Neuroscience Trials of the Future

What Psychiatry and Neuroscience could learn from the Rest of Medicine

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Disclosures

- Consultant and/or Speaker for
  - *Otsuka, Sunovion, Takeda, Acadia, Lundbeck, Roche.*

- Funding
  - UK, MRC & NIHR
  - EU, Innovative Medicines Initiative

Outline ..

- A challenge common to all of medicine
- What we have done in the past and why it may not have worked
- What can we learn from success elsewhere
- What implications it has for our science and our trials


THE WALL S

MARKE

SCIENCE

New Era

Targeting Drugs
For Each Uniqu
Genetic Profile


Toward Precision Medicine

Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES


ledicine

netic Profile

ALDHOLZ

NAL

ill launch a two-year, $45 million pro-
everal hundred thousand chemical sign-
gene hunters explore the vast regions of

d last month in The Wall Street Journal,
their gene-hunting partners in university

Identifying biologically valid homogenous illness groups

The support of human genetic evidence for approved drug indications

Matthew R Nelson[1], Hannah Tipney[2], Jeffery L Painter[1], Judong Shen[1], Paola Nicoletti[3], Yufeng Shen[3,4], Aris Floratos[3,4], Pak Chung Sham[5,6], Mulin Jun Li[6,7], Junwen Wang[6,7], Lon R Cardon[8], John C Whittaker[2] & Philippe Sanseau[2]

nature genetics

VOLUME 47 | NUMBER 8 | AUGUST 2015

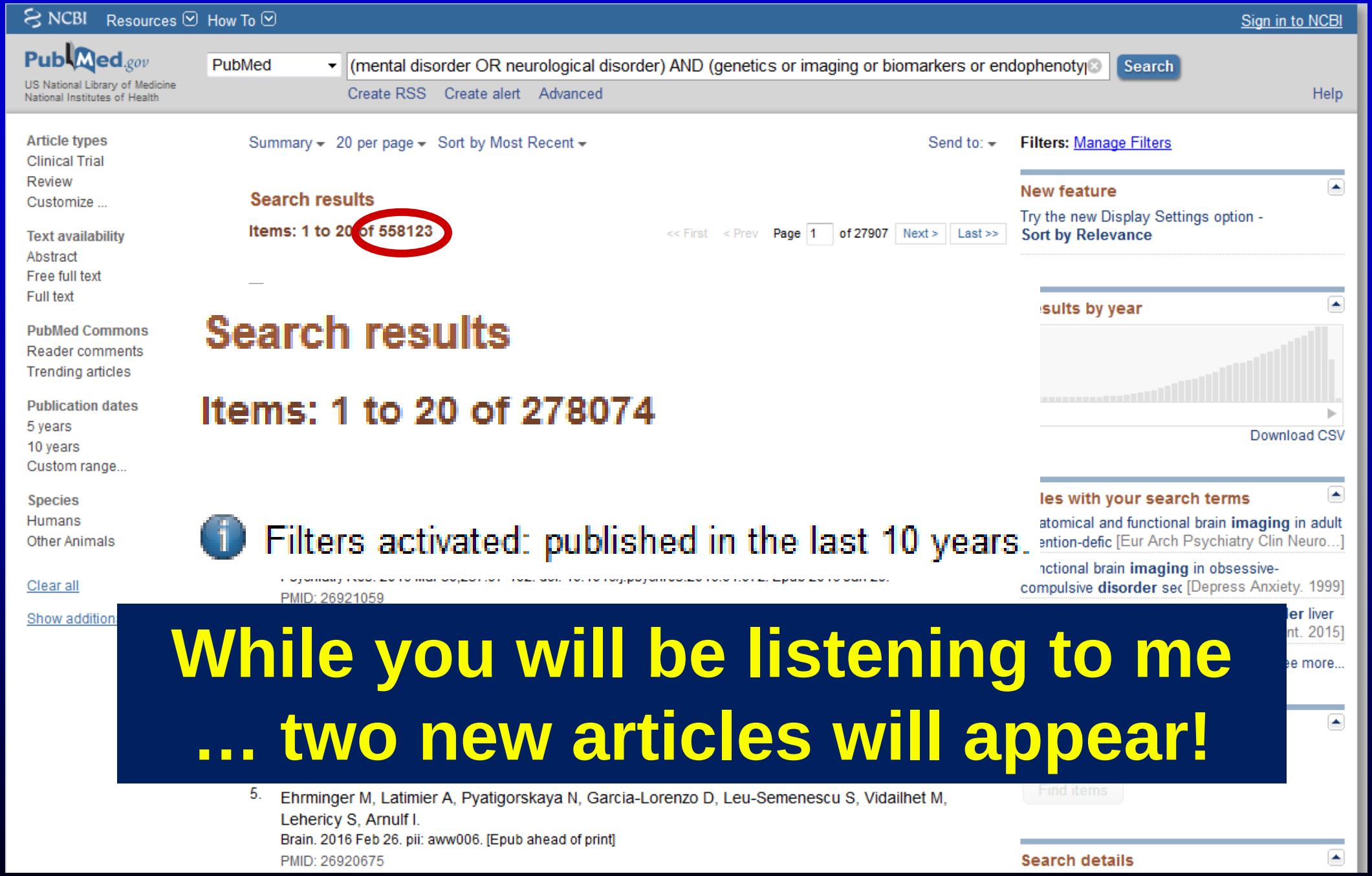
Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework

David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos

NATURE REVIEWS | DRUG DISCOVERY

VOLUME 13 | JUNE 2014 | 419

PERSPECTIVES


NCBI Resources How To
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(mental disorder OR neurological disorder) AND (genetics or imaging or biomarkers or endophenoty
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5 years
10 years
Custom range...
Species
Humans
Other Animals
Clear all
Show addition
Summary 20 per page Sort by Most Recent
Send to:
Filters: Manage Filters
Search results
Items: 1 to 20 of 558123
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Search results
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atomical and functional brain imaging in adult
ention-defic [Eur Arch Psychiatry Clin Neuro...]
nctional brain imaging in obsessive-compulsive disorder sec [Depress Anxiety. 1999]
Filters activated: published in the last 10 years.
PMID: 26921059
While you will be listening to me
... two new articles will appear!
5. Ehrminger M, Latimier A, Pyatigorskaya N, Garcia-Lorenzo D, Leu-Semenescu S, Vidailhet M, Lehericy S, Arnulf I.
Brain. 2016 Feb 26. pii: aww006. [Epub ahead of print]
PMID: 26920675
Search details

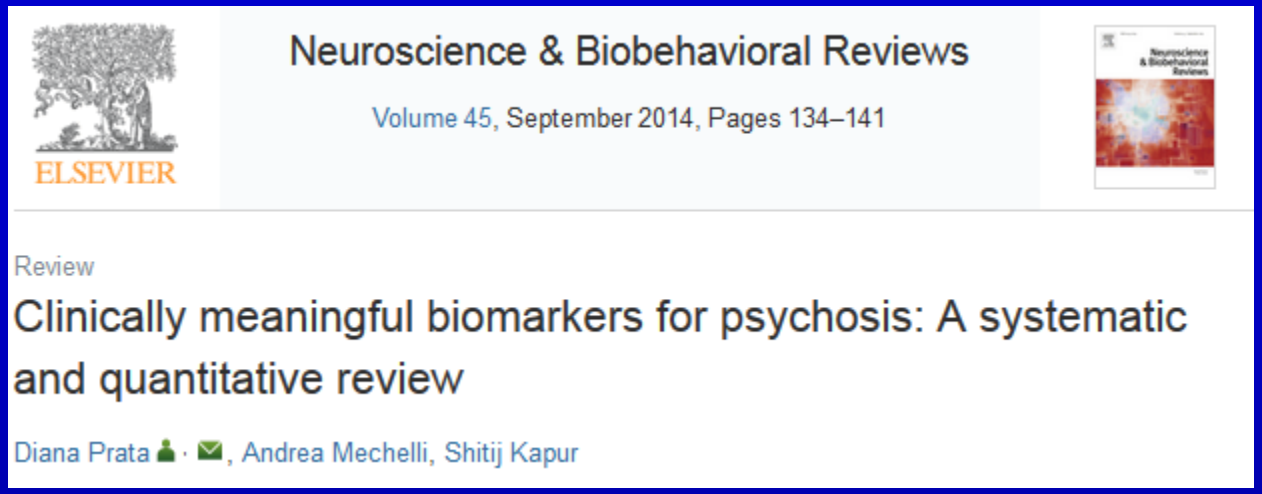
Some recent efforts at “precision” in Psychiatric Neuroscience Trials

- Iloperidone (now Fanapt™)
  - Weight gain predicting polymorphisms
- mGluR II/III agonist (Pomeglumetad™)
  - Response predicting 5-HT2 polymorphism
- GlyT-1 Inhibitor (Bitopertin™)
  - Response predicting serum CF-HR1

Volpi et al, J Clin Psychiatry, 2009

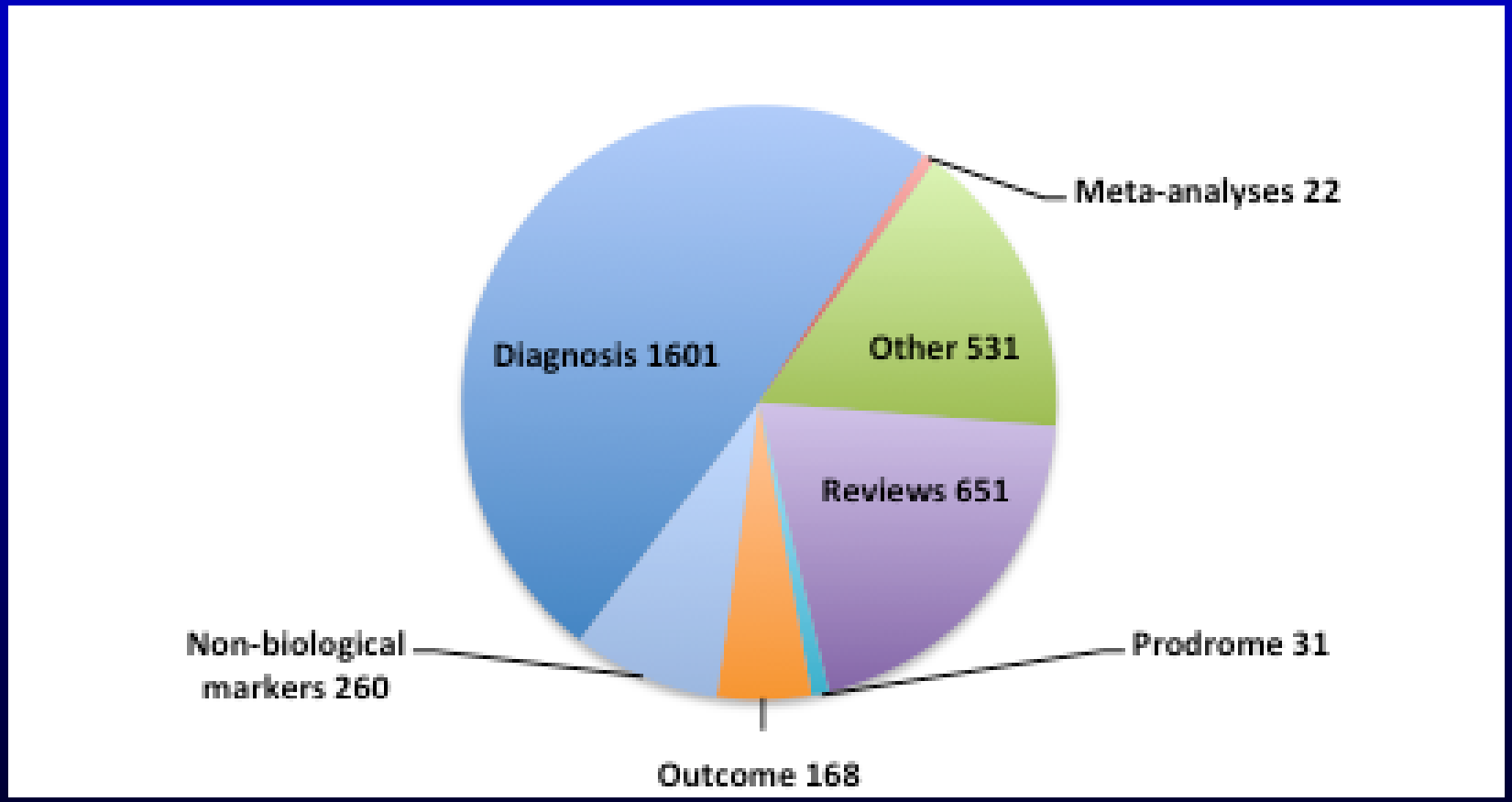
Liu et al, Pharmacogenomics, 2012

Bugarski-Kirola, poster, ACNP, 2015

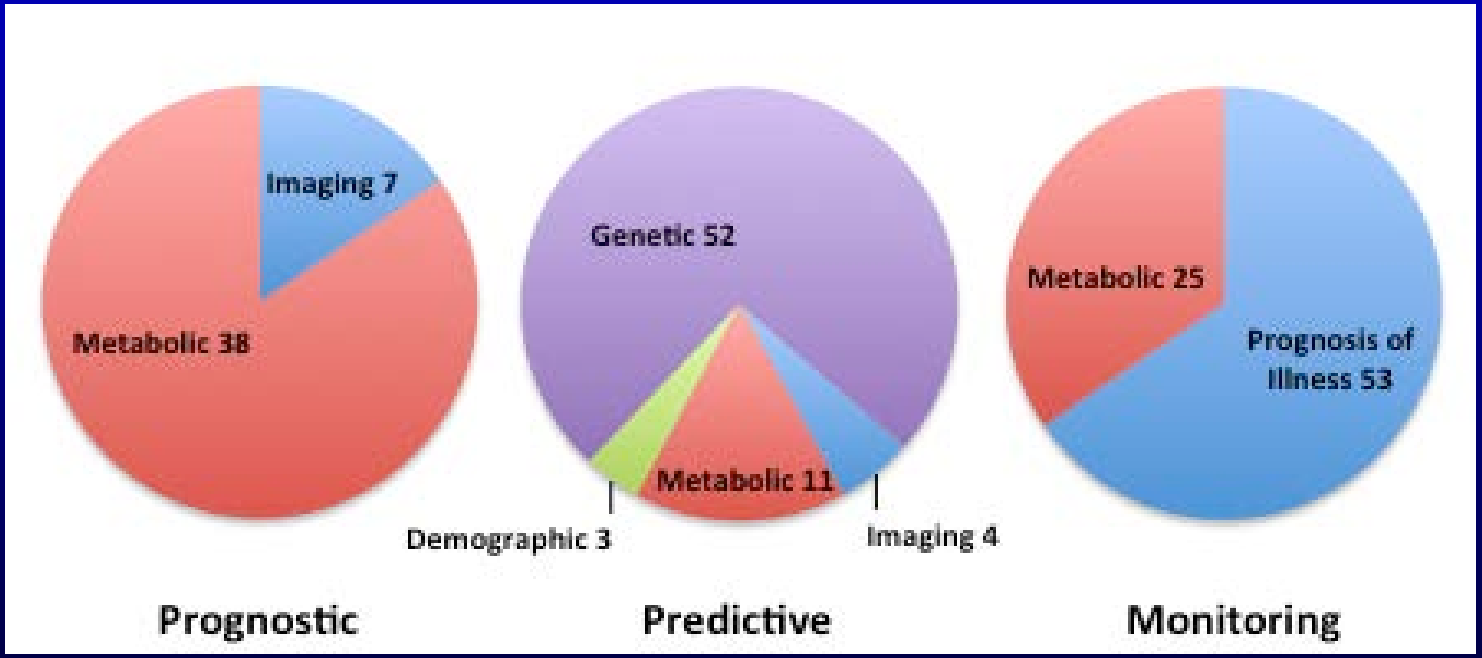


- Systematic PubMed Search for “biomarkers” and “psychosis”
- Each article classified by marker and intent
- Scoring system developed to identify the best replicated, potentially clinically significant markers

> 3,200 articles



Potentially useful markers in Neuroscience Clinical Trials



Ranking potential "Trial" Biomarkers

Biomarkers (N)		Quality of Evidence (QoE)						Effect Size					
Criteria		Score	-	1	2	3	4	Score	-	1	2	3	4
		Positive result	✔	✔	✔	✔	✔	QoE ≤ 1	✔				
		Controlled study		✔	✔	✔	✔	Marginal		✔			
		A priori definition			✔	✔	✔	Small			✔		
		Adequate power				✔	✔	Medium				✔	
		(+ 1) study of QoE ≥ 3					✔	Large					✔
Prediction of treatment response	Genetic (236)		70	165	0	1	0		235	0	0	0	1
	Metabolic (10)		4	6	0	0	0		10	0	0	0	0
	Imaging (7)		6	1	0	0	0		7	0	0	0	0
	Demographic (4)		1	3	0	0	0		4	0	0	0	0
	Total (257)		***81***	***175***	***0***	***1***	***0***		***256***	***0***	***0***	***0***	***1***
Monitoring of treatment response	Metabolic (92)		73	19	0	0	0		92	0	0	0	0
	Imaging (4)		3	1	0	0	0		4	0	0	0	0
	Total (96)		***76***	***20***	***0***	***0***	***0***		***96***	***0***	***0***	***0***	***0***

The biomarker in psychosis

- HLA-DQB1 6672 G>C SNP predicts agranulocytosis from Clozapine
  - Odds Ratio of 16.8
  - Specificity of 99.7%

- But,
  - Sensitivity of 21%
  - So does not change clinical care

Lessons Learnt

Significant Publication Bias

ORIGINAL ARTICLE

ONLINE FIRST

Excess Significance Bias in the Literature on Brain Volume Abnormalities

John P. A. Ioannidis, MD, DSc

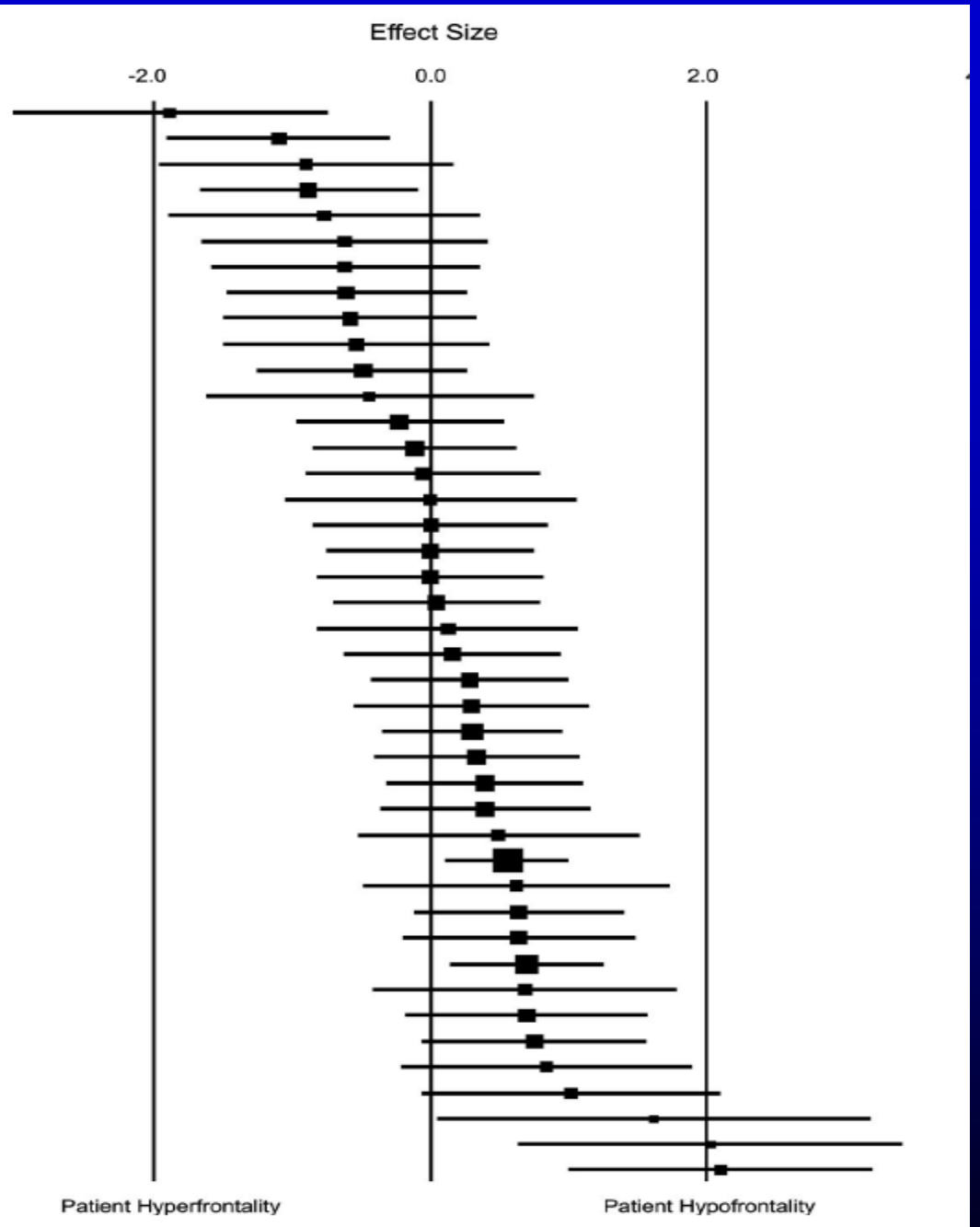
Conclusion: There are too many studies with statistically significant results in the literature on brain volume abnormalities. This pattern suggests strong biases in the literature, with selective outcome reporting and selective analyses reporting being possible explanations.

Arch Gen Psychiatry.
Published online April 4, 2011.
doi:10.1001/archgenpsychiatry.2011.28

Lessons Learnt

Too many “Approximate” replications

Study	Effect	Sample Size	
		Control	Patient
Sabri et al, 2003	-1.89	10	11
Callicott et al, 2000*	-1.09	18	13
Manoach et al, 2000*	-0.90	9	9
Callicott et al, 2000*	-0.88	18	13
Quintana et al, 2003	-0.77	8	8
Manoach et al, 2000*	-0.62	9	9
Jansma et al, 2004*	-0.62	10	10
Stevens et al, 1998*	-0.61	12	12
Manoach et al, 1999	-0.58	10	12
Jansma et al, 2004*	-0.53	10	10
Cairo, 2003*	-0.49	15	15
Manoach et al, 2001	-0.44	7	7
Cairo, 2003*	-0.22	15	15
Perlstein et al, 2003*	-0.12	15	16
Kim et al, 2003	-0.05	12	12
Kindermann et al, 2004	0.00	10	7
Hugdahl et al, 2004	0.00	12	12
Walter et al, 2003	0.00	15	15
Meyer-Lindenberg et al, 2001	0.00	13	13
Cairo, 2003*	0.05	15	15
Jansma et al, 2004*	0.13	10	10
Callicott et al, 2003	0.16	14	14
Volz et al, 1999	0.29	20	14
Stevens et al, 1998*	0.30	12	12
Honey et al, 2002	0.30	20	19
Perlstein et al, 2003*	0.34	15	16
MacDonald & Carter, 2003	0.40	17	17
Cairo, 2003*	0.40	15	15
Glahn, 2000*	0.49	9	9
Barch et al, 2002	0.55	48	38
Carter et al, 1998	0.62	8	8
Perlstein et al, 2003*	0.64	15	16
Barch et al, 2001	0.64	12	14
Honey et al, 2003	0.70	27	30
Wykes et al, 2002	0.68	6	12
Mendrek, 2000	0.70	12	12
Salgado-Pineda et al, 2004	0.75	14	14
Glahn, 2000*	0.84	9	9
Glahn, 2000*	1.02	9	9
Callicott et al, 1998	1.62	6	6
Mendrek, 2000	2.02	8	8
Menon et al, 2001	2.09	13	11



Lessons Learnt

Too many studies, too little “power”

Power failure: why small sample size undermines the reliability of neuroscience

Katherine S. Button[1,2], John P. A. Ioannidis[3], Claire Mokrysz[1], Brian A. Nosek[4], Jonathan Flint[5], Emma S. J. Robinson[6] and Marcus R. Munafò[1]

NATURE REVIEWS | NEUROSCIENCE

VOLUME 14 | MAY 2013 | 365

- The first implication of “power failure”
  - Miss findings (working at 18-30% power)
- The *Winner’s Curse*
  - Find exaggerated effects
  - The chance of replication goes down

Lessons Learnt

Little discussion of “Clinical Significance”

European Neuropsychopharmacology

Volume 25, Issue 10, October 2015, Pages 1578–1585

Biomarkers of treatment outcome in schizophrenia: Defining a benchmark for clinical significance

Stephen Z. Levine[a], Jonathan Rabinowitz[b], Rudolf Uher[c], Shitij Kapur[d]

Depression Tools.org

Home

Clinical Significance Calculator

Biomarkers and clinical significance

Biomarkers are measures taken from blood or ot
measurement. Biomarkers include genetic variations
activity among others. It is hoped that biomarkers can
select treatments that are more likely to work for a giv
medicine. However, for a biomarker to be clinically me

Type of Biomarker

--please select one--

--please select one--
binary
genetic
continous

Please enter the effect size as number of Hamilton Rating Scale for Depression (HRSD) points outcome difference per unit of biomarker

Calculate

Reference: Please refer to the article that describes the data simulations and methods behind the clinical significance calculator: http://www.futuremedicine.com/doi/abs/10.2217/pgs.11.161

Citations: Uher R, Tansey KE, Malki K, Perlis RH (2012) Biomarkers predicting treatment outcome in depression: what is clinically significant? Pharmacogenomics 13(2):233-40.

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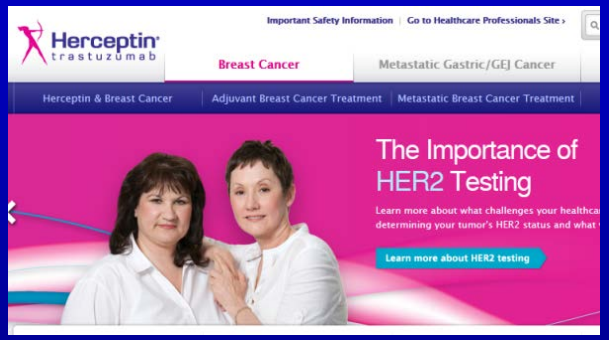
Lessons from successes in Medicine



From Biological Discoveries to Precision Medicines and New kinds of Trials

Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/*neu* Oncogene

DENNIS J. SLAMON,* GARY M. CLARK, STEVEN G. WONG, WENDY J. LEVIN, AXEL ULLRICH, WILLIAM L. MCGUIRE

Source: **SCIENCE** Volume: **235** Issue: **4785** Pages: **177-182** Published: **JAN 9 1987**

Studies of the HER-2/*neu* Proto-oncogene in Human Breast and Ovarian Cancer

DENNIS J. SLAMON,* WILLIAM GODOLPHIN, LOVELL A. JONES, JOHN A. HOLT, STEVEN G. WONG, DUANE E. KEITH, WENDY J. LEVIN, SUSAN G. STUART, JUDY UDOVE, AXEL ULLRICH, MICHAEL F. PRESS

Carcinoma of the breast and ovary account for one-third of all cancers occurring in women and together are responsible for approximately one-quarter of cancer-related deaths in females. The HER-2/*neu* proto-oncogene is amplified in 25 to 30 percent of

Source: **SCIENCE** Volume: **244** Issue: **4905** Pages: **707-712** Published: **MAY 12 1989**

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VOLUME 344

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USE OF CHEMOTHERAPY
FOR METASTATIC BF

HER2

DENNIS J. SLAMON, M.D., PH.D.,
VIRGINIA PATON, PHARM.D., ALEX BA
JANET WOLTER, M.D., MARK

.D.,
M.D.,

THE

EMPEROR

OF ALL

MALADIES

A BIOGRAPHY OF CANCER

SIDDHARTHA

MUKHERJEE

Articles

ljuvant

ancer: a randomised

Lancet 2007; 369: 29–36

See Comment page 3

Royal Marsden Hospital, London, UK (Prof I Smith MD, Prof M Dowsett PhD); Institute of Cancer Research, London (Prof I Smith, M Dowsett); Frontier Science (Scotland), Kingussie, UK (M Procter MSci); Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA (Prof R D Gelber PhD);

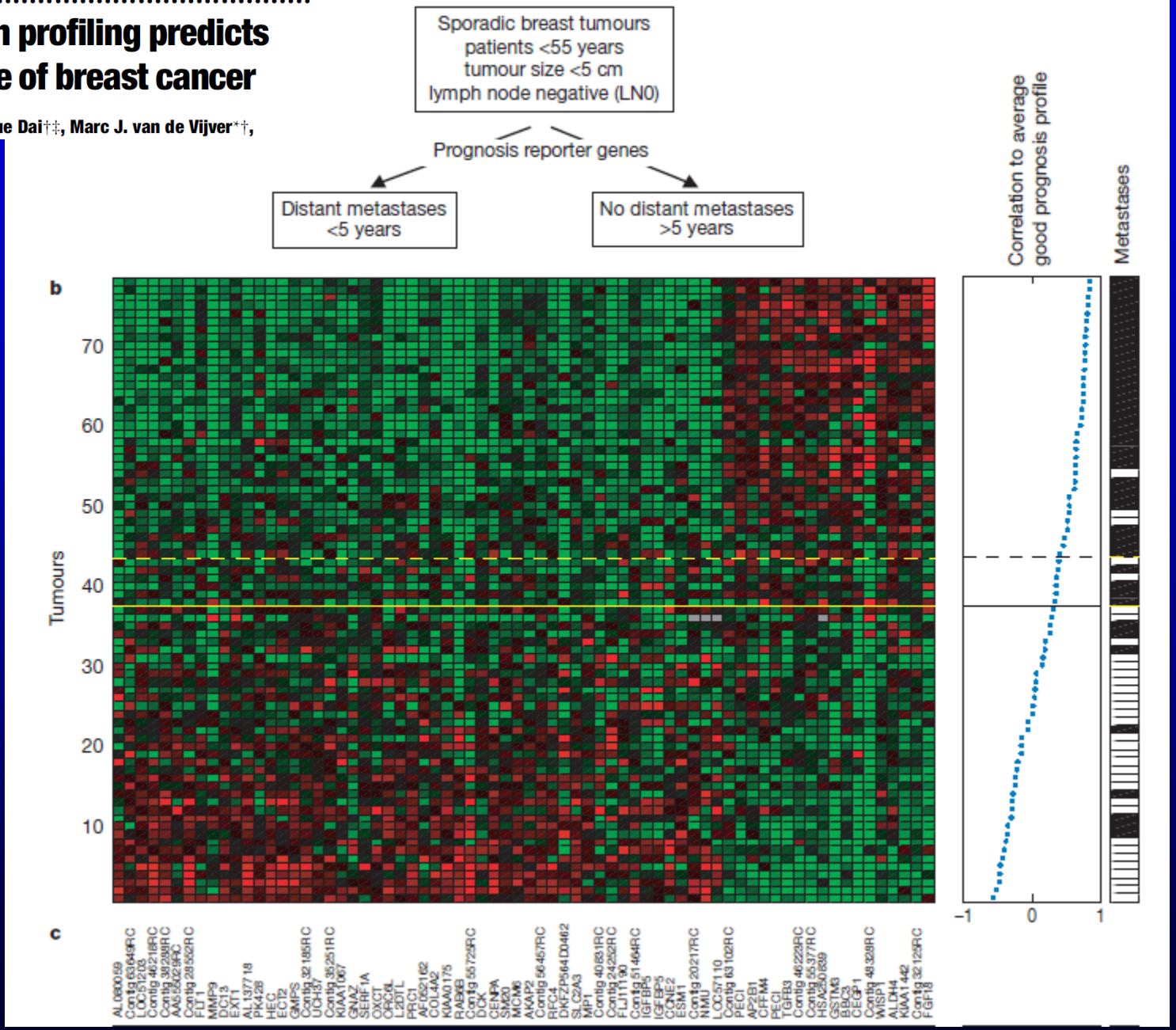
wsett, Aron Goldhirsch, Michael Untch, Gabriella Mariani, Jose Baselga, Manfred Kaufmann, David Cameron, Richard Bell, Jonas Bergh, Robert Coleman, Andrew Wardley, Nadia Harbeck, Roberto I Lopez, Peter Mallmann, Karen Gelmon, Nicholas Wilcken, Erik Wist, Pedro Sánchez Rovira, Martine J Piccart-Gebhart, for the HERA study team

Data-driven Findings

The critical importance of precise replication

Gene expression profiling predicts clinical outcome of breast cancer

Laura J. van 't Veer*†, Hongyue Dai†‡, Marc J. van de Vijver*†,



Precise Replications

Gene expression profiling predicts clinical outcome of breast cancer

Laura J. van 't Veer*†, Hongyue Dai†‡, Marc J. van de Vijver*†,

NATURE | VOL 415 | 31 JANUARY 2002 | www.nature.com

allow for patient-tailored therapy strategies. Here we used DNA microarray analysis on primary breast tumours of 117 young patients, and applied supervised classification to identify a gene expression signature strongly predictive of a short interval to distant metastases ('poor prognosis' signature) in patients with-

IGINAL ARTICLE

A Gene-Expression Signature as a Predictor of Survival in Breast Cancer

Marc J. van de Vijver, M.D., Ph.D., Yudong D. He, Ph.D., Laura J. van 't Veer, Ph.D., Hongyue Dai, Ph.D., Augustinus A.M. Hart, M.Sc., Dorien W. Voskuil, Ph.D., George J. Schreiber, M.Sc., Johannes L. Peterse, M.D., Chris Roberts, Ph.D., Matthew J.

N Engl J Med 2002; 347:1999-2009 | December 19, 2002 |

Validation and Clinical Utility of a 70-Gene Prognostic Signature for Women With Node-Negative Breast Cancer

Marc Buyse, Sherene Loi, Laura van't Veer, Giuseppe Viale, Mauro Delorenzi,

Journal of the National Cancer Institute, Vol. 98, No. 17, September 6, 2006

original article

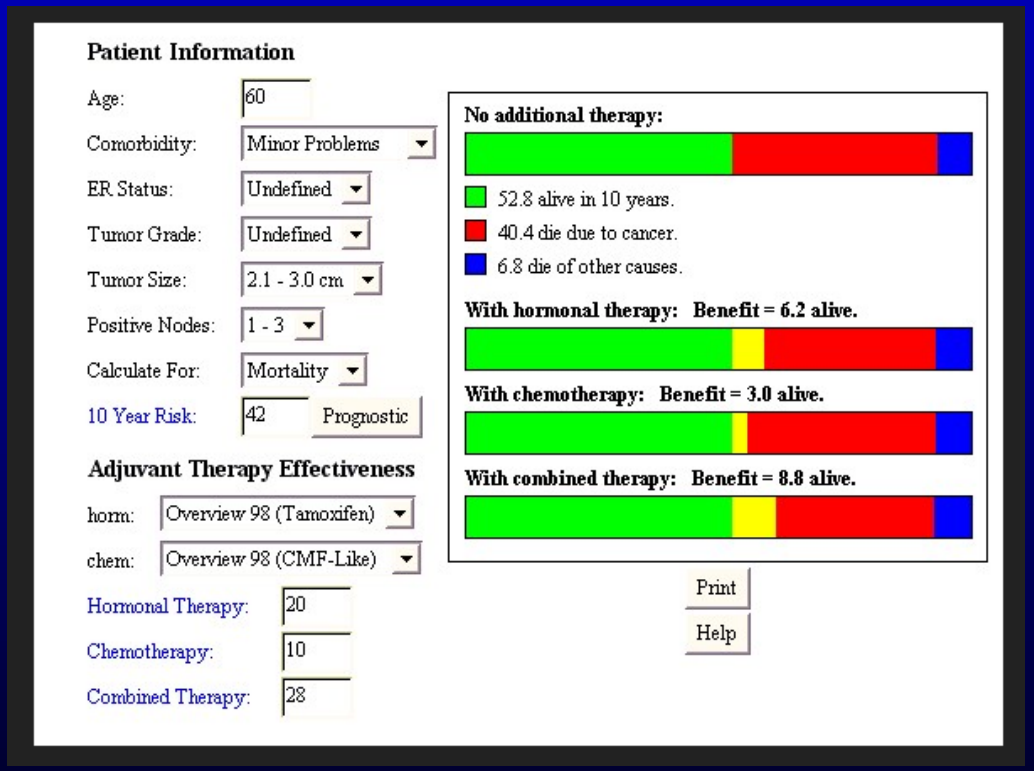
Annals of Oncology 21: 717–722, 2010
doi:10.1093/annonc/mdp388
Published online 13 October 2009

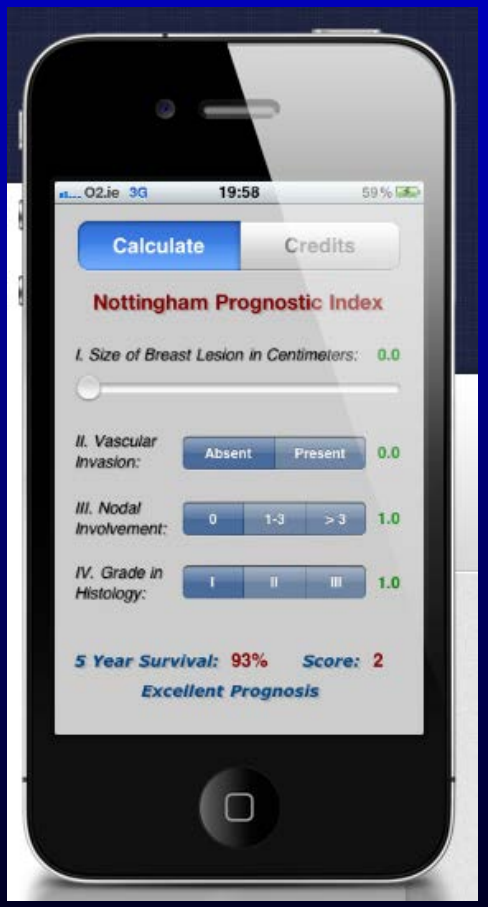
The 70-gene prognosis signature predicts early metastasis in breast cancer patients between 55 and 70 years of age

S. Mook[1], M. K. Schmidt[2], B. Weigelt[3], B. Kreike[4], I. Eekhout[1], M. J. van de Vijver[1], A. M. Glas[5],

Trials must lead to “Clinically useful & Innovative Option”

There is always a standard of care





MINDACT Trial

Breast Cancer Suspicion

Confirmation, Surgery, Pathology, ER Status
Clinical Predication & Mammaprint

Clinical - Low
Mammaprint – Low

NO CHEMOTHERAPY
NO NEED FOR TRIAL

Clinical High/Mammaprint Low
Clinical Low/Mammaprint High

RANDOMISE TO DB-RCT
CHEMOTHERAPY/PLACEBO

Clinical – High
Mammaprint – High

CHEMOTHERAPY
NO NEED FOR TRIAL

Some lessons from the frontiers of 'Precision Medicine' Trials

- It is working in several areas in medicine - but it requires patience and persistence.

- A 'precision' psychiatry/neurology will enrich and modify, rather than replace current psychiatric and neurological practise.

- To reap these benefits we will need to change the:
  - *Size and scale of our efforts (PGC, ASD)*
  - *Standardisation of measures (ADNI)*
  - *Develop a framework for assessing the clinical significance of potential innovative options*

S Kapur, A G Phillips and T R Insel Molecular Psychiatry , 2012

Thank you for your attention ..