Personalizing Medicines for Neuroscience Indications

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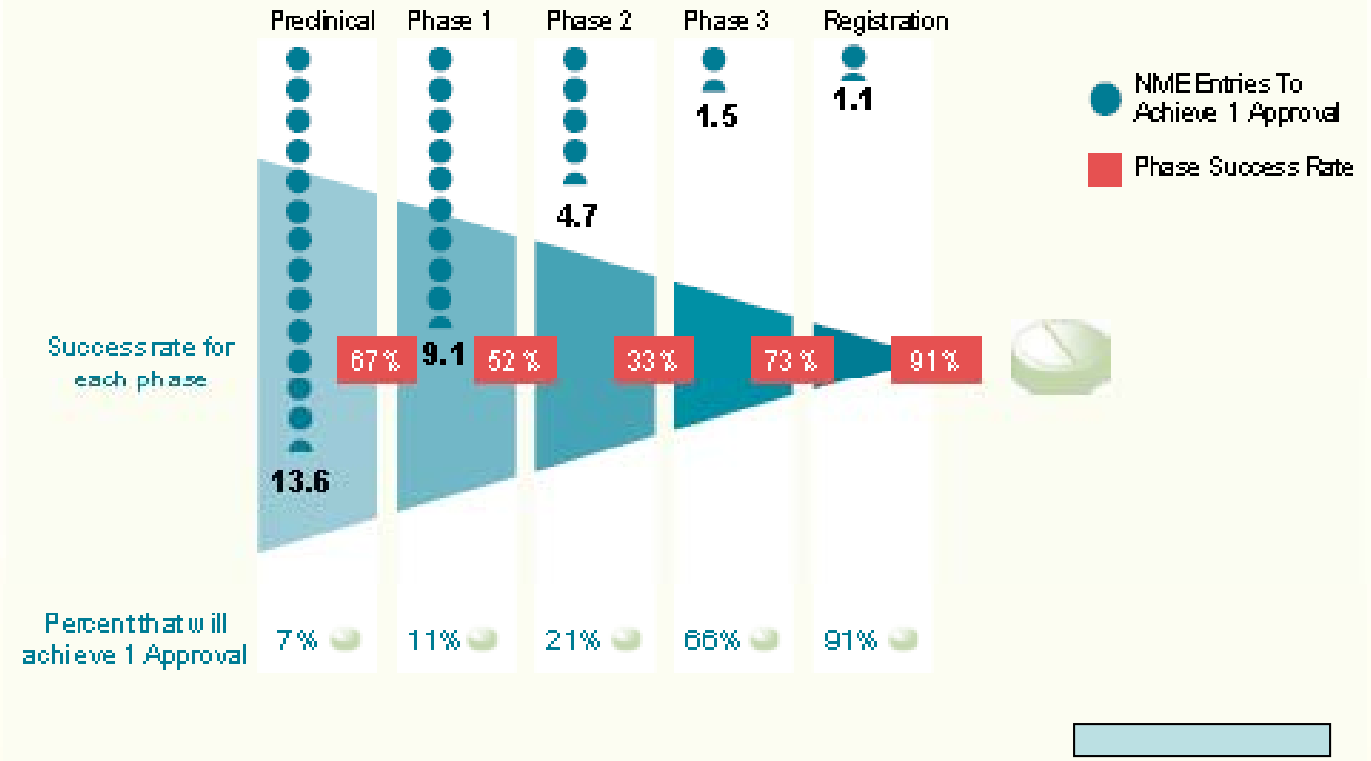
Development Success Rates

NME Success Rates By Phase And Overall 2004-2008 Industry



Success Rate = (number of successes) / ((number of terminations) + (number of successes))

What is Personalized Medicine (PM)?

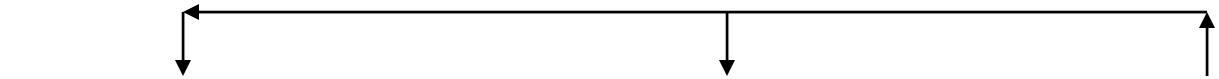
- **"Personalized medicine is the tailoring of medical treatment to the individual characteristics of each patient.**

- **It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.**
  - Classification requires variability in some measurable phenotype or genotype

- **Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not."**

Priorities for Personalized Medicine,
President's Council of Advisors on Science and Technology PCAST, Sept 15, 2008

Personalizing Medicines: Alternative (or Complementary) Methods to Symptomatic Diagnostic Classification of Patients



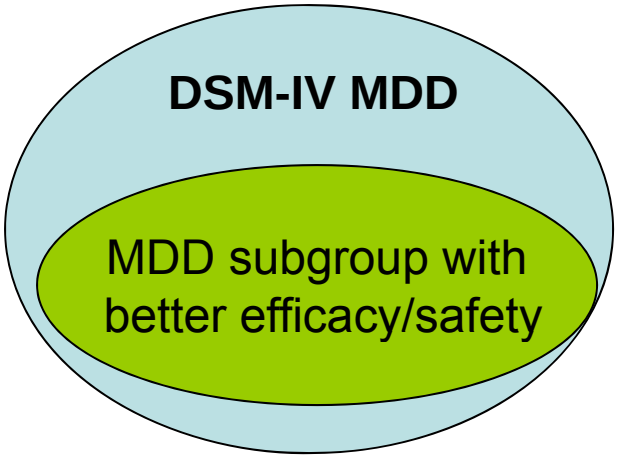
Current Practice:

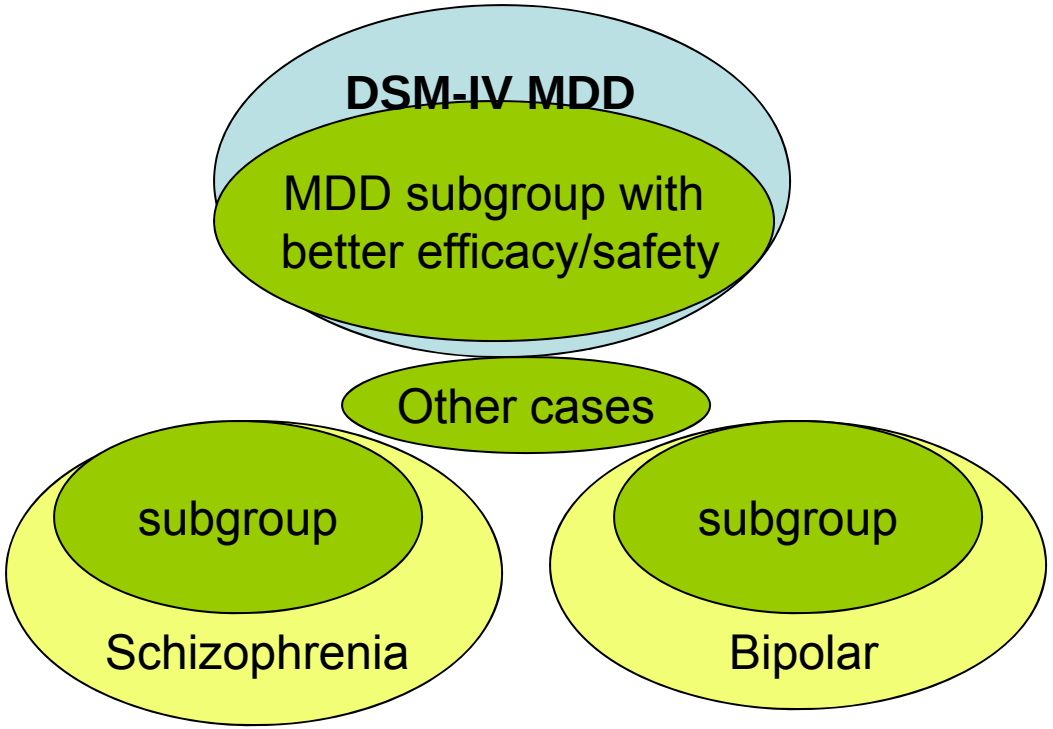
Symptomatic diagnosis (DSM) and patient history; And lab tests/technology to exclude "medical" cause → **Select Medicine And treat** → **Response: Efficacy and safety (symptoms, functioning)**

Future Practice:

Biomarker/gene/technology +/- Symptomatic diagnosis (DSM) and patient history; And lab tests/technology to exclude "medical" cause → **Select Medicine And treat** → **Response: Efficacy and safety (symptoms, functioning); Biomarker/technology?**

Classifying (selecting) Individuals: Subsetting current disorders





•Classification identifies a subset Of a DSM disorder

•Classification identifies pieces of several DSM disorders and cases Intermediate to those disorders

Classification requires variability in some measurable phenotype or genotype

PM: Variation is identified by companion diagnostics

- **A companion diagnostic facilitates the appropriate prescription of a drug for a particular patient**
  - Supply clinical information regarding drug dosing and safety
  - Predict a patient's response to optimize treatment regimes
  - Goal: Included in the therapeutic label insert, preferably as required

- **Companion diagnostics require co-development with the drug candidate**
  - **FDA Drug-Diagnostic Co-Development Concept Paper provides discussion**

- **Genentech's FDA Citizen Petition (FDA-2008-P-0638)**
  - **Requests that FDA require that all in vitro diagnostic tests intended for use in drug or biologic therapeutic decision making be held to the same scientific and regulatory standards**

- **Need to start companion diagnostic development early as a conscious and deliberate process. It cannot be 'backed into' Phase III**
  - **Where a companion diagnostic is not available or readily developable when initiating a drug discovery project, can companion diagnostics be discovered during the drug development process?**

PM: Growing Rx cabinet is using a a companion Diagnostic

- Testing required by FDA

– **Selzentry/HIV AIDS**	**Pfizer**	**CCR5 tropism**
– **Erbitux/colon cancer**	**Imclone**	**IHC EGFR +/-**
– **Vectibix/colon cancer *EMA**	**Amgen**	**EGFR and KRas mutations**
– **Herceptin/breast cancer**	**Genentech/Roche**	**FISH/IHC Her 2**

- Testing recommended by FDA

– **Camptosar/colon cancer**	**Pfizer**	**UGT1A1 variant**
– **Ziagen/ HIV AIDS**	**GSK**	**HLA-B 5701 variant**
– **Imuran/autoimmune**	**GSK**	**Thiopurine methyltransferase**
– **Tegretol/epilepsy & bipolar**	**Various**	**HLA-B 1502 Asian variant**
– **Tarceva/NSCLC**	**Genentech/OSI**	**IHC EGFR +/-**
– **Warfarin**	**Various**	**CYP2C9 and VKORC1**

- Informational tests

– **VFEND/fungal infections**	**Pfizer**	**CYP2C19**
– **Strattera/attention deficit**	**Eli Lilly**	**CYP2D6**
– **Xeloda/cancer**	**Roche**	**Dihydropyrimidine dehydrogenase**
– **Gleevec/cancers**	**Novartis**	**Philadelphia chromosome, c-KIT**
– **Fanapt/schizophrenia**	**Vanda**	**CYP2D6**

Updated from Nature Biotechnology. 26. 509-517. 2008

Herceptin (trastuzumab) is a monoclonal antibody that targets HER2

- HER2: Human Epidermal Growth Factor Receptor 2
- 25% of breast cancers are HER2 positive
- Herceptin mediates antibody dependent cellular cytotoxicity
- HER2+ breast cancer was studied in the clinical development program
  - HER2 overexpression (≥3+ by IHC) or gene amplification by FISH
- Herceptin in indicated as adjuvant therapy for HER2+ breast cancer (node + or -, ER/PR neg or one high risk feature) and certain cases of HER2+ metastatic breast cancer

Erbitux (cetuximab) is a monoclonal antibody that targets the EGFR

- EGFR- Epidermal Growth Factor Receptor
- Erbitux binds to the EGFR and competitively inhibits the binding of EGF and other ligands, inhibiting cell growth, inducing apoptosis, decreasing matrix metalloproteinase and vascular endothelial growth factor (VEGF) production
- Signal transduction through EGFR results in activation of wild type kras protein.
- In cells with activating kras somatic mutations, mutant kras protein is continuously active and is thought to be independent of EGFR regulation.

Erbitux Indications

- Squamous cell carcinoma of the head and neck
  - EGFR has been detected in nearly all SCCHN tumor specimens
  - SCCHN trials run without testing EGFR status
- EGFR-expressing metastatic colorectal cancer after failure of or intolerance to certain other chemotherapies
  - Study subjects required to have “immunohistochemical evidence of EGFR tumor expression”
  - Response rate did not correlate with either the percentage of cells positive for EGFR or the intensity of EGFR expression.
- “Retrospective subset analyses…have not shown a treatment benefit for Erbitux in patients whose tumors had kras mutations in codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations.”

National Comprehensive Cancer Network (NCNN) guidelines also recommend that Erbitux be used only in EGFR+ tumors with wild-type KRAS gene

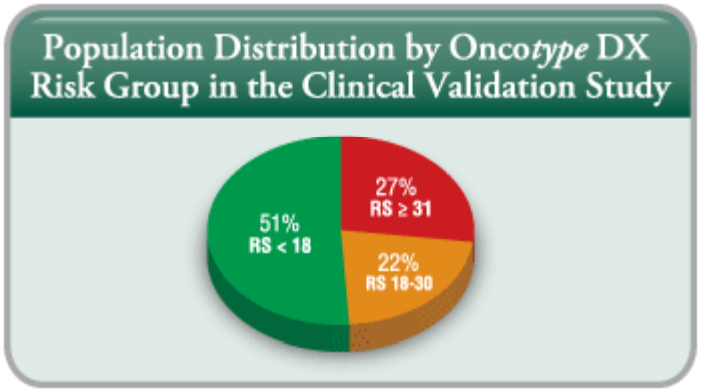
Lessons from Herceptin and Erbitux

- Individual differences in patient genotypes or phenotypes are necessary for personalized medicine to be possible.
  - Only treat patients who have the drug target.
- Since the target must be present in order for the targeted therapeutic to affect the disease, individuals who lack the target need not be studied.
- Assuming the target is present, the degree of expression of the target may or may not make a difference in outcome
  - Yes for herceptin IHC, not for Erbitux IHC
- Secondary molecular factors (kras mutations with Erbitux) can impact upon drug efficacy and complicate personalizing medications.
- Secondary non-molecular factors may also be important to understanding drug efficacy and thus risk:benefit
  - node status, “high risk features”, some metastatic cases
- It helps to have a well-defined molecular pathophysiology for the disease, and plausible linkage between the molecular pathophysiology and an outcome measure that patients, physicians, and regulators care about.

Expression profiling of tumors to predict metastasis/recurrence—FDA approved tests

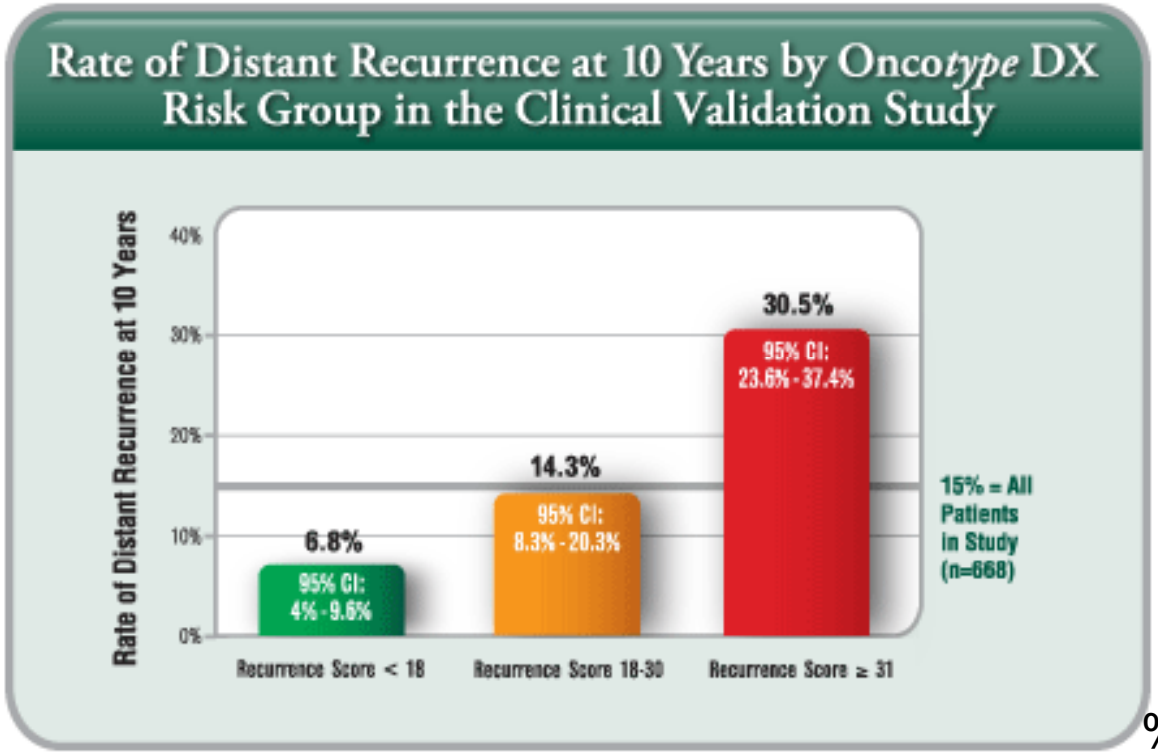
- Mammaprint: (cost = $4200)
  - Expression profile of 70 genes improves prediction of metastasis in breast CA patients who are < 61 years old, Stage I or II, tumor size ≤ 5cm, lymph node negative, no limitation on treatment.
- Oncotype DX (cost = $3900)
  - Expression levels of 21 genes within a tumor are used to predict who with Stage I or II, ER+, lymph node -, invasive breast CA will suffer a recurrence within 10 years
  - Included as an option in NCCN and ASCO guidelines for planning whether to use adjuvant chemotherapy
  - Covered by Medicare and most private insurers

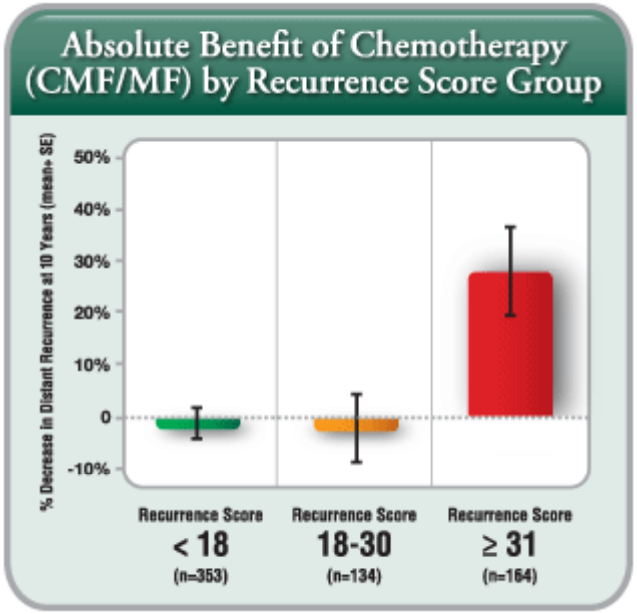
Oncotype DX: Predicting breast CA recurrence and benefit of chemotherapy



More lessons:

1) Non-molecular factors are important for personalizing medicines
2) Consider cost of the test relative to benefit
3) Consider %subjects that benefit versus cost and medical need





% decrease in distant recurrences

Labeled Genetic Tests--Neuroscience

- Carbamazepine (Black box warning)
  - HLA B*1502 allele increases the risk of serious dermatologic reactions (toxic epidermal necrosis and Stevens-Johnson syndrome)
  - “Patients with ancestry in genetically at risk (Asian)populations should be screened for the presence of HLA B*1502 prior to initiating treatment…”
  - Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk.

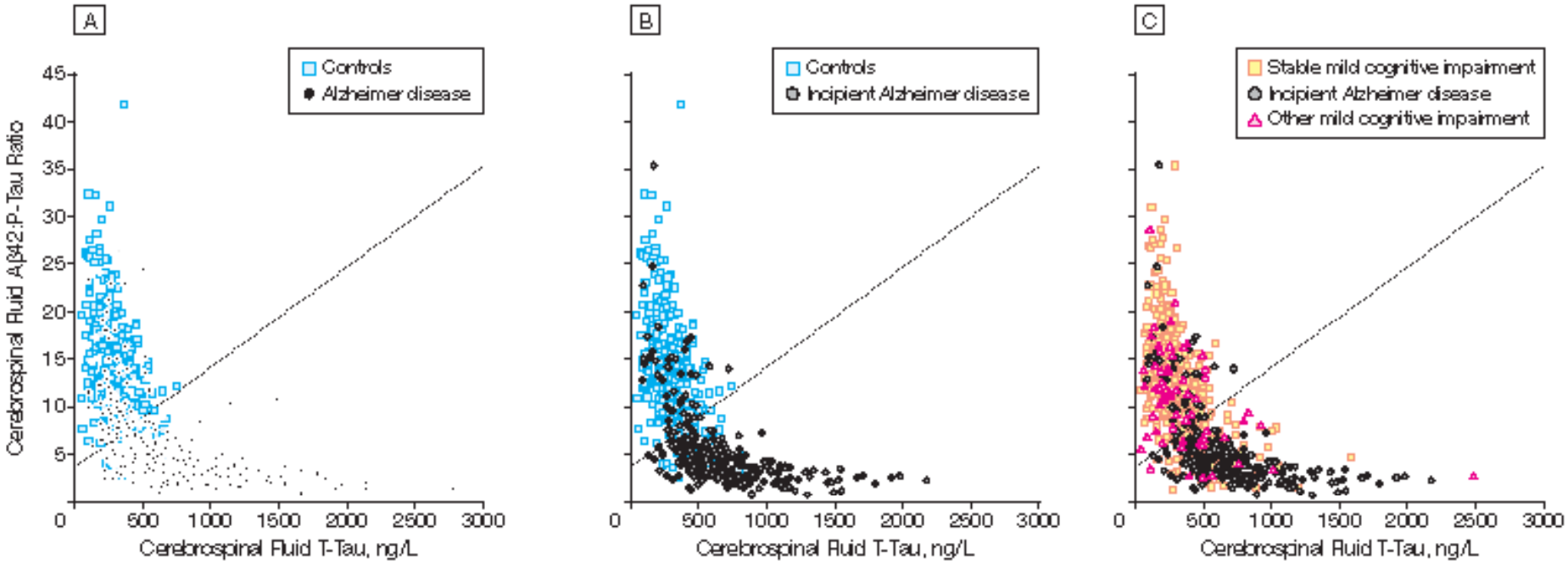
Identifying patients with Alzheimer's Disease before they are demented

- A number of pharmaceutical companies are working to develop treatments for AD that slow or stop disease progression
- These treatments would preserve more function if they can be initiated prior to patients becoming demented
- Can patients with AD pathology be identified prior to becoming demented who have a predictable rate of conversion to dementia?
  - "incipient AD", "pre-clinical AD", "amnestic MCI" etc

Biomarkers under investigation for identifying pre-clinical AD

CSF Marker	AD vs HV	Predicts MCI conversion to AD	Specificity	Note
Aβ42	decreased	yes	No: Decreased in FTD, CJD, GSSS, ALS, DLB	Plaques as traps of Aβ42?
Total-tau	increased	?	No. increased in FTD, stroke, CJD, etc	
P-tau (231, 181, 199)	increased	Yes (p-tau231)	Yes. (231, 199)	Tau hyper phosphorylated in AD
Tau/Aβ42	increased	yes		
Aβ40	No difference	No		
Plasma Aβ42	No difference	mixed		Not correlated with brain or CSF levels or plaque

Data from the Mattsson, 2009 multicenter study



Sensitivity = 85%

Sensitivity = 83%
Specificity = 88%

Specificity = 72%

Mattsson, JAMA, 2009, 302: 385-393.

Summary and Questions : Diagnosing Incipient (pre-clinical, pre-demented, prodromal) AD

- Predictive value of biomarkers combined was greater than that of individual biomarkers (Mattson study)
- Specificity of the combined biomarkers in the Mattson multicenter trial was lower than found previously in single center studies (intercenter variability; nonstandard sample handling, MCI dx)
  - Are these markers ready for use in clinical trials? Ready for use in clinical screening and/or diagnosis?
  - Is the 11% annual rate of conversion to AD sufficient to conduct clinical trials?
- ADNI study will integrate neuroimaging, CSF and clinical variables to try to improve diagnosis of incipient AD.
  - Will structural MRI, FDG-PET, or PIB be added to CSF biomarkers to improve identification of incipient AD?
- Personalized medicine may allow for extension of treatments into the preventative space—
  - what are the implications for prevention or earlier treatment of other neurological and psychiatric disorders?
- What are the earliest/risk phenotypes in other disorders?
  - Schizophrenia—cognitive deficits appear before frank psychosis
- Why are CSF and imaging biomarkers closer to being used for personalizing medicines for AD than similar biomarkers/technologies for psychiatric disorders?
  - Are CSF collection and MRI feasible for use in psychiatric disorders?

BMS-708163: A clinical trial in “patients with prodromal alzheimers disease” (NCT 00890890)

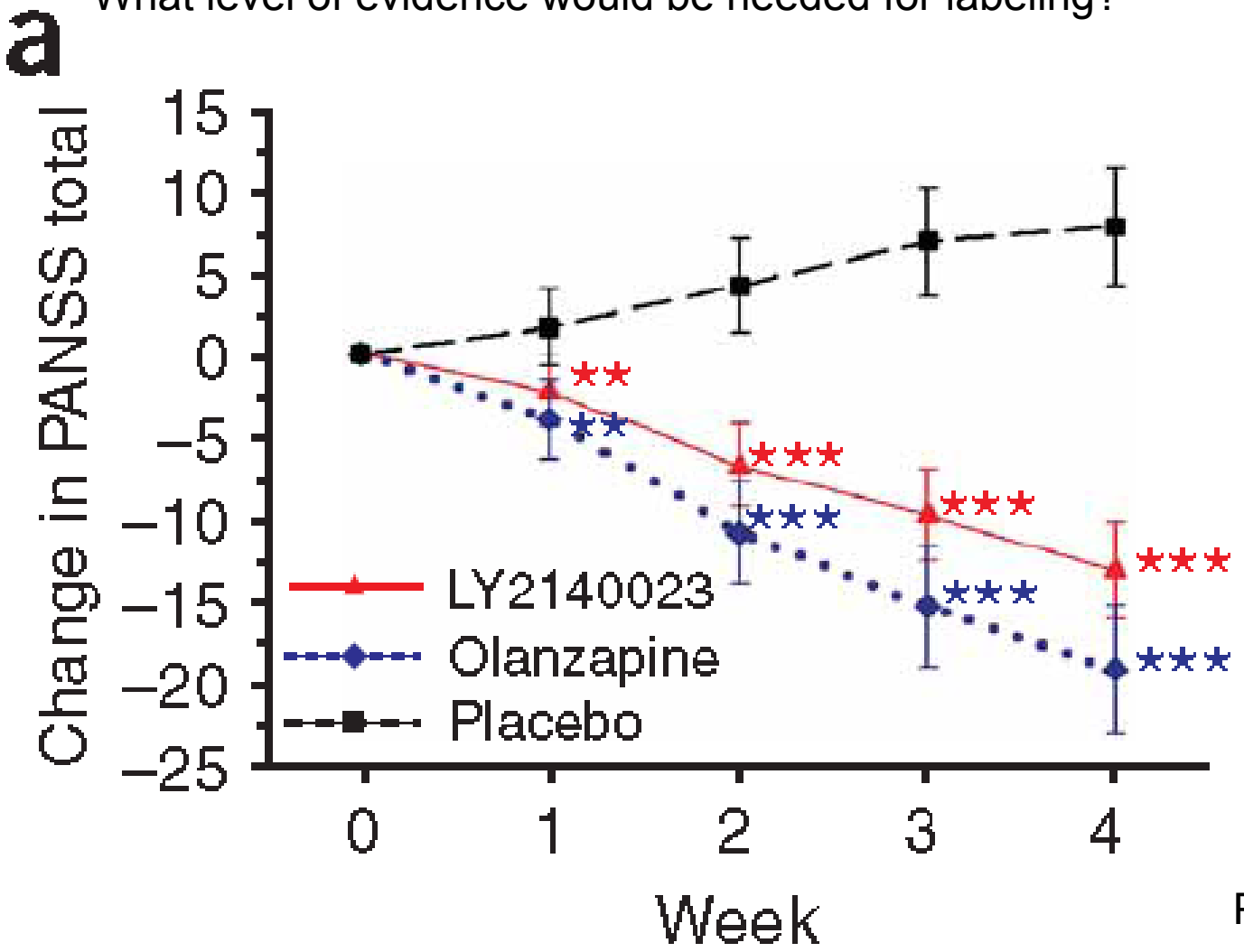
- Treatment period of 24-weeks and a follow-up period of 28 weeks.
- Primary endpoint: safety
- Secondary endpoints:
  - CSF biomarkers (Aß40,Aß42, total Tau, phosphorylated Tau) and volumetric MRI
  - Assess drug effects on progression to dementia (based on confirmed progression using DSM-IV criteria)
  - CDR-SB
- Inclusion Criteria
  - MMSE 24-30
  - CSF Abeta 42 levels < 200pg/mL
- Study size: 270 pts in Canada, Denmark, Finland, France, Netherlands, Sweden, US
- Estimated Study Completion Date: October 2012

Personalizing medicines for schizophrenia: Issues

- Neural networks, which support behavior and subjective experience, may be disrupted by a variety of molecular mechanisms,
- More complex relationship between molecular pathology and symptomatic outcomes than seen in CA or AD.
  - Significant phenotypic variability in schizophrenia
  - Progress is being made in identifying genetic risk factors for schizophrenia, but it seems to be pointing toward many genes with very small effects in the population
  - Classification using combinations of genes/proteins (molecular profiling) may be necessary
- Biomarker methods and technologies used may be seen as overly invasive, costly or not consistent with current psychiatric practice
  - Practice can change over time, driven by evidenced based medicine and consensus standards of care.

LY2140023: mGluR2/3 agonist drug candidate for treating schizophrenia

Will a different group of schizophrenics respond to LY vs to D2 antagonists?
If so, how will they be identified?
What level of evidence would be needed for labeling?



Patil, 2007

What methods should be used to classify groups of schizophrenics to try to improve risk/benefit of treatments?

Many options:

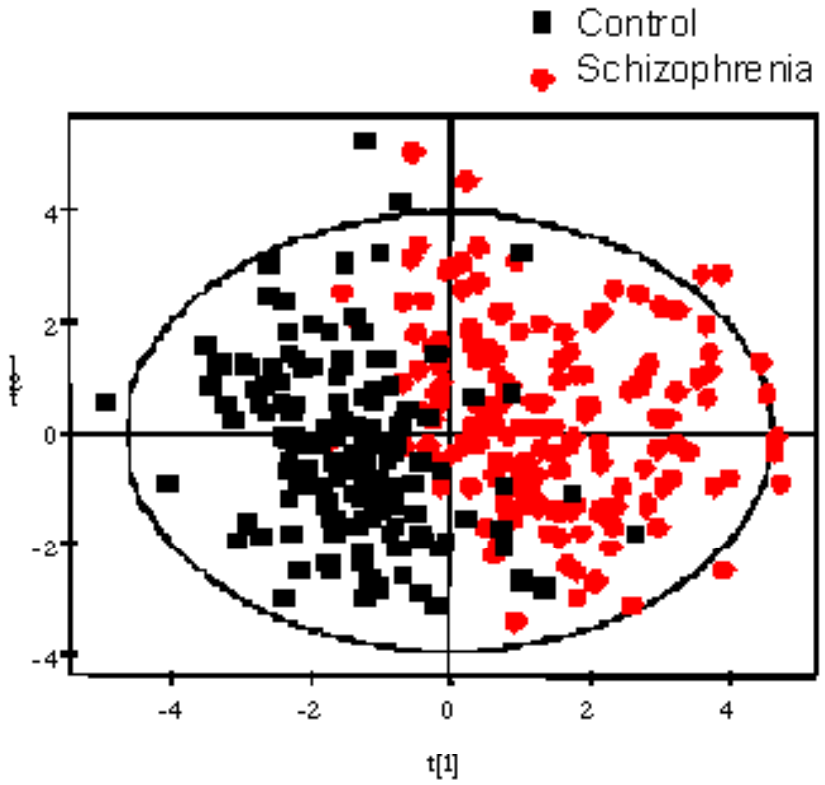
- 'Omics options: Genes/gene expression, Proteins, Metabolites
  - Glutamatergic vs dopaminergic markers for LY2140023? Or choose an unbiased approach (GWAS)?
- CSF proteins—
  - S100, SNAP-25, GSK-3β, transthyretin—inconsistent, preliminary results
- Electrophysiologic (EEG)—gamma, theta or delta synchrony
- Evoked potentials– P300, P50,etc.
- Cognitive tests
- fMRI/other functional imaging
- Multimodal/multilevel methods
  - Will this approach be necessary in order to connect molecular mechanisms to neural processes or networks to symptoms and functional outcome?
- Don't ignore the pharmacogenetics of ADME
  - This can be an important source of variation in response

Things to think about in choosing a classification method

- Ease of use of the classification method across multiple sites and ultimately in the doctor's office
- Look for large effect sizes when doing retrospective analyses. They will need to be followed by prospective analyses and effect sizes will likely drop.
- Available (or obtainable) sample size will impact ability to detect effects of classified variables on treatment outcome
- Variability in clinical phenomena (phenotype, endophenotype, genotype) and variability in the proposed classification measure needs to be understood to pursue personalized medicines
- Should one pursue linking the drug mechanism to the proposed classification measure to provide a stronger scientific rationale (hypothesis-driven, biased approach), or choose an unbiased approach (GWAS), or both?

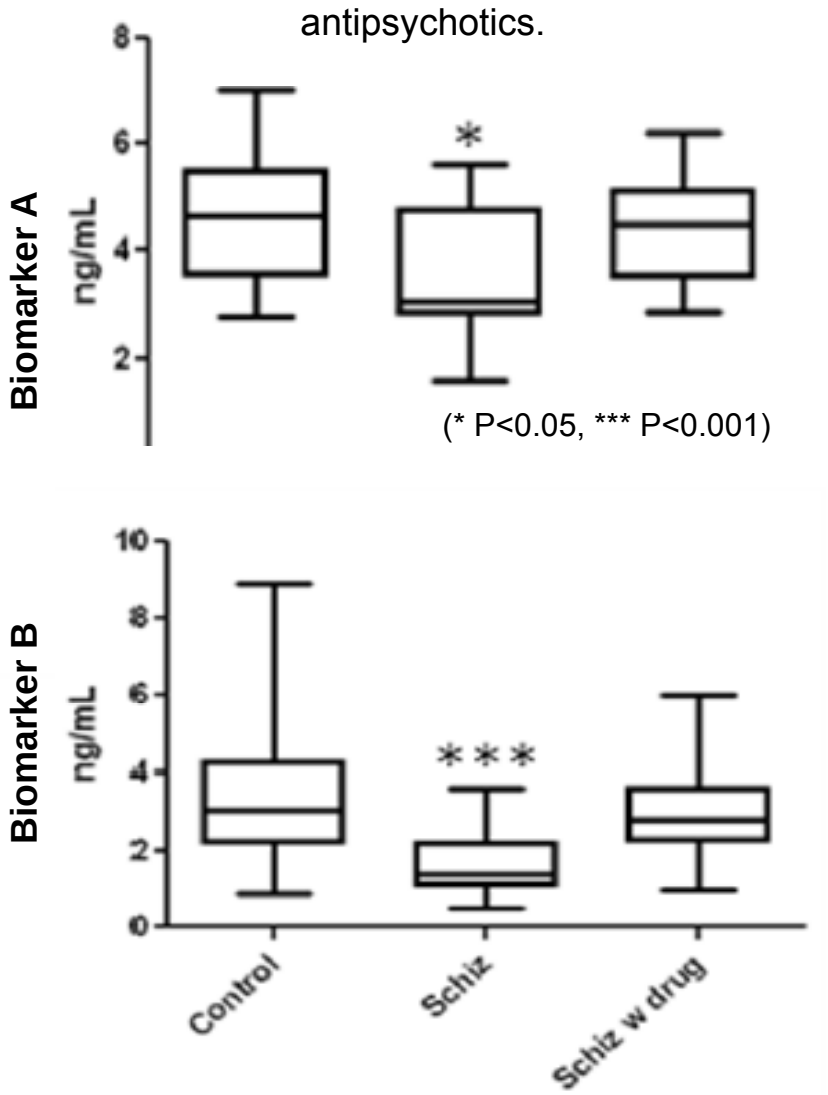
Proteomic “Fingerprint” Example from Psynova

Analysis of disease classification performance using 50 candidate panel



- Sensitivity 88%
- Specificity 86%

Box plot data of two candidate biomarkers apparently down regulated in baseline drug naive, first onset schizophrenic patients vs healthy controls. The biomarkers appear to be normalized in schizophrenics following 6 weeks of drug treatment with atypical antipsychotics.



Time for Questions and Discussion

Implications of Personalized Medicine for DSM-V and vice-versa

- Will PM methods of classifying patients for treatment make our current (DSM) way of diagnosing patients obsolete?
- Will dimensional assessments of patients, if included in DSM-V, facilitate (at least) genotypic classification of patients for developing personalized medicines?
- Will methods of diagnosis/classification transition variably over time, depending on the particular disorder/phenomena under study?

Technologies under investigation for identifying pre-clinical AD

Technology	AD vs HV	Predicts MCI conversion to AD	Specificity	Note
MRI (MTL or HC volume)	decreased	yes	probably	Also 2-5x increaed rate of whole brain atrophy
FDG-PET	Decreased regional (TPC, PCC, HC) metabolism	yes	?	
Amyloid imaging (PIB-PET)	Increased binding in AD	?	Increased in some healthy elderly; some MCI increases in AD range; early marker of AD pathology? Specificity demonstrated vs FTD.	PIB binding correlates with rate of atrophy, decreased CSF Aβ42, cerebral metabolism, memory impairment

Proteomics methods for identifying pre-clinical AD

- Nonbiased profiling of fluids (CSF)
- Methods:
  - Two-dimensional gel electrophoresis, liquid chromatography, or protein chip analysis followed by mass spectrometry and database searches to identify proteins
- Human CSF proteome
  - 2594 proteins (Pan, 2007)
  - 798 proteins, 563 peptide forms (Zougman, 2008)
- Status
  - Differences between AD and controls identified;
  - Panels created to differentiate AD from healthy controls, PD, DLB
  - Evidence of ability to identify MCI that will progress to AD dementia
  - Large validation studies and corroboration by alternative techniques needed
  - Plasma proteomics promising, but development well behind CSF for AD

Herceptin as adjuvant treatment in HER2+ breast CA

	DFS events	Hazard ratio (95% CI) p value	Deaths	Hazard ratio p value
Studies 1 + 2[s]				
AC→TH (n =1872)	133	0.48[a] (0.39, 0.59) p=< 0.0001[b]	62	0.67 p=NS[d]
AC→T (n = 1880)	261		92	
Study3				
Chemo→ Herceptin (n =1693)	127	0.54 (0.44, 0.67) p=< 0.0001[c]	31	0.75 p=NS[d]
Chemo→ Observation (n = 1693)	219		40	

HER2+ = HER2 overexpression (≥3+ IHC) or gene amplification by FISH
DFS events = Disease free survival events (recurrence) during 1 year of therapy.
Events = recurrence, occurrence of contralateral breast CA, other primary cancer, death