

# Using Diagnostics to Monitor the Effectiveness of Treatment



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# Quick Preview of Topics to be Presented in This Lecture

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- Treatment effectiveness & IT highlighted as key planks in healthcare reform; definitions and diagrams underpinning this assumption
- History of the use of diagnostics to monitor/control drug therapy; companion diagnostics and their linkage to emerging biotech drugs
- Federal government launches plan for research programs in treatment effectiveness; Big Pharma seeks to quash or control
- Diagnostics essential in any plan to monitor/control treatment effectiveness (TE); optimal means to gather objective documentation
- Elements of action plan to bring dx to forefront in therapeutic effectiveness programs; role of professional societies in plan

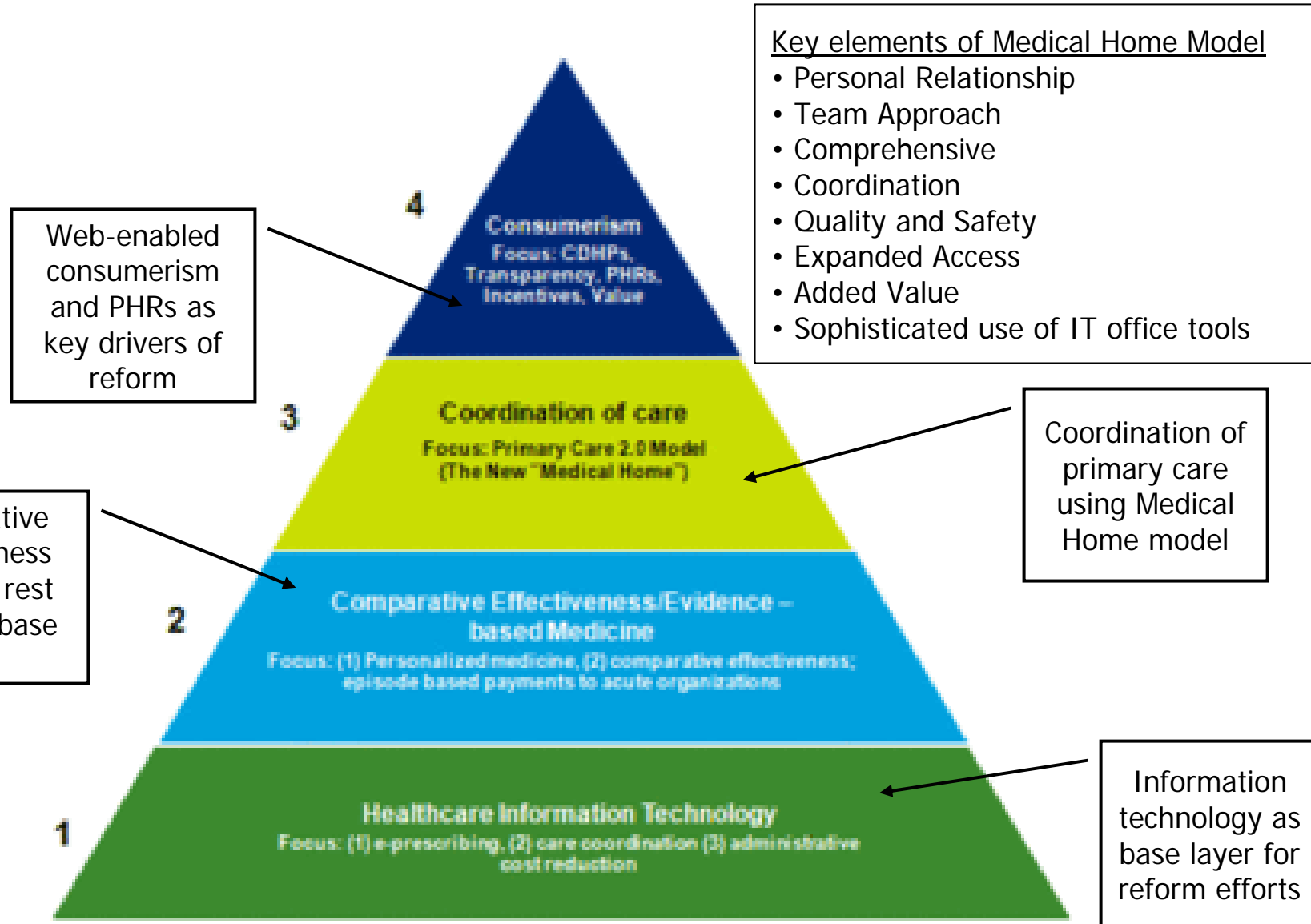
# General Themes and Ideas to Be Presented During This Lecture



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- Amount of money per year for drug therapy in the U.S. dwarfs amount spent for drugs and other types of medical therapy
- Explosion of technology/science for serum biomarkers, tissue biomarkers, & medical imaging; new drug development lagging
- Questions have arisen about how to fund the increasing cost of dx in an era when healthcare care costs are being constrained
- Overarching theme of this lecture: use of diagnostics to monitor treatment effectiveness to improve quality & lower cost-of-care
- *Transfer portion of resources from therapeutic silo to diagnostic solo; justified by role of diagnostics in monitoring effectiveness*

# Deloitte Center for Health Solutions: The Healthcare Reform Pyramid



# Placing Treatment Effectiveness (TE) in a Broader Healthcare Context



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- Changes discussed here re: TE constitute nothing less than major shift in healthcare delivery; parallels shifts occurring on other fields
- TE movement analogous to changes occurring in legal field; transition from billable-hours to evidence of achieving client goals
- Long history in healthcare of billing by procedure/time; this results in over-utilization & waste due to misplaced financial incentives
- In general, diagnostic services have largely been unengaged in direct TE assessment; emerging opportunity to participate
- TE will cause major changes in computerized reporting by LIS; tighter integration of data to objectively document rx outcomes

# A Closer Look at the Definition of Treatment Effectiveness



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- Broadly speaking, therapeutic effectiveness defined as positive outcome for patient as a direct result of therapeutic regimen
- The approach encompasses wide array of rx interventions in addition to drugs such as bed rest, physical therapy, prostheses
- About \$700 billion each year allocated to healthcare spending that can't be proven to lead to better health outcomes (source: CBO)
- Implicit in TE concept is movement away from payments based solely on actions/procedures and toward outcome-based payments
- Lab testing & medical imaging can provide evidence of favorable results; urgent need for consensus on successful outcomes criteria

# Defining Diagnostics: Lab Medicine, Pathology, and Medical Imaging



- Throughout lecture, will refer to diagnostics as general category; term encompasses lab medicine, pathology, & medical imaging
- I am strong advocate for merging these three disciplines into field of Diagnostic Medicine in order to achieve the following gains
  - Reduced cost and higher quality of diagnostic services
  - Greater political power due to criticality of services
  - Overlap already occurring with molecular imaging
  - Integration of specialized systems: LIS + RIS+ PAC = DIS
- Change will *not* occur spontaneously; need retrospective studies showing gains that might have been achieved with such integration



# Evidence-Based Medicine Morphs into Treatment Effectiveness by Episodes of Care

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- Must confess that I have labeled EBM in past as distracting despite known fact that many common treatments/procedures unproven
- I now understand overlap between EBM and comparative effectiveness; latter approach based on evidence of success in rx
- Tall order ahead of us: define measures of effectiveness, define episodes of care, & retool our information systems to measure TE
- Because challenge is so great, must be done in increments with special focus on common conditions with accepted practice norms
- Minnesota pushing for “bundles of care”; hospitals & doctors define and price a package of care to allow comparison shopping by pts.

# Treatment Effectiveness vs. Comparative Effectiveness Research



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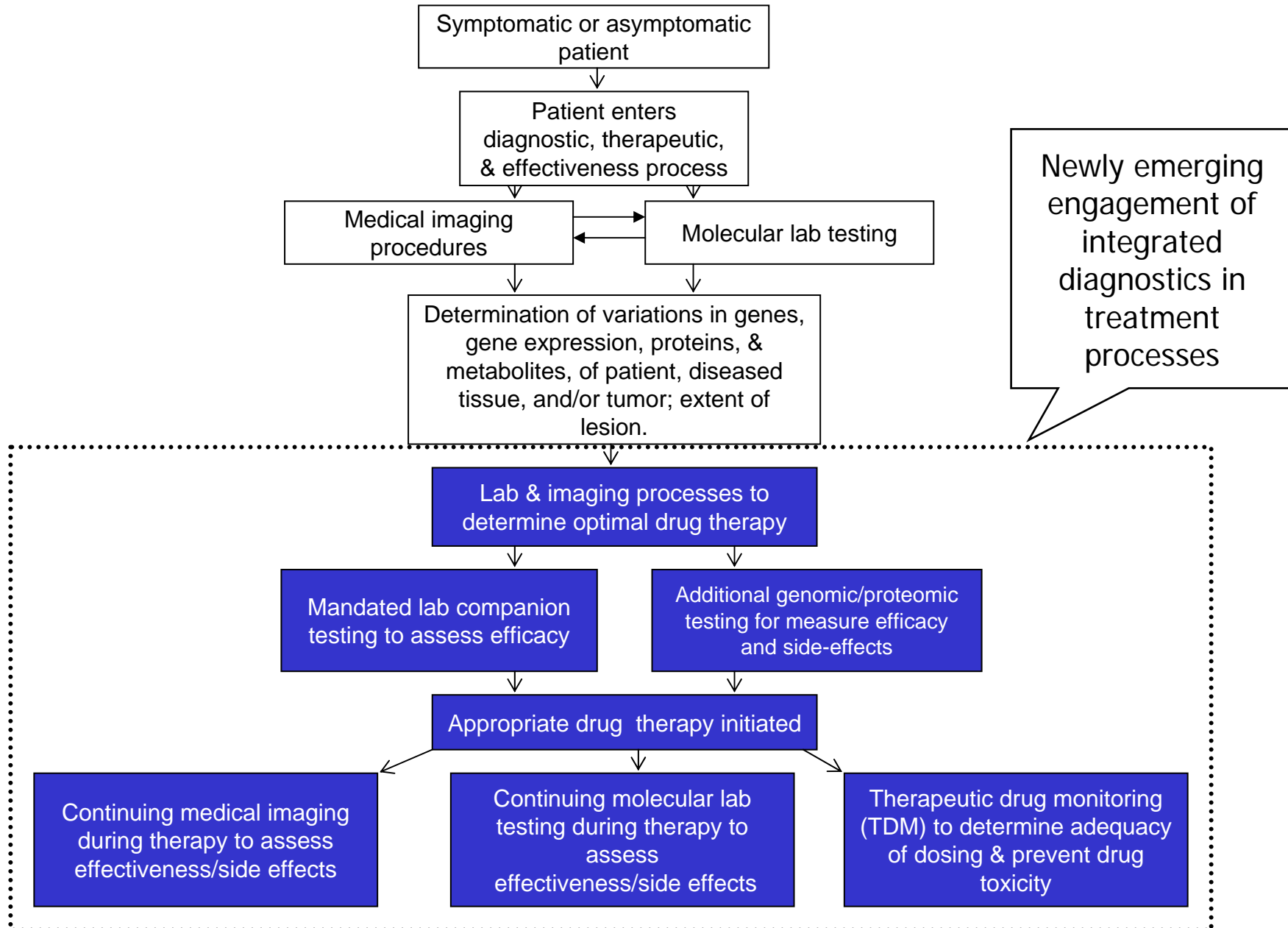
- Comparative effectiveness studies involve head-to-head comparisons of similar interventions & management strategies to treat disease
- Results of such studies will be resisted by physicians if seen merely as cost-saving measures rather than means to improve quality
- Medical treatment norms vary by region across country; interventionist norms cost more but may not yield better outcomes
- Consumers often only passive recipients of comparative effectiveness research; consumer advocacy groups can help mobilize members
- Concern on part of drug & device manufacturers that this research, like FDA regulation, may erect new barriers to product innovation

# Close Overlap of Personalized Medicine with Therapeutic Effectiveness



- Personalized medicine, perhaps better stated as targeted therapy, often defined as *right treatment for right patient at right time*
- Standardized approach to chemo not suitable for all pts. because of genotypic variation of tumor cells; rationale for use of companion dx
- For oncology patients & those with disease-mediated cellular injuries, personalized medicine comparable to tx effectiveness
- Biomarkers are easiest & cheapest way to monitor rx effectiveness; cells communicate with proteins when damaged, atypical, or healing
- PET scans will also be important in assessing regression of tumors and metastases; dynamic imaging technique allows *in-vivo* window

# Diagnostic Work Flow Diagram Underlying Personalized Medicine



# Linkage Between Treatment Effectiveness and Preventive/Predictive Medicine



- I predict that preventive/predictive medicine will soon begin to receive attention; greater emphasis can reduce cost-of-care
- Predictive medicine largely based on genomic/proteomic lab testing with some follow-up/confirmation with medical imaging
- P/P medicine closely also aligned with treatment effectiveness because earlier treatment assumed to be more effective
- In past, preventive medicine has not been adequately funded because MDs focus on treatment of disease & not prevention
- Inevitable that the pursuit of P/P medicine will be integrated into government programs emphasizing ROI & outcomes

# Early Health Model Folds Pre-Symptomatic & Pre-Clinical Dx into Health Continuum

- Ideas being promoted by GE Medical and Siemens; aligns with their large investments/integration of IVD and imaging
- Basic concept is pre-symptomatic, pre-clinical diagnosis based on biomarker panels & new imaging techniques
- EHM changes the rules of the game for MDs, healthcare insurance companies, and pharmaceutical companies
- Suggestion that EHM results in lower cost for healthcare but not yet proven; this idea needs research confirmation
- *EHM moves dx to the center of many healthcare processes because patients exhibit no overt signs/symptoms of disease*

# State of Wellness (Absence of Diagnosable Disease)

➤ Definitions and Diagrams

Wellness Domain

Preventive  
Medicine/  
Alternative  
Medicine



Genomic  
Medicine/  
Predisposition  
to Disease

Early Health Model Domain

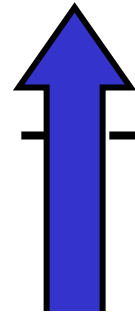


Overt Disease Domain

State of Diagnosable Acute Disease  
(Short-Term, Self-Limiting)



State of Chronic Diagnosable Disease  
(Long Duration and/or  
Frequent Recurrence)



Direction  
of Emerging Diagnostics,  
Science, & Technology

# Biomarker Panels (IVDMIAs) and the Analysis/Monitoring of Rx Effectiveness



- New discoveries in molecular dx driving trend toward test panels comprised of multiple biomarkers + computerized algorithm
- These panels referred to by the FDA as IVDMIAs; term now in standard usage; *in-vitro diagnostics multiplex indexes assays*
- FDA pushing IVDMIA manufacturers to seek approval & allow scrutiny of algorithms being used in conjunction with test panels
- Suspicion about the retrospective clinical trial methodologies being used to validate the clinical value of IVDMIAs brought to market
- We will need far greater expansion of this IVDMIA lab test category if we are to succeed in using molecular diagnostics to assess TE



# FDA's Interest in IVDMIAs; Why Regulation Could Stifle Innovation

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- Development of IVDMIA algorithms is dynamic process; concern that regulation will slow product development via slow approval
- Can retrospective studies of IVDMIAs piggybacking on subjects & serum/tissue banks of other clinical studies be properly designed?
- For IVDMIAs designed to diagnose cancer or assess cancer prognosis, what is an “acceptable” sensitivity and specificity
- Pressure on clinicians from patients. to order a particular IVDMIA that they may have read about in news although contraindicated
- “Tissue of Origin” test (Pathwork Diagnostics); original *approved* version has been superseded by newer *unapproved* version

# Big Ideas That Can Be Distilled from These Definitions and Diagrams



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- Diagnostics moving front-and-center in healthcare enterprise because of shift to early health model (pre-symptomatic dx)
- Major dx specialties (pathology, clinical lab, radiology) and also patients will derive quality/cost benefits from specialty merger
- Growing overlap of dx specialties may cause conflict & destructive competition at specialty interface without merger
- Diagnostic medicine inexorably drawn into personalized medicine; practitioners will render valued opinions about rx/px
- Integrated Diagnostic Centers will emerge in healthcare delivery for reasons of cost, efficiency, convenience; control up for grabs

# History of Use of Lab Diagnostics to Monitor Drug Therapy

- Long history of use of lab methods for therapeutic drug monitoring (TDM); used most often to track drug metabolism
- Pharmacy PhDs often attached to hospital clinical teams to monitor questions of drug dosage and pharmacokinetics
- In era of genomics/proteomics, recent consideration of *companion diagnostics* used in association with biotech drugs
  - Dx to determine patient candidacy for initiating therapy with a particular drug; used for patient serum OR tumor cell analysis
  - For several years, companion dx poster-child has been HER2/Neu status of breast cancer for Herceptin treatment
  - Newer example is K-RAS status of tumor cells to determine candidacy for *Erbix* or *Vectibix*; K-RAS must be “wild” type



# Role of Companion Diagnostics in Clinical Trials and Subsequent Drug Labeling

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- Generally no need to demonstrate drug effectiveness post FDA approval, companies must only demonstrate during clinical trials
- Cost of bringing biotech drug to market is enormous; companies thus anxious to improve odds of success in getting past trials
- Proof of drug effectiveness in trials enhanced if able to screen subjects with companion dx to select those likely to respond
- If pursue such a strategy, company obligated to label drug to select for patient/tumor profile similar to research subjects
- Drug companies now approaching dx companies early in drug development for parallel development of companion lab test

# Government Launching Research Program to Assess Treatment Effectiveness

- The \$787 billion economic stimulus bill provides money to compare effectiveness of different rx for the same illness
- Researchers will receive \$1.1 billion to compare drugs, medical devices, surgery that are used to treat specific conditions
- Spending on health care totaled \$2.2 trillion in 2007 & without reforms will rise to 25 percent of the G.D.P. in 2025
- Medicare currently covers any rx that is “reasonable & necessary”; agency can’t take costs into account for payment
- Britain & France have bodies that assess health technologies & compare the effectiveness and cost of different treatments

# Big Pharma Fights Stimulus Provision Mandating Study of Effectiveness



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- Big Pharma mobilizing to gut government funding for comparative effectiveness research; portraying as gov. rationing
- Obama supported such research in campaign because will help government programs direct their payments to effective therapy
- When AHRQ suggested in 1995 that too many unnecessary back surgeries, doctors and industry groups attacked the conclusion
- Drug and device manufacturers derive huge benefits from unnecessary use of their products, particularly if common event
- Goal of industry is to control how effectiveness data is created, reviewed, evaluated, and accessed by consumers & officials

# Will Government Plans for Comparative Effectiveness Morph into Boondoggle



- Cases stand out in our minds (e.g., Celebrex) where expensive drugs with side effects have been inappropriately promoted by MDs
- Drug companies retain enormous marketing & lobbying clout despite recent efforts to limit their largesse to physicians
- Large gap between effectiveness findings from various research studies and the modes of practice of physicians in community
- Look at expenditures for “alternative medicine” and herbal remedies in U.S.; consumers certainly don’t require rigid proofs
- What is required is some “middle way” approach; most attention should be paid to oncology because expensive & lives at stake



# Diagnostics Essential in Any Plan to Assess Treatment Effectiveness

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- Very simple point to be made here; diagnostics of various types will be key element in any mandated plan to assess rx efficiency
- Currently provides much of the objective outcome evidence; sophistication will only increase with better IVDMA offerings
- Significant challenge to convince lab professionals to engage in downstream treatment monitoring and to partner with clinicians
- Another challenge: move diagnostics “upstream” to preventive/predictive medicine; new technology will be driver
- Diagnostics industry also needs to stake claim on resources that might have been wasted on treatments deemed as ineffective

# Mobilizing Lab & Pathology Societies to Lobby for Expanded Role/Visibility of Dx



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- Diagnostics an underappreciated industry; subservient to therapeutics controlled by clinicians & their relationship to pts.
- Healthcare consumers have vital interest in lab testing because test results are very accessible for them; easy to understand
- Witness the growth of the web-based direct-access-testing (DAT) market which is now being linked to the growth of PHRs
- Lab/pathology societies mired in old-think; lobbying mainly for test reimbursement; should focus more on rx effectiveness
- Status of diagnostics could be enhanced by merger and closer collaboration of pathology, lab med, and medical imaging



# Barriers to Use of Diagnostics in Monitoring Effectiveness of Drug Therapy

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- Generally speaking, pathologists only infrequently involved in therapeutic decisions or monitoring of therapy after started
- Exception to this rule occurs in cancer rx, particularly hematopathology; malignant cell analysis important in rx
- Many pathologists lacks the clinical skill sets to become more intimately involved in making therapeutic clinical decisions
- Need closer integration of IVD & lab software industries; need new applications to assess TE based on episodes-of-care
- May be difficult, but should also seek “rules” active at time of test ordering to optimize real-time effective use of diagnostics

# Ten Possible Next Steps to Engage Dx Industry in “Effectiveness” Programs

- Seek closer alignment of path., lab medicine, & radiology
- Stimulate development of Diagnostic Information Systems
- Develop integrated reports emphasizing clinical outcomes
- Promote research in, and deployment of, IVDMIAAs
- Actively resist FDA pressure for more regulation of IVDMIAAs
- Lobby professional societies to endorse treatment effectiveness
- Encourage more involvement of pathologists with drug therapy
- Support EHM, predictive, & preventative medicine
- Encourage entry of pathology trainees with more clinical skills
- Consider development of Integrated Diagnostic Centers



# Summary and Take-Home Points for This Lecture

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- Healthcare reform will be driven by information technology, comparative effectiveness research, and PHR adoption
- Pathology/lab medicine will play major role in documenting treatment effectiveness & pre-diagnostic, pre-symptomatic dx
- Big Pharma & device manufacturers mobilizing to quash government funded medical effectiveness research programs
- Increasing attention to possible merger of pathology, lab medicine, & radiology; greater involvement with therapy
- Molecular diagnostics & IVDMIAs + companion diagnostics essential ingredients in growth of personalized/predictive medicine