

Biomarkers in Imaging and Their use in clinical trials

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Outline

- Biomarkers in clinical trials: Pro
- Biomarkers in clinical trials: Con
- Summary: what's needed for imaging biomarkers
- Biomarkers and molecular imaging: using molecular imaging agents as tools for developing therapeutic agents

Issues in Bringing New Medical Products to Market

- Rigorous, legally mandated FDA approval process
- Many years and hundreds of millions of \$ for typical new drug approval
- More and more candidate compounds being developed
- Finite resources
- One potential aid: Biomarkers (sometimes known as surrogate endpoints)

Definition of a biomarker

A laboratory measurement or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes on a clinically meaningful endpoint.

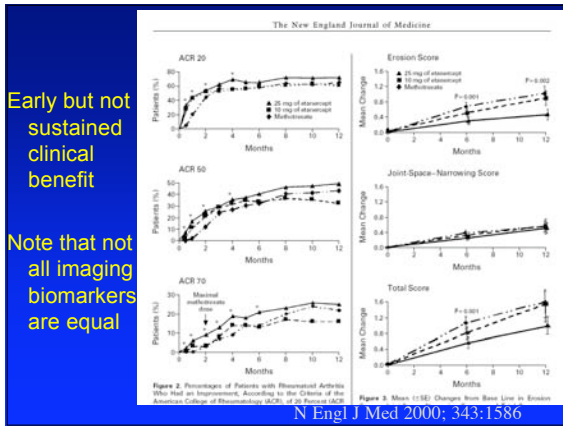
Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, eds. Clinical Measurement in Drug Evaluation. New York, NY: John Wiley & Sons Inc; 1995.

Imaging in Drug Development

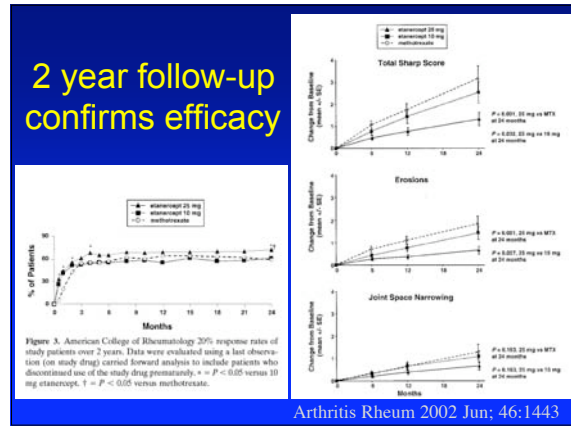
- Not about science, but about \$
- Estimates of \$10-\$30M savings per project with 'advanced technologies'
- Numerous successes for imaging so far:
 - Multiple Sclerosis (e.g., T2 lesion burden)
 - Oncology (e.g., liver lesion size)
 - Arthritis (e.g., erosions in Rheumatoid Arthritis)
 - Osteoporosis (e.g., bone density and fractures)
 - Cardiovascular (e.g., percent stenosis)
 - Many others...

Etanercept (Enbrel)

- Nov 1998 - Approved for RA pts who fail methotrexate
- June 2000 - Approved for RA patients as first line Rx for RA
- Basis for expanded approval: imaging improvement, but not clinical improvement at 1 year.
- Follow-up at 2 years, though (post-approval!) validated the FDA's decision



Early but not sustained clinical benefit
Note that not all imaging biomarkers are equal



2 year follow-up confirms efficacy

Financial impact of imaging biomarker for etanercept

- 1999 sales: \$366.9 million
- 2001 sales: \$761.9 million
- 2002 sales up 31% over 2001 in 1st quarter
- Probable benefit from imaging biomarker use: >> \$200 M

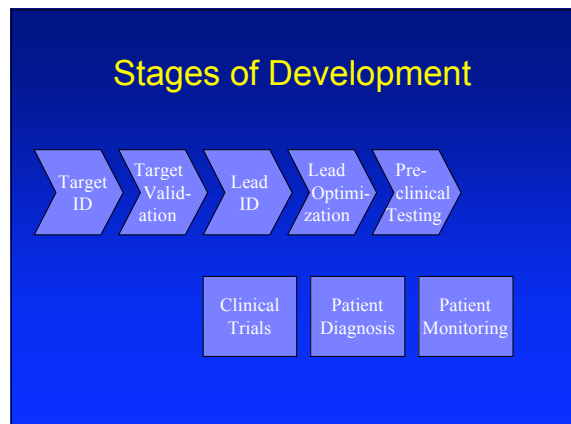
Biomarkers Under Existing Statutes and Regulations

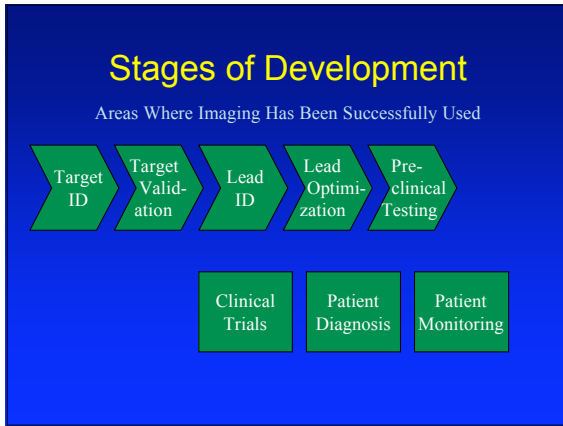
- 21 C.F.R. § 314.500: "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses"
- Broadening and codification under Food and Drug Administration Modernization Act (FDAMA), Section 112
- FDAMA "least burdensome means" provisions for medical devices

1996 Rationale for Imaging

FDA BACKGROUNDER
BRING A NEW DRUG TO MARKET FASTER
Accelerated Approval and Expanding Access
October 21, 1996

"Based on accumulating evidence, FDA now believes it is appropriate to approve products that show evidence of tumor shrinkage for patients who have no satisfactory alternative therapy. Companies can more quickly demonstrate tumor regression than improvements in survival time or quality of life and can do so in studies that are relatively easy to carry out. Allowing companies to provide additional evidence of increased survival or improved quality of life associated with that therapy after marketing approval may, in many situations, substantially shorten (sometimes by years) the total time needed for marketing approval."





Imaging biomarkers are seeing increasing use...

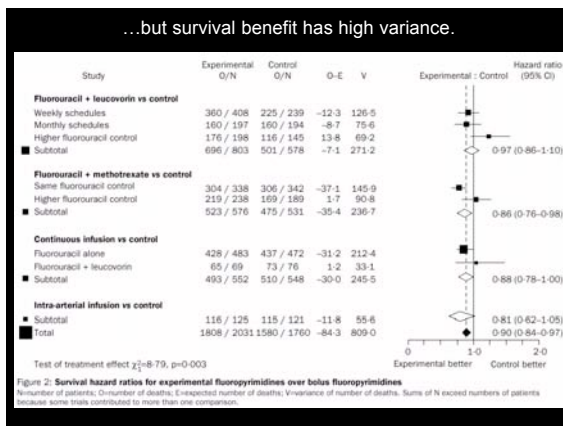
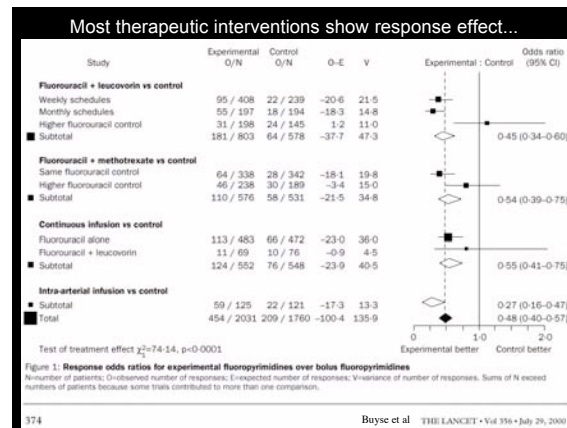
FDA APPROVES ELOXATIN FOR COLORECTAL CANCER

The Food and Drug Administration (FDA) today announced the approval of Eloxatin (oxaliplatin) injection for use in combination with infusional 5-fluorouracil (5-FU) and leucovorin for the treatment of patients with colorectal cancer whose disease has recurred or become worse following initial therapy with a combination of irinotecan with bolus 5-FU and leucovorin. The combination including Eloxatin was shown to shrink tumors in some patients and delay resumed tumor growth. These are the first results on the efficacy of the combination on survival.

Biomarkers are helpful...but cannot solve every problem!

- Oxaliplatin approved in 46 days
- But earlier rejection in 1999 when no overall survival endpoint was used:

"For approval of a first-line indication, it is necessary to demonstrate an advantage in overall survival." - ODAC, March 2000
- Oxaliplatin now approved for second-line therapy on the basis of imaging



Survival is correlated, but imperfectly...

- Numerous reasons for imperfect correlation (e.g., other Rx, small response rates, high variance)
- Surrogate may nevertheless allow identification of novel therapeutics that otherwise would require large clinical trials

Figure 4: Treatment effects on survival versus treatment effects on tumour response. Each circle represents a trial, the area of which is proportional to the number of observations in the trial.

Choice of metric may not be all that simple

- Important to choose a relevant target ... and lesion volume or lesion enhancement may not be that target (despite obvious appeal)
- Example: brain tumors and post-contrast enhancement on MRI

Schematic of relationships between disease and surrogate endpoint

A diagram showing a box labeled 'Disease' with an arrow pointing to a box labeled 'True Clinical Outcome'. Below this, a long yellow arrow labeled 'Time' points to the right.

After Fleming & DeMets, Ann Int Med 1996:605

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Surrogate not in causal pathophysiologic pathway.
Example: bone density after fluoride versus fracture

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Schematic of relationships between disease and surrogate endpoint

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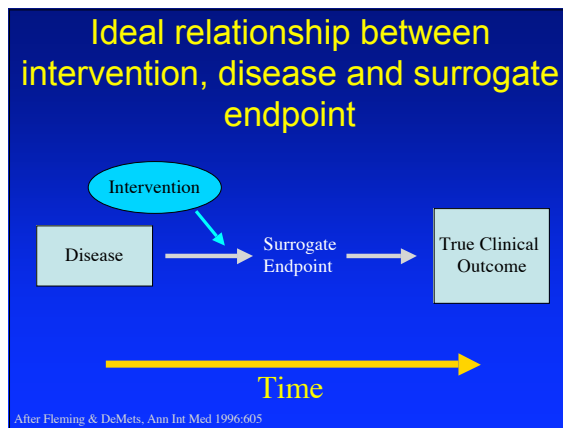
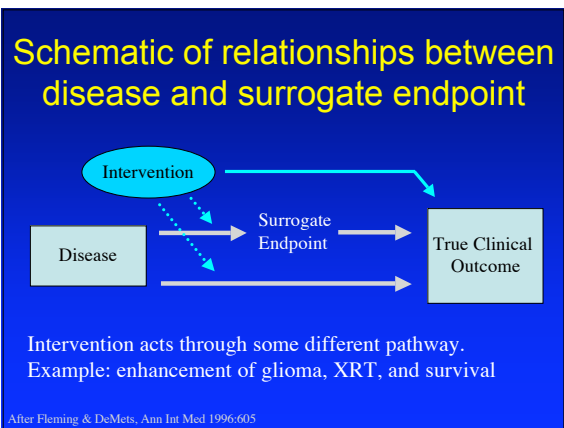
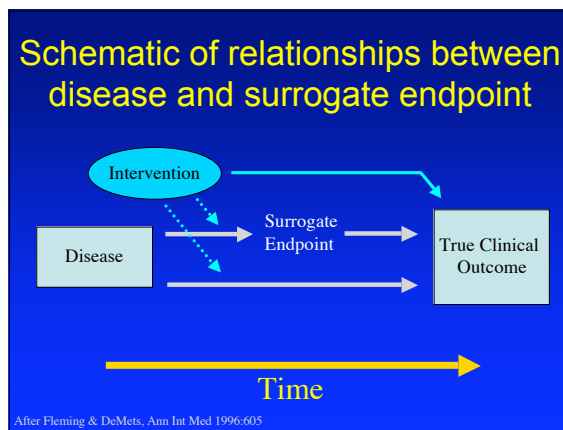
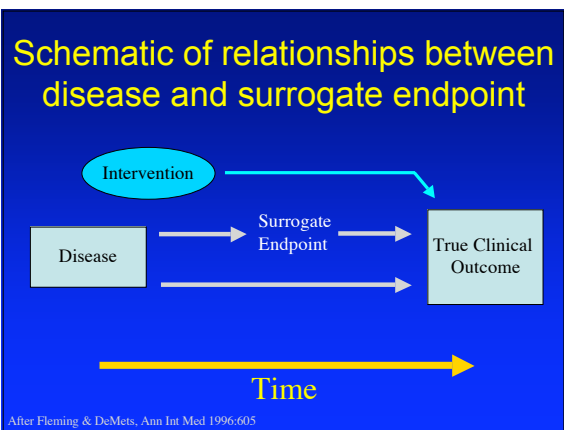
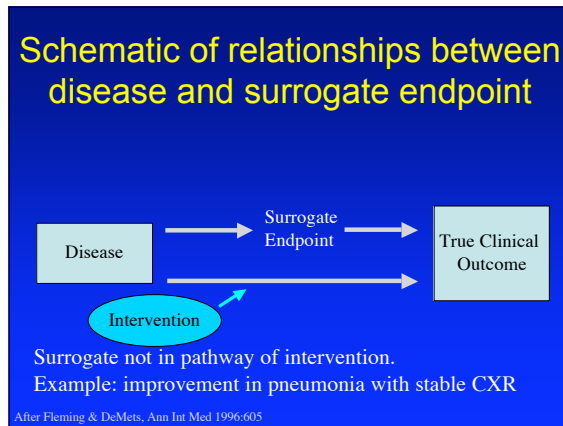
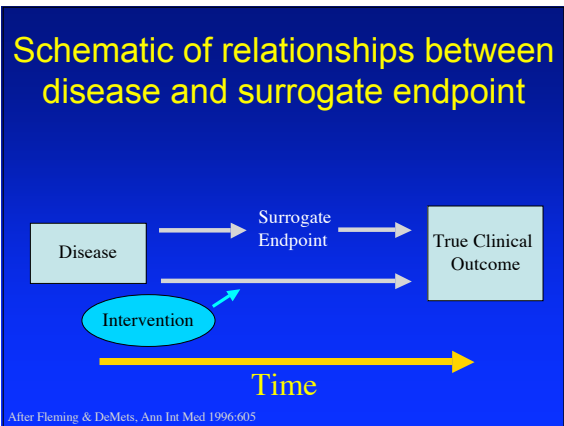
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Surrogate not in only causal pathophysiologic pathway.
Example: tumor shrinkage after chemotherapy vs survival
Famous example: CAST

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What are the implications for imaging biomarkers?

Next steps:

- Cataloging and Validation
- Reduced variance for known relationships
- New biomarkers, especially for safety

One next step: formation of the MGH Center for Biomarkers in Imaging

- An umbrella organization for the MGH Dept of Radiology (extramural research activities ~\$35M in FY2001)
- Attempt to catalog biomarkers
- Goal: to identify the appropriate stage for each biomarker and the degree of validation currently in existence.

CBI's activities

- Consulting
 - from portfolio review to **education**, esp regulatory agencies
- Biomarker Development & Validation
 - especial focus on error bars
 - a conduit to individual labs
- Phase II / Phase III central interpretation
 - “blinded readers”

Biomarker	Disease	Imaging Technique	Investigator	Disease Category
18 F-Fluorodeoxyglucose	Pancreatic carcinoma	PET	Fachman	Oncology / Neoplasm
99mTc labeled monoclonal antibody	Colorectal carcinoma	SPECT	Fachman	Oncology / Neoplasm Gastrointestinal
Abnormal lymphatic uptake of tracer	Lymphatic extension of pelvic malignancy (gynecological oncology)	MRI (using ultrasmall superparamagnetic iron oxide (ferumoxtran-DS))	Hahn P, Weisleder B, Hansinghary M, Mueller P	Oncology / Neoplasm
ACid activation (cortisol conjugate cortisol disease)	Attention deficit hyperactivity disorder	MRI PET	Rosen B	Neurological
Altered lung architecture	Pulmonary fibrosis	CT	McLeod T, Shepard J	
Anatomic disruption of arterial wall	Aortic dissection	US CT MRI Angiography	Gonzalez R, Walman A	Cardiology / Vascular

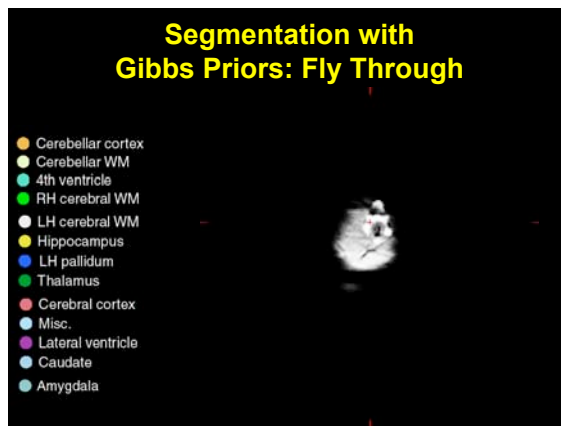
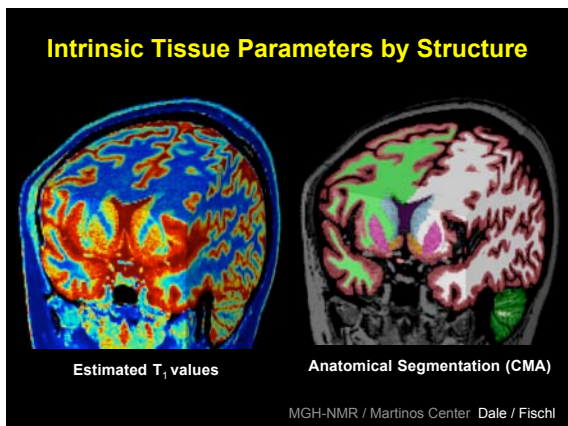
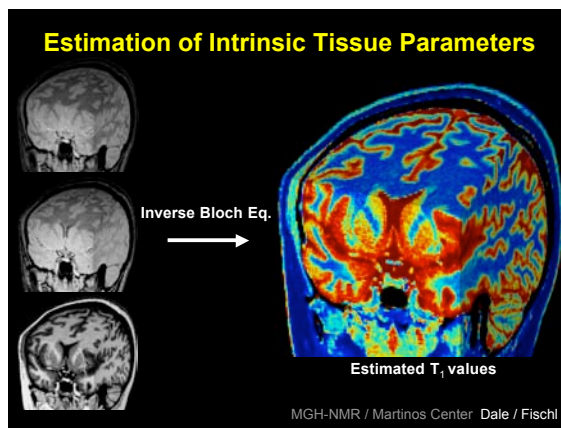
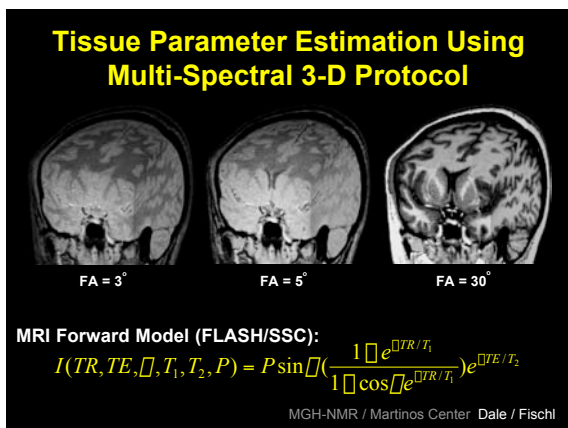
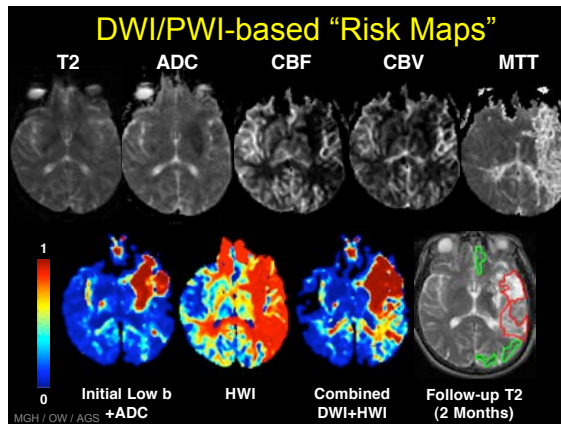
Imaging Biomarkers may be even more powerful early on...

Areas Where Imaging Has Been Successfully Used

Stages of Development


Examples of recent specific advancements

- Variance reduction in **analysis**
 - Stroke imaging and 'change from baseline'
 - Improved methods for choosing lesion boundaries
- Variance reduction in **acquisition**
 - Distortion measurement
 - Autoslice
- Improved techniques for **new biomarkers**
 - Diffusion in schizophrenia
 - Human 3T and 7T

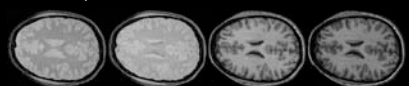


**Towards Site-Independent Analysis:
NIH-sponsored Biomedical Imaging
Research Network ("BIRN")**

Scanner/Protocol/Subject-Specific Spatial Distortions

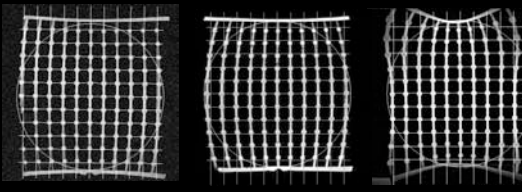


Scanner/Protocol-Specific Tissue Contrast



Goal: Develop optimized imaging protocols and post-processing algorithms that allow for precise, quantitative analysis and comparison of data across sites, studies and time.

MRI Distortions due to Gradient Non-Linearities



Siemens Whole-Body Symphony/Sonata
Max displ. 2.5/3.2mm


GE Whole-Body CRM NV/CVI
Max displ. 4.2/8.6mm

Siemens Head-Only Allegra/AC-44
Max displ. 5.7/20.2mm

MGH-NMR / Martinos Center Dale / Fischl

Auto Slice Registration:
prescribing where slices should be placed
without human intervention

5 scans separate localizer scans, pre-registration

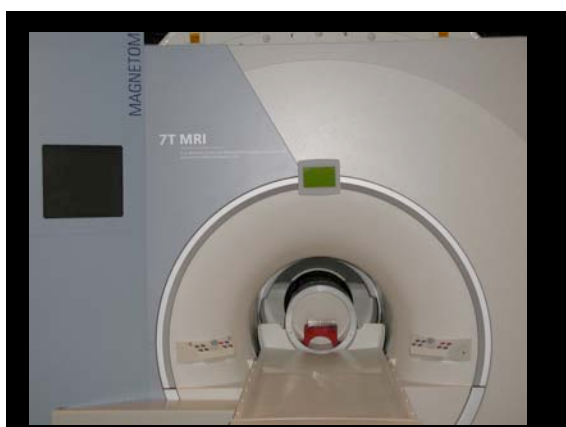


Low-resolution localizers, post-registration

Dale / Van der Kowe / Schmitt
MGH / CorTechs / Siemens

Specific MRI approaches for psychopharmacology:
Brain Ultrastructure & Diffusion

- Apparent Diffusion Coefficient as measured w/MRI is sensitive to numerous physiological parameters
- Ultrastructure in particular may be relevant



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