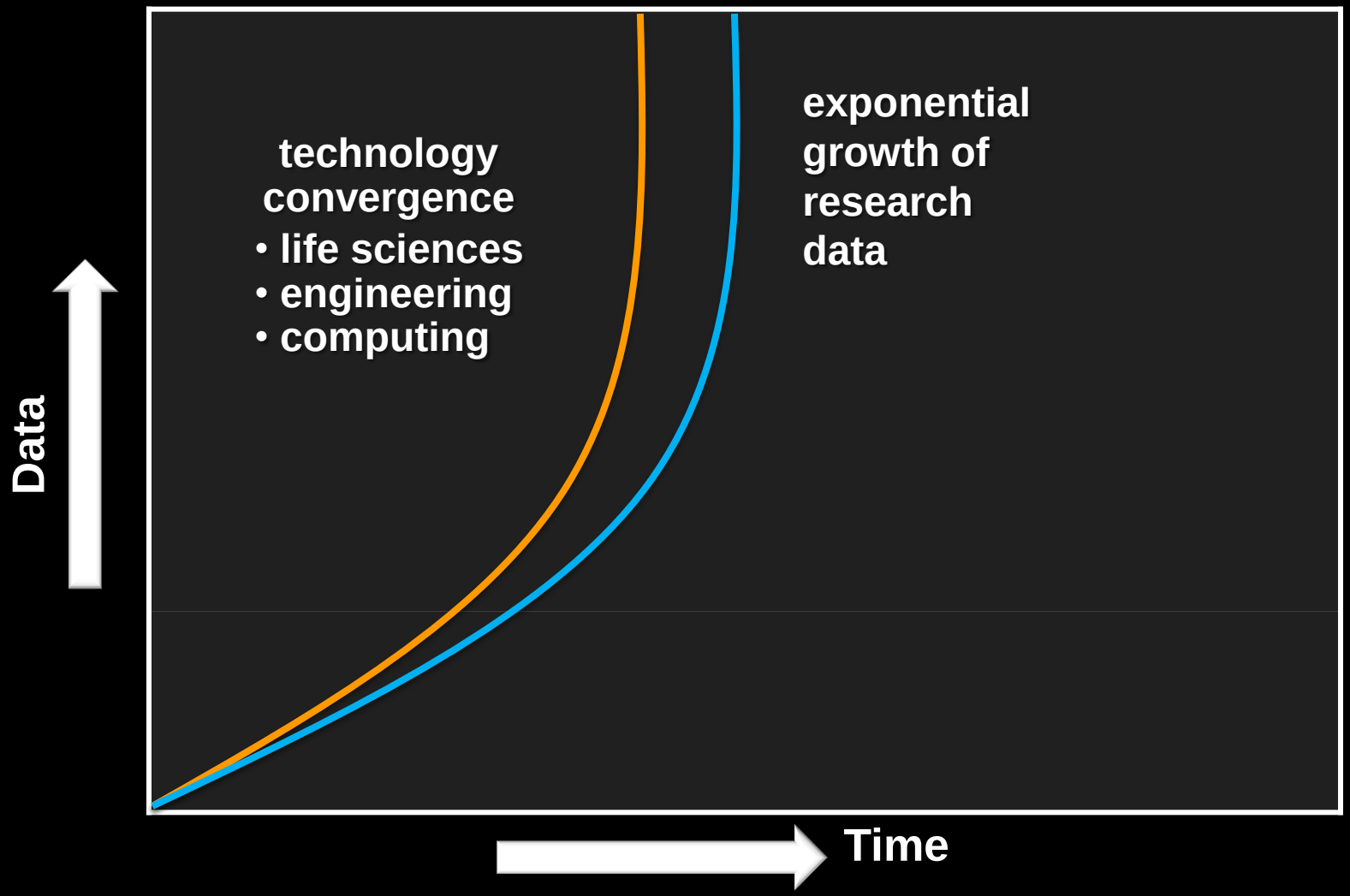
Molecular Diagnostics and Pharmacogenetic Profiling to Identify Individuals at Risk for Rx Adverse Events

- broader, more complex profiling platforms than MDx assays for ID of drug targets
- ID of slow metabolizer genotypes
- unknown effects of genetic and environmental confounders in AD(M)E beyond genetic variation in drug-metabolism (I-III) repertoire
- complex patterns of ethnic variation and haplotype associations impose continuum of metabolic phenotypes

The Human Microbiome: A Barely Understood Influence in health

- complex meta-system
  - host, microbes, viruses, other organisms, metabolites, xenobiotics
  - is there a core microbiome?
  - how do perturbations affect disease and vice-versa?
  - does the microbiome influence xenobiotic metabolism and the metabolite spectrum?

The Trajectories for Molecular Medicine



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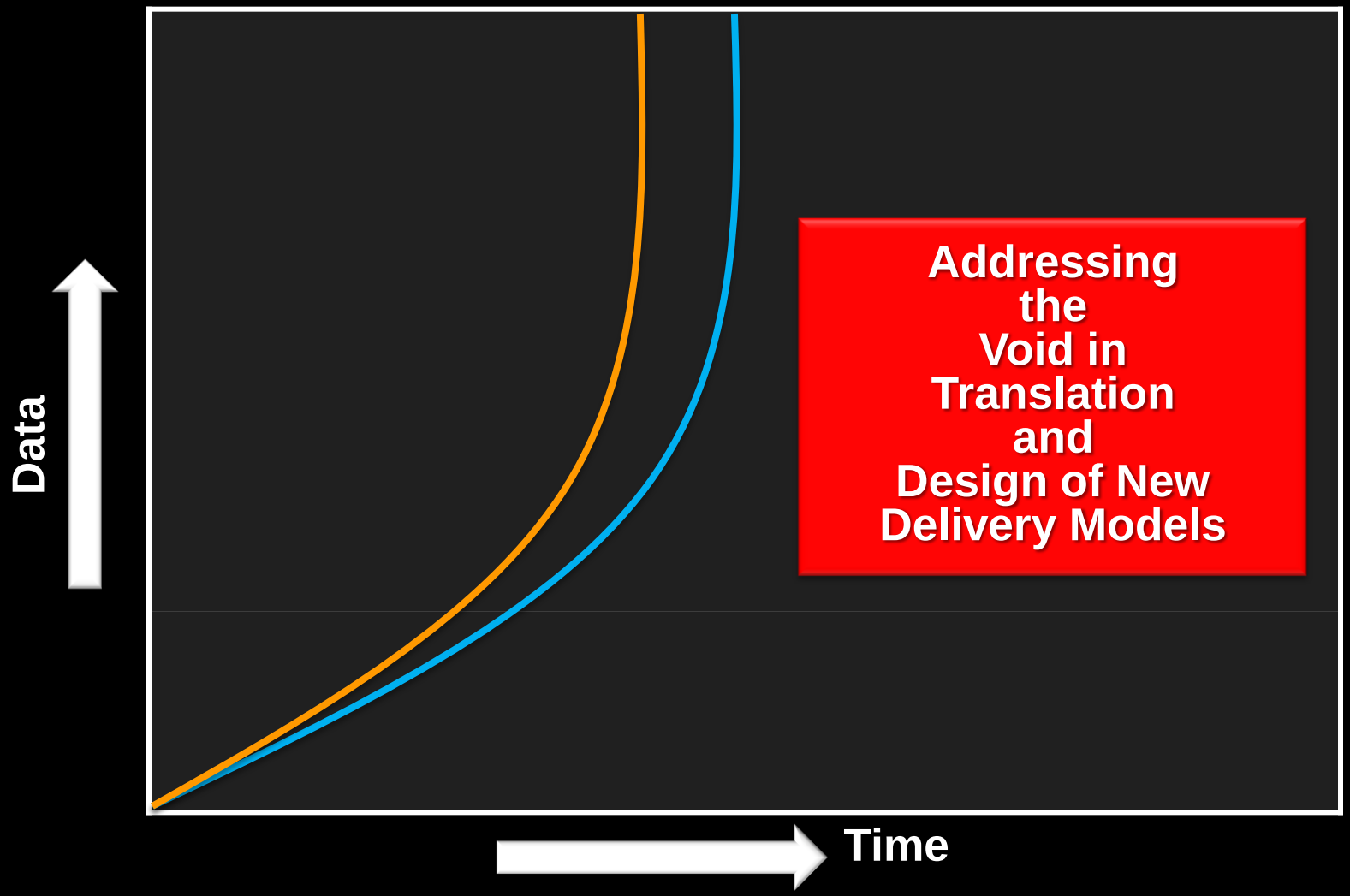

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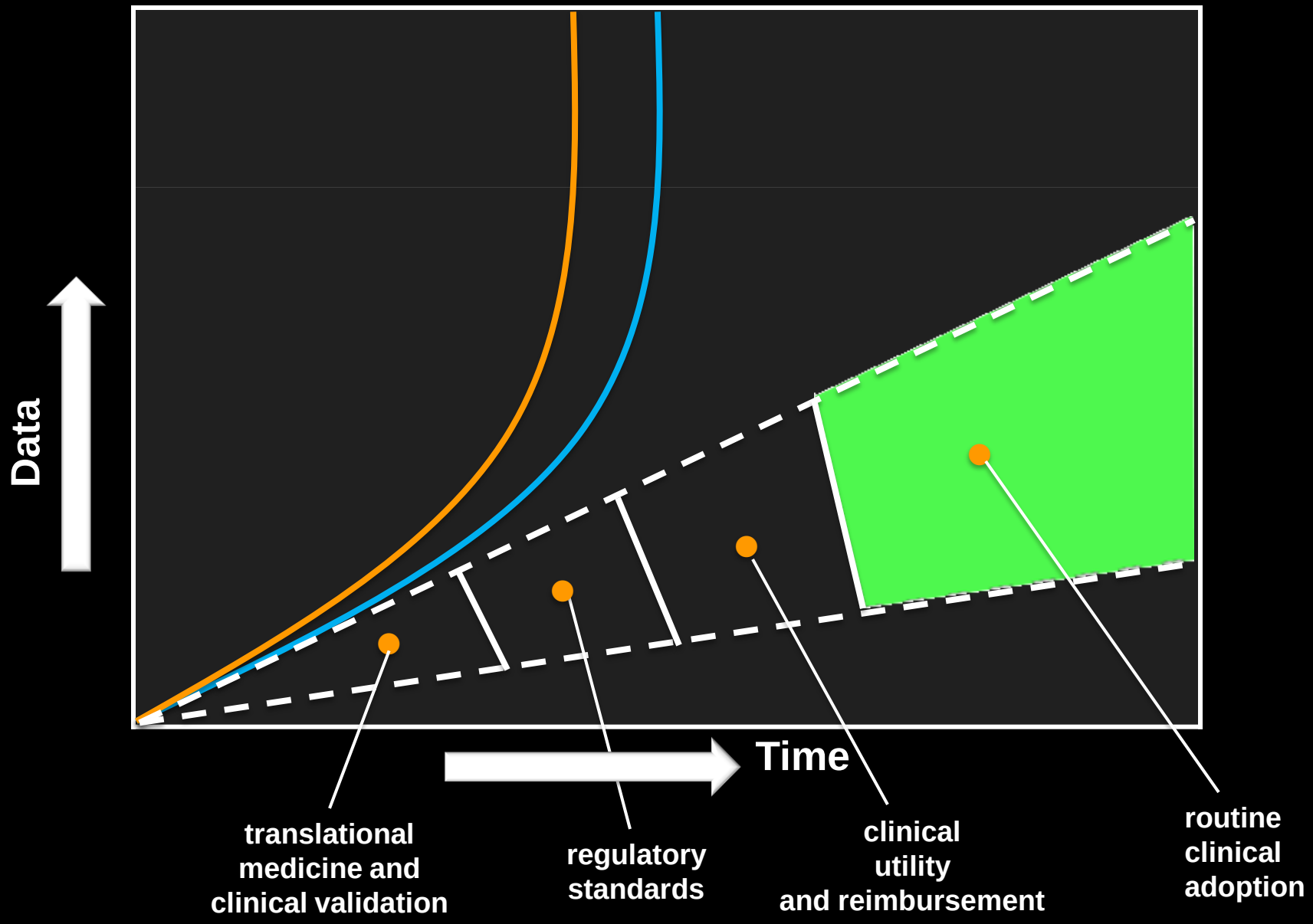


Adoption of New Technologies in Healthcare

- not merely innovation in technology
- parallel evolution and adoption of new business, financial and organizational models
- harmonizing incentives for diverse constituencies
- critical role of public policies in defining market entry barriers
  - regulation, reimbursement
  - professional standards and sustaining status quo
  - changes in administrative procedures
- cost-based, event-/procedure-based incentives versus value-based pricing, integrated care and disease management

The Evidence Dilemma in Adoption of Next-Generation Molecular Diagnostic Tests and the Evolution of Personalized Medicine

“The stark reality is that although academic conception of new biomarkers is fertile, their gestation is generally interminable”

Dr. Janet Woodcock
FDA
Clin. Pharm. Therap. (2009) 86, 13

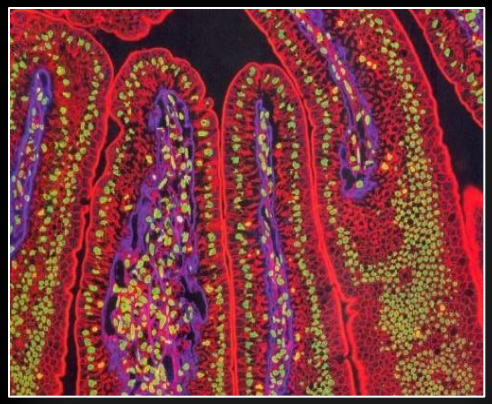
Deriving Value from “-Omics”

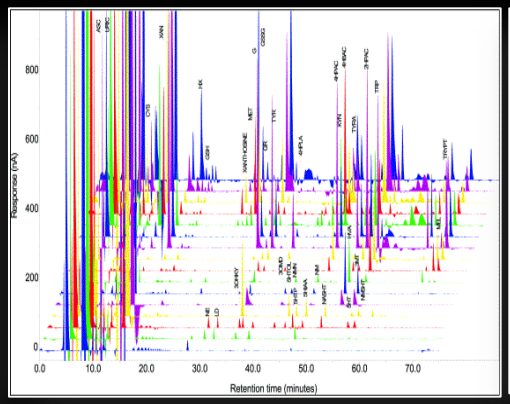
- useful only when correlated with additional parameters
  - clinical outcomes
  - clinical utility
  - actionable information
  - demonstrable economic value

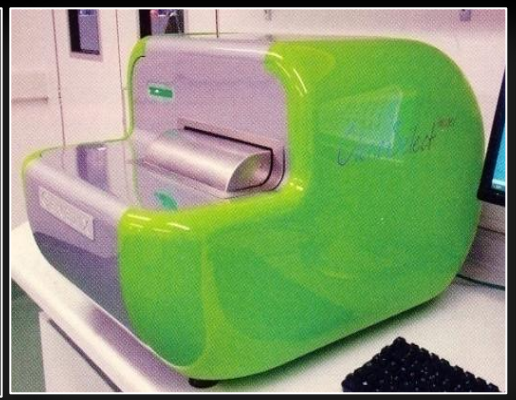
Disease-Associated Biomarkers

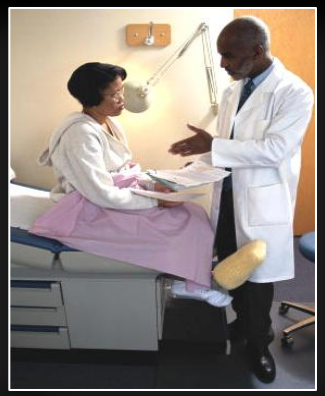
- literature dominated by anecdotal studies
  - academic laboratories
  - small patient cohorts
  - poor replication and confirmatory studies
- lack of standardization
- very few biomarkers subjected to rigorous validation
  - case-control studies with sufficient statistical power
  - inadequate stringency in clinical phenotyping
- widespread lack of understanding of regulatory requirements
  - complexities imposed by multiplex tests
  - new regulatory oversight (IVDMIAs)

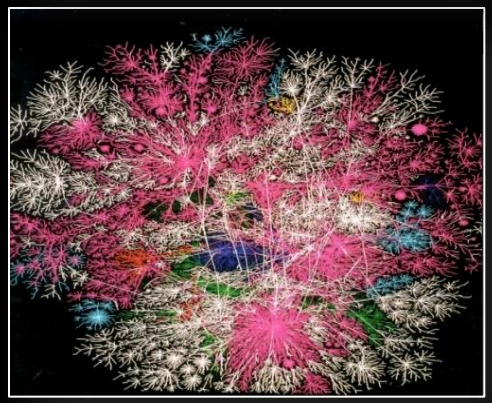
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches

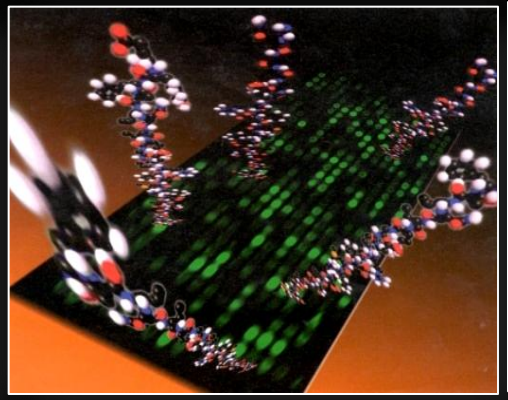


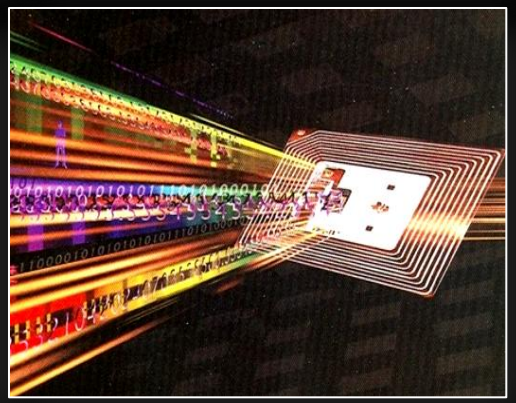












Biospecimens and Molecular Pathway Analysis

Biomarker Validation and Multiplex Assays

Instrumentation and Informatics

Clinical Impact and Patient Monitoring

The Imperative for Rigorous Clinical Sampling Protocols in Biomarker Profiling and Validation of IVD Tests

- statistical powering
- rigorous case-control studies
  - retrospective
  - prospective (piggy back on clinical trials)
- prospectively defined endpoints
  - diagnostic marker(s)
  - Rx responsiveness and resistance markers
  - staging, stratification, progression markers
- regulatory validation of software algorithms for multiplex tests

Sample Sizes Required to Render False Positive Results Unlikey When Testing Association Between a Genetic Variant and Cancer

Genetic relative risk†	Probability of association	Sample size for cases‡
1.25	0.001	2128
	0.0001	2580
	0.00001	3026
1.15	0.001	5789
	0.0001	7022
	0.00001	8234

from: S.G. Baker et al. (2006) BMJ 332, 1150

*Based on a two sided type I error of 0.05, a power of 0.90, and a false positive report probability of 0.05

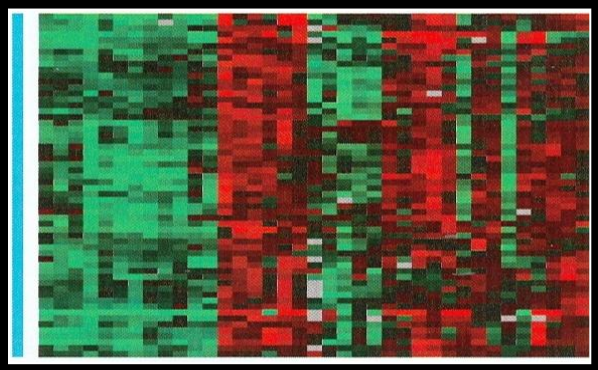
†Relative risk of cancer in people with genetic variant compared with those without.

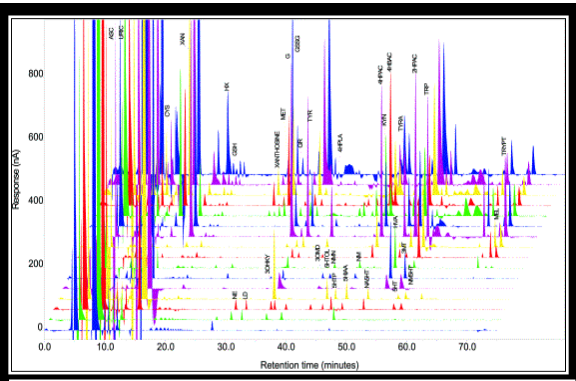
‡An equal number of controls is also needed.

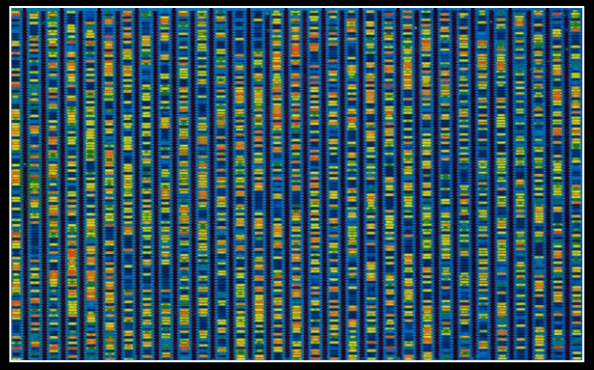
Development of Molecular Diagnostics and Biomarkers for Personalized Medicine: The Need for End-to-End R&D Solutions

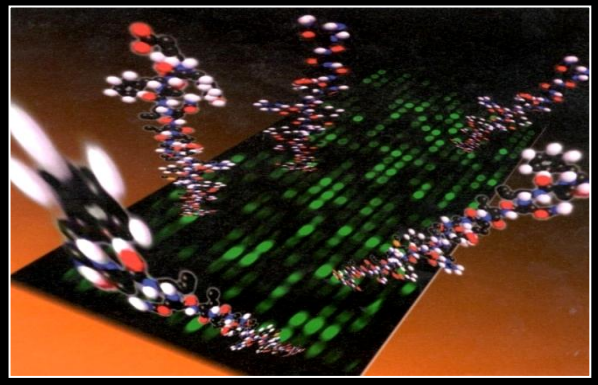
Complex Biosignature Profiling

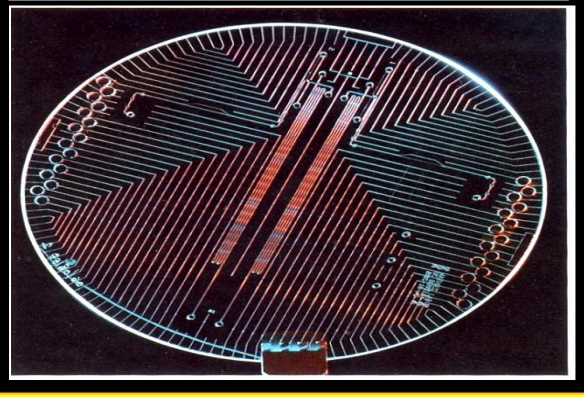
genomics	proteomics	immunosignatures

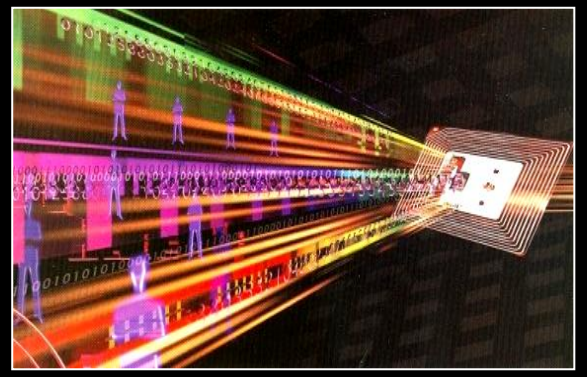












Signature Detection, Deconvolution and Multivariate Analysis

multiplex assays	novel test devices (POC)	new algorithms

Increased Legislative Interest in Standards, Oversights and Regulation of Molecular Diagnostic Testing

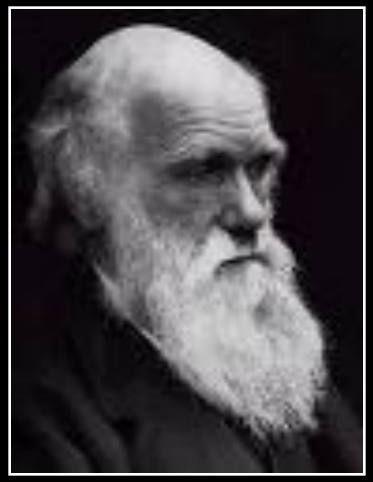
- (2008) In Vitro Diagnostic Multivariate Index Assays (IVDMIAs)
- (2009) Quality, Regulation and Clinical Utility of Laboratory-Developed Tests
- (2009) Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions
- (2009) Secretary's Advisory Committee on Genetics, Health and Society (SACGHS)
- (2009) SB 42: Post-CLIA Bioinformatics Services

Ominous Signal?

"Under the current CLIA framework,
only the analytical validity of the test is assessed,
while the clinical validity and clinical utility
of the test are not"

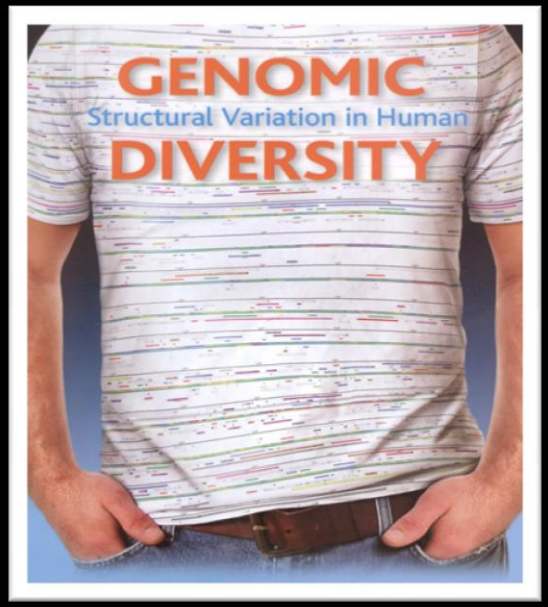
DHSS Agency for Healthcare Quality and Research
Report on Laboratory Developed Tests
September 2009

Mapping Genetic Variation and Identification of Gene Loci Associated with Complex Human Diseases



"Our ignorance of the laws of variation is profound"

Charles Darwin



Mapping the Allelic Architecture of Common Traits and Gene Constellations for Disease Predisposition and Progression

- family-based linkage studies and ‘candidate genes’

- SNPs, haplotypes and genome-wide association studies (GWAS)

- common variants confer small risk increments (OR 1.1 to 1.5)
- explain only small component of disease risk
- majority of associated loci in intronic and inter-genic regions of unknown function
- relationship of CNVs to associated loci yet to be defined

- focus on larger number of variants with low minor allele frequencies (MAF) and smaller effects

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- **comprehensive exome and whole genome sequencing**

Daunting Scale, Time and Cost of Comprehensive Mapping of Loci Associated with Complex Human Diseases

- high cost GWAS studies on few thousand individuals
  - largely uninformative in identification of the collective actions of multiple rare alleles with individual weak effects
- very large sample sizes needed for adequate statistical power to identify low frequency loci
  - 200,000 – 500,000 ($1-3 billion)
- skepticism that coarse-grained nature of routinely collected clinical/lab/billing metrics are insufficient to establish research-quality phenotypes for robust correlative whole genome sequencing

The Imperative for New Initiatives to Establish Large Scale, Standardized Scientific and Clinical Resources for Translational Research

The Rise of Big Biology: Nature Genetics (September/October 2009)

Genetic variant near *IRS1* is associated with type 2 diabetes, insulin resistance and hyperinsulinemia

Johan Rung[1,28,29], Stéphane Cauchi[2,29], Anders Albrechtsen[3,29], Lishuang Shen[1,28], Ghislain Rocheleau[1,4,28], Christine Cavalcanti-Proença[2], François Bacot[1], Beverley Balkau[5], Alexandre Belisle[1], Knut Borch-Johnsen[6], Guillaume Charpentier[7], Christian Dina[2], Emmanuelle Durand[2], Paul Elliott[8], Samy Hadjadj[9], Marjo-Riitta Järvelin[8,10], Jaana Laitinen[11], Torsten Lauritzen[12], Michel Marre[13], Alexander Mazur[1], David Meyre[2], Alexandre Montpetit[1], Charlotta Pisinger[14], Barry Posner[15,16], Pernille Poulsen[6], Anneli Pouta[8,17], Marc Prentki[18], Rasmus Ribel-Madsen[6], Aimo Ruokonen[19], Anelli Sandbaek[12], David Serre[1,28], Jean Tichet[20], Martine Vaxillaire[2], Jørgen F P Wojtaszewski[21], Allan Vaag[6,22], Torben Hansen[23,24], Constantin Polychronakos[4,25], Oluf Pedersen[23,26], Philippe Froguel[2,27] & Robert Sladek[1,4,15]

Genome-wide association study identifies variants in the *ABO* locus associated with susceptibility to pancreatic cancer

Laufey Amundadottir[1,2,55*], Peter Kraft[3,4,55], Rachael Z Stolzenberg-Solomon[2,55], Charles S Fuchs[5,6,55], Gloria M Petersen[7], Alan A Arslan[8–10], H Bas Bueno-de-Mesquita[11], Myron Gross[12], Kathy Helzlsouer[13], Eric J Jacobs[14], Andrea LaCroix[15], Wei Zheng[16], Demetrius Albanes[2], William Bamlet[7], Christine D Berg[17], Franco Berrino[18], Sheila Bingham[19], Julie E Buring[20,21], Paige M Bracci[22], Federico Canzian[23], Françoise Clavel-Chapelon[24], Sandra Clipp[25], Michelle Cotterchio[26], Mariza de Andrade[7], Eric J Duell[27], John W Fox Jr[28], Steven Gallinger[29], J Michael Gaziano[30], Edward L Giovannucci[3,6,31], Michael Goggins[32], Carlos A González[33], Göran Hallmans[34], Susan E Hankinson[3,6], Manal Hassan[35], Elizabeth A Holly[22], David J Hunter[3,6], Amy Hutchinson[2,36], Rebecca Jackson[37], Kevin B Jacobs[2,36,38], Mazda Jenab[27], Rudolf Kaaks[23], Alison P Klein[39,40], Charles Kooperberg[15], Robert C Kurtz[41], Donghui Li[35], Shannon M Lynch[42], Margaret Mandelson[15,43], Robert R McWilliams[44], Julie B Mendelsohn[2], Dominique S Michaud[3,45], Sara H Olson[46], Kim Overvad[47], Alpa V Patel[14], Petra H M Peeters[45,48], Aleksandar Rajkovic[49], Elio Riboli[45], Harvey A Risch[50], Xiao-Ou Shu[16], Gilles Thomas[2], Geoffrey S Tobias[2], Dimitrios Trichopoulos[3,51], Stephen K Van Den Eeden[52], Jarmo Virtamo[53], Jean Wactawski-Wende[54], Brian M Wolpin[5,6], Herbert Yu[50], Kai Yu[2], Anne Zeleniuch-Jacquotte[9,10], Stephen J Chanock[1,2,55], Patricia Hartge[2,55] & Robert N Hoover[2,55]

Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer's disease

Jean-Charles Lambert[1–3], Simon Heath[4], Gael Even[1,2], Dominique Campion[5], Kristel Sleegers[6,7], Mikko Hiltunen[8], Onofre Combarros[9], Diana Zelenika[4], Maria J Bullido[10], Béatrice Tavernier[11], Luc Letenneur[12], Karolien Bettens[6,7], Claudine Berr[13], Florence Pasquier[3,14], Nathalie Fiévet[1,2], Pascale Barberger-Gateau[12], Sebastiaan Engelborghs[7,15], Peter De Deyn[7,15], Ignacio Mateo[9], Ana Franck[16], Seppo Helisalmi[8], Elisa Porcellini[17], Olivier Hanon[18], the European Alzheimer's Disease Initiative Investigators[19], Marian M de Pancorbo[20], Corinne Lendon[21], Carole Dufouil[22,23], Céline Jaillard[24], Thierry Leveillard[24], Victoria Alvarez[25], Paolo Bosco[26], Michelangelo Mancuso[27], Francesco Panza[28], Benedetta Nacmias[29], Paola Bossù[30], Paola Piccardi[31], Giorgio Annoni[32], Davide Seripa[33], Daniela Galimberti[34], Didier Hannequin[5], Federico Licastro[17], Hilkka Soininen[8], Karen Ritchie[13], Hélène Blanché[35], Jean-François Dartigues[12], Christophe Tzourio[22,23], Ivo Gut[4], Christine Van Broeckhoven[6,7], Annick Alpérovitch[22,23], Mark Lathrop[4,35] & Philippe Amouyel[1–3,14]

Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility

Julius Gudmundsson[1,21], Patrick Sulem[1,21], Daniel F Gudbjartsson[1], Thorarinn Blondal[1], Arnaldur Gylfason[1], Bjarni A Agnarsson[2,3], Kristrun R Benediktsdottir[2,3], Droplaug N Magnusdottir[1], Gudbjorg Orlygsdottir[1], Margret Jakobsdottir[1], Simon N Stacey[1], Asgeir Sigurdsson[1], Tiina Wahlfors[4], Teuvo Tammela[5], Joan P Breyer[6], Kate M McReynolds[6], Kevin M Bradley[6], Berta Saez[7,8], Javier Godino[7], Sebastian Navarrete[9], Fernando Fuertes[9], Laura Murillo[10], Eduardo Polo[11], Katja K Aben[12,13], Inge M van Oort[14], Brian K Suarez[15], Brian T Helfand[16], Donghui Kan[16], Carlo Zanon[1,17], Michael L Frigge[1], Kristleifur Kristjansson[1], Jeffrey R Gulcher[1], Gudmundur V Einarsson[18], Eirikur Jonsson[18], William J Catalona[16], Jose I Mayordomo[7,8,19], Lambertus A Kiemeney[12–14], Jeffrey R Smith[6,20], Johanna Schleutker[4], Rosa B Barkardottir[2], Augustine Kong[1], Unnur Thorsteinsdottir[1,3], Thorunn Rafnar[1] & Kari Stefansson[1,3]

A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2

Honglin Song[1,43,*], Susan J Ramus[2,43], Jonathan Tyrer[1], Kelly L Bolton[1,3], Aleksandra Gentry-Maharaj[2], Eva Wozniak[2], Hoda Anton-Culver[4], Jenny Chang-Claude[5], Daniel W Cramer[6], Richard DiCioccio[7], Thilo Dörk[8], Ellen L Goode[9], Marc T Goodman[10], Joellen M Schildkraut[11], Thomas Sellers[12], Laura Baglietto[13,14], Matthias W Beckmann[15], Jonathan Beesley[16], Jan Blaakaer[17], Michael E Carney[10], Stephen Chanock[3], Zhihua Chen[1,2], Julie M Cunningham[9], Ed Dicks[1], Jennifer A Doherty[18], Matthias Dürst[19], Arif B Ekici[20], David Fenstermacher[12], Brooke L Fridley[9], Graham Giles[13,14], Martin E Gore[21], Immaculata De Vivo[2,2], Peter Hillemanns[8], Claus Hogdall[23], Estrid Hogdall[24], Edwin S Iversen[25], Ian J Jacobs[2], Anna Jakubowska[26], Dong Li[4], Jolanta Lissowska[27], Jan Lubiński[26], Galina Lurie[10], Valerie McGuire[28], John McLaughlin[29], Krzysztof Mędrek[26], Patricia G Moorman[11], Kirsten Moysich[30], Steven Narod[31], Catherine Phelan[12], Carole Pye[1], Harvey Risch[32], Ingo B Runnebaum[19], Gianluca Severi[13,14], Melissa Southey[33], Daniel O Stram[34], Falk C Thiel[15], Kathryn L Terry[6], Ya-Yu Tsai[12], Shelley S Tworoger[22], David J Van Den Berg[34], Robert A Vierkant[9], Shan Wang-Gohrke[35], Penelope M Webb[16], Lynne R Wilkens[10], Anna H Wu[34], Hannah Yang[3], Wendy Brewster[36], Argyrios Ziogas[4], Australian Cancer (Ovarian) Study[37], The Australian Ovarian Cancer Study Group[37], The Ovarian Cancer Association Consortium[38], Richard Houlston[38], Ian Tomlinson[39], Alice S Whittemore[28], Mary Anne Rossing[18], Bruce A J Ponder[1], Celeste Leigh Pearce[34], Roberta B Ness[40], Usha Menon[2], Susanne Krüger Kjaer[24], Jacek Gronwald[26], Montserrat Garcia-Closas[17], Peter A Fasching[15,41], Douglas F Easton[42], Georgia Chenevix-Trench[16], Andrew Berchuck[11], Paul D P Pharoah[1] & Simon A Gayther[2]

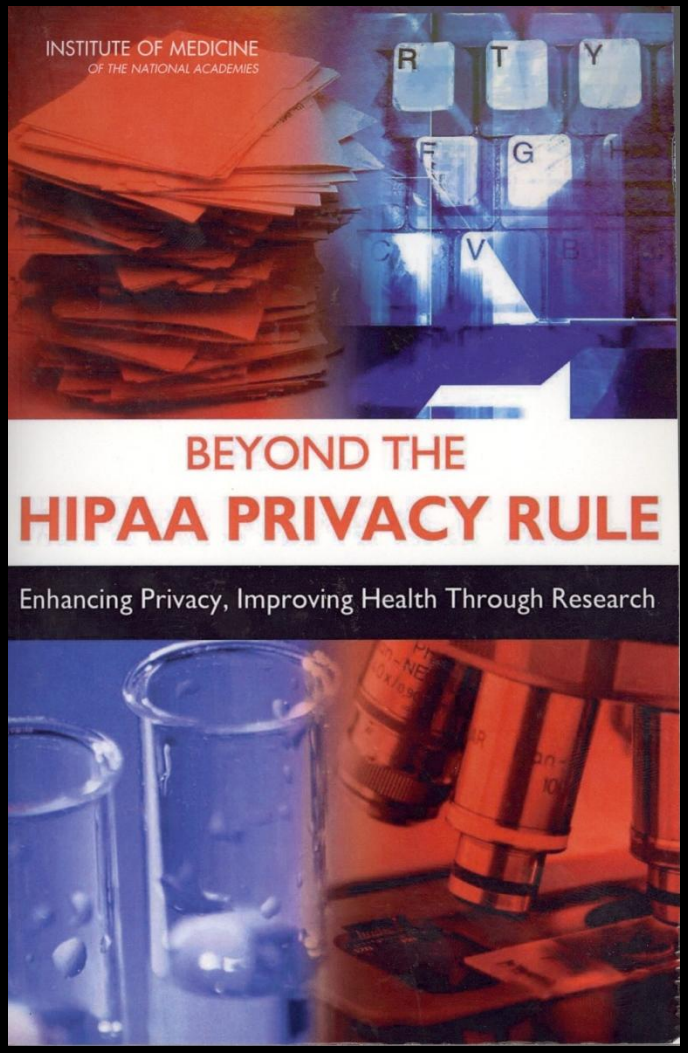
Genome-wide association study identifies 19p13.3 (*UNC13A*) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis

Michael A van Es[1,38*], Jan H Veldink[1,38], Christiaan G J Saris[1], Hylke M Blauw[1], Paul W J van Vught[1], Anna Birve[2], Robin Lemmens[3–5], Helenius J Schelhaas[6], Ewout J N Groen[1], Mark H B Huisman[1], Anneke J van der Kooi[7], Marianne de Visser[7], Caroline Dahlberg[2], Karol Estrada[8], Fernando Rivadeneira[8,9], Albert Hofman[9], Machiel J Zwarts[6], Perry T C van Doormaal[1], Dan Rujescu[10], Eric Strengman[11], Ina Giegling[10], Pierandrea Muglia[12], Barbara Tomik[13], Agnieszka Slowik[13], Andre G Uitterlinden[8,9], Corinna Hendrich[14], Stefan Waibel[14], Thomas Meyer[15], Albert C Ludolph[14], Jonathan D Glass[16], Shaun Purcell[17], Sven Cichon[18,19], Markus M Nöthen[18,19], H-Erich Wichmann[20–22], Stefan Schreiber[23,24], Sita H H M Vermeulen[25], Lambertus A Kiemeney[26,27], John H J Wokke[1], Simon Cronin[28,29], Russell L McLaughlin[29,30], Orla Hardiman[29,30], Katsumi Fumoto[31], R Jeroen Pasterkamp[31], Vincent Meininger[32], Judith Melki[33], P Nigel Leigh[34], Christopher E Shaw[34], John E Landers[35,36], Ammar Al-Chalabi[34], Robert H Brown Jr[35,36], Wim Robberecht[3–5], Peter M Andersen[2], Roel A Ophoff[11,37] & Leonard H van den Berg[1]

Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease

Denise Harold[1,45*], Richard Abraham[1,45], Paul Hollingworth[1,45], Rebecca Sims[1], Amy Gerrish[1], Marian L Hamshere[1], Jaspreet Singh Pahwa[1], Valentina Moskvina[1], Kimberley Dowzell[1], Amy Williams[1], Nicola Jones[1], Charlene Thomas[1], Alexandra Stretton[1], Angharad R Morgan[1], Simon Lovestone[2], John Powell[3], Petroula Proitsi[3], Michelle K Lupton[3], Carol Brayne[4], David C Rubinsztein[5], Michael Gill[6], Brian Lawlor[6], Aoibhinn Lynch[6], Kevin Morgan[7], Kristelle S Brown[7], Peter A Passmore[8], David Craig[8], Bernadette McGuinness[8], Stephen Todd[8], Clive Holmes[9], David Mann[10], A David Smith[11], Seth Love[12], Patrick G Kehoe[12], John Hardy[13], Simon Mead[14], Nick Fox[15], Martin Rossor[15], John Collinge[14], Wolfgang Maier[16], Frank Jessen[16], Britta Schürmann[16], Hendrik van den Bussche[17], Isabella Heuser[18], Johannes Kornhuber[19], Jens Wiltfang[20], Martin Dichgans[21,22], Lutz Frölich[23], Harald Hampel[24,25], Michael Hüll[26], Dan Rujescu[25], Alison M Goate[27], John S K Kauwe[28], Carlos Cruchaga[27], Petra Nowotny[27], John C Morris[27], Kevin Mayo[27], Kristel Sleegers[29,30], Karolien Bettens[29,30], Sebastiaan Engelborghs[30,31], Peter P De Deyn[30,31], Christine Van Broeckhoven[29,30], Gill Livingston[32], Nicholas J Bass[32], Hugh Gurling[32], Andrew McQuillin[32], Rhian Gwilliam[33], Panagiotis Deloukas[33], Ammar Al-Chalabi[34], Christopher E Shaw[34], Magda Tsolaki[35], Andrew B Singleton[36], Rita Guerreiro[36], Thomas W Mühleisen[37,38], Markus M Nöthen[37,38], Susanne Moebus[39], Karl-Heinz Jöckel[39], Norman Klopp[40], H-Erich Wichmann[40–42], Minerva M Carrasquillo[43], V Shane Pankratz[44], Steven G Younkin[45], Peter A Holmans[1], Michael O'Donovan[1], Michael J Owen[1] & Julie Williams[1]

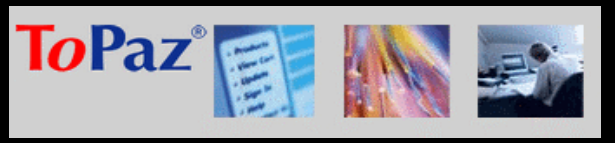
IOM Committee on Health Research and the Privacy of Health Information (2009)

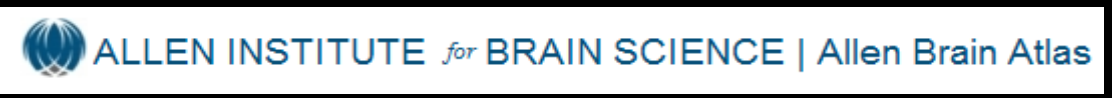


- HIPAA fails to protect privacy and impedes research
- consent does not protect against security breaches
- proposal that research be exempt from HIPAA
- adopt prior federal standard for human subjects research: The Common Rule
- eliminates need for reconsent and reauthorization for future and use of sample/data

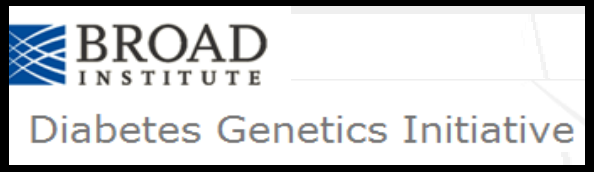
Standards for ‘Omics’ Data Cross-Domain Integration, Open-Source Data Sharing and Computational Analysis

The Rise of Open-Source Networks and Consortia





FDA/Severe Adverse Events (SAE) Consortium



Clinical Semantics Group

OBO Foundry Ontologies

Nature Biotechnology 25, 1251 - 1255 (2009)

Cell Ontology (CL)

Gene Ontology (GO)

Foundational Model of Anatomy

ZFIN

Zebrafish Anatomical Ontology

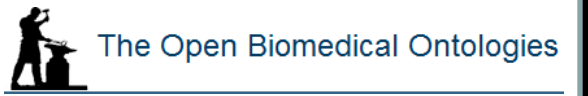
Chemical Entities of Biological Interest (ChEBI)

Disease Ontology (DO)

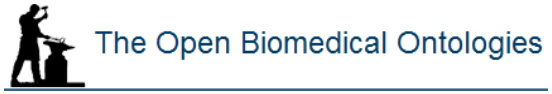
Plant Ontology (PO)

Sequence Ontology (SO)

Ontology for Clinical Investigations (OCI)



Common Anatomy Reference Ontology



Environment Ontology

Ontology for Biomedical Investigations

Phenotypic Quality Ontology (PATO)

Protein Ontology (PRO)

OBO Relation Ontology

RNA Ontology (RnaO)

Changing the Sociology of the Life Sciences and Clinical Research Communities

Creating a New Network of Connected Expertise to Accelerate Innovation in Healthcare R&D

- ever faster generation of new information
- diversification of innovation sources
- current R&D ecosystem is too fragmented to fully leverage novel content and shared learning
- global sourcing
- rise of new business models of ‘expertise networks’ that eclipse current monolithic single company innovation models

If You Build It Will They Pay?
Adoption of Disruptive Innovation

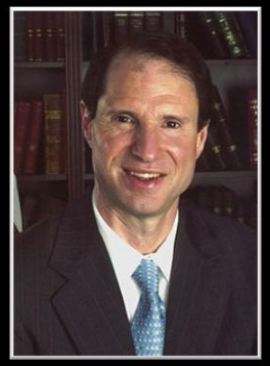
- new technology/service that simplifies a complex/costly problem
- business model that allows market adoption of the simplified solution at low(er) cost
- incentivized supply and demand to networks to reinforce the disruption

Reimbursement for Diagnostic Tests

The Imperative for Value-Based Pricing versus Current Cost-Based Models

- inadequate US Medicare coding and payment mechanisms
  - out moded, out-dated, lacking in transparency, inconsistently applied
- inappropriate assignment of existing CPT codes to new tests
- engagement of third party payers who derive economic/clinical value from new Dx

The CMS Date of Service Rule (Implemented 1/08) a.k.a The '14 Day Rule'



Sen. R. Wyden
(D-Ore)

- "presents a barrier to the use and development of personalized medicine"
- Senate Finance Committee Proposed Amendment (10/09) to eliminate and allow non-hospital labs to bill Medicare

PMC Personalized Medicine Coalition

- "We couldn't support a bill that would disadvantage hospital labs"
  Amy Miller, Policy Director
- "This will lead to closing and down-sizing of academic labs. It would benefit a very small number of laboratories and harm a very large number of hospitals"
  Mary Williams, COO

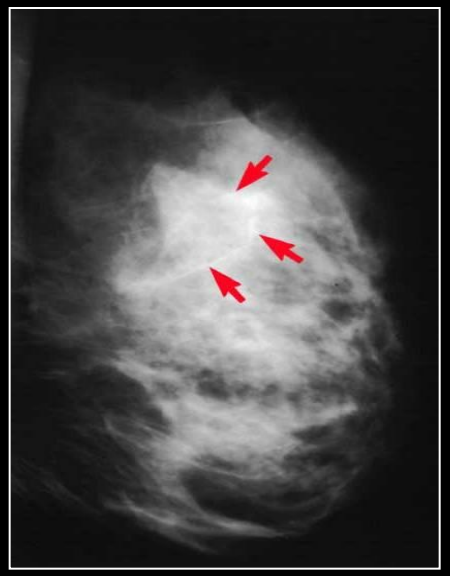
15th ANNIVERSARY AMP.org Association for Molecular Pathology

Demonstrating the Clinical Utility of Diagnostic Profiling

- right disease (subtype)
- right risk: benefit decision
- right treatment
- right patient

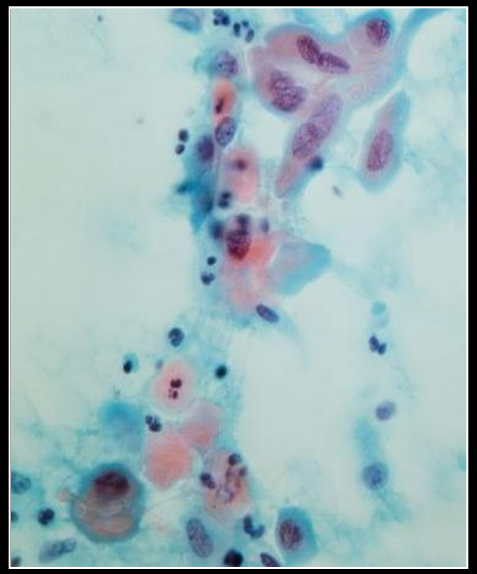
Have We Ignored the Biology of Tumor Progression in Our Approaches to Cancer Screening

Prostate



Breast

Colon



Cervix

Have We Ignored Differences in Patterns of Tumor Progression in the Design of Breast and Prostate Cancer Screening Programs?

- L. Esserman et. al. (2009) JAMA 312, 1685-92
- Gil Andriole (2009) NEJM 360, 1310
- screening increases detection of early disease

but

incidence of regional disease not reduce commensurately

- suggests potential overtreatment for low risk indolent lesions

and

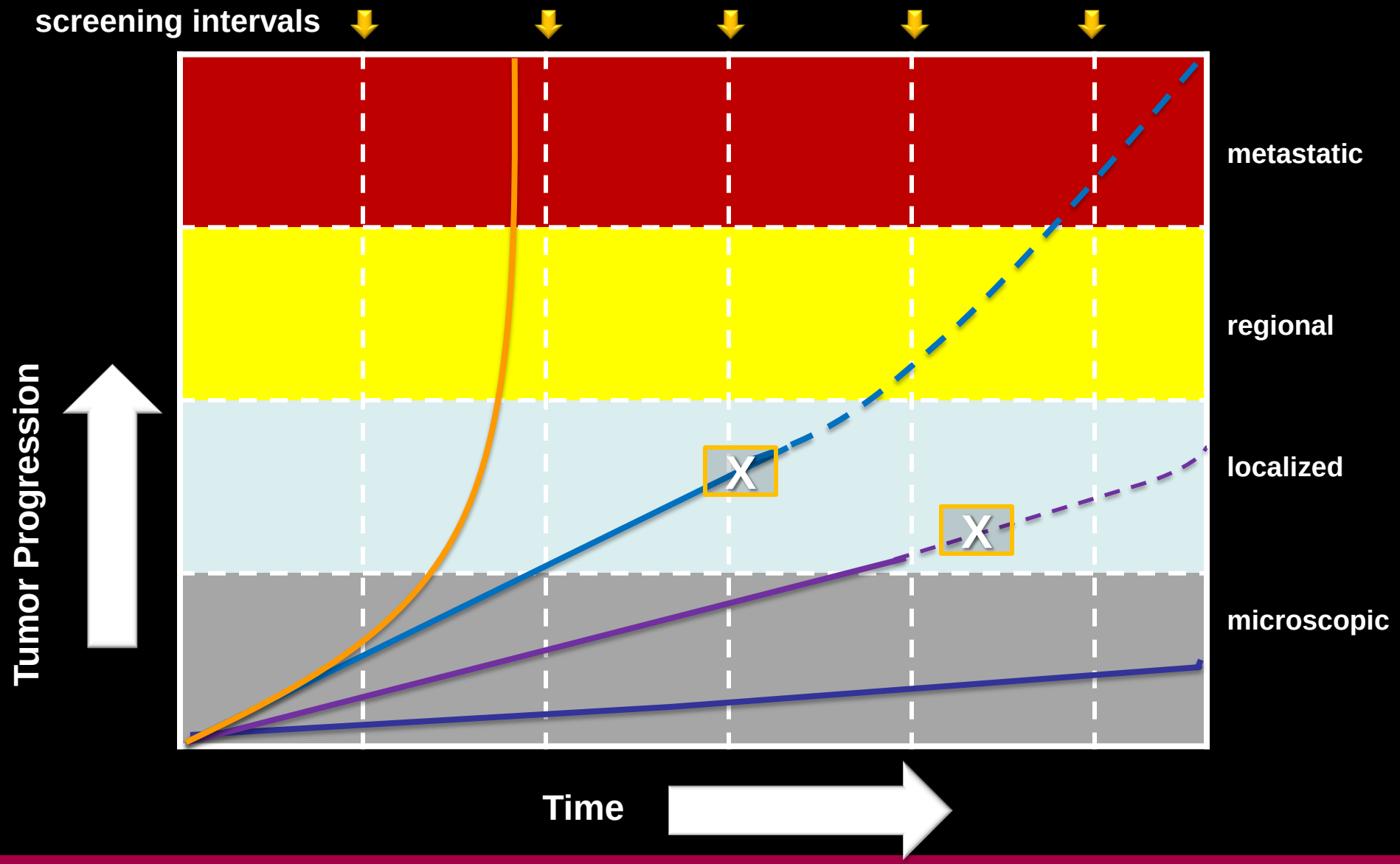
screening intervals insufficient to detect aggressive lethal tumors arising as ‘inter-interval’ events

- concept consistent with detection of small fraction of small, early breast cancers classified as low risk by NCI criteria but high mortality risk by NKI 70 gene test

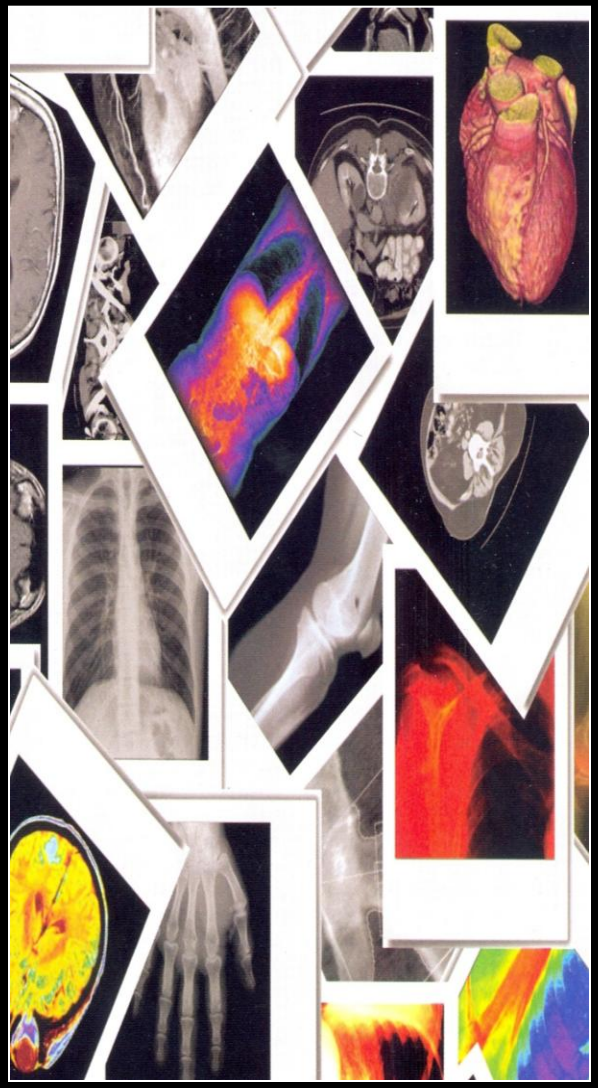
and

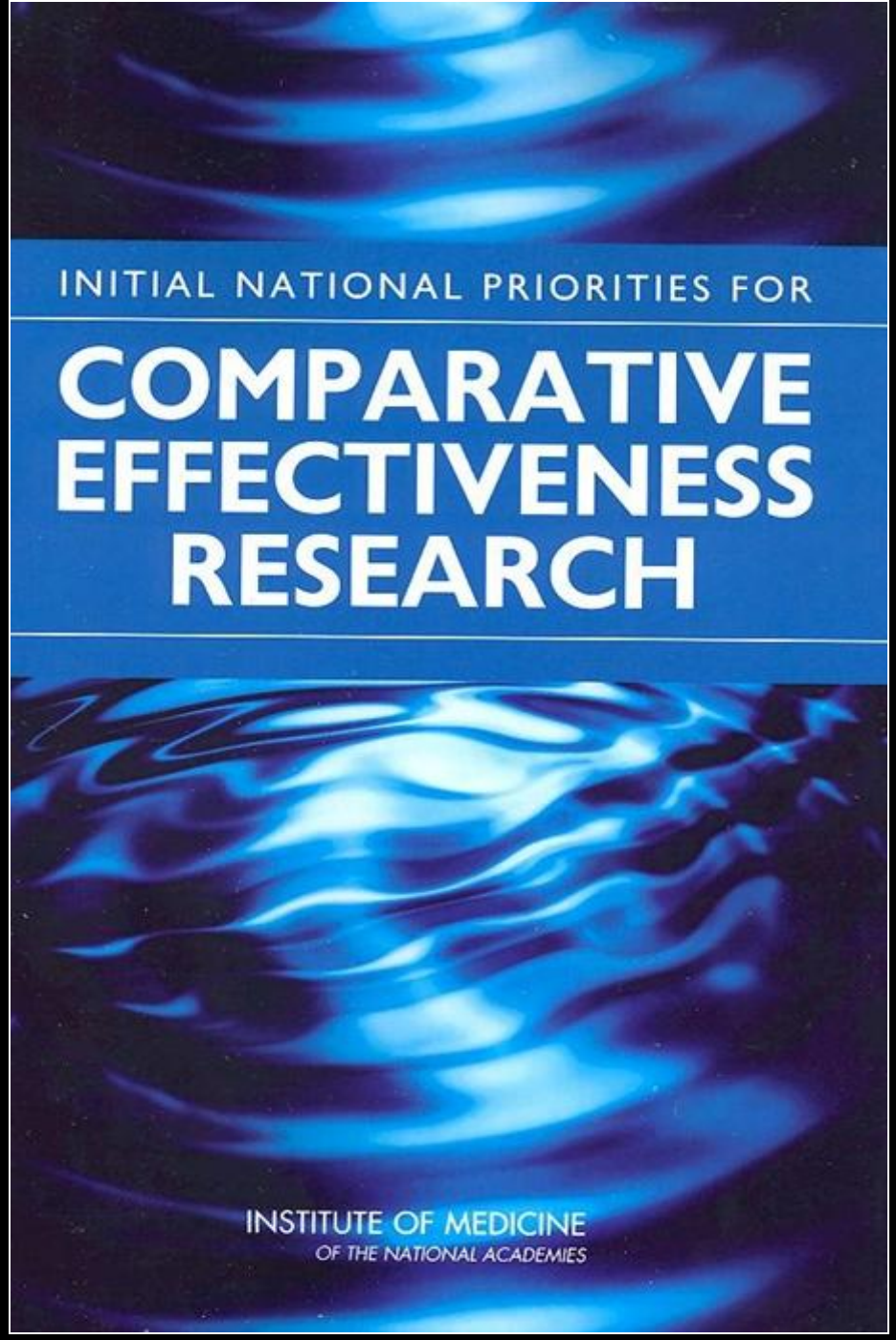
I-SPY trial data with 85% malignancies were inter-interval cancers and only 15% detected in routine screening

Effectiveness of Cancer Screens Based on Different Patterns of Tumor Biology and Screening Intervals



How Much New Technology Can We Afford?





The NEW ENGLAND JOURNAL of MEDICINE

(2009) 360, 1925

Does Comparative-Effectiveness Research Threaten Personalized Medicine?

Alan M. Garber, M.D., Ph.D., and Sean R. Tunis, M.D.

Newsweek
SEPTEMBER 21, 2009

THE CASE FOR KILLING GRANNY

CURBING EXCESSIVE END-OF-LIFE CARE IS GOOD FOR AMERICA
BY EVAN THOMAS

I WAS A TEENAGE DEATH PANELIST
BY JON MEACHAM

PLUS

THE WAY OUT OF AFGHANISTAN
BY FAREED ZAKARIA

THE ROOTS OF THE NEXT CRASH
BY NIALL FERGUSON

OBAMA'S CREDIBILITY GAP
BY GEORGE F. WILL

UK National Institute for Health and Clinical Excellence (NICE)

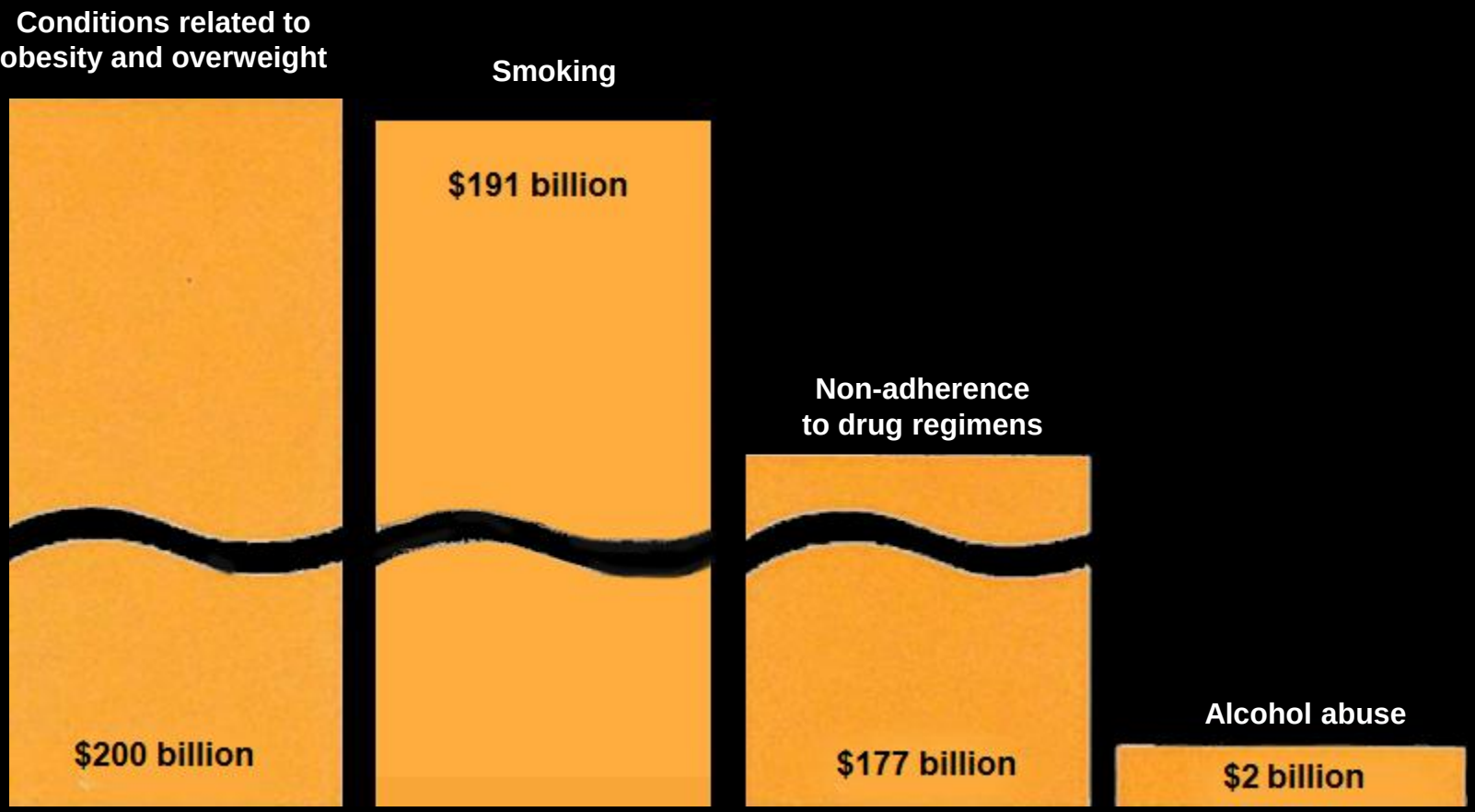
Nice Gets Nasty (or Rational?)

Personalized Medicine: A Broader Perspective

Promotion of Wellness

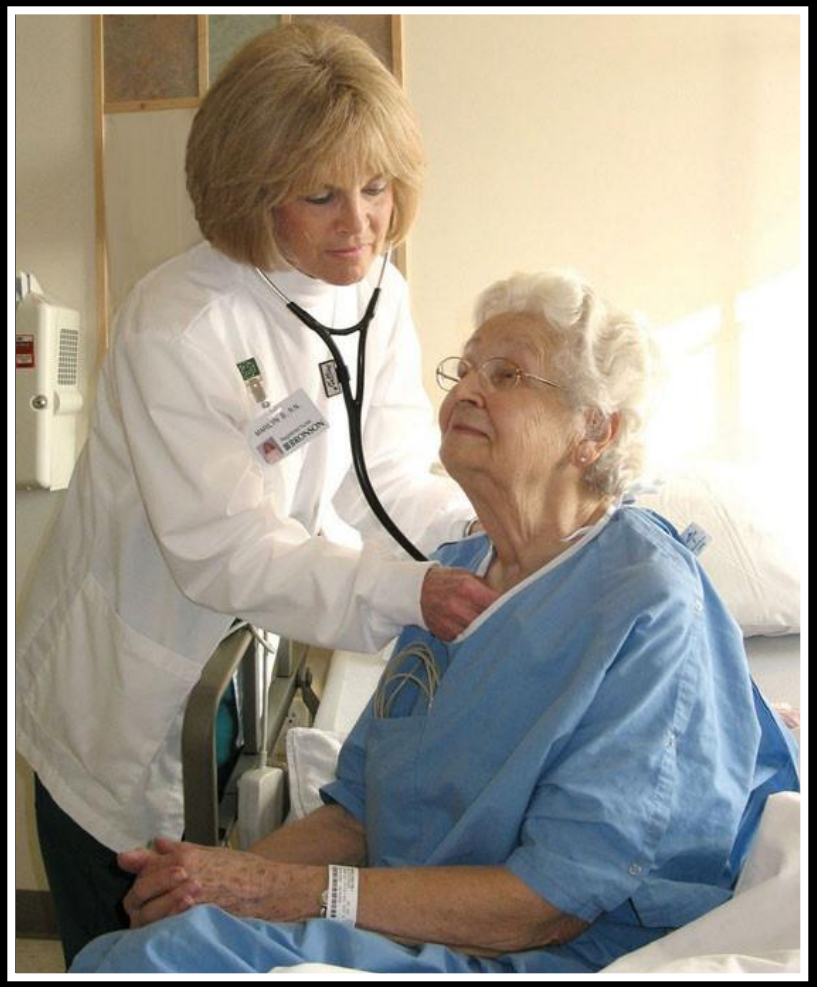
- increased consumer responsibility for wellness
- remote monitoring of individual health status
- crucial role of healthcare information systems
  - integrated Rx care for complex chronic conditions
  - outcomes and comparative effectiveness
  - earlier detection of disease episodes and risk mitigation
  - wellness versus illness

Annual Excess Healthcare Costs Related to Consumer Behavior



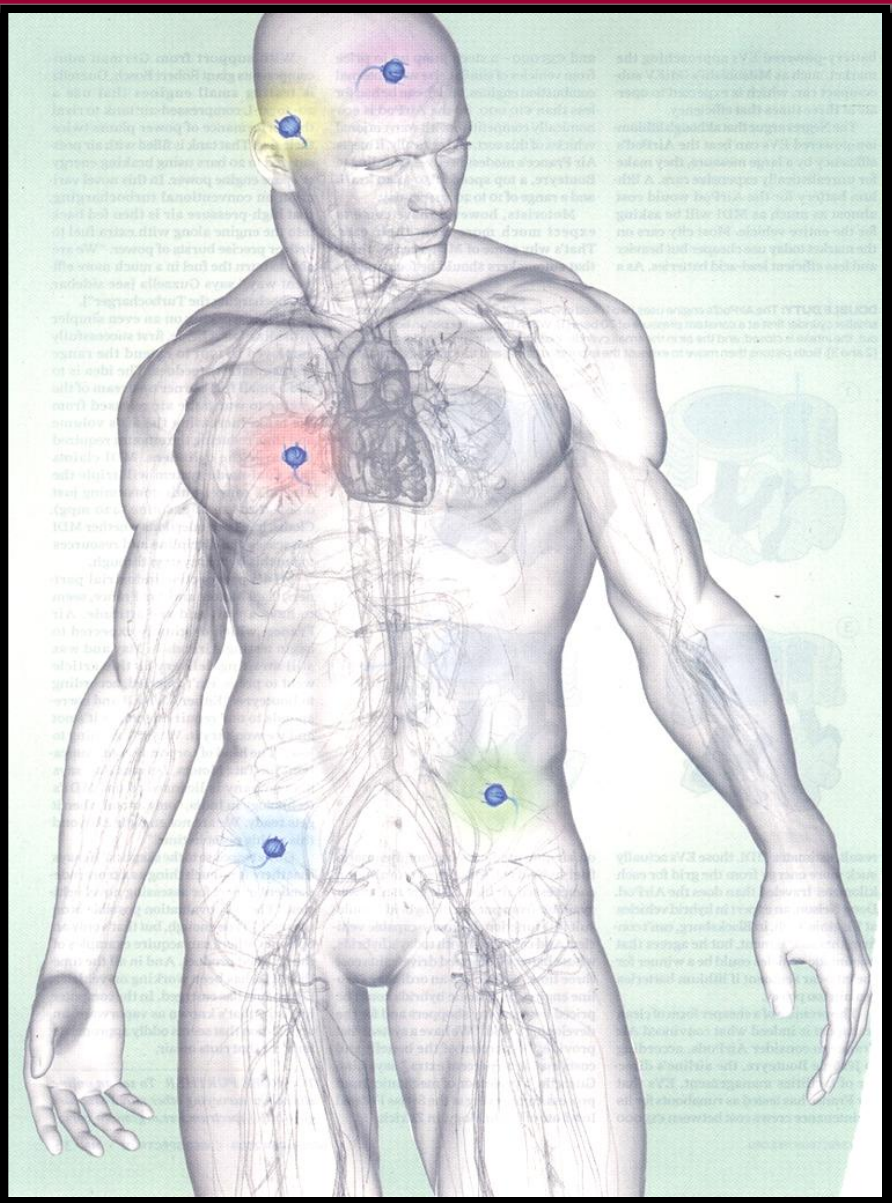
Source: RTI International & Center for Disease Control and Prevention (200), Datamonitor (2007), Americas Health Insurance Plans (2007), Commonwealth Fund (2007), Agency for Health Research and Quality (2003), Analysis by PricewaterhouseCoopers' Health Research

Demographic Trends and the Clinical and Economic Burden of Complex, Chronic Conditions/Co-Morbidities



- 23% Medicare beneficiaries have 5 or more conditions
- polypharmacy and AEs
- poor patient compliance
- multiple physician/venue encounters
- poor communication/ coordination between siloed healthcare services
- procedure-based reimbursement versus care continuum integrated

On Body: In Body Sensors/Devices
For Real Time and Remote Monitoring of Individual Health Status



On Body: In Body Sensors and Devices

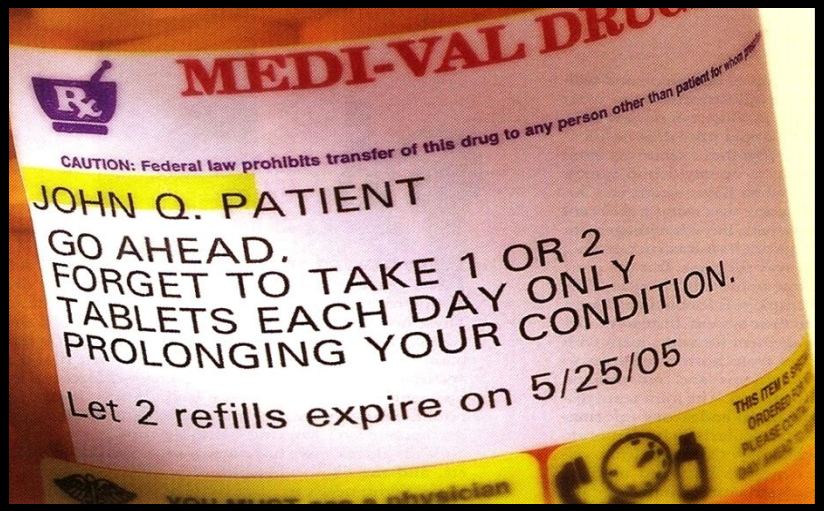
Objective

- remote monitoring of health status

Applications

- multi-feature monitoring and broad-band wireless networks
  - ubiquitous sensing
- enhanced autonomy for in-home aged
- proactive alerting and intervention to mitigate health incidents
- monitoring of patient compliance
- coupled linkage to remote Rx dispensing for efficient disease management

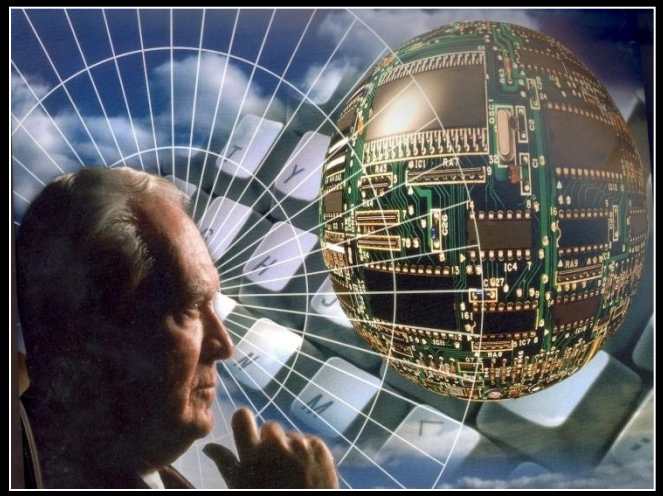
The Costs of Non-Compliance with Rx Regimens

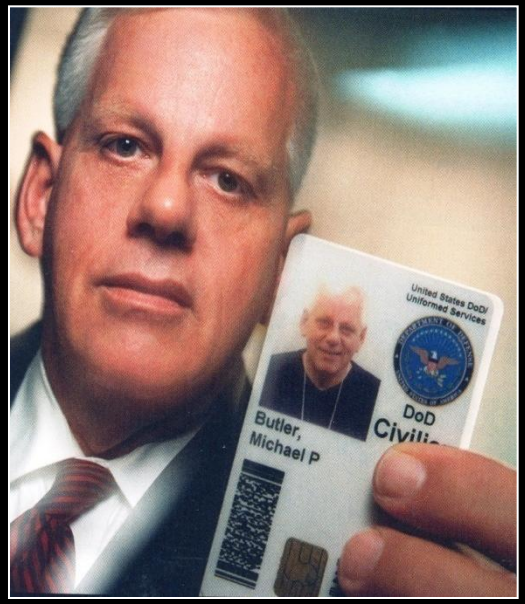


- **$177 billion projected cost**
- **20 million workdays/year lost (IHPM)**
- **40% of nursing home admissions**
- **projected 45-75% non-compliance (WHO)**
- **50-60% depressed patients (IHPM)**
- **50% chronic care Rx (WHO)**

Paper Kills!:
The Inefficiencies and Risks Created by Sustained Dependence on Paper Healthcare Records

The Infocosm: Emerging Networks of Global Connectivity





Wireless Technologies: Consumer and Clinical Markets Converge

Connecting Patients (and Consumers) to Optimum Healthcare Resources

CarePages℠ connect, share...care.

Microsoft® HealthVault™ BETA

Google™

WebMD® Better information. Better health.

revolutionhealth

PMRs and patient support networks for linkage to clinical trials and expertise

integrated care of chronic conditions and specialty Rx distribution

Pharma and Healthcare Social Media (Non-Brand Sponsored) Patient Communities

Pharma and Healthcare Social Media Brand Physician and Nurse Communities

ASKLEPIOS
THE CANADIAN PHYSICIAN'S COMMUNITY

HCPs' social network operated by the Canadian Medical Association

coliquio
medizin, einfach wissen

Social network serving the German speaking countries

dermRounds

social and professional networking site dedicated to connecting dermatologists, and others in the field of dermatology

DocCheck Faces

HCPs' Social network physicians, dentists, pharmacists, and veterinary surgeons

doc 2 doc beta
connecting doctors worldwide

online doctors community

Doctors.net.uk

UK-registered doctors in primary and secondary care

DoooX®
the healthcare community

medical and healthcare communities

DOCTORNETWORKING.COM
Network for physicians

Network for physicians

DoctorsHangout.com

Personal& Professional Networking for Doctors& Medical Students Worldwide

doctrs

exclusive social net for Physicians

iMedX

connects physicians with information, opportunities, and each other.

MedicSpeak

network of doctors and medical students communication, collaborations, exchange of ideas and sharing of knowledge.

Medscape Physician Connect

Engage your peers through our FREE global physician community

MedicalExchange
MEDTING

interactive platform on web for the medical professionals

New Media | Medicine

medical students', and pre-medical students' social network

nurse connect

online nursing community and networking site

QBGYN.net
The Universe of Women's Health

research and support community

ozmosis
The Trusted Physician's Network

Trusted Physician's Network

present diabetes

multi-disciplinary diabetes Learn, share, collaborate

present PODIATRY

Podiatric Residency Education Online community

HealthMap
Global Disease Alert Map
English | Español | Français | Português | Русский | 中文 |
NEJM H1N1 Case Reports | About | Twitter | Blog | Donate | Store | Feedbac
Map
Satellite
Earth
Terrain
Greenland
Iceland
Canada
North Atlantic Ocean
Россия
Russia
Mongolia
China
Japan
Algeria
Libya
Egypt
Mali
Niger
Chad
Sudan
Brasil
Brazil
Perú
Bolivia
Chile
Argentina
Angola
Madagascar
South Africa
South Pacific Ocean
South Atlantic Ocean
Indian Ocean
Australia
Papua New Guinea

The Expanding Universe of Health Information Resources: Redefining Physician:Patient Relationships

• MD-centric monopoly	→	• patient-centric markets
• paternalistic decisions and passive patients	→	• engaged patients/consumers
• institutional control	→	• individual custody
• paper records	→	• EHR/PMRs
• fragmented information and portability barriers	→	• seamless integration and mobility
• centralized testing analysis and expert interpretation	→	• increasingly decentralized, automated analysis and decision algorithms • remote health status monitoring

Changing Minds and Changing Behaviors

Resistance

- delusional merits of status quo
- unwarranted external scrutiny
- claimed risk by change
- loss of status, income, autonomy
- skepticism
- ‘victims’

- incentives
- alignment
- ownership
- tangible individual/ group rewards
- political/media/ public pressures

Adoption

New Vistas in Biotechnology with Potential for Major Therapeutic Advances

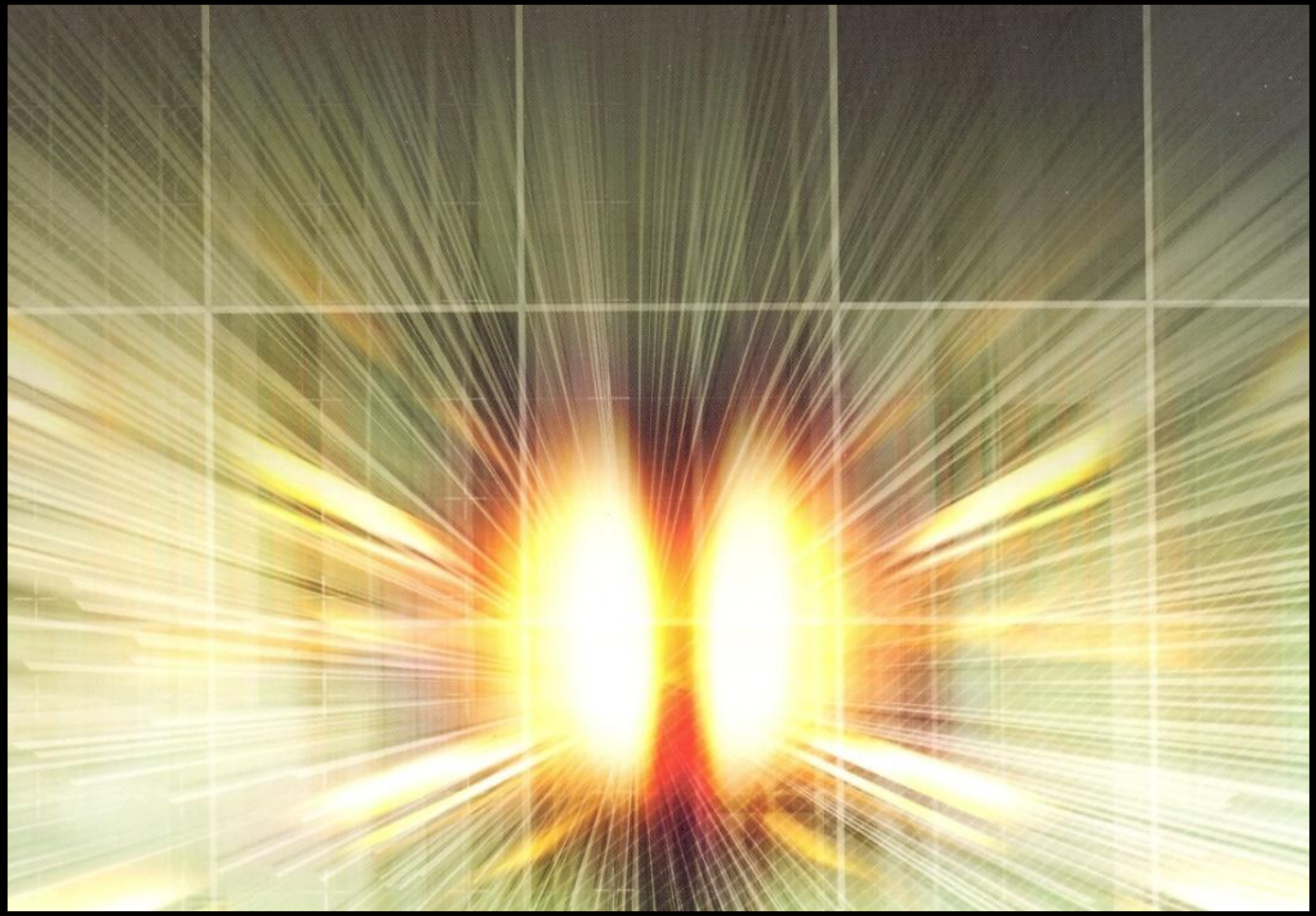
- selective modulation of gene expression via siRNA

- regenerative medicine: programming cellular differentiation and autologous cell therapy

- synthetic biology: cells as novel Rx/vaccine delivery systems or diagnostic sentinels

- tissue engineering: novel biomatrices for repair and remodeling

Technology Acceleration and Convergence in Healthcare Delivery



The Coming Convergence in Healthcare Delivery

Technologies

- biotechnology, medicine, engineering, computing, telecommunications and social media

Clinical Practice

- molecular medicine and increasingly customized care
- diagnostic, drug and device combinations
- POC testing and remote monitoring
- reduced error and improved compliance
- improved outcomes

Realigned Incentives

- integrated care for complex chronic diseases
- earlier disease detection and risk reduction
- wellness versus illness
- remote health status monitoring

The Coming Convergence in Healthcare Delivery

Consumers

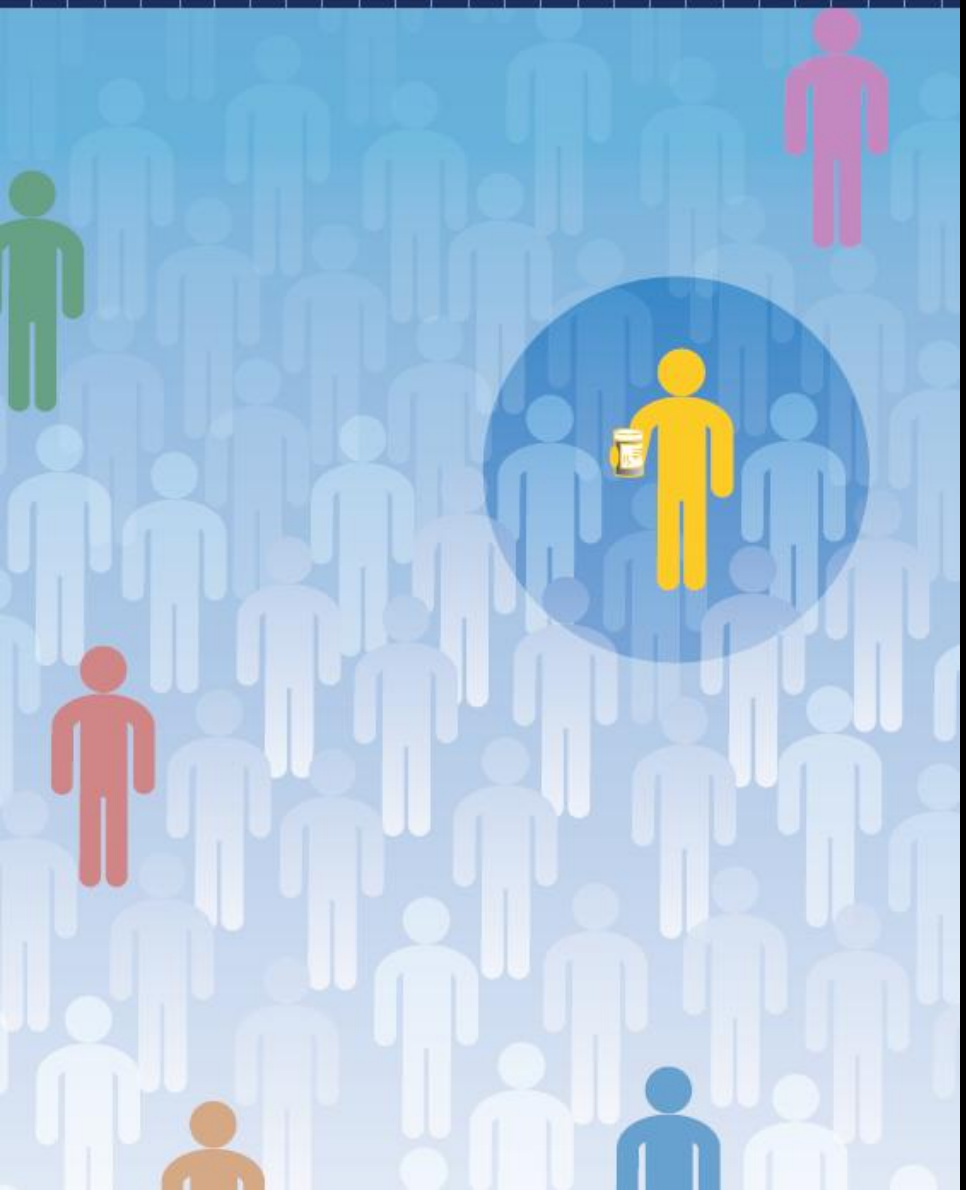
- increased personal responsibility for health
- new incentives for wellness/compliance
- health status monitoring

Connectivity

- integrated care networks for chronic disease
- social media networks and informed consumers
- new supplier networks of specialized turnkey expertise
- value added ‘content’ services for clinical data mining
- clinical decision-support systems

The Burrill Report on Personalized Medicine

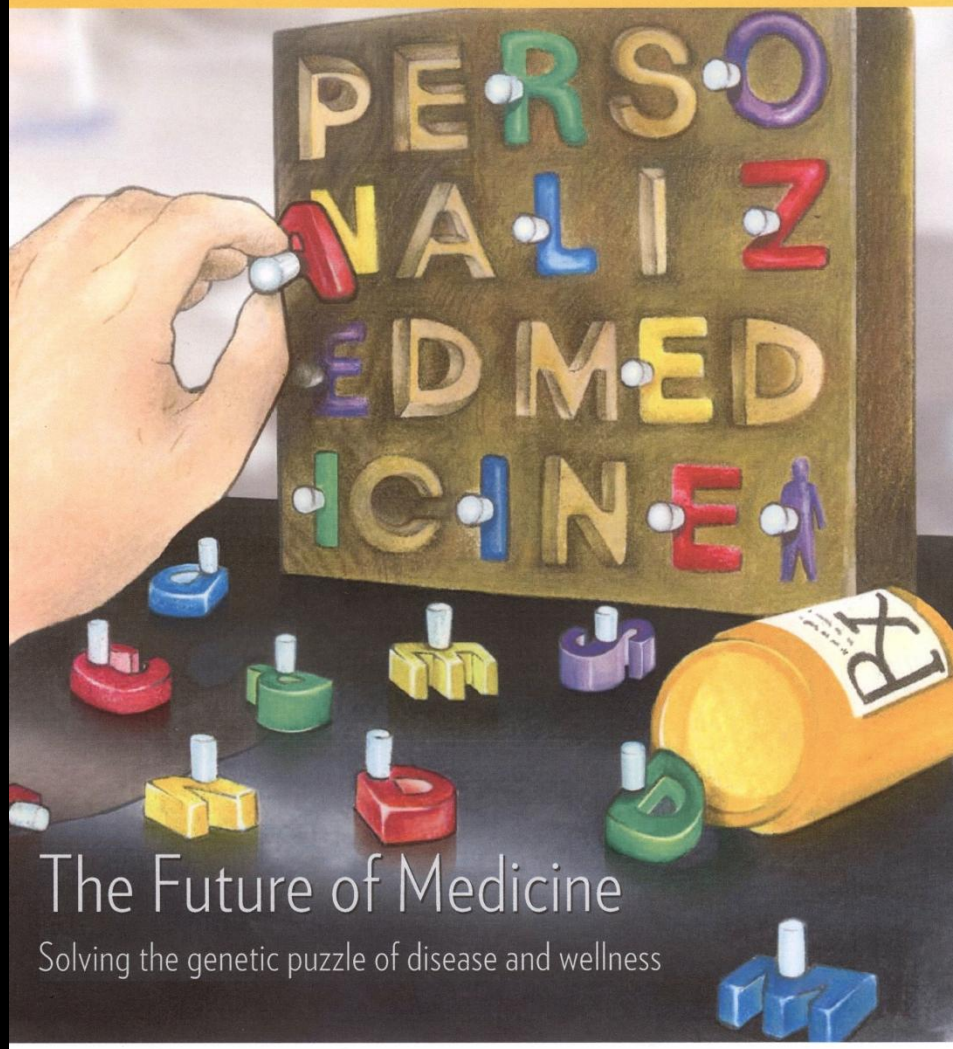
November 2008



WHERE SCIENCE AND SOCIETY MEET

The Journal of Life Sciences

FALL 2009



The Future of Medicine

Solving the genetic puzzle of disease and wellness