Being the Best: 20 Year Outlook
Event 1: Game-Changing Innovations

Getting to Personalized Medicine: Innovation and the Role of Comparative Effectiveness Research

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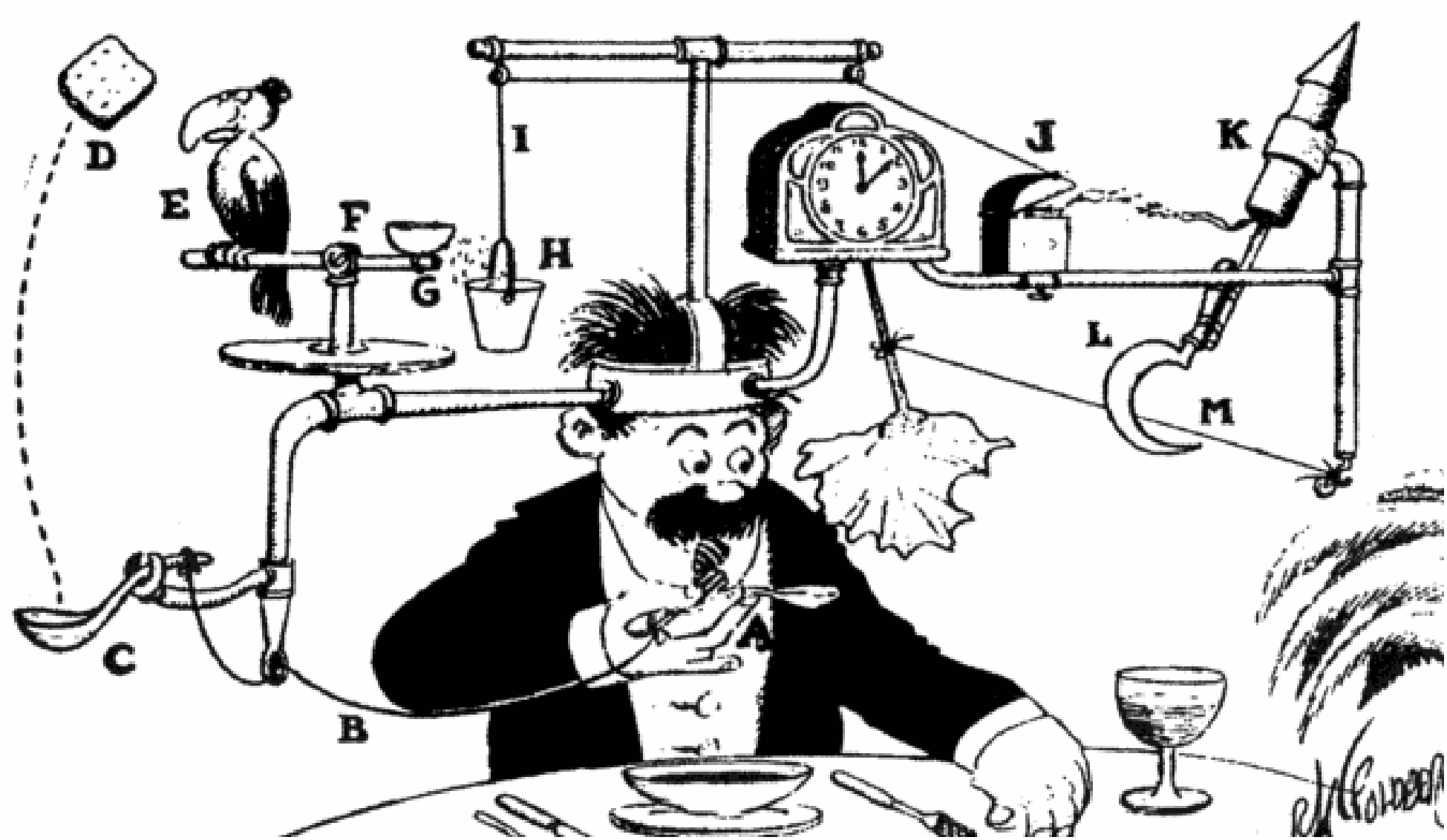
The LEWIN GROUP®
Center for Comparative Effectiveness Research

Innovation?



Rube Goldberg machine: Professor Butts and the self-operating napkin

Technologies Determined to be Ineffective or Harmful for Some/All Patients/Indications

- ABMT-HDC for breast cancer
- Anti-arrhythmic drugs
- Bevacizumab (Avastin) for breast cancer(?)
- COX-2 inhibitors
- Electronic fetal monitoring during labor without access to fetal scalp sampling
- Episiotomy (routine or liberal) for birth
- Extracranial-intracranial bypass to reduce risk of stroke
- Erythropoiesis-stimulating agents for anemia (for “normal” Hgb?)
- Gastric bubble for morbid obesity
- Gastric freezing for peptic ulcer disease
- Hormone replacement therapy for healthy menopausal women
- Intermittent positive pressure breathing
- Oxygen for premature infants
- Prefrontal lobotomy for mental disturbances
- Prostate specific antigen (PSA) testing for prostate cancer
- Radiation therapy for acne
- Thalidomide for sedation in pregnant women

Technologies that are Beneficial, Cost-Effective, but Underused

- ACE inhibitors for treatment of heart failure
- Antibiotics for gastrointestinal ulcers
- Childhood vaccinations
- Cochlear implants for severe-to-profound deafness
- Colorectal cancer screening
- HbA1c testing every 6 months in diabetic patients
- Hypertension management
- ICDs for survivors of cardiac arrest
- Influenza vaccines
- Inhaled corticosteroids in adults with asthma
- Mammography (esp. age 50+)
- Organ transplantation
- Pap smears
- Pneumococcal vaccine for high risk patients
- Smoking cessation interventions
- Warfarin to prevent strokes due to atrial fibrillation

Why Are Proven Technologies Underused?

- **Lack of awareness by patients, physicians, and others**
- **Inadequate information dissemination**
- **Actual or perceived concern about poor patient adherence (e.g., polypharmacy for HIV/AIDS)**
- **High costs / limited coverage and payment**
- **Concerns about short-term cost without regard for subsequent cost savings or cost-effectiveness**
- **Inappropriate or unsubstantiated concerns about improper use (e.g., pain therapy)**
- **Inconvenience and misperceptions by clinicians or patients**
- **Clinical inertia**
- **Insufficient supply (e.g., organs for transplantation)**
- **Disproportionate concerns about adverse effects (e.g., warfarin to reduce risk of stroke)**
- **Fear of stigma (e.g., treatment of depression)**
- **Professional conflicts by physician specialists, provider institutions, industry, and others**

As Described in *A Call to Make Valuable Innovative Medicines Accessible in the EU**

- **If a medicine leads to key improvements in health outcomes: Innovative**
  - **And if it fills an unmet medical need: Valuable**
    - **And if it results in net savings, or cost-effective and acceptable budget impact: Value for money**
- **Then, it should be largely implemented and made accessible to all in need for it**

*Background report for ministerial conference 23-24 September 2010.

Attribute Demand: Health Technologies (1)

- **Better: more effective, more accurate**
- **Safer: fewer adverse events/side effects**
- **Less painful / uncomfortable**
- **Less invasive**
- **Sooner: risk assessment/screening, diagnosis**
- **Faster: treatment, recovery; development/production**
- **Easier: expertise/training req'ts, ergonomics, delivery, adherence**
- **Targeted: to organs, tissues, cells**
- **Personalized: for individual patients**
- **Cheaper: per unit, episode of care, downstream**

Attribute Demand: Health Technologies (2)

- **Customized/options: e.g., for providers/facilities**
- **Standardized, easy care flow integration**
- **Smaller: lighter, portable**
- **Reliable: fail-safe, low maintenance; customer support**
- **Responsive/adaptable/programmable**
- **Informative/accountable: data recording, transmission**
- **Secure: protected personal/health information**
- **Closer/more convenient: hospital ⇨ clinic ⇨ doc's office ⇨ workplace ⇨ home**
- **Remotely deliverable**
- **Greener: energy-efficient, reusable, recyclable, biodegradable**

Personalized Medicine

"Personalized medicine" refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not." — President's Council of Advisors on Science and Technology 2008

Potential of Personalized Medicine

- **Predict our individual susceptibility to disease, based on genetic and other factors.**
- **Provide more useful and person-specific tools for preventing disease, based on that knowledge of individual susceptibility.**
- **Detect the onset of disease at the earliest moments, based on newly discovered biological markers and changes at the molecular level.**
- **Preempt the progression of disease, as a result of early detection.**
- **Target medicines and dosages more precisely and safely to each patient, on the basis of genetic and other personal factors.**

Source: Personalized Healthcare: Opportunities, Pathways, Resources. U.S. Department of Health and Human Services. September 2007.

Why Comparative Effectiveness Research?

- **Evidence of inappropriate use of health care technologies, including over-use, under-use, and improper use**
- **Evidence of large variations in practice**
- **Evidence submitted for market authorization by regulatory agencies often not sufficient to support clinical and policy decisions**
- **Inconsistent, insufficiently rigorous evidence for many technologies that are not subject to market authorization (i.e., many medical and surgical procedures)**
- **Lack of evidence on "head-to-head" comparisons of alternative interventions for particular health problems**
- **Lack of evidence in "real-world" practice (efficacy vs. effectiveness)**
- **Continued rapid increases in health care costs**

Main Attributes of CER

- **Direct ("head-to-head") comparisons of alternative interventions (as opposed to comparison with placebo or indirect comparisons)**
- **Applies to all types of interventions**
  - pharma, biotech, devices/equip't, medical and surgical procedures; organization, delivery, management, financing
- **Effectiveness (in realistic health care settings) rather than efficacy (in ideal circumstances)**
- **Health care outcomes (e.g., morbidity, mortality, symptoms, QoL, adverse events) rather than intermediate/surrogate endpoints**
- **Enables subgroup analyses to yield findings for particular patient groups, including priority populations**

CER Methods "Toolkit" (Evolving)

Clinical Trials

- Randomized clinical trials
- Practical (pragmatic) clinical trials
- Other non-randomized controlled trials
- Adaptive clinical trials and other trial designs
- Other, e.g., randomized consent, regression discontinuity, combined single-subject ("n of 1") trials

Observational Studies (prospective or retrospective)

- Population-based longitudinal cohort studies
- Patient registries
- Claims databases
- Clinical data networks
- Electronic health record data analyses
- Post-marketing surveillance (passive and active)

Syntheses of Existing Evidence

- Systematic reviews (comparative effectiveness reviews)
- Meta-analyses
- Modeling

"Fusion" of Data Sources Using Advanced HIT

Potential in large networks linking clinical, other data

- **Interoperable EHRs**
- **Biobanks (e.g., tissue/tumor repositories)**
- **Clinical registries**
- **Claims data**
- **Potential to conduct "virtual" clinical trials, observational (e.g., cross-sectional, longitudinal cohort) studies, advanced modeling**

However:

- **Methodological, statistical challenges remain in selection bias, information bias, other confounders**
- **Current data infrastructure for linking genetic testing data to other sources is far from adequate**

CER Using Multiple Data Sets; for example …

- **For a CER study on alternative treatments for colorectal cancer; one research team is using these observational data sets:**
  - **SEER–Medicare Linked Database (NCI, SEER registries, CMS)**
  - **CanCORS – Cancer Care Outcomes Research & Surveillance Consortium (NCI, VA)**
  - **NCCN Oncology Outcomes Database**
  - **Medicaid registries**

* Schrag et al., Dana-Farber/Harvard Cancer Center

CER and Personalized Medicine: Contradiction?

- **CER has been largely oriented toward population-based evaluations and applications. In contrast, personalized medicine (PM) focuses on using individuals' genomic information and other personal traits to inform their health care decisions.**

Subgroups and Individuals, Not Just Populations

- **The trouble with averages …**
  - Interventions that yield a statistically significant treatment effect across a study population may not necessarily work for all treated patients; they may be ineffective for some patients and harmful for others.
  - Interventions that do not yield a statistically significant treatment effect across a study population—and that may be dismissed as ineffective—may work for certain subsets of the population.
- **Need to discern subgroup and patient-specific differences**
  - Heterogeneity of treatment effects (HTEs)
  - Synergy with personalized medicine
  - Preferences for patient-reported outcomes (PROs)

CER and Personalized Medicine: Complementary

- **Population-based evidence must be complemented by personalized evidence based on discrete genomic and other personal traits of specific patients**
  - **CER should respond to and support PM**
  - **PM interventions must be supported with evidence of clinical validity and utility from diverse populations and routine health care settings**
  - **Need population-based research with sufficient power for subgroup analyses (esp. prospective) to identify and quantify relationships among genomic traits, biomarkers, therapies and health outcomes**
  - **Integrate research priorities, study design and conduct, reporting, and translation into practice**

Personalized Medicine Interventions Still Subject to Evidence Requirements

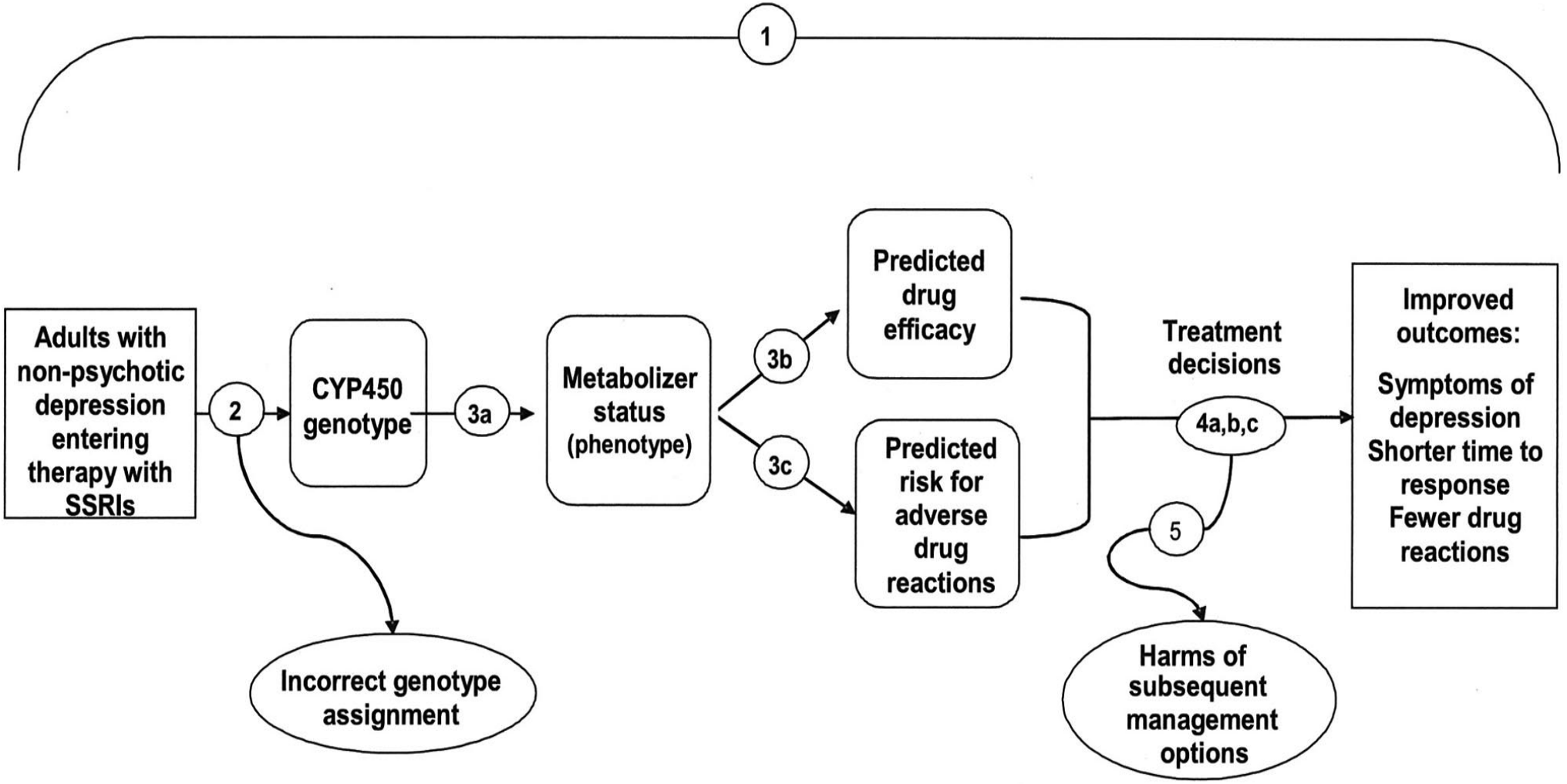
- **PM interventions don't get a "bye." Like other technologies, they remain subject to prevailing requirements for rigorous evidence demonstrating how well they work compared to standard care.**
  - **Increasingly, this means showing that an intervention has some direct, or least demonstrably indirect, favorable impact on outcomes that matter in real-world practice settings.**
  - **For genetic/genomic testing and other aspects of molecular-based PM, this means demonstrating not only technical accuracy of a test, but further downstream impact on health care decisions and outcomes.**

EGAPP Hierarchy of Data Sources and Study Designs

Level	Analytic Validity	Clinical Validity	Clinical Utility
1 (highest)	Collaborative study using a large panel of well-characterized samples Summary data from well-designed external proficiency testing schemes or interlaboratory comparison programs	Well-designed longitudinal cohort studies Validated clinical decision rule	Meta-analysis of RCTs
2	Other data from proficiency testing schemes Well-designed peer-reviewed studies (e.g., method comparisons, validation studies) Expert panel reviewed FDA summaries	Well-designed case-control studies	A single RCT
3	Less well designed peer-reviewed studies	Lower quality case-control and cross sectional studies Unvalidated clinical decision rule	Controlled trial without randomization Cohort or case-control study
4	Unpublished and/or non-peer-reviewed research, clinical laboratory, or manufacturer data Studies on performance of the same basic methodology, but used to test for a different target	Case series Unpublished and/or non-peer-reviewed research, clinical laboratory, or manufacturer data Consensus guidelines Expert opinion	Case series Unpublished and/or peer-reviewed studies Clinical laboratory or manufacturer data Consensus guidelines Expert opinion

Source: Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative : methods of the EGAPP Working Group. Genet Med 2009;11(1):3-14.

Analytical Framework: CYP450 for SSRIs



Source: Teutsch SM et al. EGAPP Working Group. Genet Med 2009;11(1):3-14.

Factors Influencing Cost-Effectiveness of Genetic Testing (1)

- **Prevalence of the genetic mutation and the disease in the population**
- **Severity and cost of the disease or outcome the test is designed to predict or diagnose**
- **Strength of the association between the genetic mutation and clinical outcomes (penetrance)**
- **Availability of effective interventions that can be implemented on the basis of genetic information and that provide a reduction in the relevant event rate compared with standard care**

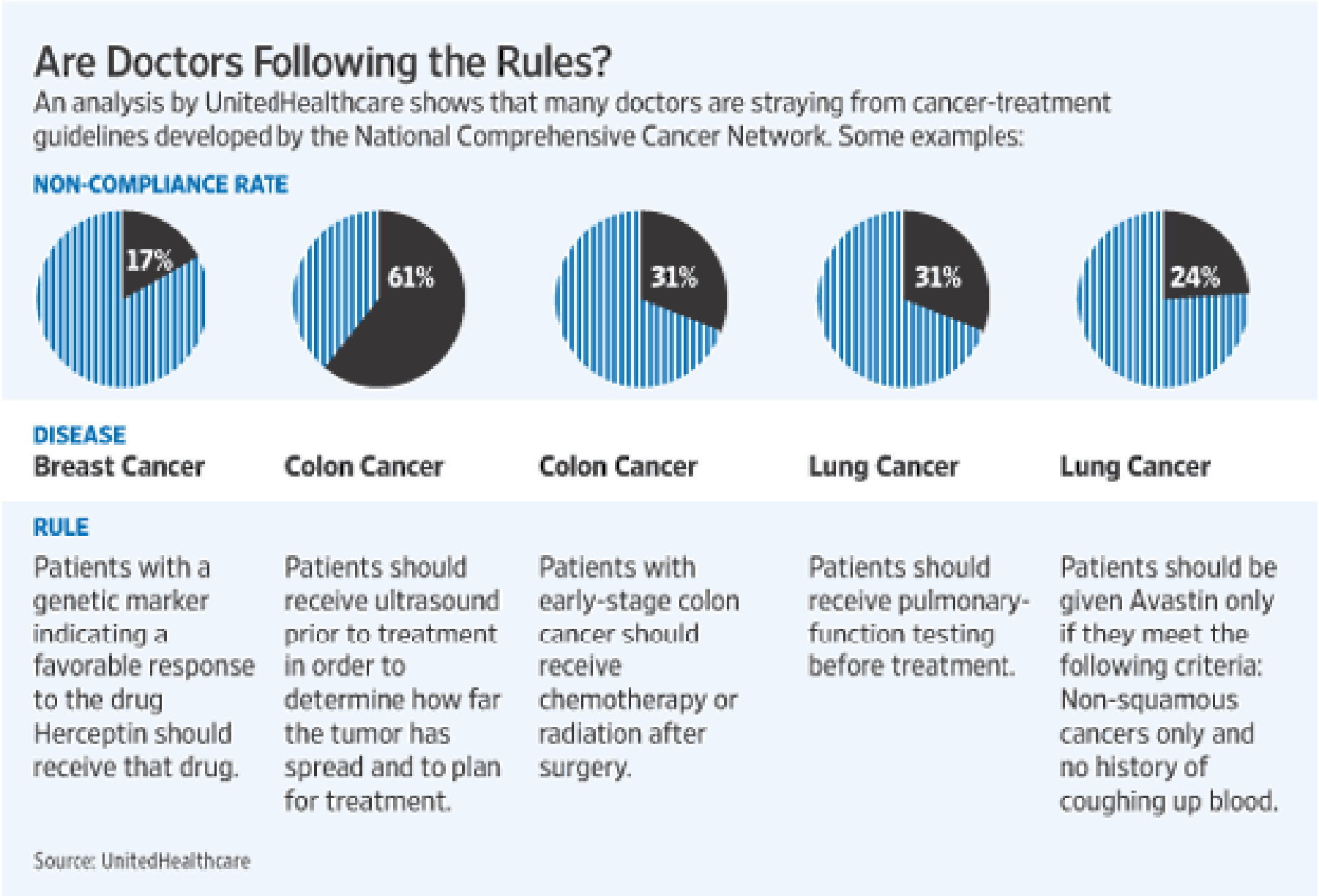
Source: Phillips KA, Veenstra DL, et al. Genetic testing and pharmacogenomics: issues for determining the impact to healthcare delivery and costs. Am J Mgd Care 2004;10(7):425-32.

Factors Influencing Cost-Effectiveness of Genetic Testing (2)

- **Whether testing is for prediction of future risk or for immediate diagnostic or prescribing decisions**
- **Cost, turnaround time, and accuracy of the test and whether the results provide information for a single condition or multiple conditions**
- **The cost of counseling (if relevant)**
- **The potential downstream and indirect costs and benefits such as the extent to which family members are tested, the potential ramifications of loss of privacy if genetic results are disclosed, etc.**

Source: Phillips KA, Veenstra DL, et al. Genetic testing and pharmacogenomics: issues for determining the impact to healthcare delivery and costs. Am J Mgd Care 2004;10(7):425-32.

Evidence-Based Policies Often Don't Translate into Practice



Source: Johnson A. Insurer plays judge on cancer care. Wall Street Journal. Feb. 9, 2010.

Medicare Evidence Development & Coverage Advisory Committee (MEDCAC): Pharmacogenomic Testing for Anticancer Therapies, Jan. 27, 2010

1. **How confident are you that there is sufficient evidence to determine whether pharmacogenomic testing affects health outcomes (including benefits and harms) for patients with cancer whose anticancer treatment strategy is guided by the results of testing as described below?**
   a) **CYP2D6 for breast cancer patients who are candidates for tamoxifen**
   b) **UGT1A1 for colon cancer patients who are candidates for irinotecan**
   c) **HER2/neu for breast cancer patients who are candidates for trastuzumab**
   d) **BCR-ABL for chronic myelogenous leukemia patients who are candidates for imatinib**
   e) **e) K-RAS for metastatic colorectal cancer patients who are candidates for cetuximab and/or panitumumab**

MEDCAC: Pharmacogenomic Testing for Anticancer Therapies, Jan. 27, 2010

2. **For those items where the answer to Question 1 is at least in the intermediate range (mean score ≥ 2.5), how confident are you that pharmacogenomic testing improves health outcomes for patients with cancer whose anticancer treatment strategy is guided by the results of testing as described below?**
   a) **CYP2D6 for breast cancer patients who are candidates for tamoxifen**
   b) **UGT1A1 for colon cancer patients who are candidates for irinotecan**
   c) **HER2/neu for breast cancer patients who are candidates for trastuzumab**
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MEDCAC: Pharmacogenomic Testing for Anticancer Therapies, Jan. 27, 2010

3. How confident are you that these conclusions are generalizable to

a. community based settings;
b. the Medicare beneficiary population?

4. Please discuss any important evidence gaps and recommend how they should be addressed.

CER Impact on Innovation?

- **CER is likely to alter "value propositions" for innovation. It will provide new opportunities and focus or redirect R&D portfolios.**
  - **The need to generate comparative evidence of health outcomes, including for patient subgroups, raises the risk of innovation and forces choices about its direction and sequence. Targeted therapies that can demonstrate comparative effectiveness may gain market advantages.**
  - **Government support of CER (trials, other studies) could reduce development costs of some new interventions. For example, government and private sector support of linked databases may help to identify new genetic determinants of drug response, related biomarkers.**

Implications for the Innovation-Friendly Yet Discerning and Accountable Health Authority (1)

1. **Determine health authority's responsibility for financing innovation, e.g.:**
   - Subsidize (many) unproven innovations?
   - Reward proven valuable innovation?
   - Support evidence generation for selected investigational uses?
2. **Marketing authorization by regulatory agency does not mean that evidence is complete; more will be needed, e.g.:**
   - Patient outcomes, not just biomarkers/intermediate outcomes
   - Effectiveness (in community settings, heterogeneous populations/subgroups)
   - Adverse events (esp. delayed or rare ones)
   - Patterns of use, costs
3. **Scientific and technical wizardry is no reason to dispense with rigorous evidence standards**
   - May adapt, refine standards for various technology types/other circumstances, as appropriate

Implications for the Innovation-Friendly Yet Discerning and Accountable Health Authority (2)

4. **Encourage/enable innovators to anticipate evidence requirements throughout technology lifecycle**
   - What gatekeepers/decision-makers will want what evidence when?
   - Improve transparency/communication/guidance re: evidence req'ts
   - Specify attributes/parameters of value
5. **CER, HTA, other developments/trends will redefine value and shift direction of innovation**
   - There will be shakeouts and successes
6. **Use provincial and other data assets for ongoing research of innovations in practice**
   - Practical trials, claims data, EHRs, registries, etc.
   - Link/integrate these sources as feasible/appropriate to increase scope of research and power of findings
7. **Collect ongoing performance data on overuse, underuse, improper use; outcomes**
   - Compare performance to standards/guidelines
   - Provide feedback to providers, industry, policy-makers, public for adaptation, corrective action (including standards/guidelines)

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