The Convergence of Clinical Medicine, Engineering and Computing: New Horizons in Healthcare Delivery

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The John F. Wilkinson Memorial Lecture
Manchester Medical Society
5 May 2010
Dr. John F. Wilkinson (1897 - 1998)
## Challenges for Healthcare Delivery Systems

<table>
<thead>
<tr>
<th>Cost</th>
<th>Demographics</th>
<th>Chronic Diseases</th>
<th>Life Style Disease</th>
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<tr>
<td>Inefficient use of Information</td>
<td>Fragmented, Compartmentalized Services</td>
<td>Protracted Adoption of Best Practices</td>
<td>Complex Services</td>
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- **Cost:** Inefficient use of Information
- **Demographics:** Fragmented, Compartmentalized Services
- **Chronic Diseases:** Protracted Adoption of Best Practices
- **Life Style Disease:** Complex Services
The Challenge of Delivery of Equitable and Effective Healthcare: Balancing Infinite Demand Versus Finite Resources

30 March 2010
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities

Health Status

- Healthy/Low Risk
- At-Risk
- High Risk

20% of the Population Generate 80% Cost

- multiple co-morbidities
- end-of-life care
- chronic disease progression
- chronic disease early stage
- acute disease

Value
Cost
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
The Three Convergent Forces Shaping the Evolution of Healthcare

- Molecular medicine and personalized medicine
- Access, cost, and quality of care
- Proficient use of information (e.health)
The Waste and Risk of Empirical Rx: Ignoring The Obvious in Clinical Practice

- diseases are not uniform
- patients are not uniform
- a “one-size fits all” Rx approach cannot continue

- inefficiency and waste of empirical Rx
- cost of futile therapy
- medical error and AEs
The Evolving Market for (Bio)Pharmaceutical Therapies

- **“Blockbuster” Rx**
  - Empirical “one-size-fits-all”
  - Population-based Rx

- **Stratified/Targeted Rx**
  - Rx targeted to patient subgroups with common molecular pathology
  - Dx-Rx combinations and Rx labeling

- **Individualized Rx**
  - Relevant disease subtype
  - AE risk profiling
  - Compliance monitoring

- **Personalized Healthcare**
  - Integrated framework of coordinated care and longitudinal care
molecular diagnostics and individual patient profiling: the key driver in molecular medicine and rational therapeutics

- mapping the causal pathology of disease versus diagnosis based on symptoms/biochemistry/histopathology classifications
- identification of molecular subtypes of disease arising in same cell/organ and common symptoms
- disease subtypes and Rx selection
  - right Rx for right disease subtype
- profiling individual genetic variation in response to drugs
  - right Rx for right patient
- eventual mapping of individual disease predisposition risk profiles based on genetic uniqueness
  - new approaches to disease prevention
Mapping the Molecular Signatures of Disease

**PROFILE**
- ID patterns of pathway and network dyregulation in disease
- "biosignatures"

**SENSE**
- Automated platforms for rapid detection of multiplex analytes

**ACT**
- Rapid analytics and customized data formats/visualization to guide optimum decisions by clinicians, patients and payors
Mapping the Molecular Signatures of Disease

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Life Sciences

Engineering

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

MDx Platforms

- massive parallelism
- miniaturization
- automation
- rapid
- POC

RIGHT Rx for RIGHT DISEASE SUBTYPE
# Molecular Diagnostics and Miniaturized Devices: A Key Future Driver in the Healthcare Value Chain

## Complex Biosignature Profiling

<table>
<thead>
<tr>
<th>genomics</th>
<th>proteomics</th>
<th>immunosignatures</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="genomics image" /></td>
<td><img src="image2.png" alt="proteomics image" /></td>
<td><img src="image3.png" alt="immunosignatures image" /></td>
</tr>
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## Signature Detection, Deconvolution and Multivariate Analysis

<table>
<thead>
<tr>
<th>automated, high throughput multiplex assays</th>
<th>novel test formats and devices (POC)</th>
<th>new algorithms for complex signal/deconvolution</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image4.png" alt="automated image" /></td>
<td><img src="image5.png" alt="novel test formats image" /></td>
<td><img src="image6.png" alt="new algorithms image" /></td>
</tr>
</tbody>
</table>
K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy

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

clinical guidelines

- regulatory endorsement in product labeling

- payor adoption
● 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)

- 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
From Pharmaceuticals to Pharmasuitables

Disease Subtyping:

Individual Variation and AE risk

Right Rx for Right Disease

Right Rx for Right Patient
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
  - number of isoforms for DMPK enzymes and scale of individual variation within populations
- 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
- growing recognition of importance of variation in HLA and immune response alleles as additional risk factor
The Hunt for Gene Loci Associated with Complex Human Diseases
The “Missing Heritability in Complex Human Diseases”

“Human Genetics faces an unexpected problem. It is plagued by what might be called Macavity Genes. Often the evidence for inheritance is clear, but, like the mystery cat, the agents responsible are just not there.”

Dr. S. Jones
Lancet 3 April 2010 p. 1153
Disease Predisposition Risk Profiling for Common, Multigenic Late-Onset Disorders

- slower evolution than many predict
- Genome-Wide Association Studies (GWAS)
  - high cost and to date low yield in terms of clinically exploit able markers
  - disease origins from multiple low penetrance alleles versus small, dominant set of high penetrance alleles
- substantial ambiguities regarding probabilistic risk of overt disease
  - epistasis
  - epigenetics
  - environmental confounders
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The premature quest to provide consumer genomic testing (CGx) for future risk of major diseases
“Our ignorance of the laws of variation is profound”

Charles Darwin
Mapping the Complexity of Genome Organization

- recognition of increasing levels of organizational and regulatory complexity
  - haplotypes
  - CNV
  - indels
  - RNA universe
  - ‘dark’ elements
  - epistasis
  - epigenetics
  - nuclear compartmentalization and \textit{trans}-expression
### miRNAs Associated with Solid Cancers

<table>
<thead>
<tr>
<th>Tumor</th>
<th>miRNA</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>miR-21, miR-125b</td>
<td>oncomiR</td>
</tr>
<tr>
<td>Breast cancer metastasis</td>
<td>miR-335, miR-206, miR-126</td>
<td>metastasis suppressor</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>let-7a, miR-143, miR-145</td>
<td>tumor suppressor</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>miR-17-92 cluster, miR-106b/93/25 cluster</td>
<td>oncomiR</td>
</tr>
<tr>
<td>Pancreatic ductal carcinoma</td>
<td>miR-196a, miR-196b</td>
<td>oncomiR</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>miR-199a/b, miR-140, miR-145, miR-204, miR-125a/b</td>
<td>tumor suppressor</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>miR-141, miR-200a/b/c</td>
<td>oncomiR</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>miR-21, miR-224, miR-34a, miR-221/222, miR-106a, miR-106a, miR-203</td>
<td>oncomiR</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>miR-122a, miR-422b, miR-145, miR-199a</td>
<td>tumor suppressor</td>
</tr>
<tr>
<td>Thyroid papillary cancer</td>
<td>miR-146b, miR-221, miR-222, miR-181b, miR-155, miR-224</td>
<td>oncomiR</td>
</tr>
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From: M. Galasso et. al. (2010) Genome Medicine 2, 12
Gene Deserts: The 8q24 Region and Cancer Susceptibility

Translation of the Major Promise of Molecular Medicine into Routine Clinical Practice

A Complex, Multi-Dimensional Challenge
The Trajectories for Molecular Medicine

- exponential growth of research data
- technology convergence
  - life sciences
  - engineering
  - computing

Data vs. Time
The Trajectories for Molecular Medicine

- **exponential growth in research data**

- **Data**

- **Time**

- **translational medicine and clinical validation**

- **regulatory standards**

- **clinical utility**

- **routine clinical adoption**

- **exponential growth in research data**
The Real World

- innovation in science and technology alone is necessary but not sufficient
- adoption requires overcoming multiple barriers
  - existing standard of care
  - cultural conservatism
  - pricing, reimbursement and other obstacles
  - regulatory hurdles
  - intellectual property
- wide variation in adoption speed by different sectors
  - healthcare (10-30 years)
  - computing (1-2 years)
  - engineering (1-10 years)
Deriving Value from “-Omics”

- useful only when correlated with additional parameters
  - clinical outcomes
  - clinical utility
  - actionable information
  - demonstrable economic value
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
Standards for ‘Omics’ Data Cross-Domain Integration, Open-Source Data Sharing and Computational Analysis
OBO Foundry Ontologies

Nature Biotechnology 25, 1251 - 1255 (2009)

- Cell Ontology (CL)
- ZFIN: Zebrafish Anatomical Ontology
- Plant Ontology (PO)
- Common Anatomy Reference Ontology
- Phenotypic Quality Ontology (PATO)
- Gene Ontology (GO)
- Chemical Entities of Biological Interest (ChEBI)
- Sequence Ontology (SO)
- Environment Ontology
- The Open Biomedical Ontologies
- Protein Ontology (PRO)
- RNA Ontology (RnaO)
- Disease Ontology (DO)
- Ontology for Clinical Investigations (OCI)
- Ontology for Biomedical Investigations
- The Relation Ontology
- OBO Relation Ontology

http://www.nature.com/nbt/journal/v25/n11/fig_tab/nbt1346_T2.html
The Rise of Open-Source Networks and Consortia
Managing Mega-Data

- **volume**
- **scale**
- **global networks**

- **heterogeneity**
- **integration**
How Much New Technology Can We Afford?
UK National Institute for Health and Clinical Excellence (NICE)
Nice Gets Nasty (or Rational?)
Wellness:

The Most Broad and Most Valuable Definition of Successful Healthcare

Consumers at the Center
After a Short Stay in America, Michelangelo's David Returned to Europe
polypharmacy and AEs
poor patient compliance
multiple physician/venue encounters
poor communication/coordination between siloed healthcare services
The Non-Compliance Problem

- non-compliance rates in both long-term and short-term treatments reach 50% of patients
- non-compliance "a worldwide problem of striking magnitude" (WHO, 2003)
- non-compliance is a major barrier for realizing the benefits evidence-based therapies
- lack of effective policies toward the problem of non-compliance at both national and European levels
Health Status Monitoring and the Promotion of Wellness

On-Body: In-Body Sensors (OBIBs) and Remote Monitoring of Health Status
On Body: In Body Sensors/Devices
For Real Time and Remote Monitoring of Individual Health Status
When Your Carpet Calls Your Doctor

Wireless health care

The Economist 10 April 2010
Personal Health Systems: On-Body: In-Body Sensors (OBIBs)

- wearable
- portable/mobile
- point-of-care
- implantable
- multi-parametric
- interoperability with electronic records

Mobile Health (mHealth)
## Major Target Markets for Wireless Medicine

<table>
<thead>
<tr>
<th>Disease</th>
<th>Parameter</th>
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<tbody>
<tr>
<td>Alzheimer’s</td>
<td>vital signs, location, activity, balance</td>
</tr>
<tr>
<td>Asthma</td>
<td>respiratory rate, FEV, air quality, oximetry, pollen count</td>
</tr>
<tr>
<td>Breast CA</td>
<td>ultrasound self-exam</td>
</tr>
<tr>
<td>COPD</td>
<td>respiratory rate, FEV, air quality, oximetry</td>
</tr>
<tr>
<td>Depression</td>
<td>medication compliance, communication</td>
</tr>
<tr>
<td>Diabetes</td>
<td>glucose, hemoglobin ATC</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>cardiac pressures, weight, blood pressure fluid status</td>
</tr>
<tr>
<td>Hypertension</td>
<td>continuous blood pressure monitoring, medication compliance</td>
</tr>
<tr>
<td>Obesity</td>
<td>smart scales, caloric in/out, activity</td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td>sleep phases, quality, apnea, vital signs</td>
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Modified from: West Wireless Health Institute, Medtech Insight, August 2009
The Infocosm: Emerging Networks of Global Connectivity
“It is a shame that the telegraph has been invented. Now suddenly anyone can get the news”

“One already has too much to think about when bathing, which is not good”

James Rothschild (1852)
Information-Based Medicine

HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
NHS Connecting for Health

NHS Connecting for Health supports the NHS in providing better, safer care, by delivering computer systems and services that improve how patient information is stored and accessed.

NHS staff, the media and patients can use this site to learn about our work and its benefits.

New & updated sections

Summary Care Records (SCR)
Faster, safer access to key health information.

Picture Archiving and Communications System (PACS)
Digital x-rays and scans.

NHS Pathways
For emergency or urgent care assessment.

Clinical Dashboards Demonstrator
Selection of pilot stage demo dashboards.

Automatic identification and data capture
Bar codes and radio frequency technology.

NHS Number: adult social care
Supporting health and social care integration.

QuickLinks

Electronic Prescription Service Release 2
Four stages of PCT readiness for Release 2.

NHS Interoperability Toolkit
Framework & standards for local integration.

Source: http://www.connectingforhealth.nhs.uk/
“I look forward to the day when a physician without mathematics will seem as incongruous an idea as that of an educated man without Latin or Greek”

Dr. Gilbert, Physician to Elizabeth I

“A physician without a computer will soon be as rare a phenomenon as one with knowledge of Latin and Greek”

Professor Ian Isherwood CBE
MANCHESTER MEDICAL SOCIETY
20 June 2003
Telecommunications and Media Industry Convergence: Implications for Healthcare
Wireless Technologies: Consumer and Clinical Markets Converge
e-Patient Revolution
Integrated Data Systems for Mobile Networks

- geolocation data (where)
- temporal information (when)
- contextual information (what)
Pharma and Healthcare Social Media Brand Sponsored Patient Communities

- **23andMe**: social networking and genetics supported by community
- **alli circles**: support community for Alli, weight loss product from GSK
- **CFvoice**: people of all ages living with cystic fibrosis
- **Epilepsy Advocates**: support community for Epilepsy by Valeant
- **Epilepsy EMPOWERMENT**: global, interactive social network for CML community by Novartis Oncology
- **Arimidex (breast cancer)**: support and patient story site
- **CML earth**: support community for breast cancer sponsored by Genentech
- **Hearing Journey**: support community supported by hearing implant company
- **WHYDOT**: support community Bayer Healthcare
- **PKU.com**: support community for patients with PKU sponsored by Biomarin

Online wellness program:
- **walkingbread**: support community epilepsy
- **myMS myWAY**: support community collaboration Bayer Healthcare and MS Soc.
- **Cystic Fibrosis**: support community Cystic Fibrosis sponsored by Gentech

Shared patient stories:
- **Diabetes community, sponsored by OneTouch**: online wellness program
- **Living with Hemophilia**: support community Bayer Healthcare
- **Changing Life with Diabetes**: support community patients with PKU sponsored by Biomarin

Focus on through social media:
- **DIABETES HANDPRINT.COM**: support community overall disease information and features
- **DEPNET.com**: everyday support
- **EPILEPSY EMPOWERMENT**: support community to share the power of Walk MS experience
- **MSwatch**: Support community patients with PKU sponsored by Biomarin
- **Canadian Multiple Sclerosis community**: Canadian Multiple Sclerosis community
- **Hearing Journe**: support community supported by hearing implant company
- **PKU.com**: support community for patients with PKU sponsored by Biomarin
“We’ll have an entire generation of people who never truly have a private moment”

Patrick Tucker
Director of Communications
World Future Society
Virtual Medicine Networks: Increasingly Integrated Care and Continuity of Care

- rapid, real time access
- clinical specialties
- health records
- lab data
- drug interactions
- electronic Rx prescribing
A New Healthcare Ecosystem Arising From Technology and Market Convergence

Integrated Technology Platforms

Dx/Devices

Rx

Hlx

passive/active data collection
analytics and network architecture
EMR/PMR
performance and outcomes analysis

Data Mining and Integration Services

Increasingly Targeted Care and Efficient Use of Finite Resources

services for integrated care

patients

consumers
Global Health: Understanding the Implications of Major Economic and Environmental Dislocations
Reaping the rewards: a vision for UK medical science

Groundbreaking advances in medical science over the last 30 years offer the next UK Government an unprecedented opportunity to reinvigorate the economy, to enhance the productivity of the NHS and to make public services more cost-effective. Bold leadership will ensure that the UK can continue to generate world-class medical science that is translated into health and wealth benefits, and can become the best location in the world for medical research in both the public and private sectors.
Sustaining UK Research Innovation

Life Sciences 2010: Delivering the Blueprint

The Current and Future Role of Technology and Innovation Centres in the UK
A Report by Dr. Hermann Hauser

Strength and Opportunity

For Lord Mandelson
Secretary of State
Department for Business Innovation & Skills
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
• remote 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
“to encourage harmony”