Innovative Medicines Initiative

NEWMEDS

Novel methods leading to New medications in Depression and Schizophrenia

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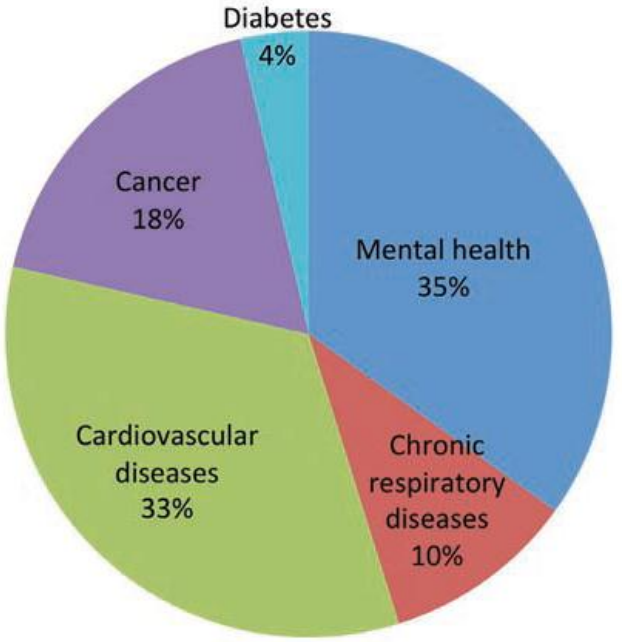
Psychiatry

a continous burden on Patients, Families, Caregivers and Society

- The global cost of mental health conditions in 2010 was estimated at US$ 2.5 trillion, with the cost projected to surge to US$ 6.0 trillion by 2030.
- **Mental Health is one of the** top drivers in loss of output
- Schizophrenia and Depression are among the top drivers in Mental Health



Source: **The Global Economic Burden of Non-communicable Diseases, 2011**

We have had very limited success in psychiatry

The NEW ENGLAND JOURNAL of MEDICINE

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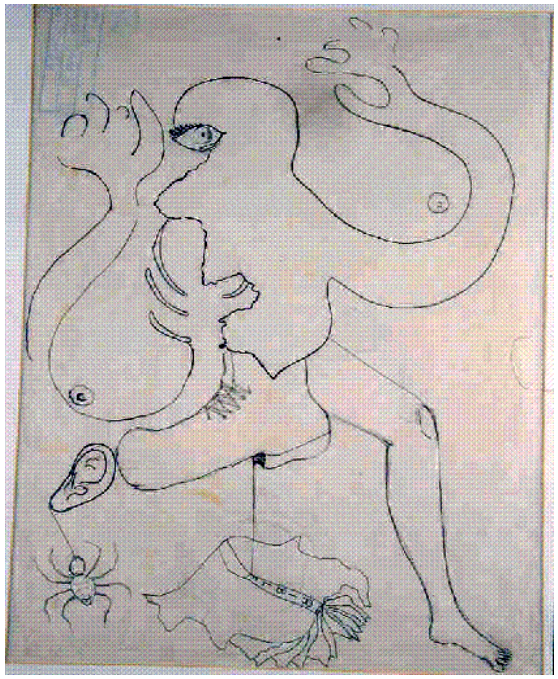
Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

Jeffrey A. Lieberman, M.D., T. Scott Stroup, M.D., M.P.H., Joseph P. McEvoy, M.D., Marvin S. Swartz, M.D., Robert A. Rosenheck, M.D., Diana O. Perkins, M.D., M.P.H., Richard S.E. Keefe, Ph.D., Sonia M. Davis, Dr.P.H., Clarence E. Davis, Ph.D., Barry D. Lebowitz, Ph.D., Joanne Severe, M.S., and John K. Hsiao, M.D., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators*

In summary, patients with chronic schizophrenia in this study discontinued their antipsychotic study medications at a high rate, indicating substantial limitations in the effectiveness of the drugs. Within this limited range of effectiveness, olanzapine appeared to be more effective than the other drugs studied, and there were no significant differences in effectiveness between the conventional drug perphenazine and the other second-generation drugs.

The Patients are heterogenous



- Mental disorders have been considered "behavioral," implying that an exclusive focus on symptoms could yield a precise diagnosis
- Research has demonstrated that diagnostic labels such as **depression** or **schizophrenia** do not specify the underlying heterogeneity of these disease appropriately.
- Attempts to subdivide these categories by considering additional symptoms, such as *anxious depression*, have until now failed to give reliably better prediction of treatment response – *Tom Insel NIMH*

Key Research Challenges in Psychiatry

Challenge

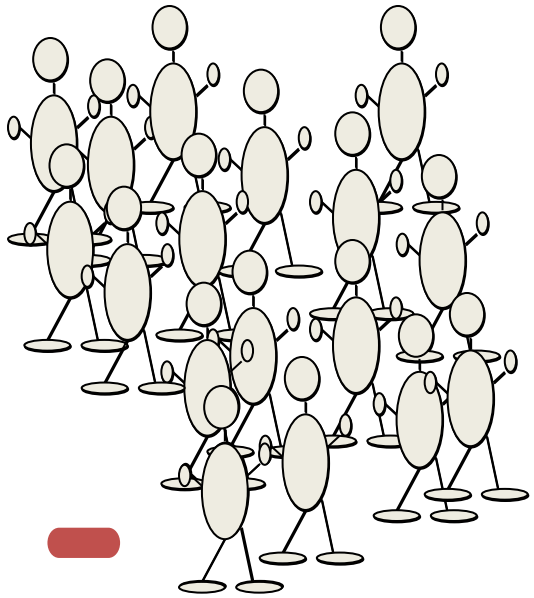
Why do patients not respond well to current medication ?

Question?

Can we identify groups of patients and medications that match better?

- Clinical phenotype
- Biological phenotype
- Animal models
- Clinical trials in a meaningful way

We are in desparate need of better tools



The need for a PPP

- The scientific questions that remain unanswered in psychiatry are extremely complex
  - One organisation cannot solve this by themselves
- A number of big pharma have recently pulled out of basic research in psychiatry (GSK, AZ)
  - More will follow due to the costs
- We need a platform where we can join forces
  - IMI has succesfully provided that platform

Three major bottlenecks….

are holding back the progress of the field

Lack of pathophysiologically **relevant animals models** to guide the drug discovery efforts

Lack of tools and tests in healthy volunteers that provide **early indications of efficacy**

The reliance of **clinical trials on symptom-based DSM-categories** which inevitably lead to heterogeneous groups of patients

Newmeds tries to address this

Headline achievements of the NEWMEDS program

WP 1, 2, 4

Animal models that truely translate the phenotype of a patient

WP 4, 5, 6

Experimental Human tools that enable early decision making

Phase 1

Phase IIa

Phase 2b

Phase 3

Sub mission

WP 7, 9

Biologically Validated Targets

WP 3, 7, 8, 9,10

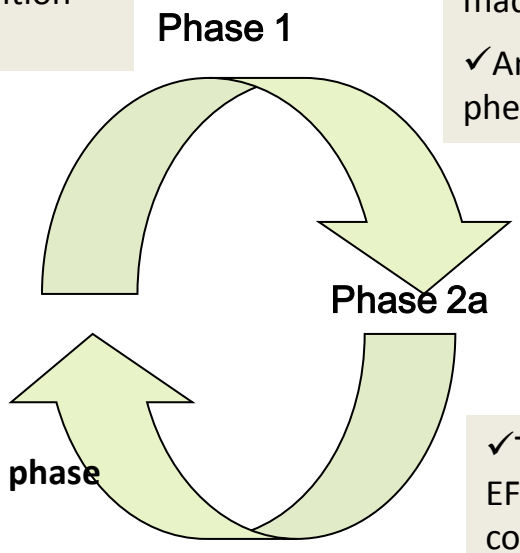
The way we do clincial trials

Discovery phase

Headline achievements of the NEWMEDS program

- ✓ Animal-human imaging methodology has been developed and is ready to be used
- ✓ Cross site validated cognition assay s in rodent

- ✓Recruitment of more than 1300 subjects, controls and subjects carrying CNVs and MRI scanning of > 300 subjects
- ✓Neuropsychological and anthropometric phenotypes associated with schizophrenia CNVs have been identified
- ✓ Links from animal models to humans carriers have been made
- ✓Animal models carrying the CNVs show distinct phenotypes



Phase 2b → Phase 3 → Sub mission

- ✓ Cognitive and electrophysiological batteries have been validated in animal models **ready to be used in humans**
- ✓14 animal models of schizophrenia evaluated in a proteomic markers

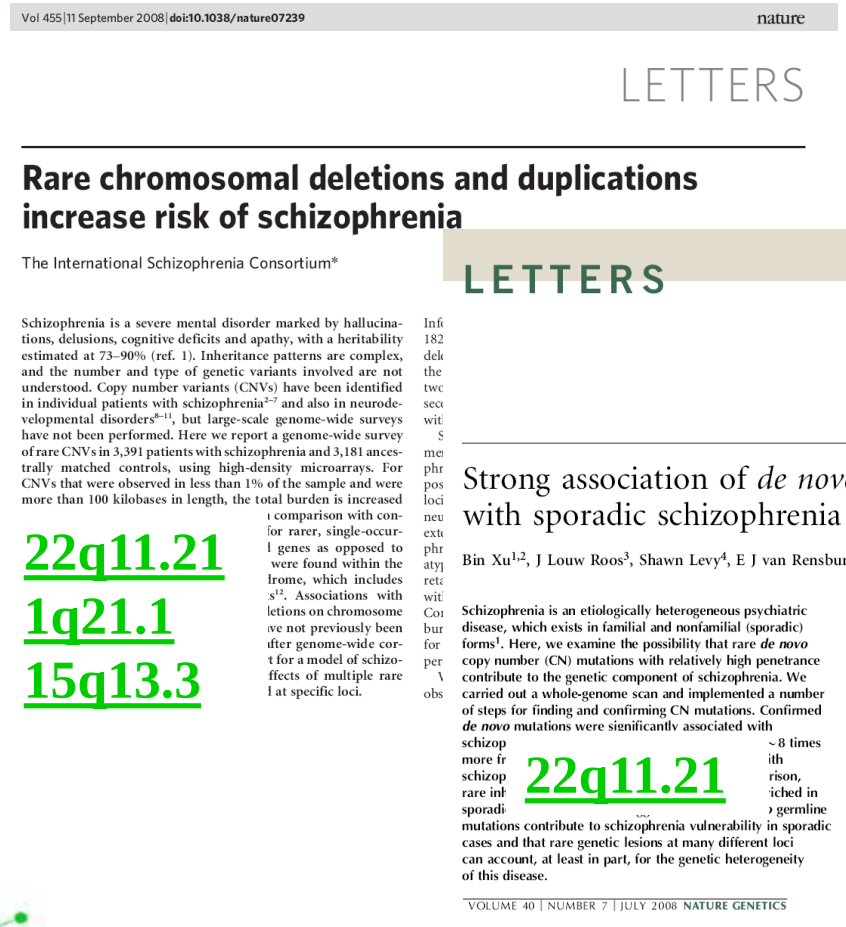
- ✓The largest database on schizophrenia trials enrolled in EFPIA studies (> 23,000 patients) from where we have collected data to improve clin trials – **Shorter and more efficient trials**
- ✓The largest database on treated depressed populations generated - **no single gene does it.**
- ✓*depressiontools.org*, an easy-to-operate web calculator to determine whether a biomarker is meaningful or not

An example from NEWMEDS..

There is clearly a genetic link……..

If you have a schizophrenic….	Your risk of getting schizophrenia is….
Identical twin	46%
Both parents	48%
Sibling or parent	12%
Aunt, Nephew, grand parent	5%
First cousin, great aunt	2%
No relatives	1%

Copy Number Variations (CNVs) could they be the link?



Vol 455|11 September 2008|doi:10.1038/nature07239 nature

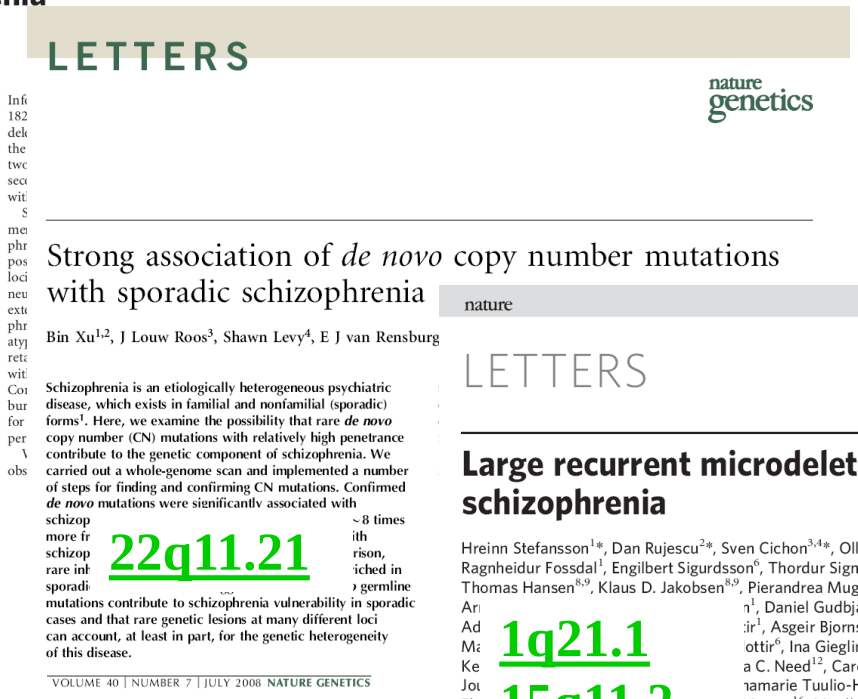
LETTERS

Rare chromosomal deletions and duplications increase risk of schizophrenia

The International Schizophrenia Consortium*

Schizophrenia is a severe mental disorder marked by hallucinations, delusions, cognitive deficits and apathy, with a heritability estimated at 73–90% (ref. 1). Inheritance patterns are complex, and the number and type of genetic variants involved are not understood. Copy number variants (CNVs) have been identified in individual patients with schizophrenia[2–7] and also in neurodevelopmental disorders[8–11], but large-scale genome-wide surveys have not been performed. Here we report a genome-wide survey of rare CNVs in 3,391 patients with schizophrenia and 3,181 ancestrally matched controls, using high-density microarrays. For CNVs that were observed in less than 1% of the sample and were more than 100 kilobases in length, the total burden is increased

22q11.21
1q21.1
15q13.3



LETTERS

nature genetics

Strong association of *de novo* copy number mutations with sporadic schizophrenia

Bin Xu[1,2], J Louw Roos[3], Shawn Levy[4], E J van Rensburg

Schizophrenia is an etiologically heterogeneous psychiatric disease, which exists in familial and nonfamilial (sporadic) forms[1]. Here, we examine the possibility that rare *de novo* copy number (CN) mutations with relatively high penetrance contribute to the genetic component of schizophrenia. We carried out a whole-genome scan and implemented a number of steps for finding and confirming CN mutations. Confirmed *de novo* mutations were significantly associated with

22q11.21

mutations contribute to schizophrenia vulnerability in sporadic cases and that rare genetic lesions at many different loci can account, at least in part, for the genetic heterogeneity of this disease.

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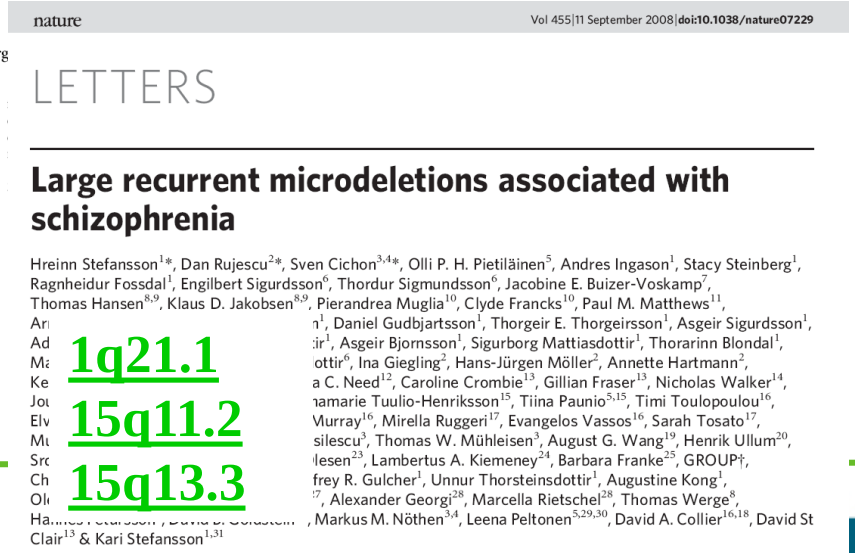

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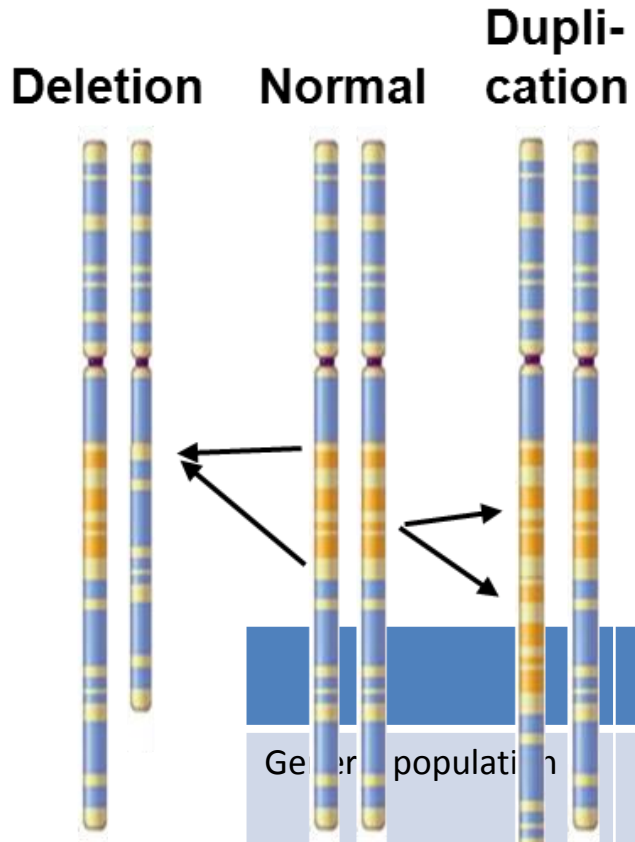
LETTERS

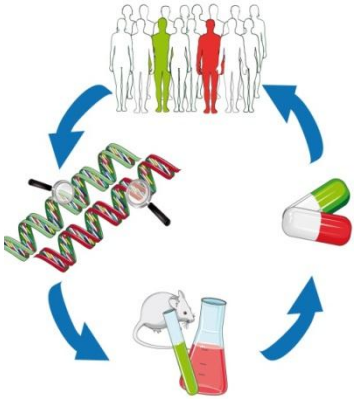
Large recurrent microdeletions associated with schizophrenia

Hreinn Stefansson[1]*, Dan Rujescu[2]*, Sven Cichon[3,4]*, Olli P. H. Pietiläinen[5], Andres Ingason[1], Stacy Steinberg[1], Ragnheidur Fossdal[1], Engilbert Sigurdsson[6], Thordur Sigmundsson[6], Jacobine E. Buizer-Voskamp[7], Thomas Hansen[8,9], Klaus D. Jakobsen[8,9], Pierandrea Muglia[10], Clyde Francks[10], Paul M. Matthews[11], Ar… …n[1], Daniel Gudbjartsson[1], Thorgeir E. Thorgeirsson[1], Asgeir Sigurdsson[1], Ad… …ir[1], Asgeir Bjornsson[1], Sigurborg Mattiasdottir[1], Thorarinn Blondal[1], Ma… …ottir[6], Ina Giegling[2], Hans-Jürgen Möller[2], Annette Hartmann[2], Ke… …a C. Need[12], Caroline Crombie[13], Gillian Fraser[13], Nicholas Walker[14], Jou… …namarie Tuulio-Henriksson[15], Tiina Paunio[5,15], Timi Toulopoulou[16], Elv… …Murray[16], Mirella Ruggeri[17], Evangelos Vassos[16], Sarah Tosato[17], Mu… …silescu[3], Thomas W. Mühleisen[3], August G. Wang[19], Henrik Ullum[20], Src… …lesen[23], Lambertus A. Kiemeney[24], Barbara Franke[25], GROUP†, Ch… …frey R. Gulcher[1], Unnur Thorsteinsdottir[1], Augustine Kong[1], Ol… …[7], Alexander Georgi[28], Marcella Rietschel[28], Thomas Werge[8], Ha… …, Markus M. Nöthen[3,4], Leena Peltonen[5,29,30], David A. Collier[16,18], David St Clair[13] & Kari Stefansson[1,31]

1q21.1
15q11.2
15q13.3

What are CNVs and Why are the CNVs so interesting?





CNVs are

Chromosomal deletions and duplications containing several genes

	Healthy	Schizophrenia
Ge er popula i n	100	1
22q11	100	30

Pursuing CNV variants as entries into psychiatry

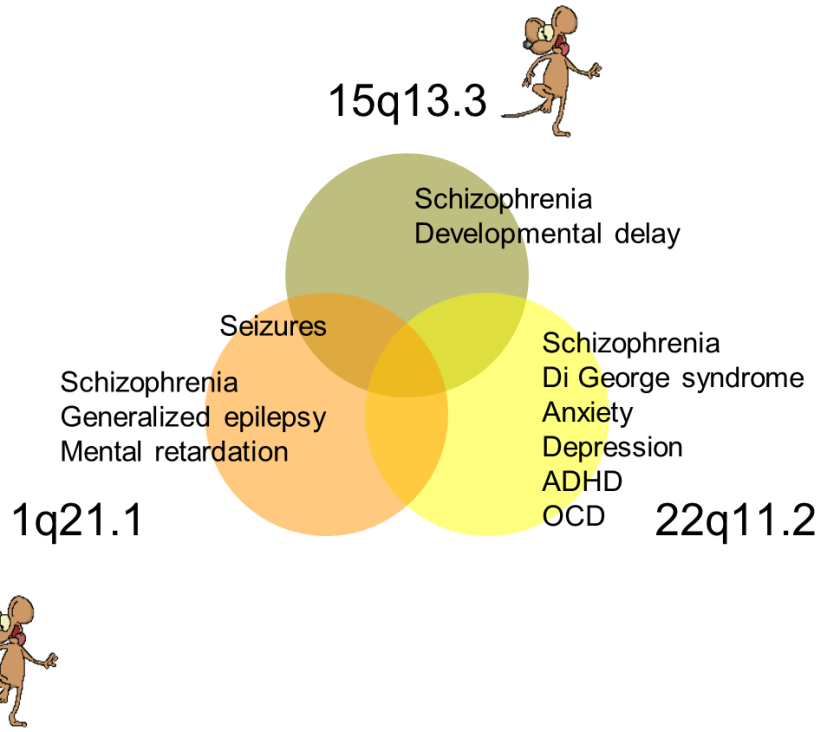
Basis: Unrelated CNVs can lead to similar functional outcome (schizophrenia)

Aim - ultimately:
Identify drug targets with a strong link to underlying biology

How:
Characterize CNV mouse models
Characterise Human carriers of CNVs
Identify schizophrenia relevant phenotypes in the mice

Outcome:
Platform to identify targets that may be used across diseases with similar biological dysfunctions

Converging symptoms and disorders

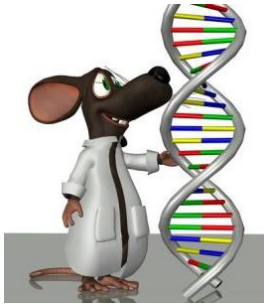


CNV carriers

We have made mice models of these syndromes

We also have access to human carriers of these CNVs

Highlight of this example



CNV mice

CNV carrier

Schizophenia patient

Phenotypes seen in both CNV animals and human carriers have been found and might represent a novel platform from which we can start to hunt for novel drugs

What next?

- Finalise the validation of our tools
  - So that drug hunting can begin !
- Find a way to best leverage what we have achieved so far and secure that work continues and commitment remains high

Will Newmeds develop new drugs??

NO

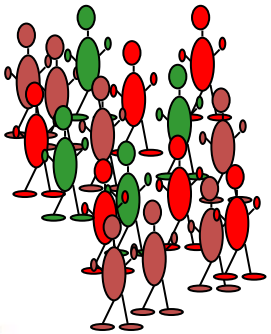
But we will provide methods and novel entries to go ”drughunting”

And when will we have a novel drug?

A novel platform to screen — 2014

A novel target to screen on next year — 2015

A novel drug candidate in 4 years — 2018



A truely novel drug in many years… — 2028

What impacts has NEWMEDS had?

Sadly,

- We have not as yet changed the lives of the patients that suffer from schizophrenia and depression

BUT we have

- Gained novel insights into the biology of these diseases
- Standardised the application of cognitive models across several industrial partners
- Developed novel tools for drug discovery [animal models, human imaging]
- Developed new web tools for analysis [image analysis, biomarker significance]
- Provided information for the design of more efficient clinical trials

- A single EFPIA company would not have done this on their own
- EFPIA companies continue to stay committed to Psychiatry

Thank you

Coordinator: H Lundbeck A/S, Copenhagen, Dr Tine Bryan Stensbøl

Leader of the Managing Entity: King's College London, London, Prof Shitij Kapur

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www.newmeds-europe.com

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(total of 125)

Former members:

Lori Badura, Gabriel Vargas, Judith Jaeger, Svante Nyberg, Enrico Domenici, Donna Palumbo, Jayne Fox, Xiaolan Hu, Sarah Smith, Karen Williams

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Servier 2012

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