# Using Diagnostics to Monitor the Effectiveness of Treatment

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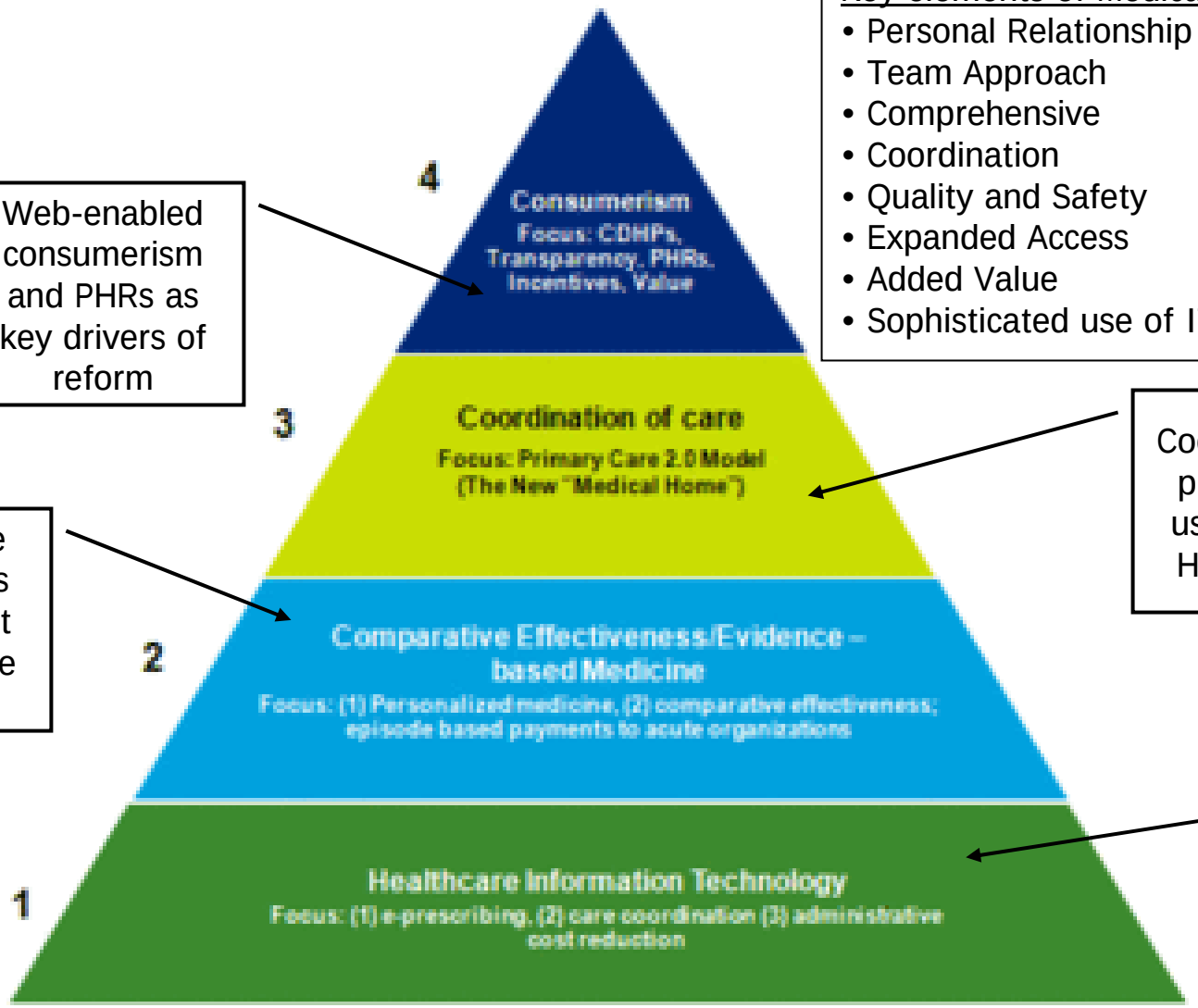
# Quick Preview of Topics to be Presented in This Lecture

- 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

- 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




Web-enabled consumerism and PHRs as key drivers of reform

Comparative effectiveness and EBM rest on an IT base layer

Coordination of primary care using Medical Home model

Information technology as base layer for reform efforts

Key elements of Medical Home Model

- Personal Relationship
- Team Approach
- Comprehensive
- Coordination
- Quality and Safety
- Expanded Access
- Added Value
- Sophisticated use of IT office tools

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

- 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

- 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

- 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.

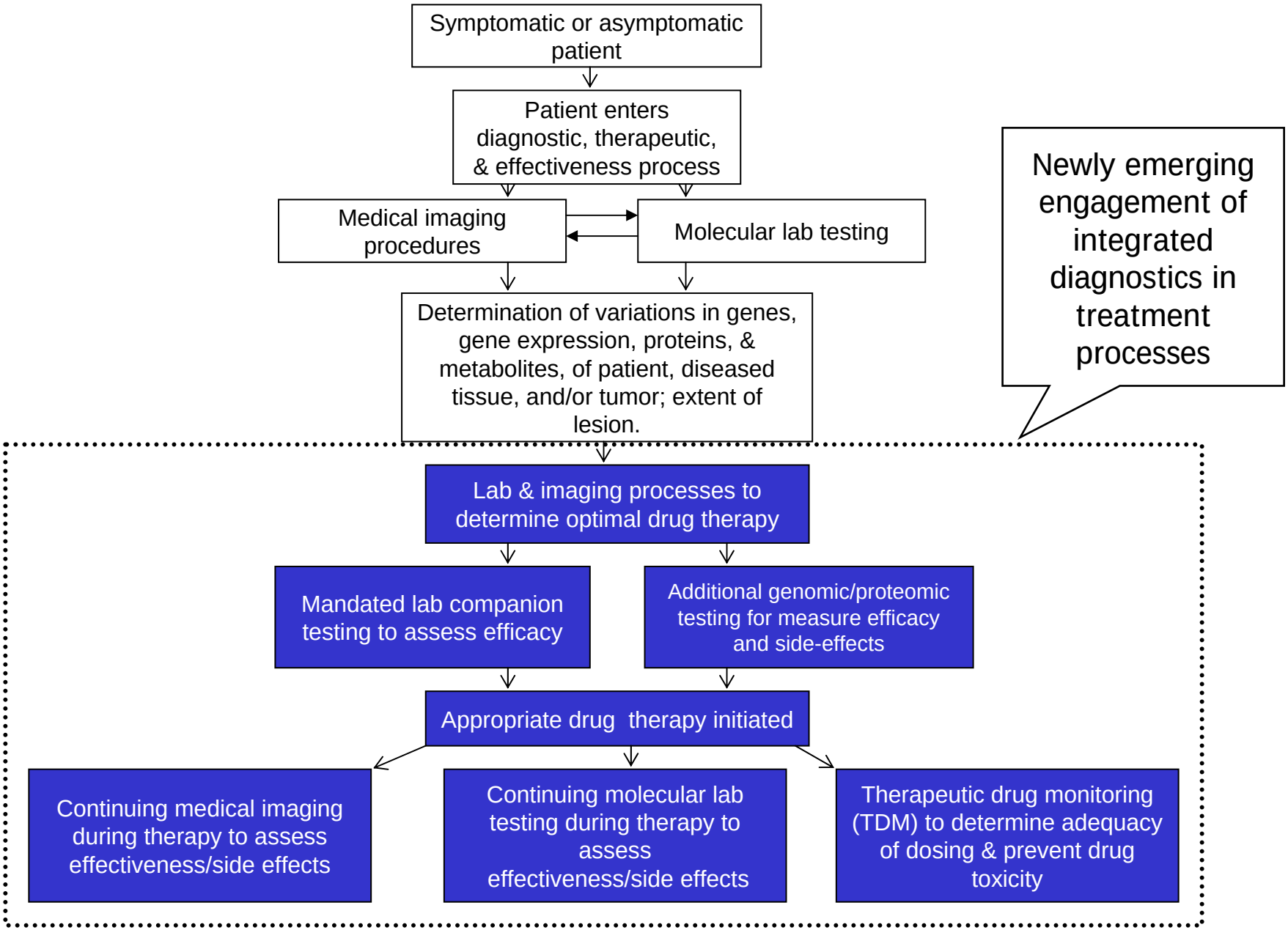
# Treatment Effectiveness vs. Comparative Effectiveness Research

- 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

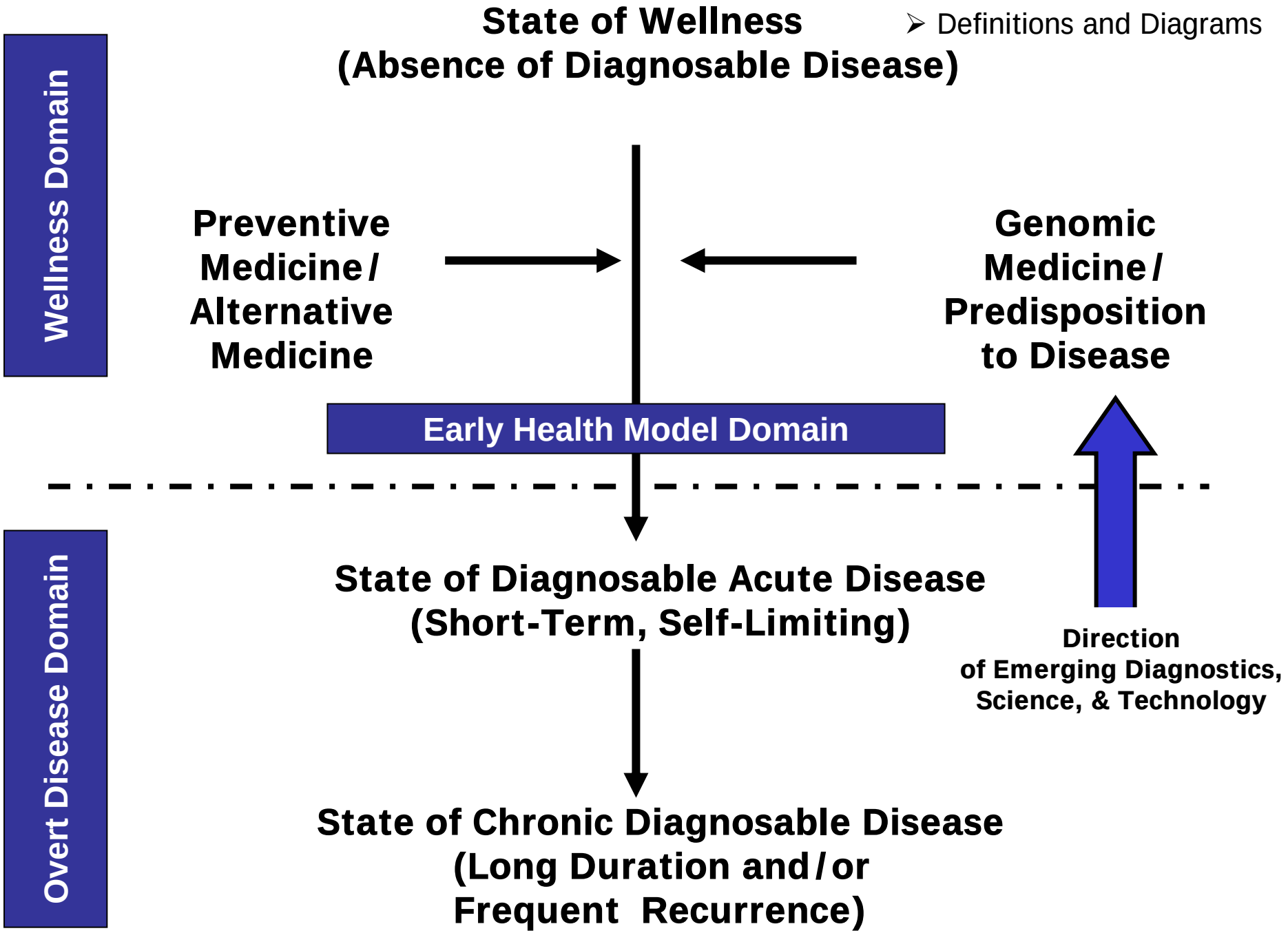


# Linkage Between Treatment Effectiveness and Preventive/Predictive Medicine

- 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)
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)
Direction of Emerging Diagnostics, Science, & Technology
State of Chronic Diagnosable Disease
(Long Duration and / or Frequent Recurrence)

# 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

- 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

- 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 *Erbitux* or *Vectibix*; K-RAS must be “wild” type

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

- 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

- 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

- 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 IVDMIA 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

- 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

- 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, IVDMIAs
- Actively resist FDA pressure for more regulation of IVDMIAs
- 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

- 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