



## Clinical, Financial, and Technological Forces For and Against Integration of *In-Vivo* and *In-Vitro* Diagnostics

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## Genesis of Idea That Radiology, Lab Medicine, & Pathology Could/Should Merge

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- Roots of merger idea can be traced back 2-3 years to IVD acquisitions & marketing campaigns by Siemens & GE
- Companies have acquired major companies & aggressively promoted *full-service diagnostics* & *early health model*
- Strategies based on idea that affinity/synergy exists between *medical imaging* and *molecular diagnostics*
- Vocabulary being used (e.g., integration, conversion, merger) suggests need for caution when promoting idea
- Now entering the "second phase" of merger discussions characterized by engagement of pathologists/radiologists

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## Understanding Pro/Con Forces at Work Important for Integration Enthusiasts

- These “forces” can be categorized as *clinical*, *financial*, & *technological*; each will be addressed later in this lecture
- Because of inertia and tradition, physicians affected by merger will require compelling arguments in favor of change
- Regardless of quality of pro/con arguments, process will undoubtedly begin with low-level collaborative projects
- Suitable models: fine-needle-aspiration (FNA) programs in hospitals; cross-disciplinary approach to tumor diagnosis
- Hospital programs like FNA serve as test beds for *hand-offs* & *information-sharing* across MDs necessary for collaboration

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## Major Topics to Be Addressed in This Lecture

- A closer look at the *integration* or *conversion* of *in-vivo* & *in-vitro* diagnostics; what is the basis for the conversation?
- Background of early health model (EHM) and molecular medicine; the intellectual underpinnings to this discussion
- Forces at work of sufficient importance that they will serve to promote integration of pathology, radiology, and IVD
- Possible trajectory for change; parallel events now and in near future that may demonstrate feasibility of specialty merger
- Set of deliverables from this Molecular Summit; ways in which the proposed “integration” agenda can be moved forward

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## Introduction to the Early Health Model: Discussion of Its Component Parts

- *Early health model* (EHM) represents major shift in healthcare delivery with new emphasis on diagnosis of *preclinical/presymptomatic* disease
- EHM, popularized by GE Medical, composed of five components:
  - *Consideration of personal health characteristics*: e.g., environmental influences, personal lifestyle, and genetic predisposition to disease
  - *Diagnosis of disease*: such an approach will include far greater emphasis on molecular diagnostics and medical imaging
  - *Prognosis of disease*: has been handled in a perfunctory manner in past; more refined approach will lead to greater patient satisfaction
  - *Treatment of preclinical/presymptomatic disease*: this approach will include use of newer biotech drugs (“personalized medicine”)
  - *Information technology*: this provides the “glue” that integrates and holds together the various the above four components of the EHM

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## Defining Molecular Medicine and Its Interplay with Early Health Model

- Siemens' *molecular medicine/full service diagnostics* campaign focuses on the molecular basis of disease
- This molecular approach will enable physicians to diagnose, determine prognosis, and treat their patients
- Understanding of *molecular medicine* enables and promotes the following advances in healthcare delivery
  - Early detection and treatment of disease; allied to EHM
  - More effective monitoring of drug treatment efficacy, which is important for future drug development
  - Selection of individualized (i.e., personalized) therapy
  - Expansion of potential for screening programs & determination of genetic predisposition to disease

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## Why Both EHM & Molecular Medicine Disruptive for Players in Healthcare Delivery

- Healthcare payers unsettled because approach adds to cost of care; struggling to pay for "routinely" diagnosed diseases
- MDs nervous because trained to diagnose disease based on existing patient signs/symptoms and not anticipated problems
- Pharmaceutical companies nervous because clinical trials for current drugs have been based on rx of symptomatic disease
- Criticality of diagnostic methods in EHM model demands integration/collaboration across labs/pathology/radiology
- Most positive response from patients; dissatisfied with current approach; told by MDs to return to office when symptomatic

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## Why EHM and Molecular Medicine So Important for Pathology and Lab Medicine

- Essence of EHM is early dx; pathology/lab medicine will have no difficulty adapting to this healthcare delivery model
- Molecular diagnostics pivotal to success of EHM; lab testing first logical step for arriving at presymptomatic diagnoses
- Directed medical imaging more cost-effective following biomarker screening or detection of circulating tumor cells
- Theoretically and in long run, EHM may reduce cost of healthcare because treating diseases in their earliest stage
- As early detection & diagnosis moves to center stage, role of clinician even more focused on choosing effective therapy

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## Forces at Work : Summary of Relevant Technologic & Scientific Issues

- Rapid advances occurring in molecular imaging with possibility of rendering specific tumor & disease diagnoses
- Large panels of "wellness" biomarkers will be performed periodically as optimal health screening method
  - The use of such panels will turn annual physical from meaningless exercise into effective surveillance tool
- Computer-based algorithms will play a critical role in the interpretation of results from large complex test panels
  - Current interest of FDA in "*in-vitro* diagnostic multivariate index assays" (IVDMIAs) worrisome; may inhibit progress
- LIS & RIS/PACS currently most robust clinical systems; integration into a DIS will produce many added benefits

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## Multiplexed Biomarker Panels Provide Diagnoses + Wellness Monitoring

- Large panels of biomarkers will become the most cost-effective method of choice for monitoring patients' wellness/disease status
- Approach based on knowledge that cells communicate by elaboration of proteins; challenge of how to interpret type/levels
- More comprehensive & sensitive than current methods such as yearly cursory physical exam + small set of routine lab studies
- Lab panels more cost-effective and less risky than intensive medical imaging; only venipuncture required to obtain samples
- Reasonable approach is to develop algorithms to more accurately assess the significance of changes in serum and cellular proteome

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## Use of Algorithms in the Analysis of Large Biomarker Panels for Disease Surveillance

- Algorithm (i.e., rule) development will be critical element in emergence of proposed integrated field of diagnostic medicine
- As new biomarkers discovered, added to existing test panels to increase positive and negative predictive values
  - Recent news about urine GOLPH2, SPINK1, & PCA3 expression & TMPRSS2:ERG fusion status for diagnosis of prostate cancer
- FDA seeking to regulate algorithms in connection with IVDMIAs; Genomic Health's Oncotype DX as a focus of regulatory attention
  - Regulatory oversight over algorithms/rules in molecular medicine would have chilling effect on pathology informatics
- Rules will also be important if lab enterprise integrated with medical imaging; hand-offs among specialists will be complicated

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## Molecular Imaging Has Potential in Future to Compete with Surgical Pathology

- Medical imaging (e.g., CT, MRI) identifies the mass/shape of a lesion but does not usually address “biology” of lesion
- By linking radio-opaque substance to molecules that bind to biomarker(s), make inferences about behavior of lesion
- Molecular imaging has potential to locate a space-occupying lesion & also provide clues about dx & prognosis
- Surgical pathology is current diagnostic gold standard; time-tested “technology” for rapid, inexpensive diagnoses
- Radiology will require pathology to validate diagnoses flowing from molecular imaging; collaboration → validation

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## Efficiency and IT Benefits Can Be Achieved by Closer Integration

- Currently, radiology & pathology/lab operate in two separate diagnostic silos with few interactions between the groups
- Closer integrated approach would yield quality & strategic benefits for *both* patients and for specialists themselves
- Radiology uses DICOM, a standard for handling, storing, printing, and transmitting information in medical imaging
- No coding system for radiology reports similar to SNOMED in pathology; report retrieval by diagnosis can be challenging
- With closer integration, radiology could adopt SNOMED & pathology a DICOM standard for image storage and retrieval

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## Emergence of the Diagnostic Information System (DIS): Blended LIS + RIS + PACS

- Long history of success with LISs, RISs, and PACS; inappropriate to view as merely feeder systems for EMRs
- Blended diagnostic department would require independent IT infrastructure for sophisticated information management
- I support development of a Diagnostic Information System (DIS); powerful synergy across these three IT systems
- PACS support will allow boot-strapping of digital imaging in pathology and emergence of digital pathology department
- Business and technical challenges of a DIS will serve to energize software vendors specializing in this software area

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## Forces at Work: Summary of Relevant Clinical Issues & Challenges

- First and foremost, integration will enhance professional dialogue/interactions, producing better/earlier diagnoses
- Earlier diagnoses may potentially lower the cost of healthcare delivery; tread carefully because may backfire
- Integration of LISs, RIS, and PACS into DIS will preclude "swallowing" of diagnostic data by inadequate EMRs
- Dialogue between clinicians and diagnosticians via conversations and reports will be clarified/enhanced
- Opportunity for input from diagnosticians regarding patient therapy; moves them to clinicians' "sweet spot"


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## Evolution of the "Organ/Disease" Specialist in a Department of Diagnostic Medicine

- I currently [optimistically] view radiologists and surgical pathologists as having more similarities than differences
- With advent of molecular imaging, radiologists developing keen interest in use of biomarkers/molecular diagnostics
- Would be impossible for individual "diagnostic medicine" specialists to efficiently manage entire gamut of diseases
- Radiologists/pathologists have evolved sub-specialty niches for subject mastery, quality issues, & training demands
- Logical arc for specialty training: *in-vivo* imaging + *in-vitro* tissue + biomarker expertise by specific organ or disease

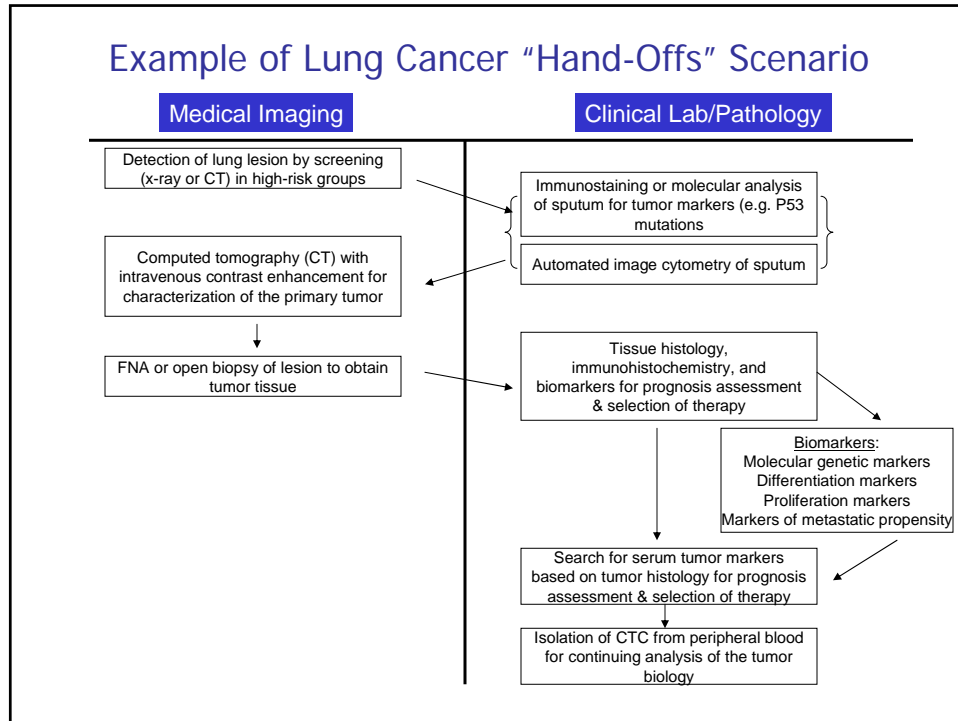
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## Need to Develop "Clinical Scenarios" for Specialty Interoperability as Proof of Concept

- Need to develop scenarios (i.e., clinical protocols) detailing hand-offs (lab/imaging) & resulting in rapid/less expensive dx's
- These scenarios will form core for new type of software directing work processes in the merged diagnostic department
- This software development will be challenging; functionality will be based on changing needs regarding patient management
- Work-flow rules as well as interpretive algorithms will be integrated into the mature DISs that ultimately come to market
- National reference labs, currently competitors of hospital labs, will be unable to provide comparable set of diagnostic services

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### Enhanced Quality of Reporting with Merged LIS/RIS/PACS Databases

- Now at earliest stage of technology allowing us to query image databases: find all previous instances of image
- From quality perspective, don't yet fully comprehend value of integrated radiology, CP, & AP reporting + analysis
- Greater value than simply retrieving prior diagnoses; with merged databases, can track success of prior treatment
- Analysis/integration of all previous *n-vivo* & *in-vitro* studies will become mandatory component of diagnostic reports
- Many current pathology residents inadequately trained to even integrate molecular dx results into surg path reports

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## Forces at Work: Summary of Relevant Financial and Political Issues

- Healthcare is a business and any merger discussion cannot proceed absent strong financial/political drivers
- Understood that medical imaging currently yields high margins whereas most lab studies commoditized
- C-suite executives gladly allocate capital to medical imaging projects; less enthusiastic about lab purchases
- Perhaps wishful thinking that some of the “magic” of medical imaging will rub off on merged enterprise
- However, if believe that “entire diagnostic enterprise” moving to center stage, best strategy is specialty merger

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## A Hard Look at the Political Issues Underpinning a Possible Merger

- Many pathology/radiology department chairmen currently feel little pressure to modify their *modus operandi* in any way
- Majority of chairmen in academic pathology departments focus on research; often reactive and disinclined to make changes
- Academic radiology leadership has been more vocal and entrepreneurial in responding to “leakage” of procedures
- Most specialty leaders are risk averse & conservative; need concrete evidence that change has major benefits for them
- Initiatives will come from “change junkies” who will derive national attention from launching “organizational innovations”

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## Constant Pressure for More Cost-Effective Healthcare Delivery; Can EHM Deliver Goods?

- Key question for pathology & lab medicine: is it possible to lower cost of healthcare as dx/rx become more sophisticated?
- One possible answer: multiplexed biomarker testing for dx and monitoring may be less expensive than imaging
- For neoplasms, earlier diagnosis and targeted therapy may avoid expensive surgery and prolonged hospital stays
- Wellness monitoring and healthy lifestyles may avoid complications of chronic diseases like diabetes and CHF
- Best policy will be to “under-promise” and “over-deliver”; EHM & molecular medicine should be sold on scientific merit

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## Potential Merger Already Being Promoted by Large Corporations

- Siemens and GE have made ~\$17B bet on molecular imaging; these investments cannot help but shape future
- Companies are developing new vocabulary to describe this convergence with major marketing/education campaigns
- Press releases for molecular imaging discuss *in-situ/in-vivo* biomarkers; clinical labs responsible for *in-vitro* biomarkers
- GE has launched “Re-Imagining” campaign directed to both MDs & consumers; new power of consumers in market
- Unknown currently to what extent new business model by for-profits can/will influence medical specialty boundaries

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## Political Gains If Specialties Coalesce and Lobby in Concert for Diagnostic Medicine

- In large tertiary hospitals, budget of a merged department could reach \$100M – potential for powerful political leverage
- Current estimate of 70% of dx's based on lab testing; add to this the diagnostic yield of current medical imaging
- Some capital acquisitions in radiology could possibly be avoided with enhanced molecular diagnostic screening
- Strengths of pathology: control over all *in-vitro* testing and surgical pathology/cytology (current gold standard for dx)
- Strengths of radiology: control over most digital imaging + evolving molecular imaging & interventional radiology

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## Development of “Diagnostics Centers” in Hospitals for Prototyping New Model

- Cancer hospitals have evolved as cross-disciplinary centers with various specialists focusing on single disease category
- Interesting political challenge to *status quo* with hospital directors rivaling authority of chairmen of departments
- Embedded “integrated diagnostic centers” would provide idea environment to test some of hypotheses floated here
  - Diagnoses arrived at faster and with less expense
  - Integrated diagnostic reports more useful for clinicians
  - Trainees could interpret both images and biopsy specimens
  - Biomarker panels could be used to direct imaging studies
  - Diagnostic specialists could extend expertise to rx choices

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## Possible Trajectory for Discussions & Eventual Convergence of Two Specialties

- First area for discussion will be opportunities for hand-offs and work-flow with goal of more rapid diagnosis development
- Second area for discussion will be IT convergence; examples include common viewers & integrated image databases
- Third area will be planning and development of early examples of integrated reports; test with clinicians for value
- Fourth area will be discussions at level of departmental chairs & hospital executives regarding political power-sharing
- In parallel, surgical pathology training programs need to be modified to emphasize criticality of molecular diagnostics

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- Possible trajectory for discussions & merger of specialties; technical, political, and financial issues that come into play
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## Deliverables from Molecular Summit: Moving the "Diagnostic Medicine" Merger Agenda

1. Consensus development that notion of conversion/merger is *reasonable* and worth further discussion and analysis
2. Develop deeper understanding of both advantages and disadvantages of integration for further analysis
3. Identification of key individuals who can fan out and articulate a potential merger scenario to decision-makers
4. Identification of existing and emerging hospital programs and centers that can serve as models for future initiatives
5. Spawn additional conferences and committees within professional organizations to extend this discussion

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## Summary and Take-Home Points from Lecture

- New vocabulary now being hatched to encompass diagnostic/prognostic/therapeutic continuum
  - *Early health model* and *molecular medicine* integrate medical imaging, molecular imaging, molecular dx, & surgical path.
- With new biology (genomics + proteomics), diagnoses will be rendered quickly; art of medicine in prognosis + therapy
- Molecular imaging evolving quickly; amalgam of sophisticated imaging technologies + *in-situ* biomarkers
- Integration of pathology/lab medicine/radiology into "Dept of Dx Medicine" makes political, economic, & quality sense
- First step might be development of interdisciplinary "diagnostic centers" allowing low-risk experimentation

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