Employing Complex Datasets for More Effective Decision-Making in Drug Development

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Big Data, Multimodality & Dynamic Models in Biomedical Imaging
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Disclosures

- Both presenters:
  - Current employees of GlaxoSmithKline and hold stock

- Fred Wilson:
  - Previously a consultant to ECNP R&S, GlaxoSmithKline, IPPEC, King's College London, Lundbeck A/S, Mentis Cura ehf and Pfizer Inc.
  - Received travel expenses as a guest speaker on EEG from Orion Pharma Ltd
  - Previously an employee of Pfizer and held stock options

Outline

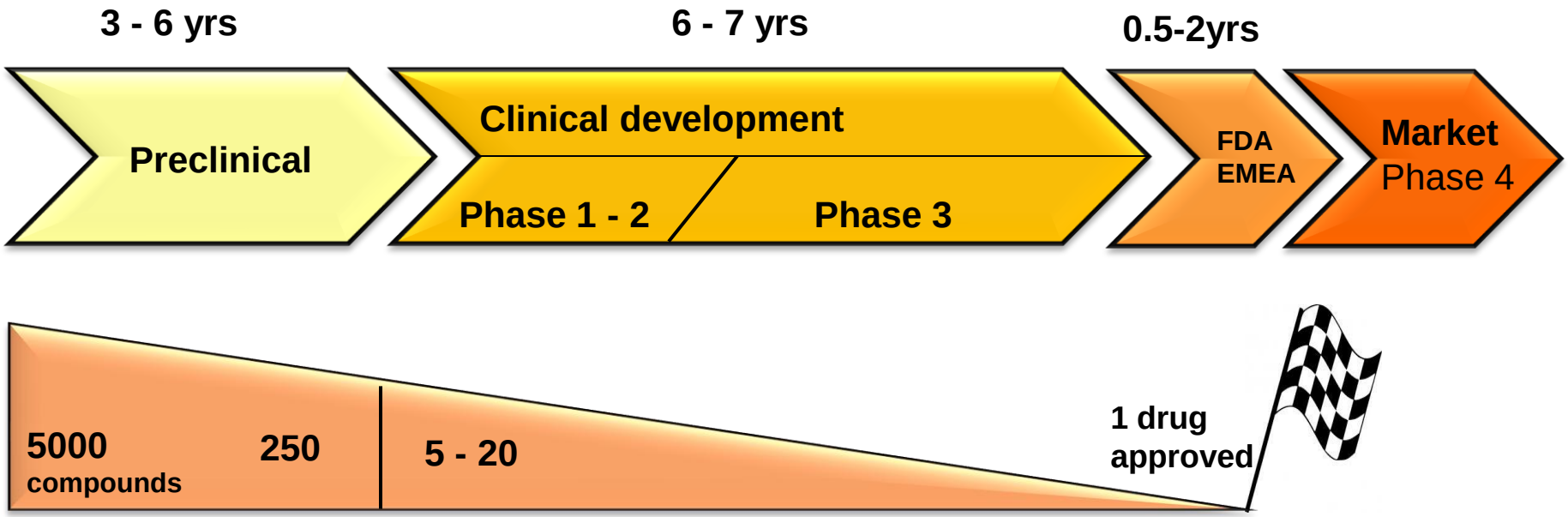
- Motivation:
  - Attrition in the drug development pipeline
  - What do we mean by complex data and decision-making?

- Improving decision-making in early drug development:
  - The role of biomarkers – what do we need to measure?
  - Example: electroencephalography (EEG) as a pharmacodynamic biomarker

- Quality control and data linkage in multi-site clinical studies:
  - Improving on existing visual and other basic measures
  - Extracting additional information from existing datasets

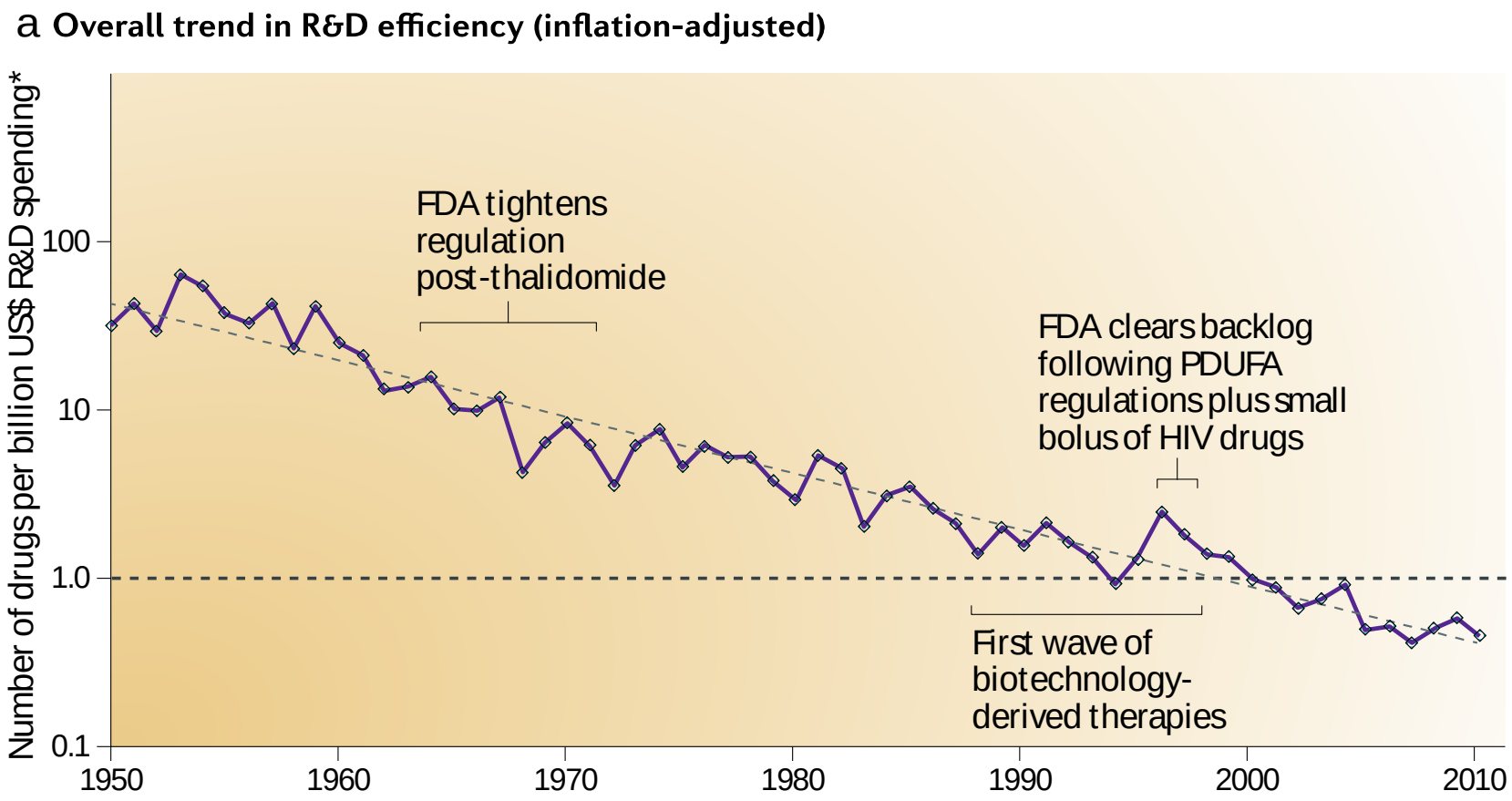
- Conclusions

Drug development – a lengthy and “risky” process



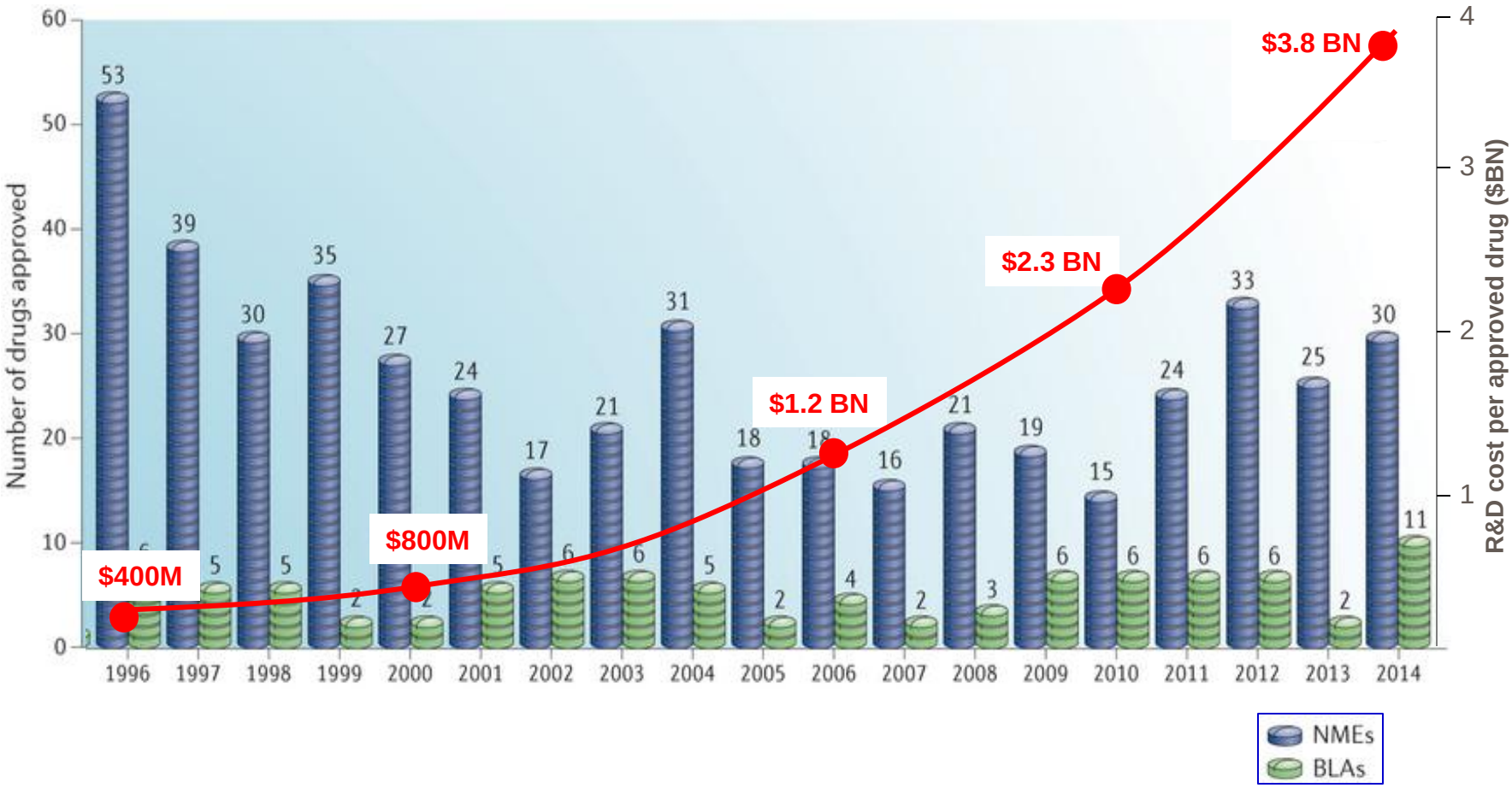
Motivation

– The situation is economically unsustainable



Scannell *et al*, *Diagnosing the decline in pharmaceutical R&D efficiency,* Nature Reviews Drug Discovery, 2012

R&D productivity - increasing costs per approved drug



Sources:Tufts CSDD. Nature Rev Drug Discovery. PhRMA

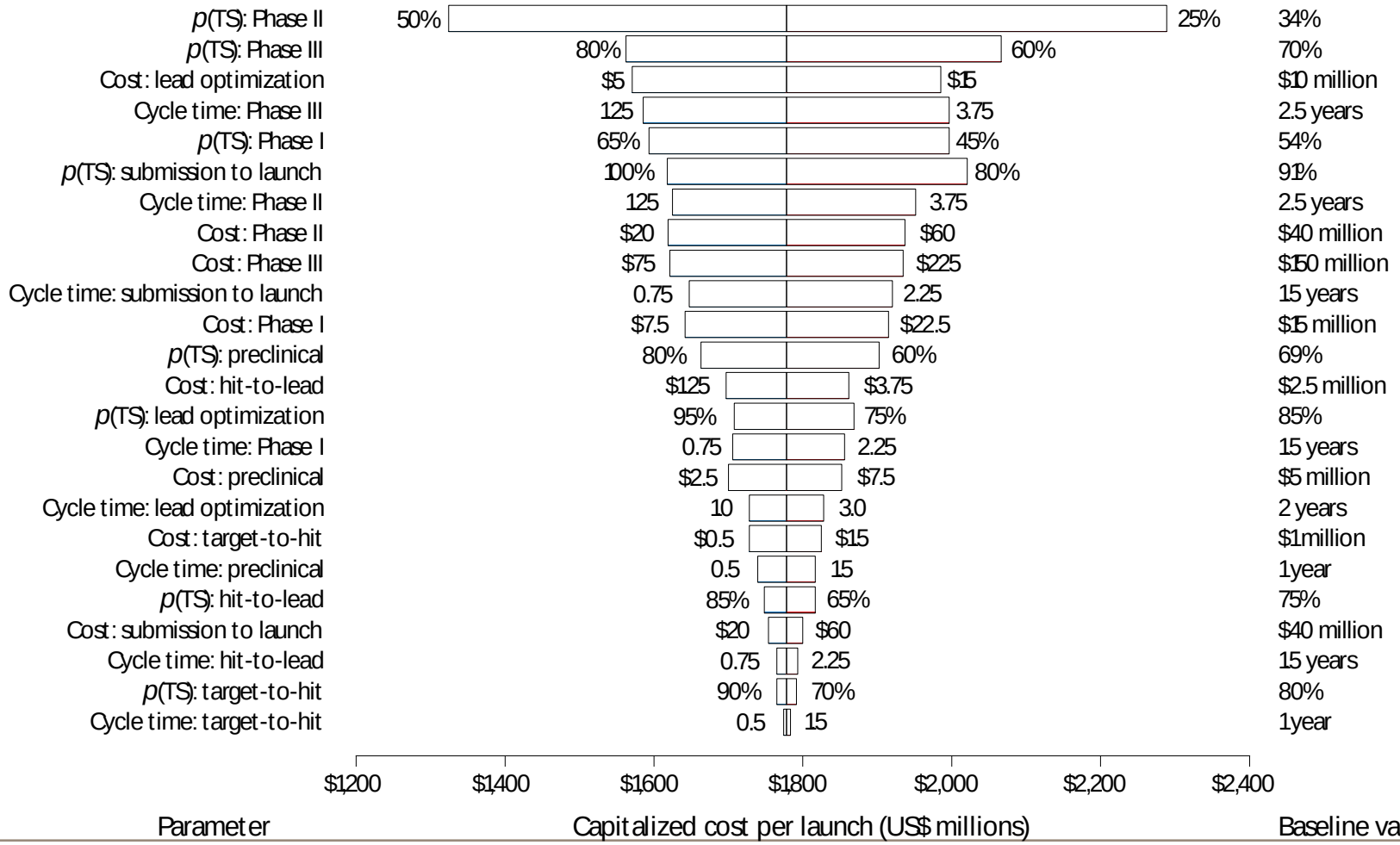
What do we mean by complex data and decision-making?

- Most biological and clinical datasets are ‘complex’:
  - Large numbers of data points
  - Multiple sources of noise (random, biological, systematic)
  - May not include large numbers of samples (so not true ‘big data’)

- ‘Decision-making’ requires data reduction to answer a specific question:
  - Typically requires a binary choice and/or reduction to a single variable, for example:
    - Is the drug binding to the target?
    - Is the drug having a biological effect? How big an effect?
    - Will this patient respond to the drug? By how much?

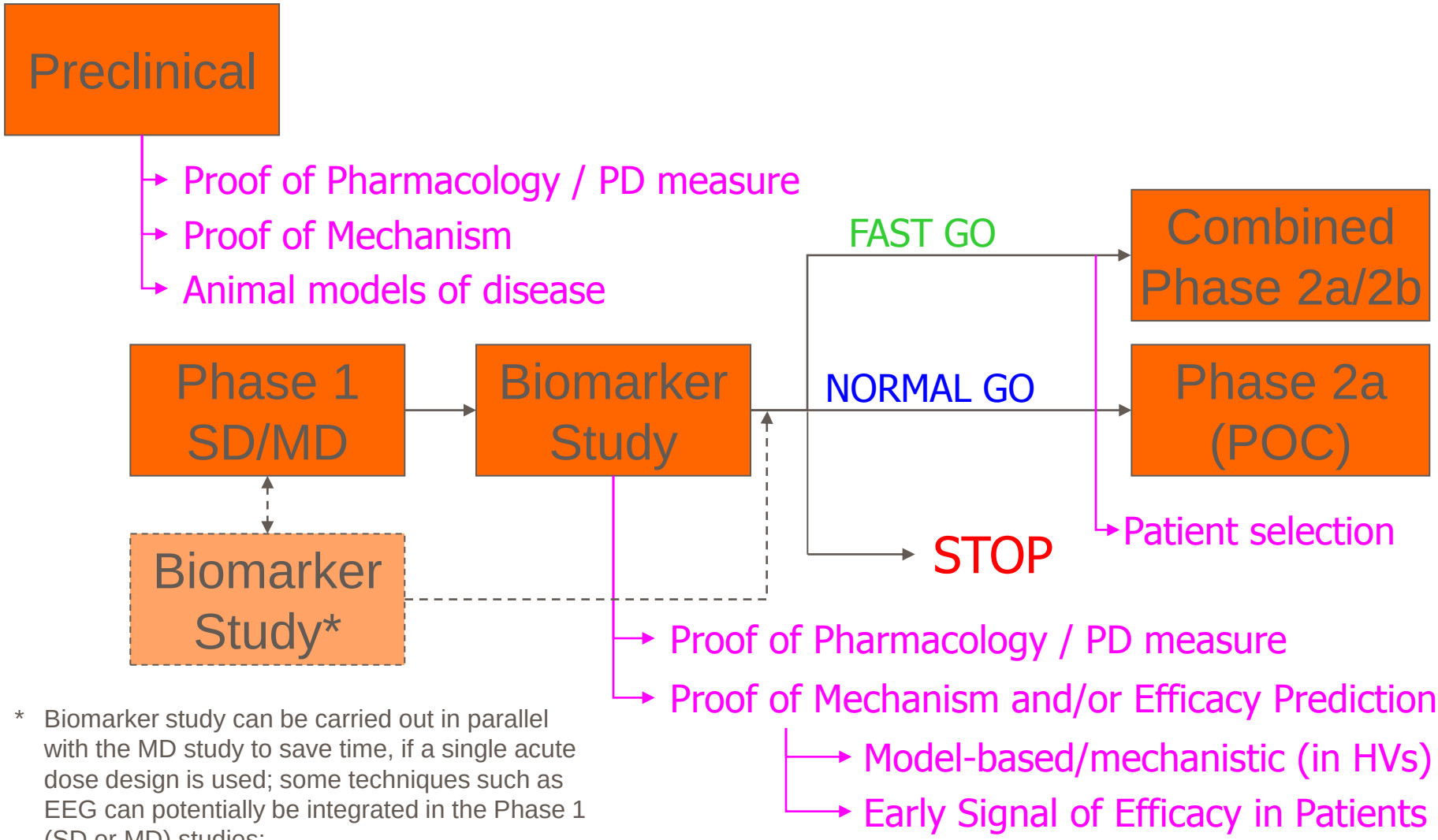
Improving decision-making in early drug development

Parametric Sensitivity Analysis



Paul et al, *How to improve R&D productivity: the pharmaceutical industry's grand challenge*, Nature Reviews Drug Discovery, 2010

De-risking Phase 2/3 using Biomarkers



* Biomarker study can be carried out in parallel with the MD study to save time, if a single acute dose design is used; some techniques such as EEG can potentially be integrated in the Phase 1 (SD or MD) studies;

Wilson, F.J. & Danjou P., 2015 Early Decision-Making in Drug Development: The Potential Role of Pharmaco-EEG and Pharmaco-Sleep, *Neuropsychobiology*, 72, pp.188-194.

Fundamental PK-PD Principles

– Recent review of 44 Phase 2 drug development projects at Pfizer

– Examined based on 3 principles:

PILLAR 1: Exposure at the target site of action

PILLAR 2: Binding to the pharmacological target

PILLAR 3: Expression of pharmacology

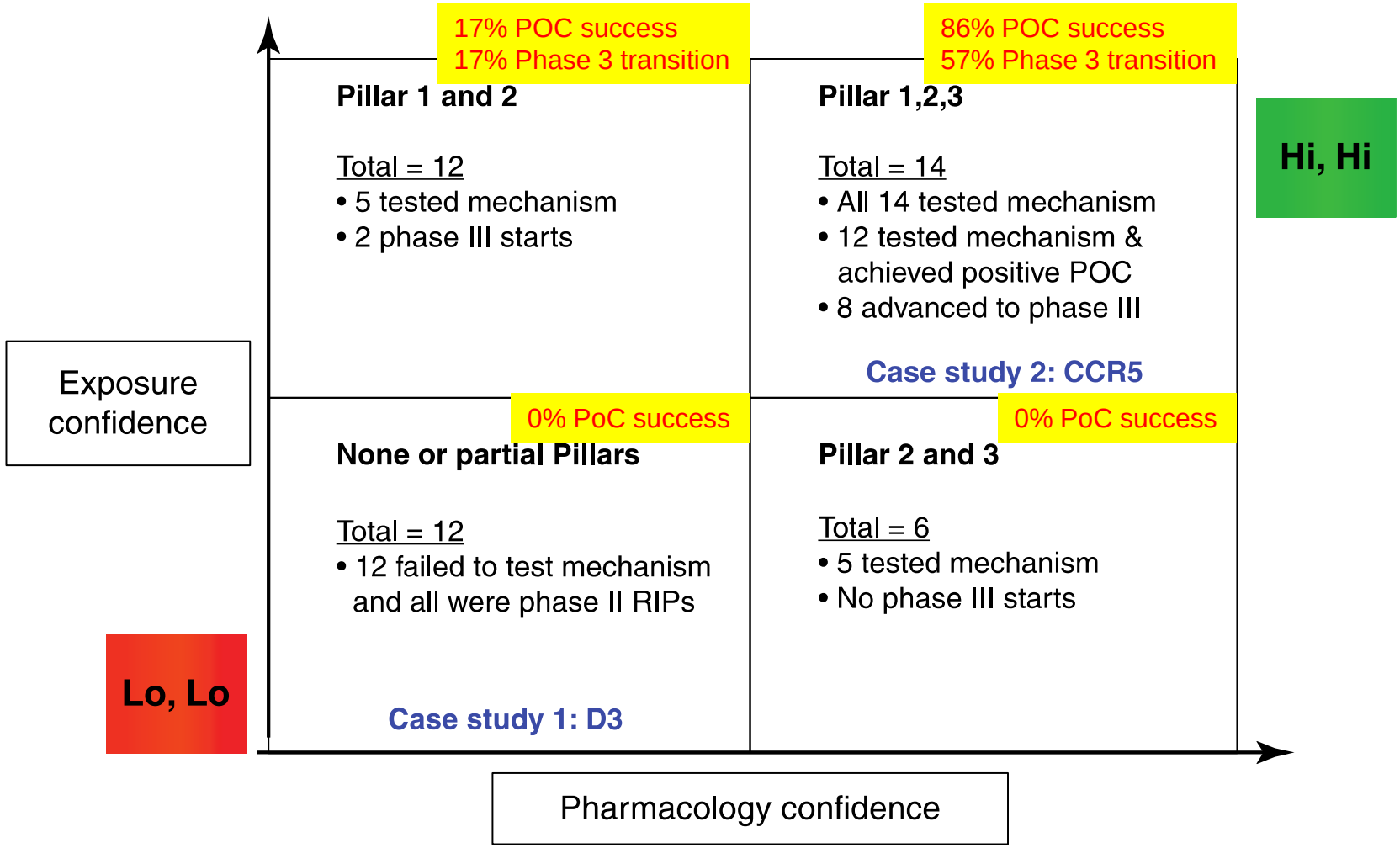
– Summarised onto two axes:

EXPOSURE CONFIDENCE: Based on Pillars 1 and 2

PHARMACOLOGY CONFIDENCE: Based on Pillars 2 and 3

Morgan et al, *Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival,* Drug Discovery Today, 2012

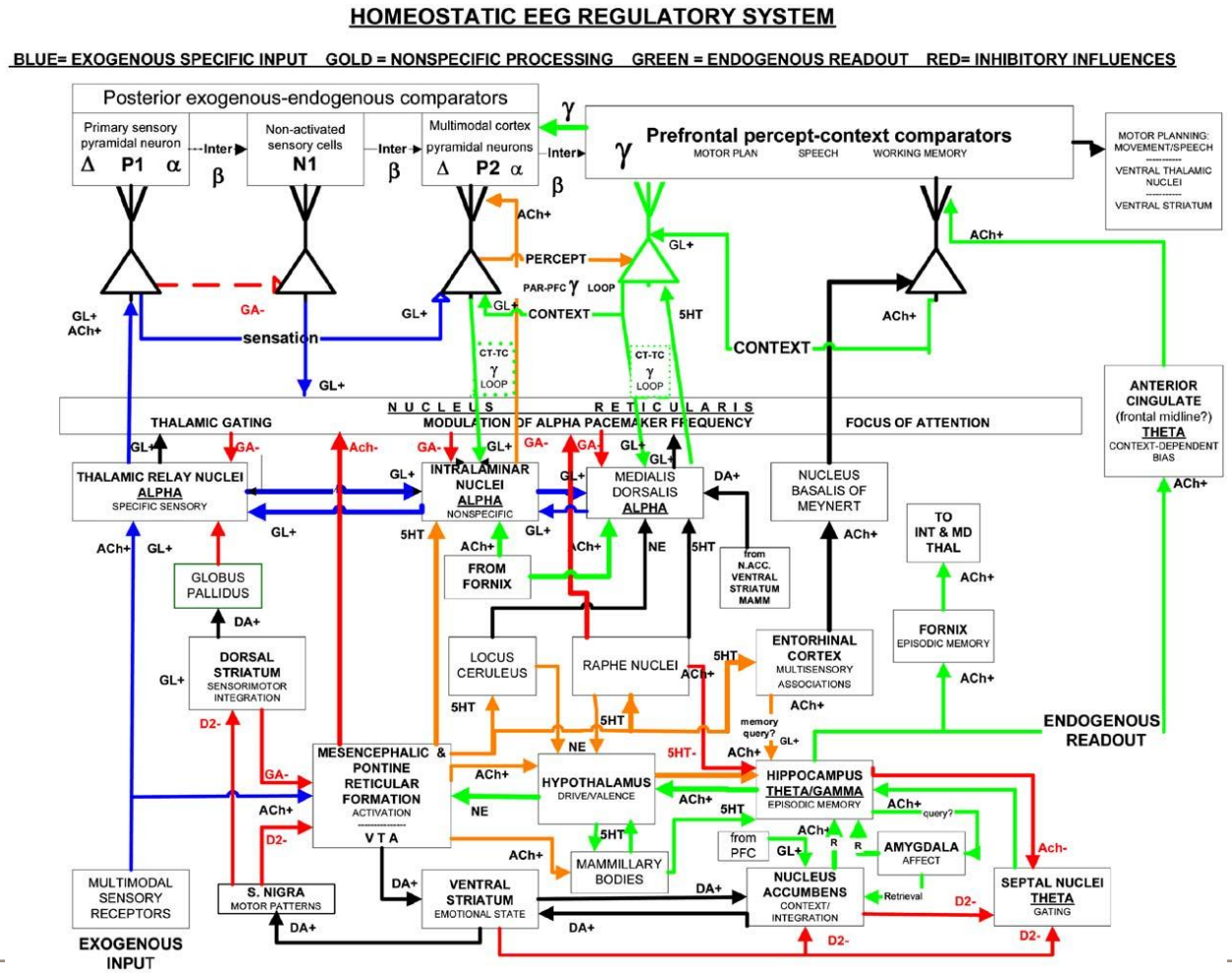
Fundamental PK-PD Principles



Morgan et al, *Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival,* Drug Discovery Today, 2012

EEG – a window onto brain function

Involves large neuronal populations that include all major neurotransmitter systems



John, E Roy; Prichep, Leslie S, *The relevance of QEEG to the evaluation of behavioral disorders and pharmacological interventions,* Clinical EEG and Neuroscience, 37(2), pp. 135-43, 2006

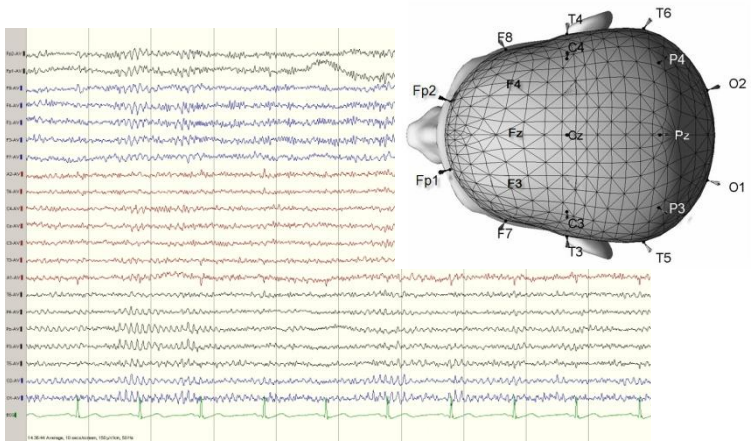
Status of pEEG as a PD biomarker

- Lots of historical issues with unclear results from pEEG
- Propose a new framework for when to use pEEG as a PD biomarker:
  - Two simple criteria:
    - Preclinical experiments produce a robust result
    - We expect this to translate (based on best current knowledge)
  - Clinical study should be designed to test for the expected effect, with other pEEG measures as secondary endpoints

Wilson, F.J. et al., 2014. Can pharmaco-electroencephalography help improve survival of central nervous system drugs in early clinical development? *Drug discovery today*, 19(3), pp.282–288.

Classical Quantitative EEG Analysis

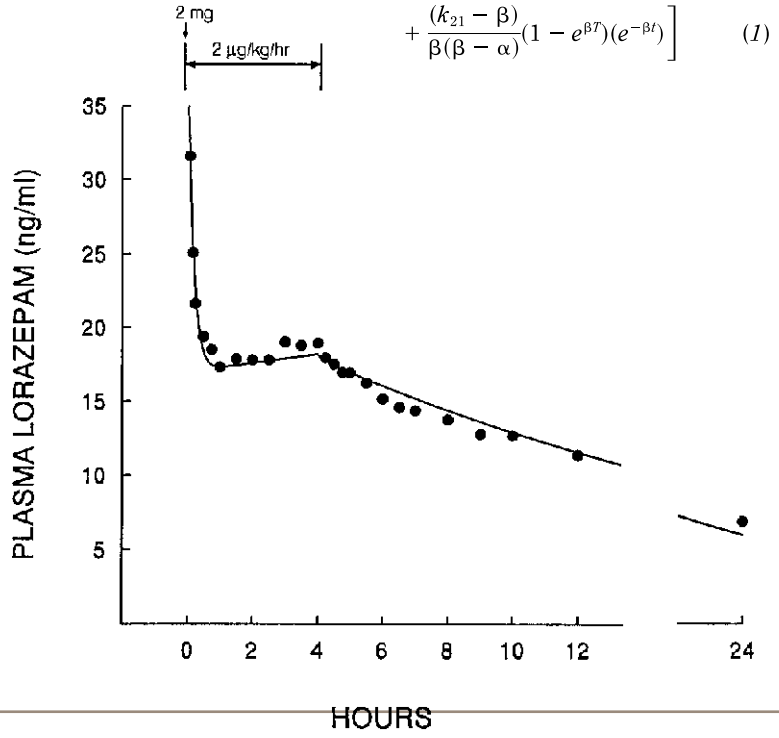
- Generate frequency spectrum of signal (e.g. using Short-Term Fast Fourier Transform)
- Split frequencies into bands (Delta, Theta, Alpha, Beta, Gamma)
- Evaluate required endpoints:
  - Total and relative spectral power in each band
  - Power ratios
  - Coherence between different regions in each frequency band
  - Other parameters e.g. peak alpha frequency

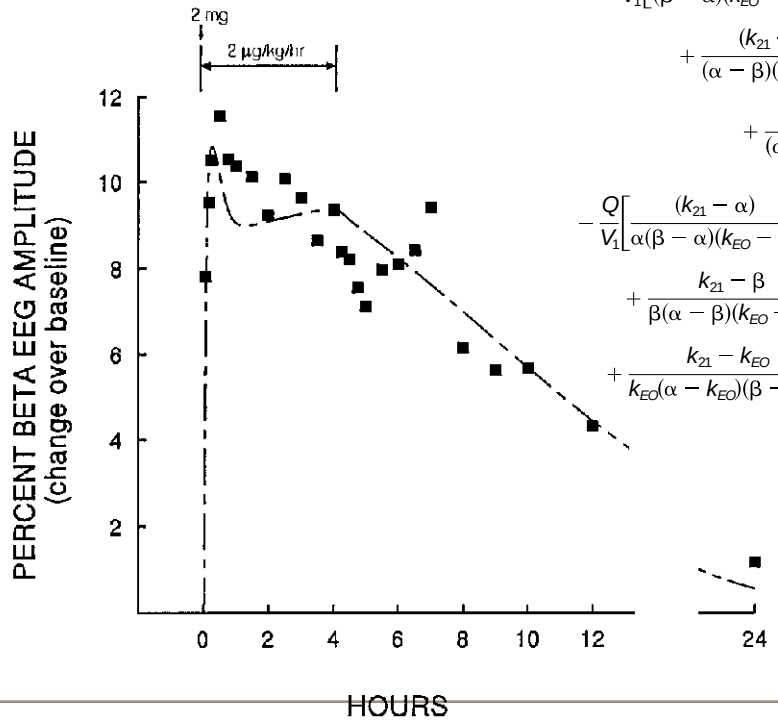


Famous Example - Benzodiazepines

– Complex PK-PD modelling with EEG works well e.g.

$$C = \frac{D}{V_1}\left[\frac{k_{21}-\alpha}{\beta-\alpha}\cdot e^{-\alpha t} + \frac{k_{21}-\beta}{\alpha-\beta}\cdot e^{-\beta t}\right] + \frac{Q}{V_1}\left[\frac{(k_{21}-\alpha)}{\alpha(\alpha-\beta)}(1-e^{\alpha T})(e^{-\alpha t}) + \frac{(k_{21}-\beta)}{\beta(\beta-\alpha)}(1-e^{\beta T})(e^{-\beta t})\right] \quad (1)$$





$$E = \frac{E_{max}\cdot(C_E\cdot k_{EO})^A}{EC_{50}{}^A + (C_E\cdot k_{EO})^A} \quad (2)$$

$$C_E = \frac{D}{V_1}\left[\frac{(k_{21}-\alpha)}{(\beta-\alpha)(k_{EO}-\alpha)}\cdot e^{-\alpha t} + \frac{(k_{21}-\beta)}{(\alpha-\beta)(k_{EO}-\beta)}\cdot e^{-\beta t} + \frac{(k_{21}-k_{EO})}{(\alpha-k_{EO})(\beta-k_{EO})}\cdot e^{-k_{EO}t}\right] - \frac{Q}{V_1}\left[\frac{(k_{21}-\alpha)}{\alpha(\beta-\alpha)(k_{EO}-\alpha)}\cdot(1-e^{\alpha T})(e^{-\alpha t}) + \frac{k_{21}-\beta}{\beta(\alpha-\beta)(k_{EO}-\beta)}\cdot(1-e^{\beta T})(e^{-\beta t}) + \frac{k_{21}-k_{EO}}{k_{EO}(\alpha-k_{EO})(\beta-k_{EO})}\cdot(1-e^{k_{EO}T})(e^{-k_{EO}t})\right] \quad (3)$$

Greenblatt DJ, von Moltke, LL, Ehrenberg, BL, Harmatz JS, Corbett KE, Wallace DW, Shader RI 2000 Kinetics and dynamics of lorazepam during and after continuous intravenous infusion *Crit. Care Med.* **28** 2750-7

The Problems with Classical Analysis

- Numerous potential endpoints (100s or 1000s):
  - 19 or more electrode positions
  - 5 frequency bands (more if subdivided)
  - Absolute and relative power values
  - Power ratios
  - Coherence measures (by scalp region and band)

- Individual endpoints lack specificity
- Readout often dependent on *post hoc* interpretation
- Impossible to define criteria *a priori* to enable clear decisions

Generalised Semi-linear Canonical Correlation Analysis (GSLCCA)

- Method developed to enhance utility of EEG as a PD biomarker by using data from the:
  - Whole spectrum (without dividing into bands)
  - Entire recording duration
  - All electrodes

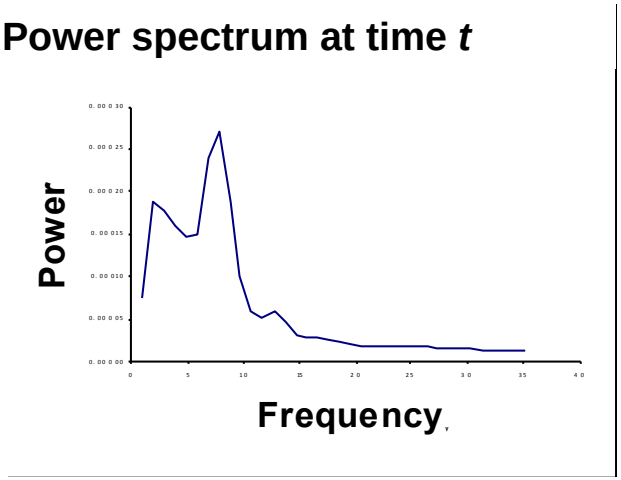
- To provide:
  - Interpretable mechanistic information
  - A PD measure

- Assuming:
  - A PD profile of a known form (i.e. a given equation with unknown parameters)

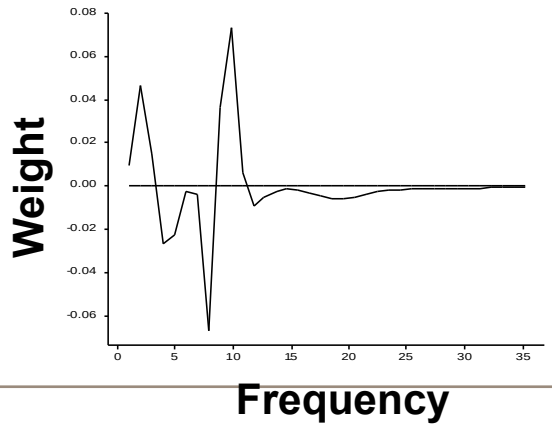
Brain, P., Strimenopoulou, F. & Ivarsson, M., 2012. Generalized Semilinear Canonical Correlation Analysis Applied to the Analysis of Electroencephalogram (EEG) Data. *Statistics in Biopharmaceutical Research*, 4(2), pp.149–161.
Brain et al, 2014. Extracting drug mechanism and pharmacodynamic information from clinical electroencephalography data using generalised semi-linear canonical correlation analysis. *Physiological Measurement,* 35(12), pp. 2459–2474.

GSLCCA - Principle

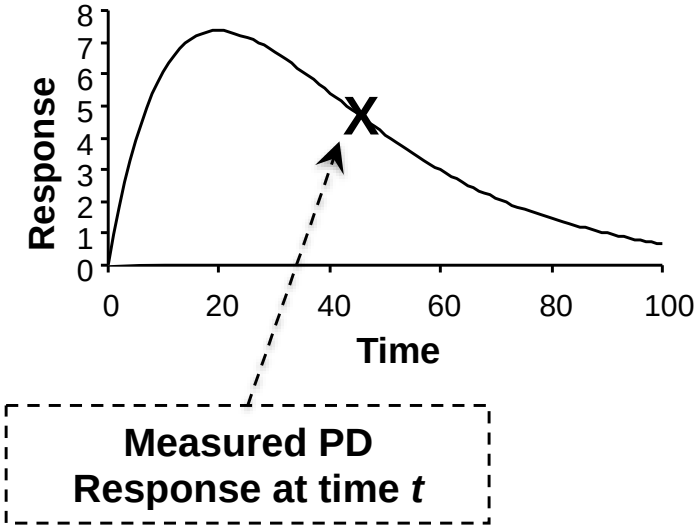
(a) Power spectrum at time *t*



(b) Signature obtained using GSLCCA

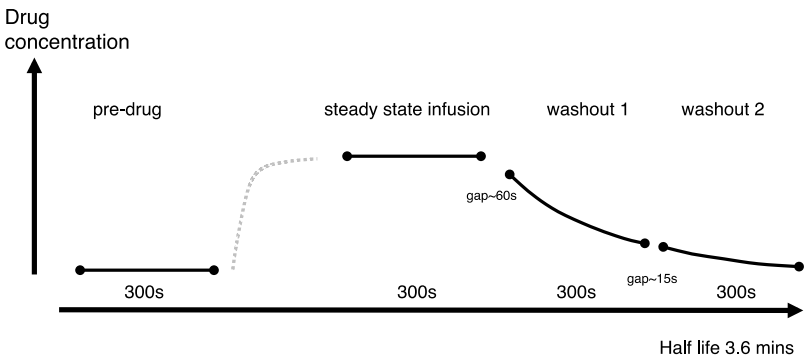


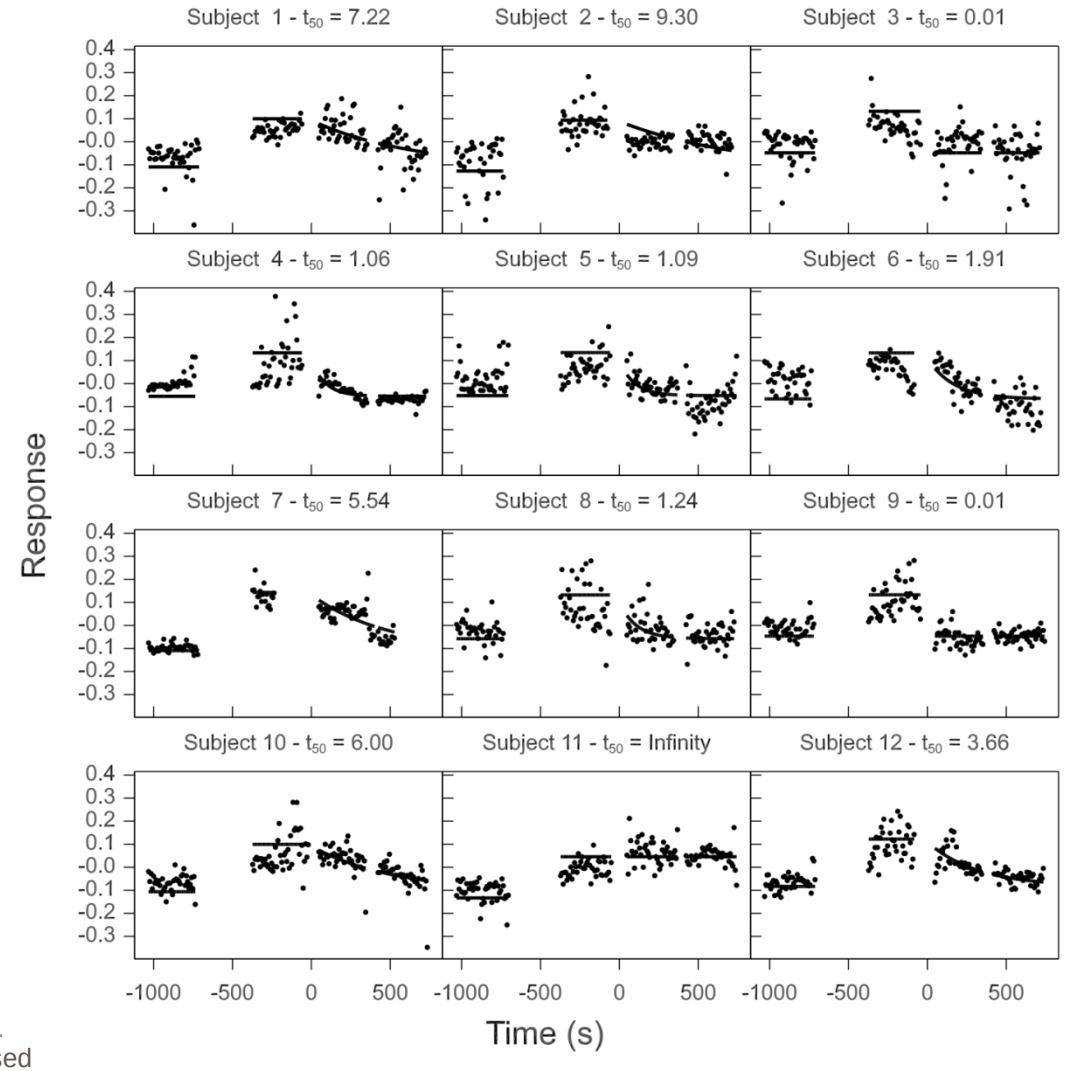
(c) Model PD response profile



GSLCCA – Example Results

Clinical study with remifentanil





Mean t_{50} = 3.04 ± 0.88 minutes

Brain et al, 2014. Extracting drug mechanism and pharmacodynamic information from clinical electroencephalography data using generalised semi-linear canonical correlation analysis. *Physiological Measurement,* 35(12), pp. 2459–2474.

Quality control and data linkage in multi-site clinical studies

Linking Imaging to Other Clinical Endpoints

Strategy for "Big Data" and Stratified Medicine

Goal of stratified medicine is to allow a clinician to determine the optimal therapy or combination of therapies for an individual at the earliest possible stage

- How can this be determined based on initial presentation of disease?
  - Integrated analysis of genomic and other data
- Imaging is primary endpoint in many clinical studies
- Incorporating imaging data to analysis is challenging
  - Raw data are essentially large volumes of pixel intensities
  - Requires semantically-rich descriptors to correlate with other data sources
  - Essentially a problem of knowledge extraction from image volumes
- Not a classical Big Data problem
  - Relatively small number of samples (subject-visits)
  - Each sample is very well-characterised

Registration-Path Imaging Studies

Multisite and standardised

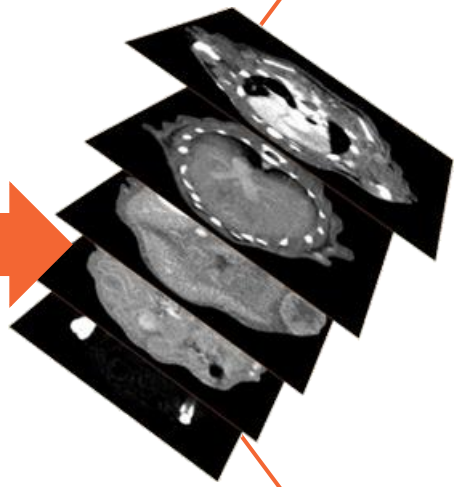
- Safety and efficacy
- Established endpoints

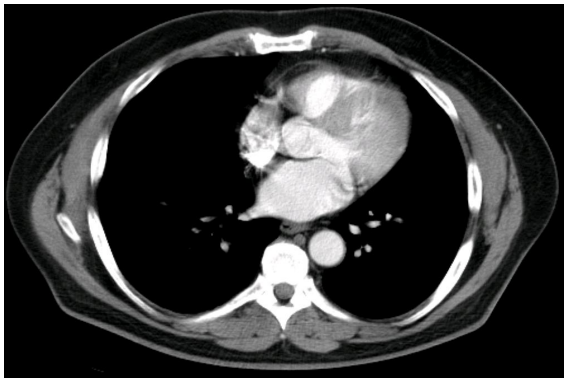
- Large(ish) sample populations
- Data acquired globally in clinical radiology departments
- Local and centralised independent radiological review

- Regulated
- Conservative

Clinical Imaging Data

Digital Imaging and Communications in Medicine (DICOM)





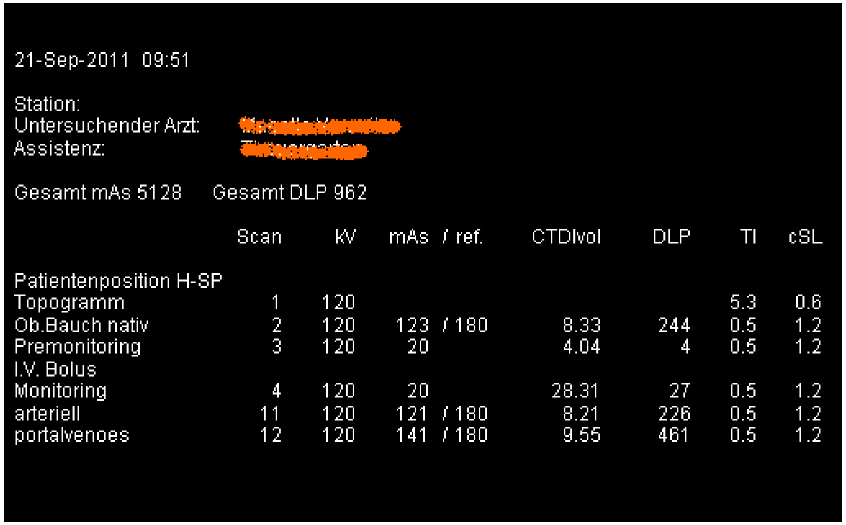
Patient's Name	001234
Patient ID	001234
Patient's Sex	Male
Study Date	05-Dec-2007
Patient's Birth Date	30-Jun-1960
Modality	CT
Referring Physician	

Image

Metadata

Sensitive Personally Identifiable Information

Pixel deidentification

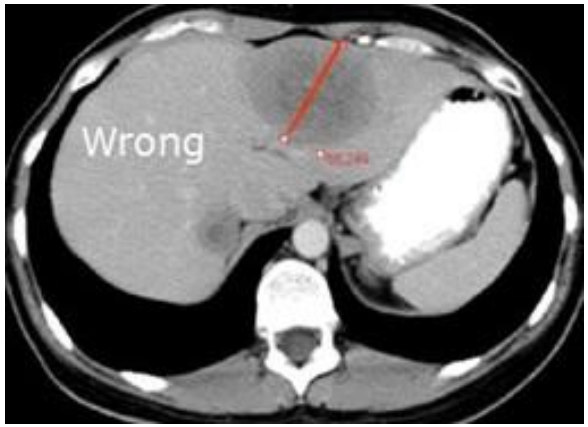


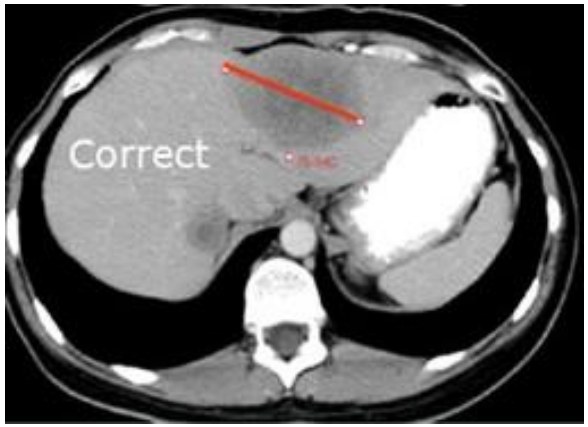
Response Evaluation Criteria in Solid Tumours (RECIST)

Standard objective measures of response to therapy

Baseline

Follow-on





http://www.recist.com/recist-in-practice/

QC and Analysis Pipeline

Opportunities for automation

- Algorithms should be general
  - Validation overhead obviates study-specific software
  - Broad applicability across TAs
- Outputs should include confidence estimate
  - Need to be able to identify false-positives
- Challenges
  - Statistical bias: value of comparing data between studies?
  - Variations in acquisition (multisite)

Classification and Automated QC

Randomised Decision Forests

Courtesy Ben Glocker

- Characterise
  - Modality
  - Anatomical region
  - Contrasting agent
  - Gender
  - Age
- QC
  - Correct person
  - Missing slices
- Feature detection
  - Artefacts
  - Anomalies

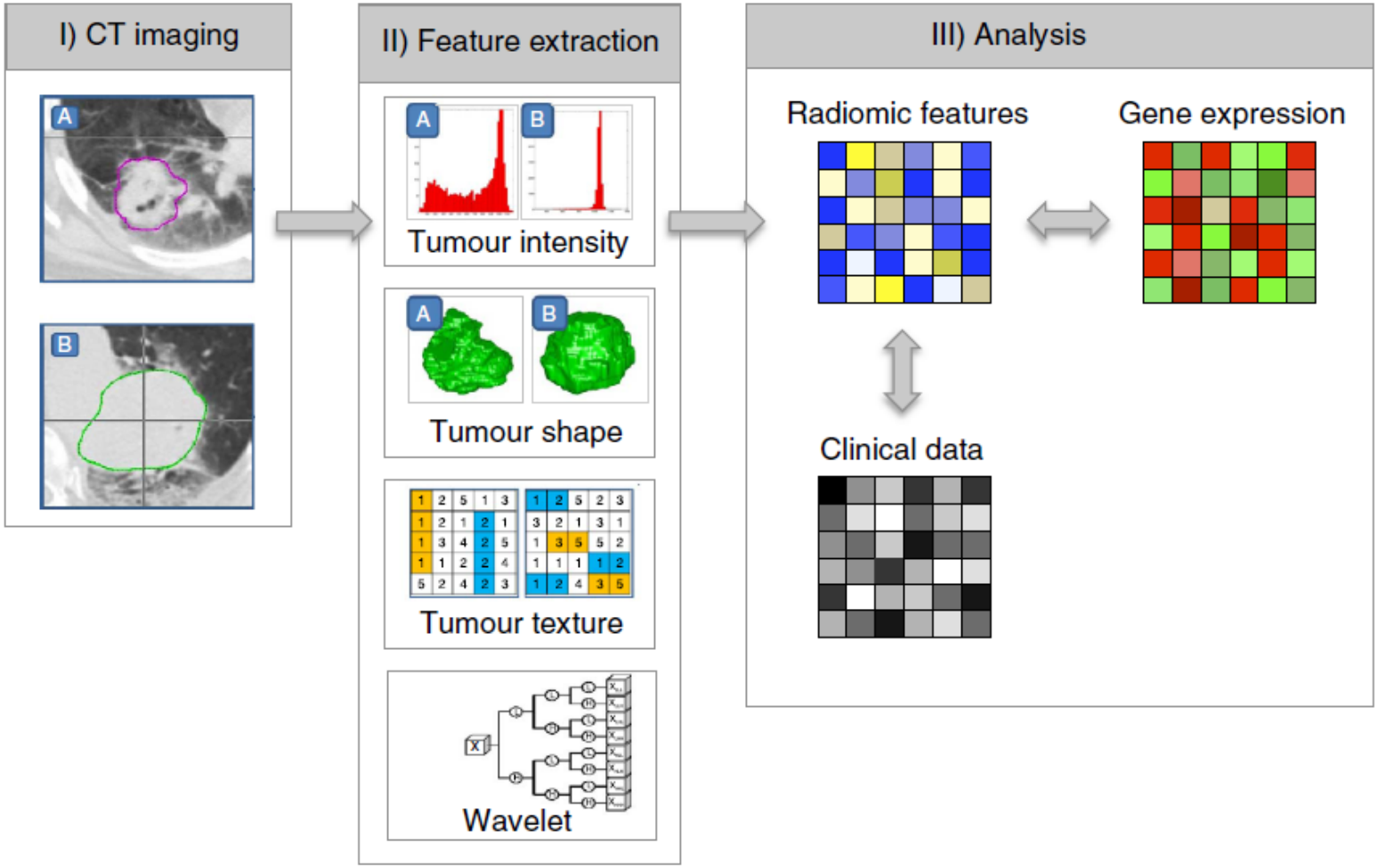
Glocker et al, Vertebrae Localization in Pathological Spine CT via Dense Classification from Sparse Annotations, in MICCAI, September 2013

Criminisi et al, Regression Forests for Efficient Anatomy Detection and Localization in Computed Tomography Scans, in Medical Image Analysis (MedIA), Elsevier, 2013

Criminisi et al, A Discriminative-Generative Model for Detecting Intravenous Contrast in CT Images, in MICCAI, September 2011.

Radiomics

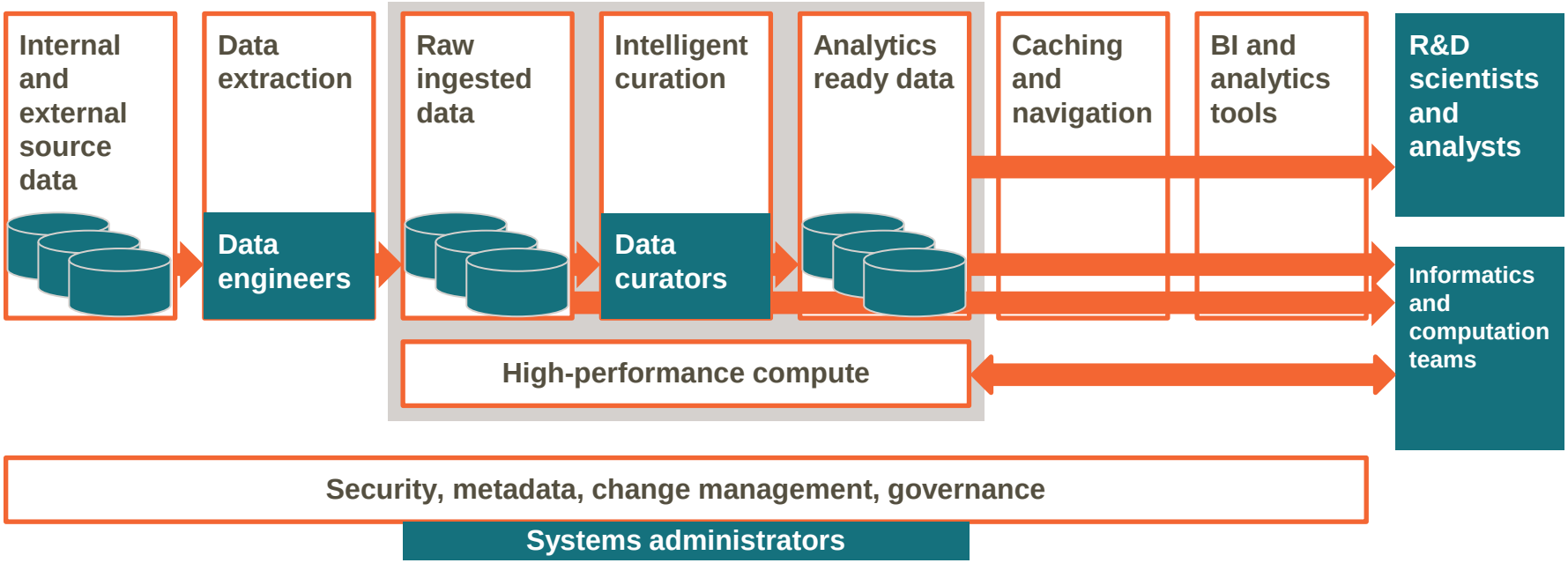
Detailed quantitative biomarkers are better predictors of survival?



Aerts et al, Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun 2014 5 4006

Integrative Data Analytics at GSK

Using technology to make data more accessible



- A scalable analytics platform for GSK R&D based on Hadoop infrastructure and supporting analytics tools
- Facilitates study of information brought together from multiple domains to uncover unique and actionable insights

Project CRAWL

Contextualisation of Real-World Drug-Use through Social Listening

http://epidemico.com/2015/04/22/2015-bio-it-world-best-practices-award-clinical-health-it-winner-project-crawl/

- Reporting of post-market adverse events relies on patient following formal process
- CRAWL extends GSK's safety activities to social media communications
- Cloud-based validated system to monitor social media for drug safety in real time
- Standardises colloquial language into medical terminology
- Removes PII and unwanted noise
- Highlights the questions being asked
- Identifies potential supply chain concerns (adulteration, counterfeiting)
- Safety listening lab monitors data

Conclusions

- Complex datasets include not only ‘Google style’ big data (i.e. billions of samples) but also other rich datasets (i.e. many data points but not necessarily large numbers of samples)

- The pharmaceutical industry still relies on very simple analysis methods

- There is significant scope for improvement!