# Basics of Translational Medicine

# Biomarkers : An essential element of developing new medicines

John Beaver

Biogen Community Lab

16 December 2020

# Overview

- How did I become a drug developer?
- What a crazy business: Why do investors give biopharma $$$ if they usually lose it all?
- What are biomarkers and are they any good for developing new medicines?
- Let’s bring this to life with some examples

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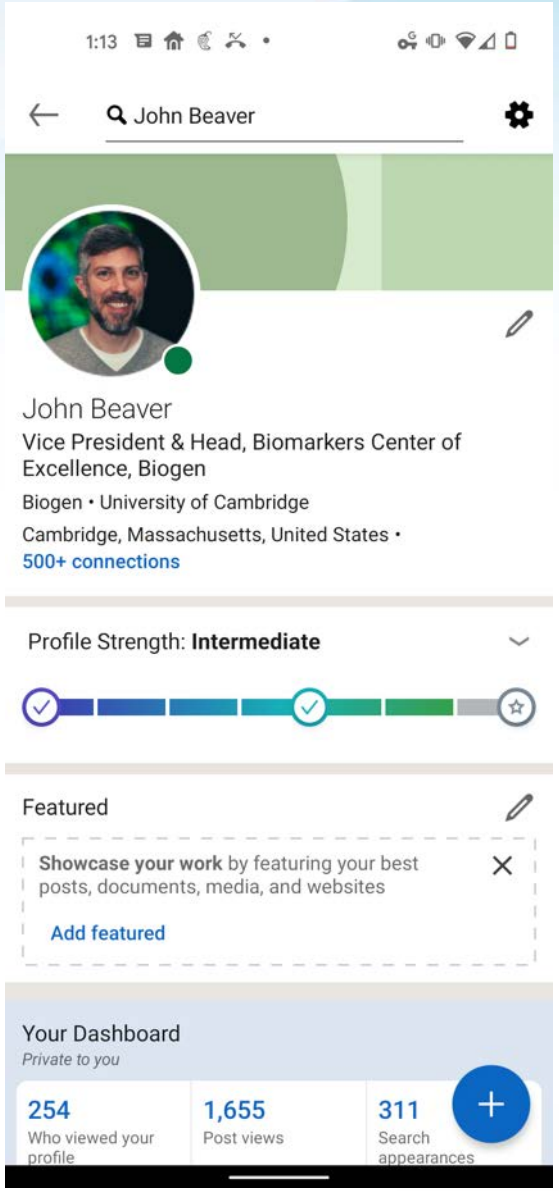
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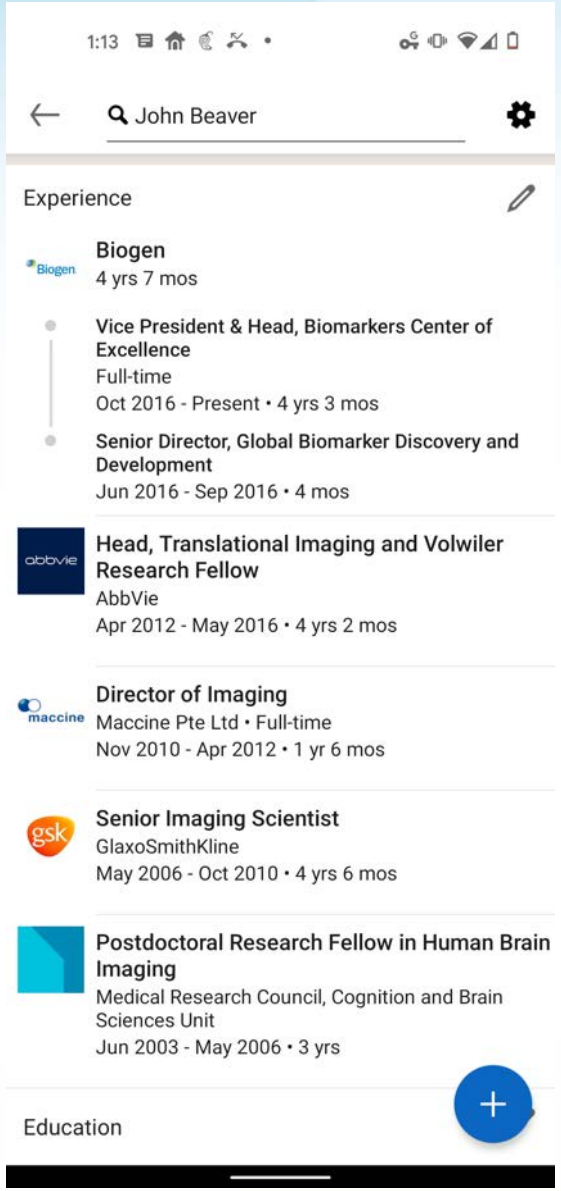
John Beaver
John Beaver
Vice President & Head, Biomarkers Center of Excellence, Biogen
Biogen • University of Cambridge
Cambridge, Massachusetts, United States •
500+ connections
Profile Strength: Intermediate
Featured
Showcase your work by featuring your best posts, documents, media, and websites
Add featured
Your Dashboard
Private to you
254
Who viewed your profile
1,655
Post views
311
Search appearances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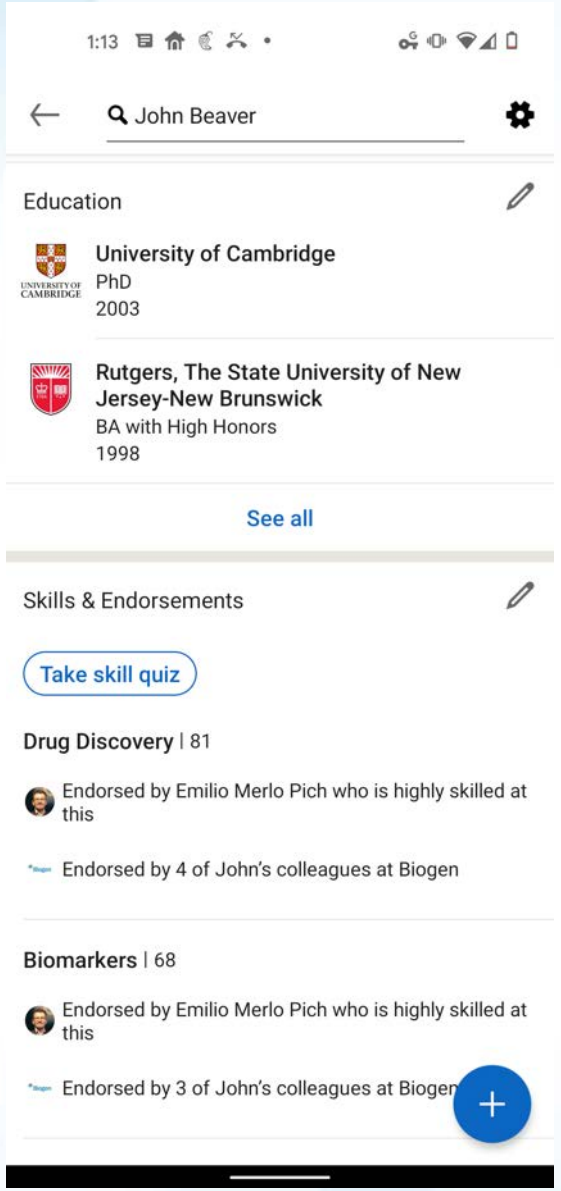
John Beaver
Experience
Biogen
4 yrs 7 mos
Vice President & Head, Biomarkers Center of Excellence
Full-time
Oct 2016 - Present • 4 yrs 3 mos
Senior Director, Global Biomarker Discovery and Development
Jun 2016 - Sep 2016 • 4 mos
Head, Translational Imaging and Volwiler Research Fellow
AbbVie
Apr 2012 - May 2016 • 4 yrs 2 mos
Director of Imaging
Maccine Pte Ltd • Full-time
Nov 2010 - Apr 2012 • 1 yr 6 mos
Senior Imaging Scientist
GlaxoSmithKline
May 2006 - Oct 2010 • 4 yrs 6 mos
Postdoctoral Research Fellow in Human Brain Imaging
Medical Research Council, Cognition and Brain Sciences Unit
Jun 2003 - May 2006 • 3 yrs
Education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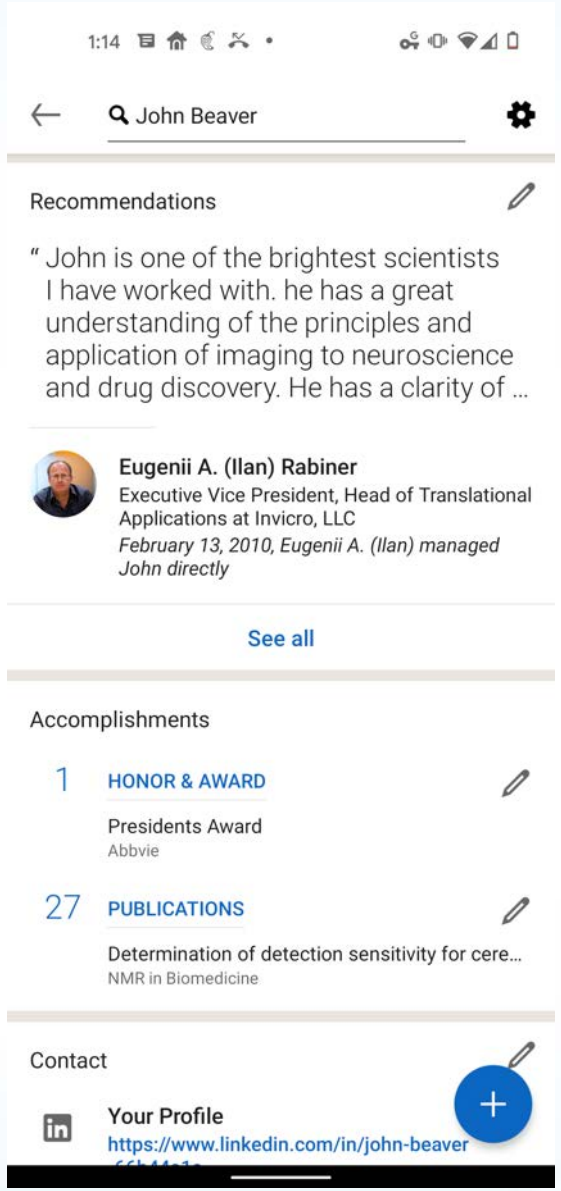
John Beaver
Education
University of Cambridge
PhD
2003
Rutgers, The State University of New Jersey-New Brunswick
BA with High Honors
1998
See all
Skills & Endorsements
Take skill quiz
Drug Discovery | 81
Endorsed by Emilio Merlo Pich who is highly skilled at this
Endorsed by 4 of John's colleagues at Biogen
Biomarkers | 68
Endorsed by Emilio Merlo Pich who is highly skilled at this
Endorsed by 3 of John's colleagues at Biogen


1:14
John Beaver
Recommendations
" John is one of the brightest scientists I have worked with. he has a great understanding of the principles and application of imaging to neuroscience and drug discovery. He has a clarity of ...
Eugenii A. (Ilan) Rabiner
Executive Vice President, Head of Translational Applications at Invicro, LLC
February 13, 2010, Eugenii A. (Ilan) managed John directly
See all
Accomplishments
1 HONOR & AWARD
Presidents Award
Abbvie
27 PUBLICATIONS
Determination of detection sensitivity for cere...
NMR in Biomedicine
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https://www.linkedin.com/in/john-beaver

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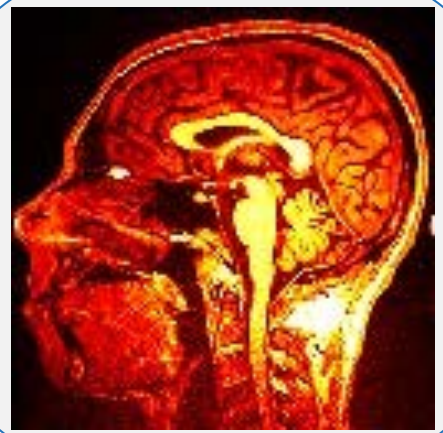
# How did I become a drug developer?


4.5yrs @ Biogen



This is my brain!

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# What a crazy business: High Risk Enterprises Face Unique Challenges

## OIL & GAS

**Challenges**

If I can even get the claim: Does the claim hold oil? Can I reach it? What new technology will be needed to do so? What will it cost to get it out? Will the price of oil be high enough to turn a profit when I do? ….

## PHARMA & DIAGNOSTICS

**Challenges**

Does the target play a critical role in the disease? What questions do we need to answer to understand this role? Can we design a molecule to interact with the target? Can we get it to the target? Is it safe? Does it do what we want it to do when it hits the target? Is the impact meaningful? Will it be reimbursed? ….

## FILM INDUSTRY

**Challenges**

Can I successfully market the product before shooting even the first frame? Can I afford the minimum investment ($60M-$200M) to guarantee success for content production? Can I get it done in time and without any actors getting hurt (or worse)? Can we secure distribution channels? ….

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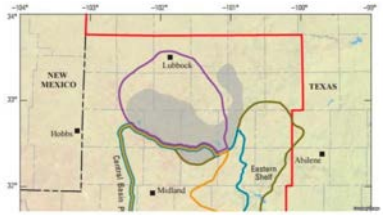
# The Rewards and the Failures can be Staggering

## OIL & GAS

**Examples**

2013: Royal Dutch Shell Pulls out of Chukchi Sea $4.1B loss

2016: Discovery of Wolfcamp Formation, TX Shale Deposit (est. 900B bls)

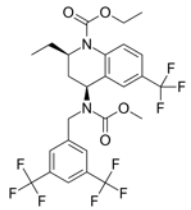


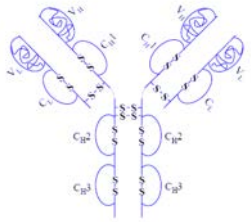

## PHARMA & DIAGNOSTICS

**Examples**

2006: torcetrapib (Pfizer) Kills P3 due to safety est. loss $800M

2002: Humira (Abbvie) 2017 revenues of $18B. Now off-patent.





## FILM INDUSTRY

**Examples**

2013: ***47 Ronin*** $250M production budget. Est loss $150M

1939: ***Gone with the Wind*** <$4M production budget. 2014 ROI >$3.4B



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# Bringing New Medicines to Patients Demands a Successful Business Able to Overcome Immense Challenges

- Do I understand this **biological mechanism**?
- Can I create the **right molecule** to manipulate this mechanism?
- Is my molecule **safe** to administer at all?
- When administered (and how, exactly, do I do that?), how much should I give and does it **reach the target**?
- Did **enough of it get there and stay there for long enough**? Is it **still safe** at that dose?
- Did I give it to the **right patient**?
- Does it have the **desired clinical effect**, and did I look at the right time?
- Does it cause a **meaningful change in disease course**?
- Will **prescribers prescribe it** and will **payors pay for it**?

We Must Convince:

- Ourselves
- Our Investors
- Regulators
- Patients
- Prescribers
- Payors

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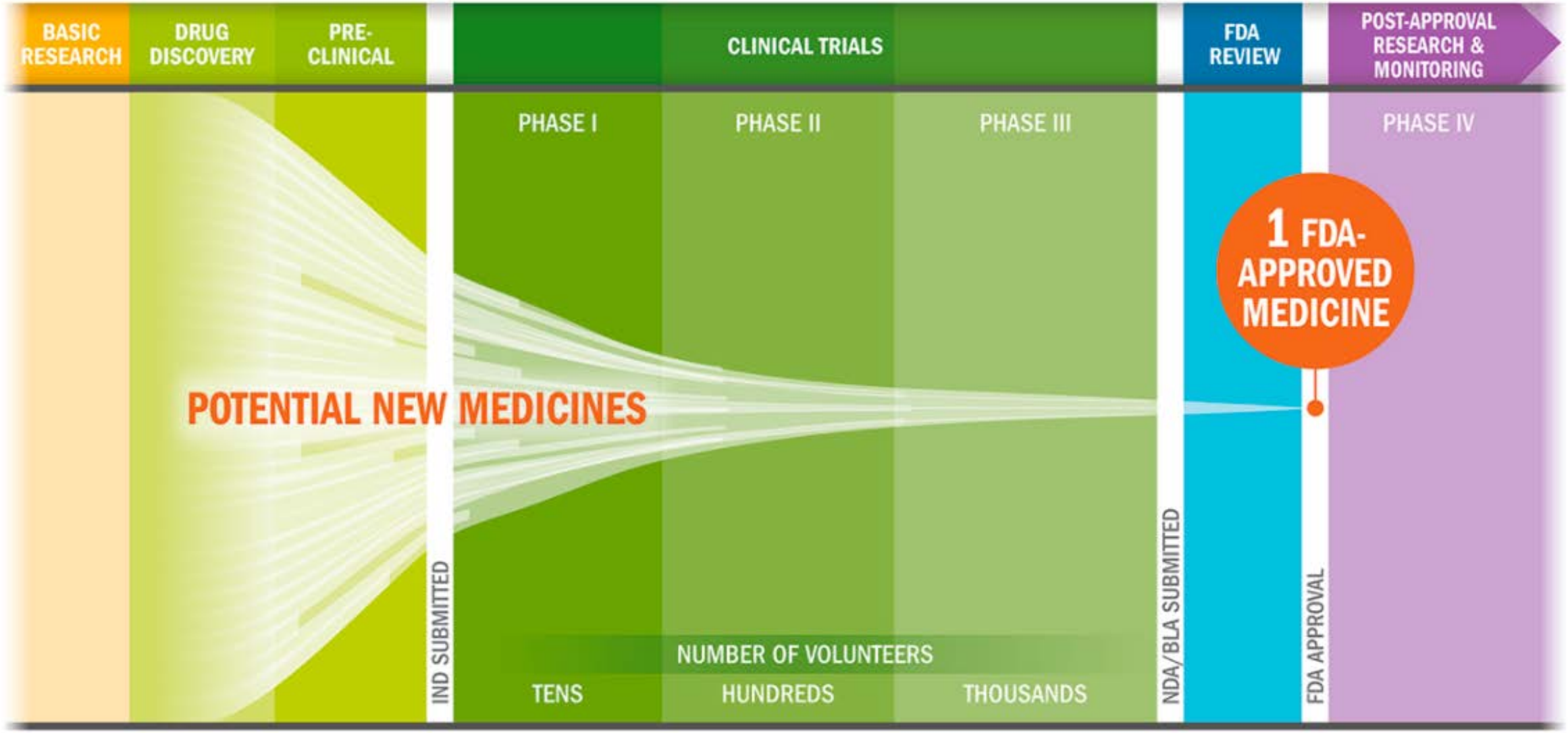
# Risky Business




www.phrma.org

9 -15 years with average costs of $2.6B (2013)

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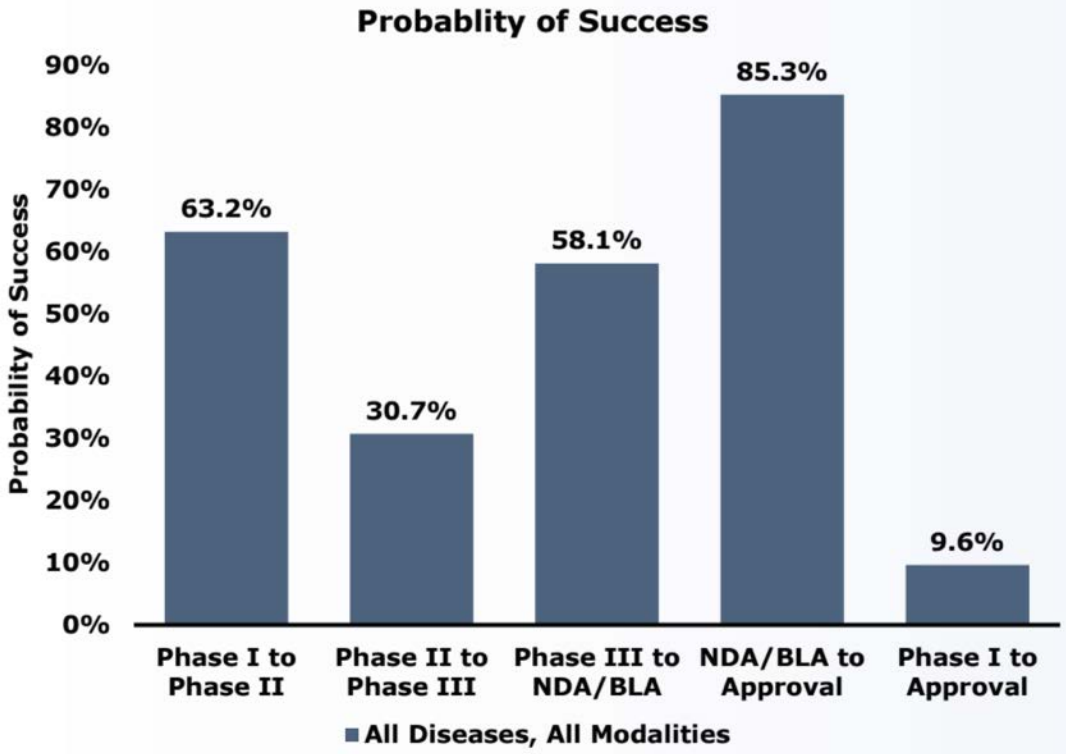
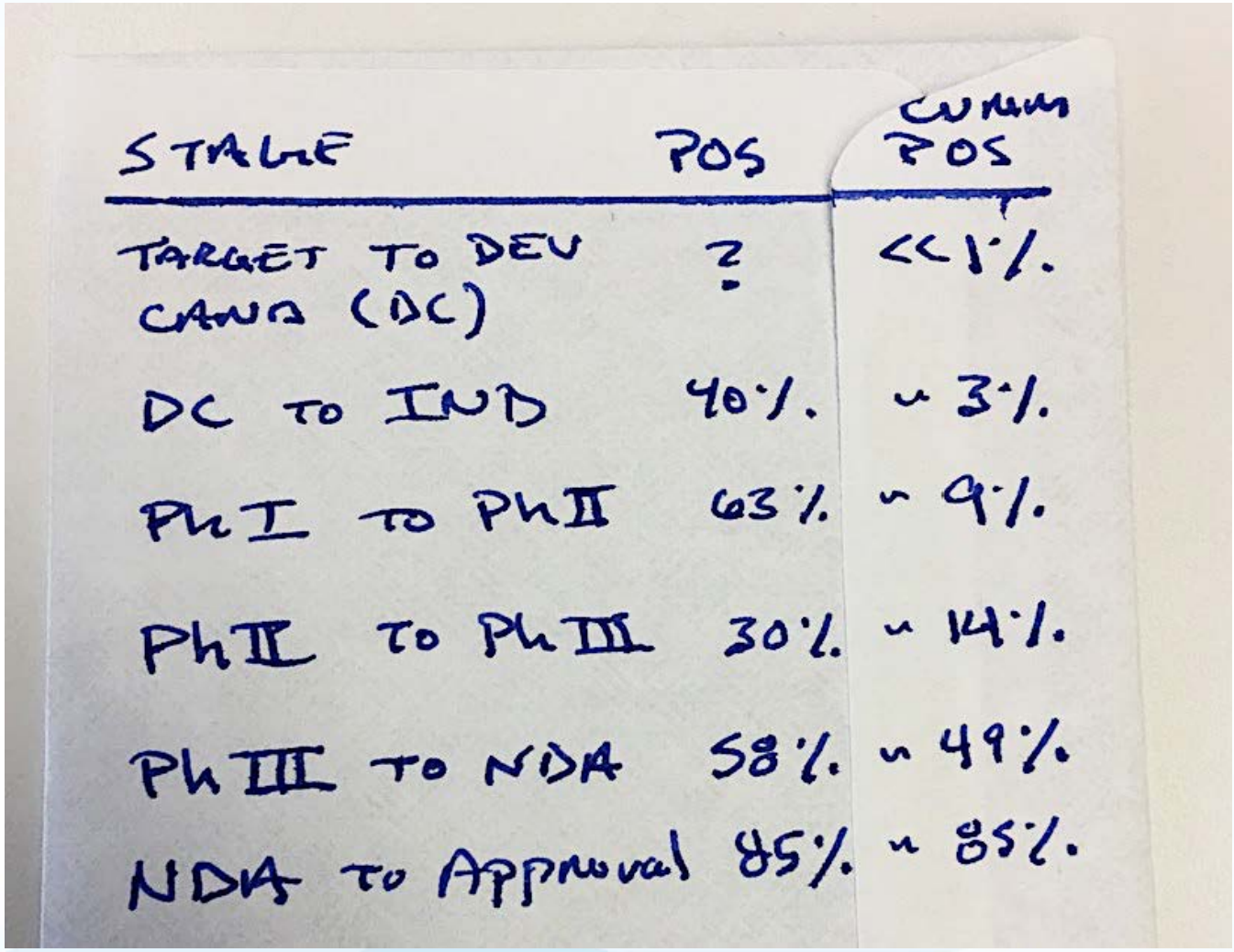
# Back of the Envelope Calculation:

*What are the chances of a new drug becoming a medicine for patients?*




Clinical Development Success Rates 2006-2015 - BIO, Biomedtracker, Amplion 2016

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# Probability of Success can be increased by addressing key questions with biomarkers


Biomarker Applications

- *In vivo* Bio Distribution
- Patient Stratification
- Target Engagement
- Pharmaco-Dynamic
- Clinical
- Safety

- Do I understand this **biological mechanism**?
- Can I create the **right molecule** to manipulate this mechanism?
- Is my molecule **safe** to administer at all?
- When administered (and how do I do that?), does it **reach the target**?
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# So, what is a biomarker anyway?

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention

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# Biomarkers in drug development
# Focus on Targets, Technologies, Translation

Avoid going ‘blind’ into clinical studies

- Target engagement: Does the medicine reach the intended target(s)?
- Patient Stratification: Which patients will benefit from the medicine?
- Dose Selection: What is the minimum dose required to occupy the target?
- Mechanism: Does binding the target elicit a relevant physiologic response?

Biomarkers – Imaging, Electrophysiological, Biochemical, Behavioral, PGx

**PET**

**Positron Emission Tomography**

**CT**

**Computed Tomography**

**MRI**

**Magnetic Resonance Imaging**

**SPECT**

**Single Photon Emision Computed Tomography**

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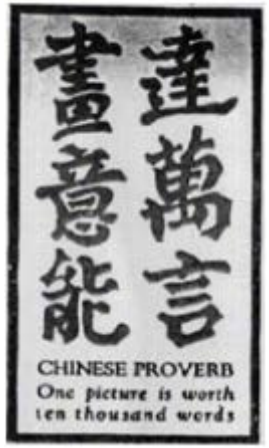
# Images effectively communicate medical science

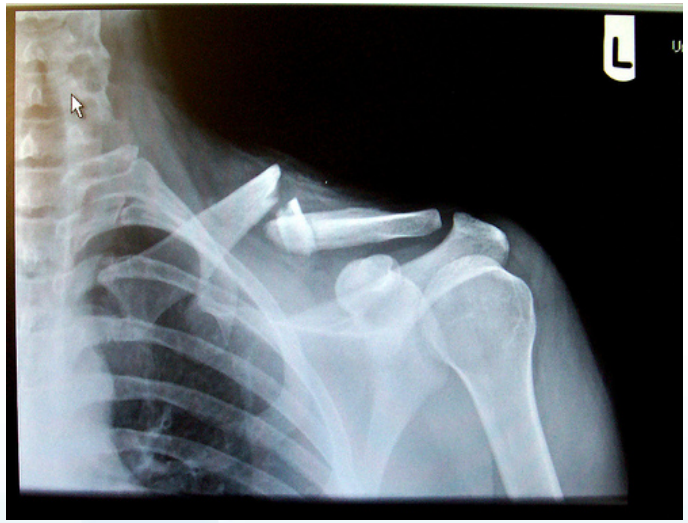
Most science is communicated via graphs, charts and plots

- Difficult for non-experts to understand the key message
- Typically lack visual impact




Medical images can show directly and clearly the effect of a treatment on disease

- Most people have had previous exposure to medical images and can understand their message (e.g., XRays for bone fracture)

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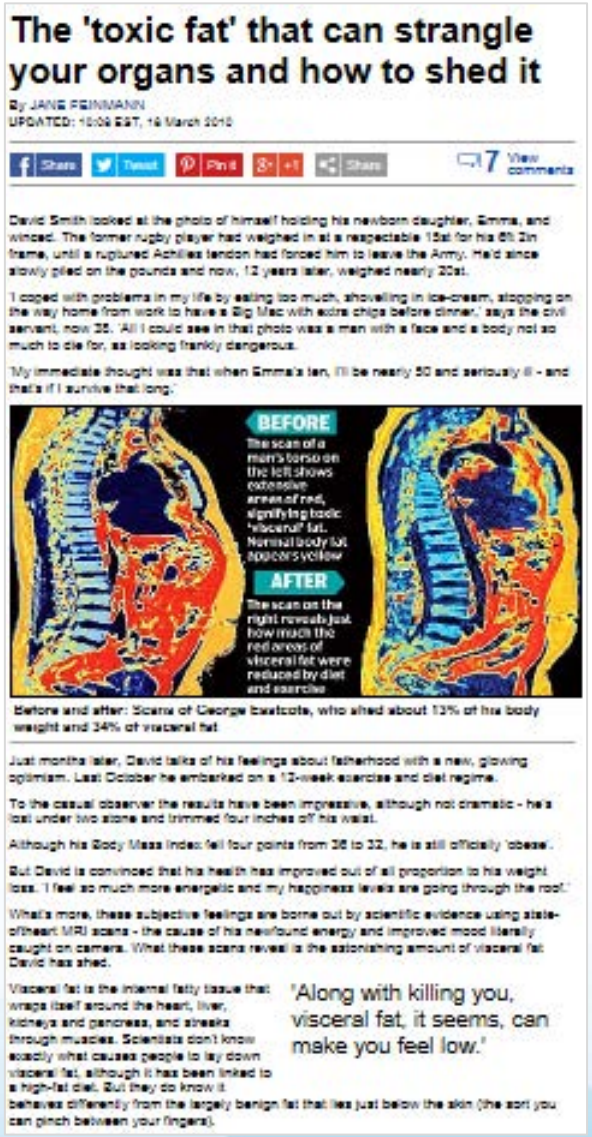
# Example: GSK's drug Alli

- GSK launch of weight-loss drug Alli in Europe
- Used medical imaging to change the public's perception of Alli from a 'vanity drug' (i.e., a slimming tablet) to a medicine with a clear health benefit
  - Provided scientific evidence of health benefits in a way the public could easily understand
  - Strategy: a small Magnetic Resonance Imaging (MRI) study individuals to visualize Alli's effects on fat related to health risks in overweight/obese individual
  - Cost: ~$250k USD
  - Product launch was highly successful across EU, supported by extensive press coverage of MRI study showing Alli's impact on 'toxic fat'

*Daily Mail front page coverage of GSK's study*
(UK's highest circulation daily)



**The 'toxic fat' that can strangle your organs and how to shed it**

By JANE FEINMANN
UPDATED: 19:09 EST, 19 March 2010

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David Smith looked at the photo of himself holding his newborn daughter, Emma, and winced. The former rugby player had weighed in at a respectable 15st for his 6ft 2in frame, until a ruptured Achilles tendon had forced him to leave the Army. He'd since slowly piled on the pounds and now, 12 years later, weighed nearly 20st.

'I coped with problems in my life by eating too much, shovelling in ice-cream, stopping on the way home from work to have a Big Mac with extra chips before dinner,' says the civil servant, now 36. 'All I could see in that photo was a man with a face and a body not so much to die for, as looking frankly dangerous.

'My immediate thought was that when Emma's ten, I'll be nearly 50 and seriously ill - and that's if I survive that long.'

BEFORE
The scan of a man's torso on the left shows extensive areas of red, signifying toxic 'visceral' fat. Normal body fat appears yellow

AFTER
The scan on the right reveals just how much the red areas of visceral fat were reduced by diet and exercise

Before and after: Scans of George Eastcote, who shed about 13% of his body weight and 34% of visceral fat

Just months later, David talks of his feelings about fatherhood with a new, glowing optimism. Last October he embarked on a 12-week exercise and diet regime.

To the casual observer the results have been impressive, although not dramatic - he's lost under two stone and trimmed four inches off his waist.

Although his Body Mass Index fell four points from 36 to 32, he is still officially 'obese'.

But David is convinced that his health has improved out of all proportion to his weight loss. 'I feel so much more energetic and my happiness levels are going through the roof.'

What's more, these subjective feelings are borne out by scientific evidence using state-of-the-art MRI scans - the cause of his newfound energy and improved mood literally caught on camera. What these scans reveal is the astonishing amount of visceral fat David has shed.

Visceral fat is the internal fatty tissue that wraps itself around the heart, liver, kidneys and pancreas, and streaks through muscles. Scientists don't know exactly what causes people to lay down visceral fat, although it has been linked to a high-fat diet. But they do know it behaves differently from the largely benign fat that lies just below the skin (the sort you can pinch between your fingers).

'Along with killing you, visceral fat, it seems, can make you feel low.'

*"… these subjective feelings are borne out by scientific evidence using state-of-the-art MRI scans - the cause of his newfound energy and improved mood literally caught on camera. What these scans reveal is the astonishing amount of visceral fat David has shed."*

*"Dr Haslam points to David Smith's example to show how quickly we could all turn our health around in this way.*
*'There's no doubt that with a BMI of 36, David's health was at risk - and yet within three months his life expectancy will have improved dramatically."*

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# Pharmacotherapy for obesity

Alli (Orlistat 60mg) is a medicine for weight loss


**alli** – your new partner in weight loss

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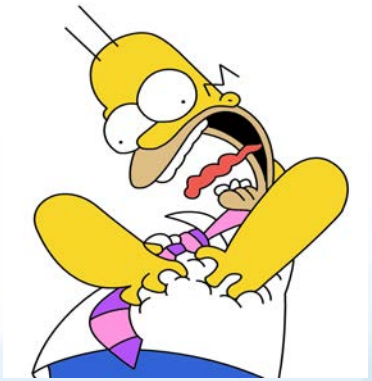
# Body Mass Index is a poor predictor of disease risk

## Visceral vs Subcutaneous Fat Deposits

- Visceral adipose tissue (VAT) and intramuscular adipose tissue (IMAT) have more profound adverse health effects than subcutaneous fat
- Insulin Resistance, Chronic inflammation, Oxidative Stress, Coronary Disease

"[Sumo wrestlers] have low cholesterol, they have low insulin resistance and a low level of triglycerides," said Bell. "Their fat is all stored under the skin, on the outside."*

Klein S. Absence of an Effect of Liposuction on Insulin Action and Risk Factors for Coronary Heart Disease
New England Journal of Medicine 350:2549-2557.

Ruberg F. The Relationship of Ectopic Lipid Accumulation to Cardiac and Vascular Function in Obesity and Metabolic Syndrome *Obesity* (2009) doi:10.1038/oby.2009.363

Boden G. Interaction between free fatty acids and glucose metabolism. CurrOpin Clin Nutr Metab Care 2002;5:545–9.

*Associated Press, 2007

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# Hepatic Steatosis (Liver fat)

Fat accumulation in the liver (IHL) is more strongly associated than VAT with:

- Insulin resistance and type II diabetes, Increased triglyceride levels, 2-3x higher coronary disease risk

Underlying mechanism not fully understood

How to measure?

- Adiposity and Liver Fat do not correlate
- Liver biopsy
- Blood test of γGT


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**Fat liver, not belly, may be best indicator of health problems**

Posted 10/25/2009 8:00 PM | Comments 3 | Recommend 4 E-mail | Save | Print | Reprints & Permissions |

By Nanci Hellmich, USA TODAY

WASHINGTON — For years, scientists have warned people that having an apple-shaped figure or a beer belly is a health risk.

They said people with wide girths are more likely to have visceral or intra-abdominal fat, which increases their risk of diabetes, heart disease, stroke and some types of cancer.

But new research presented Sunday at the

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Chitturi S, Abeygunasekera S, Farrell GC et al. NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology 2002; 35:373–9.

Fabbrini, Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity, *PNAS September 8, 2009 vol. 106 no. 36 15430-15435*

Seppala-Lindroos A, Vehkavaara S, Hakkinen AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metab 2002;87:3023–8.

Chitturi S. Fatty liver now, diabetes and heart attack later? The liver as a barometer of metabolic health. Journal of Gastroenterology and Hepatology. Vol 22, Iss 7, 967-969


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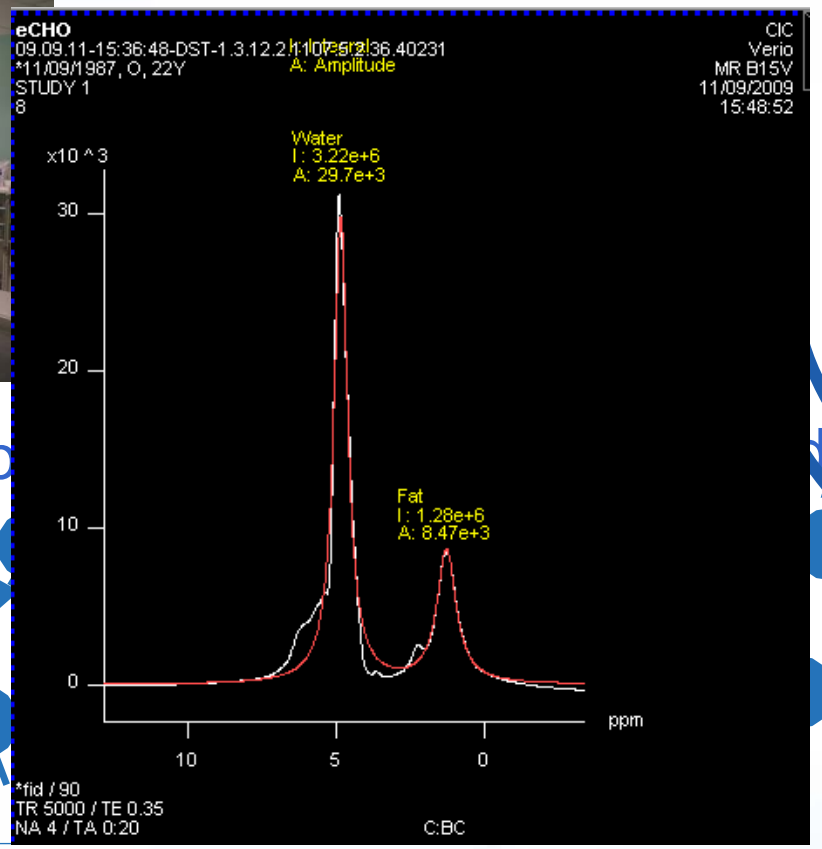
# MRI of Water and Fat







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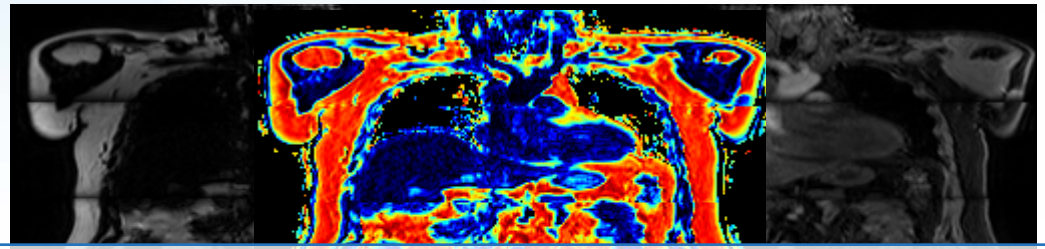
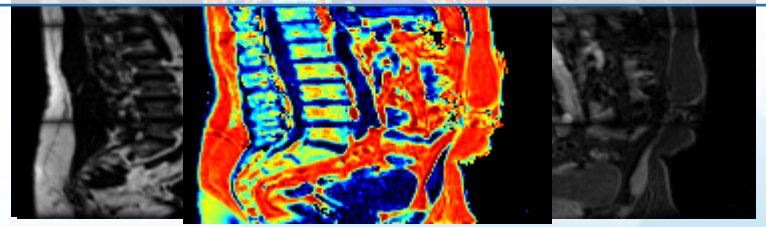
# Breath-held 3D Body Fat MRI



MRI provides the only *non-ionizing, non-invasive* method of assessing fat in its various compartments (subcutaneous-SAT, visceral-VAT, pericardial) and tissue fat content (liver-IHL, muscle-IMAT).

Quantitative regional measures of body fat may be more sensitive/specific for a range of metabolic diseases and for direct and indirect effects of therapeutics than simple measures such as weight / BMI.



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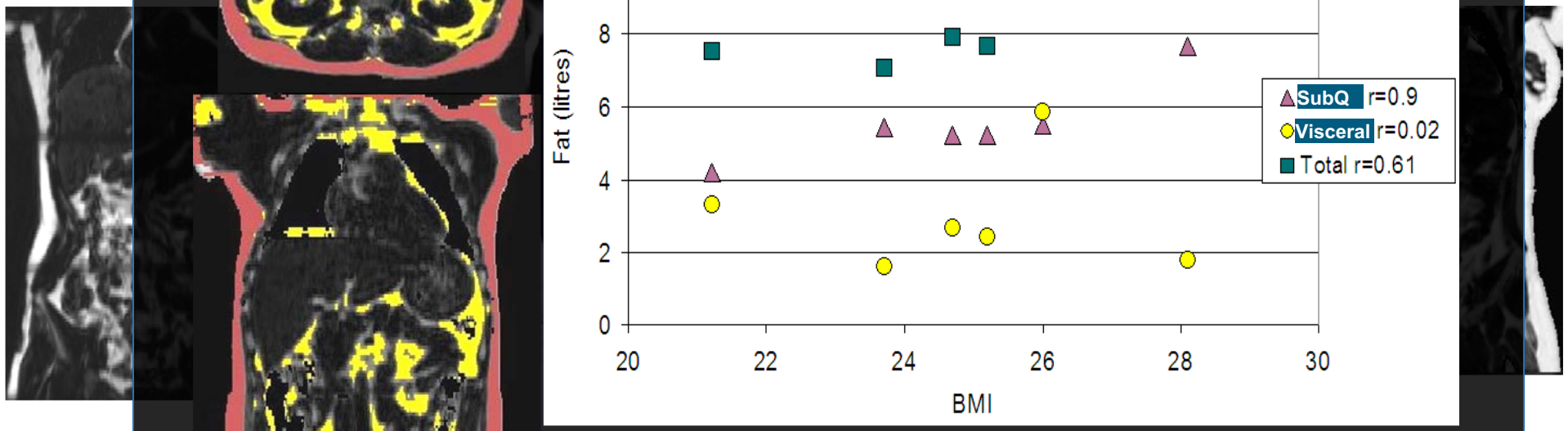
# MRI data on body fat imaging

Six adult healthy volunteers, M/F, 30-42 y/o.

'Fat fraction' im






- La
spite of similar o
'build' of all the volunteers

- Subcutaneous fat correlates with BMI
- Visceral fat has *poor correlation w/ BMI*

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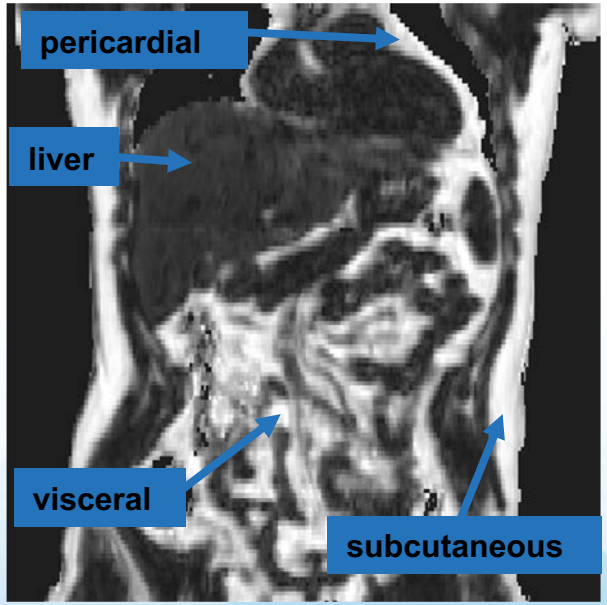
# Biomarker Study with Alli

Serial MR study of the effects of Alli over 3 months

- Monthly
  - Physical: Weight (BMI), Waist Circ, BP, HR
  - Blood: Triglycerides, LDL/HDL Cholesterol
  - AEs: Alli known to cause GI upset
- Baseline and after 3 months of treatment with Alli
  - Multiple MR measures of fat compartment content at each timepoint

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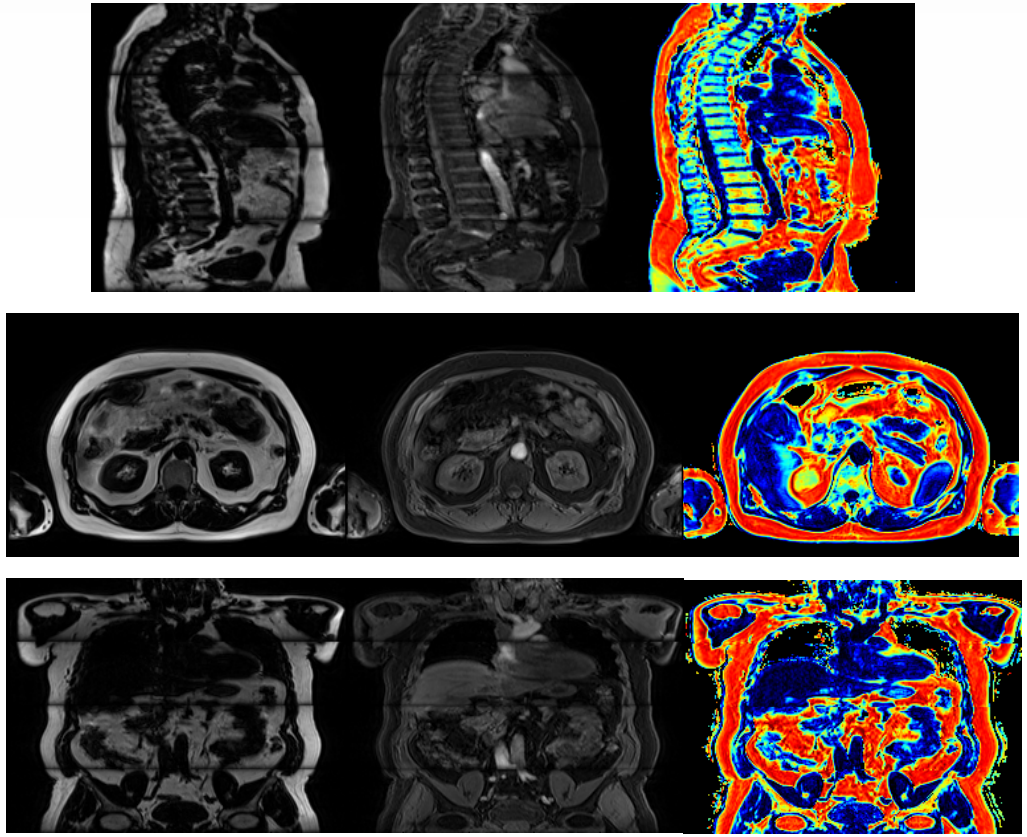
# Bioamrker Study with Alli

## 3D Spatially resolved fat/water in torso

- Whole abdomen in 3 or 4 15s breath-held scans
- Total abdominal fat, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT),  pericardial fat volumes (L)



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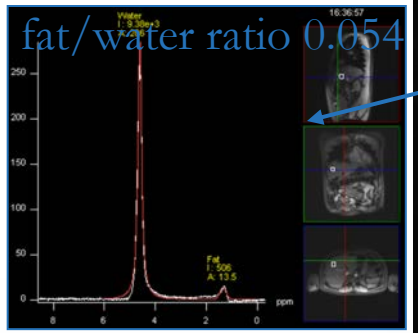
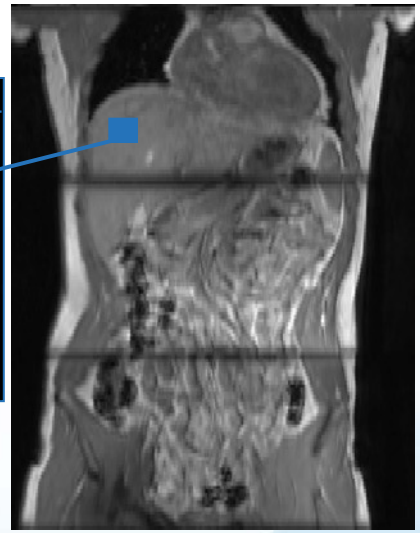
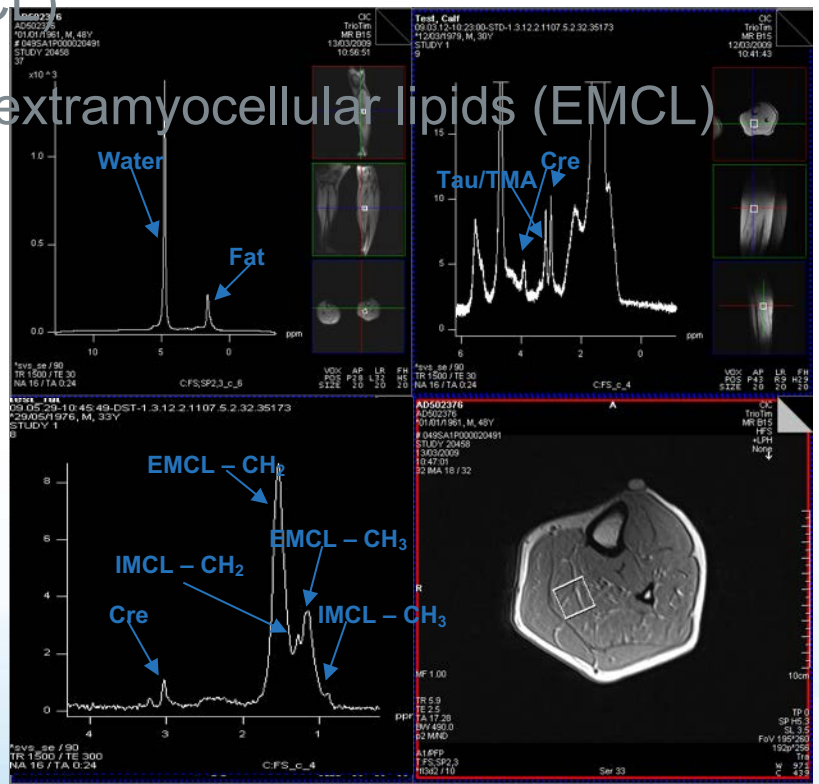
# Biomarker Study with Alli

## MR Spectroscopy in (normally) low-fat regions

- Liver (Intrahepatocellular lipids - IHL)
- Muscle (Soleus and Tibialis Anterior)
  - Fat inside muscle cells-intramyocellular lipids (IMCL)
  - Fat in adipocytes scattered between muscle cells-extramyocellular lipids (EMCL)



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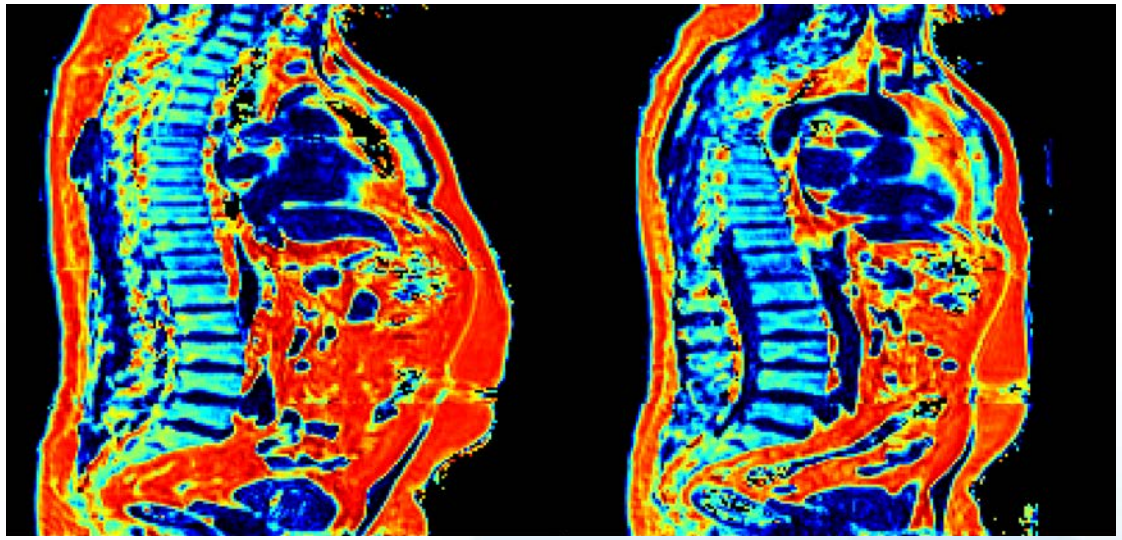
# Results

24 out of 27 subjects completed, BMI = 27-35

- Avg subject lost 5.24 Kg (5.6% mass, $p<0.0001$)
- Avg BMI down by 1.72 pts ($p<0.0001$)
- Avg Waist Circ. Down 4.54cm (4.3%, $p<0.0001$)



Before Diet+Alli

3 mos Diet+Alli

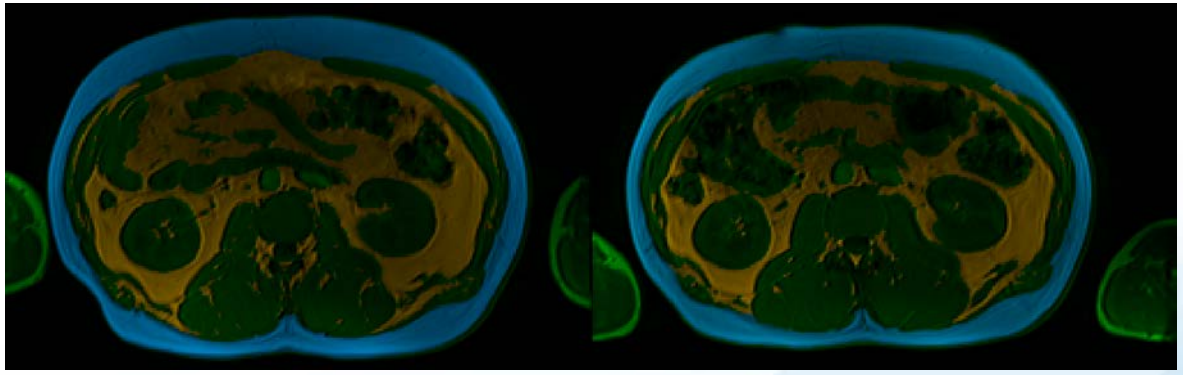
Biogen

# Results – MR Endpoints

| Endpoint | n | % Change | 95% CI | Corresponding Absolute Change | 95% CI | p-value |
|---|---|---|---|---|---|---|
| Visceral Adipose Tissue (L) | 20 | -10.6 | (-18.6, -1.8) | -0.60 | (-1.05, -0.10) | 0.0225 |
| Subcutaneous Adipose Tissue (L) | 19 | -11.7 | (-15.4, -7.8) | -1.01 | (-1.33, -0.68) | <0.0001 |
| Total Abdominal Fat (L) | 19 | -12.2 | (-16.9, -7.3) | -1.79 | (-2.48, -1.07) | 0.0001 |
| IHL Fat-Water Ratio (%) | 22 | -43.3 | (-56.7, -25.7) | -1.41 | (-1.85, -0.84) | 0.0003 |
| Pericardial Fat (L) | 21 | -9.8 | (-17.9, -0.9) | -0.022 | (-0.040, -0.002) | 0.0342 |

Before Diet+Alli

3 mos Diet+Alli



Visceral: 5.330 to 3.961L : 25.68% fat loss
SubQ: 6.855 to 5.519L : 19.49% fat loss

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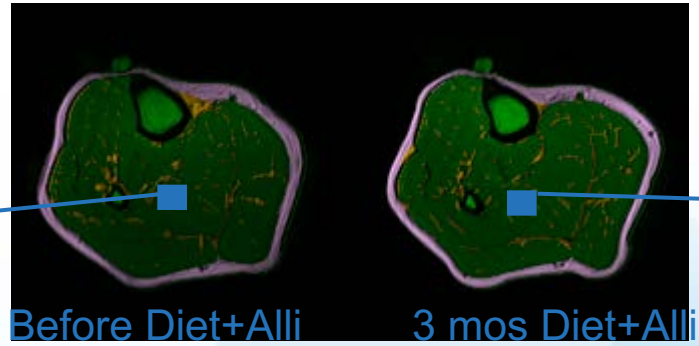
# Results – Cardiovascular Sampling

| Endpoint | n | Mean Change | 95% CI | Corresponding % Change | 95% CI | p-value |
|---|---|---|---|---|---|---|
| Cholesterol (mmol/L) | **24** | **-0.546** | **(-0.780, -0.311)** | **-10.5** | **(-15.0, -6.0)** | **<0.0001** |
| High Density Lipids (mmol/L) | **24** | **-0.063** | **(-0.112, -0.013)** | **-5.2** | **(-9.4, -1.0)** | **0.0168** |
| Low Density Lipids (mmol/L) | **24** | **-0.438** | **(-0.640, -0.235)** | **-13.4** | **(-19.7, -7.2)** | **0.0002** |
| Triglycerides (mmol/L) | 24 | -0.087 | (-0.262, 0.087) | -5.4 | (-16.2, 5.4) | 0.3074 |
| Systolic Blood Pressure (mmHg) | **24** | **-6.04** | **(-10.33, -1.75)** | **-4.8** | **(-8.2, -1.4)** | **0.0082** |
| Diastolic Blood Pressure (mmHg/L) | **24** | **-4.92** | **(-7.25, -2.59)** | **-6.3** | **(-9.3, -3.3)** | **0.0003** |
| Heart Rate (beats/min) | **24** | **-5.46** | **(-8.78, -2.14)** | **-8.6** | **(-13.8, -3.3)** | **0.0027** |

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# Study Summary Findings – It Works!

Significant reductions from baseline to 3 month visit seen in Weight, BMI and waist circumference

- Waist Measurement associated with SAT, not VAT/IHL

Significant reductions in nearly all MRI endpoints

- Comparable reductions in SAT and VAT ~11%
- Strong correlations with weight loss
- No change seen in IMAT

Significant and largest reduction in IHL (-43%, p=0.0003)

Changes in IHL *significantly* associated with changes in blood pressure, heart rate and cholesterol

Changes in VAT *only* associated with weight and HDL cholesterol

Results also available including only those with BMI >= 28, near-identical values/changes.

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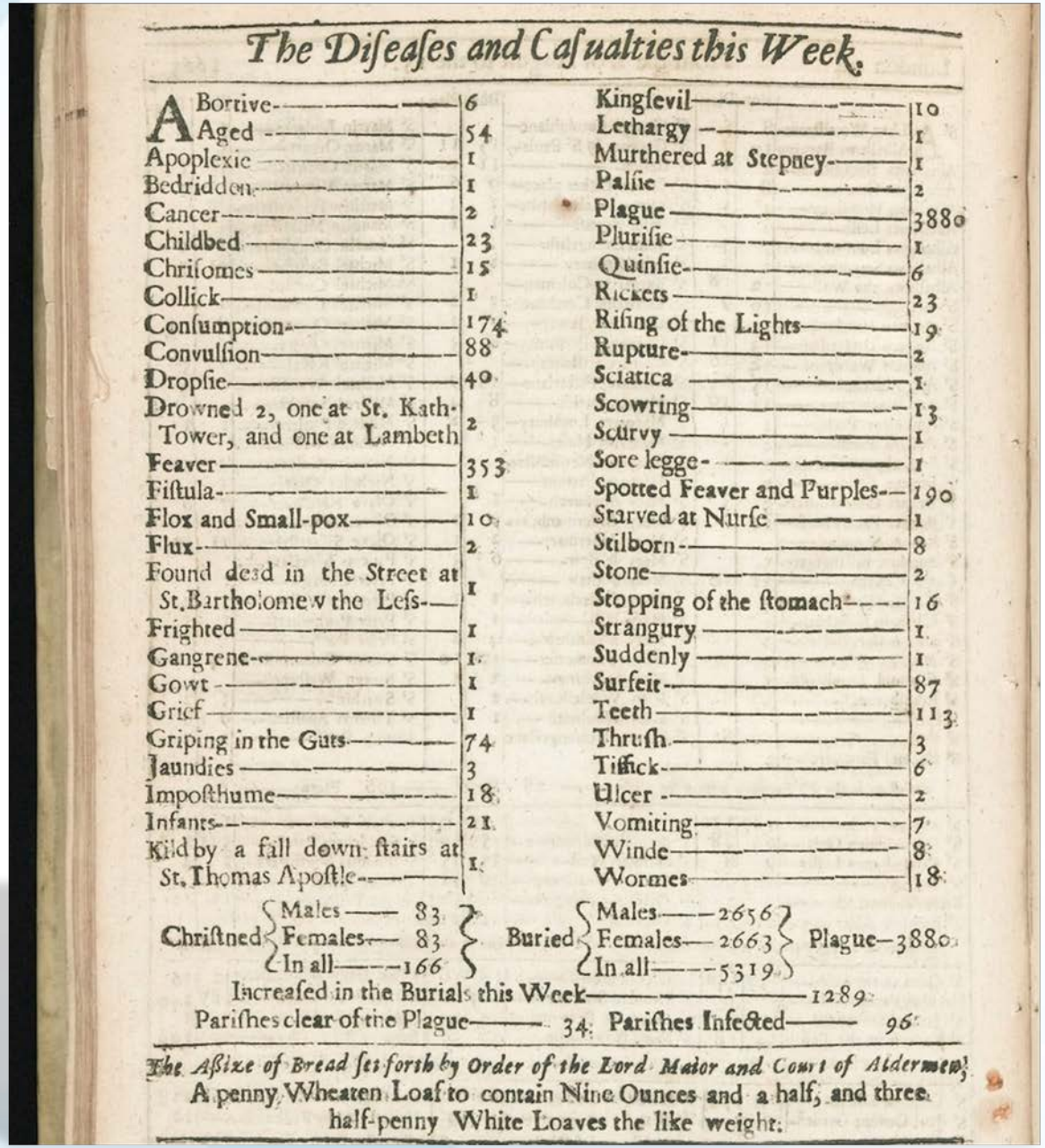
# Moving toward a pathology based classification of neurological disease

# London, 1665:
# Classification of disease



The Diſeaſes and Caſualties this Week.

| | | | |
|---|---|---|---|
| Abortive | 6 | Kingſevil | 10 |
| Aged | 54 | Lethargy | 1 |
| Apoplexie | 1 | Murthered at Stepney | 1 |
| Bedridden | 1 | Palſie | 2 |
| Cancer | 2 | Plague | 3880 |
| Childbed | 23 | Pluriſie | 1 |
| Chriſomes | 15 | Quinſie | 6 |
| Collick | 1 | Rickets | 23 |
| Conſumption | 174 | Riſing of the Lights | 19 |
| Convulſion | 88 | Rupture | 2 |
| Dropſie | 40 | Sciatica | 1 |
| Drowned 2, one at St. Kath. Tower, and one at Lambeth | 2 | Scowring | 13 |
| | | Scurvy | 1 |
| Feaver | 353 | Sore legge | 1 |
| Fiſtula | 1 | Spotted Feaver and Purples | 190 |
| Flox and Small-pox | 10 | Starved at Nurſe | 1 |
| Flux | 2 | Stilborn | 8 |
| Found dead in the Street at St. Bartholomew the Leſs | 1 | Stone | 2 |
| | | Stopping of the ſtomach | 16 |
| Frighted | 1 | Strangury | 1 |
| Gangrene | 1 | Suddenly | 1 |
| Gowt | 1 | Surfeit | 87 |
| Grief | 1 | Teeth | 113 |
| Griping in the Guts | 74 | Thruſh | 3 |
| Jaundies | 3 | Tiſſick | 6 |
| Impoſthume | 18 | Ulcer | 2 |
| Infants | 21 | Vomiting | 7 |
| Kild by a fall down ſtairs at St. Thomas Apoſtle | 1 | Winde | 8 |
| | | Wormes | 18 |

| | | | | |
|---|---|---|---|---|
| Chriſtned | Males 83 | Buried | Males 2656 | Plague 3880 |
| | Females 83 | | Females 2663 | |
| | In all 166 | | In all 5319 | |

Increaſed in the Burials this Week 1289

Pariſhes clear of the Plague 34 Pariſhes Infected 96

The Aſſize of Bread ſet forth by Order of the Lord Maior and Court of Aldermen;
A penny Wheaten Loaf to contain Nine Ounces and a half, and three half-penny White Loaves the like weight.

Shown by Sir John Bell
At PMWC2015 Oxford

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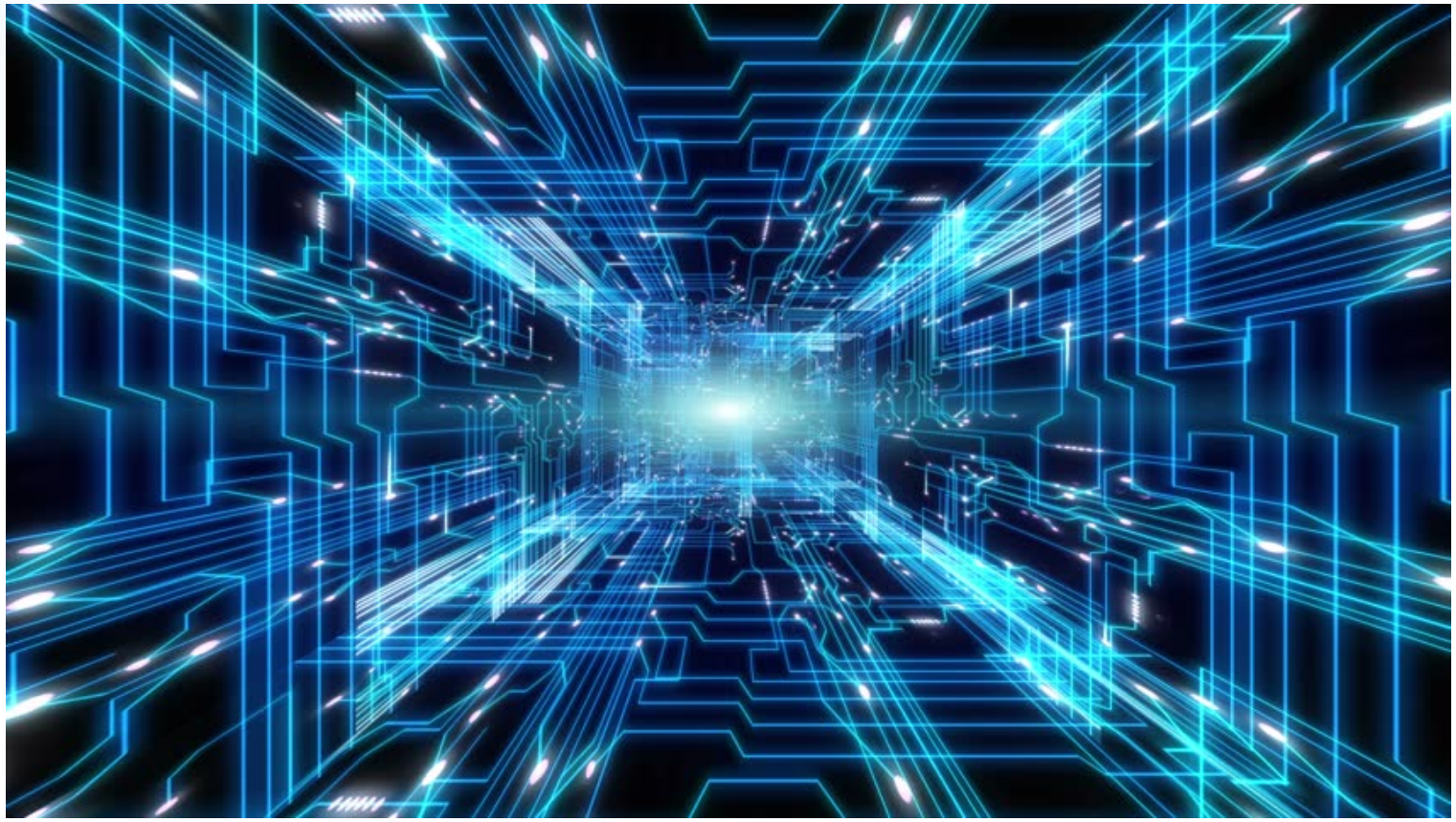
## Fast forward ~350 years…

## Where is clinical  neurology now?



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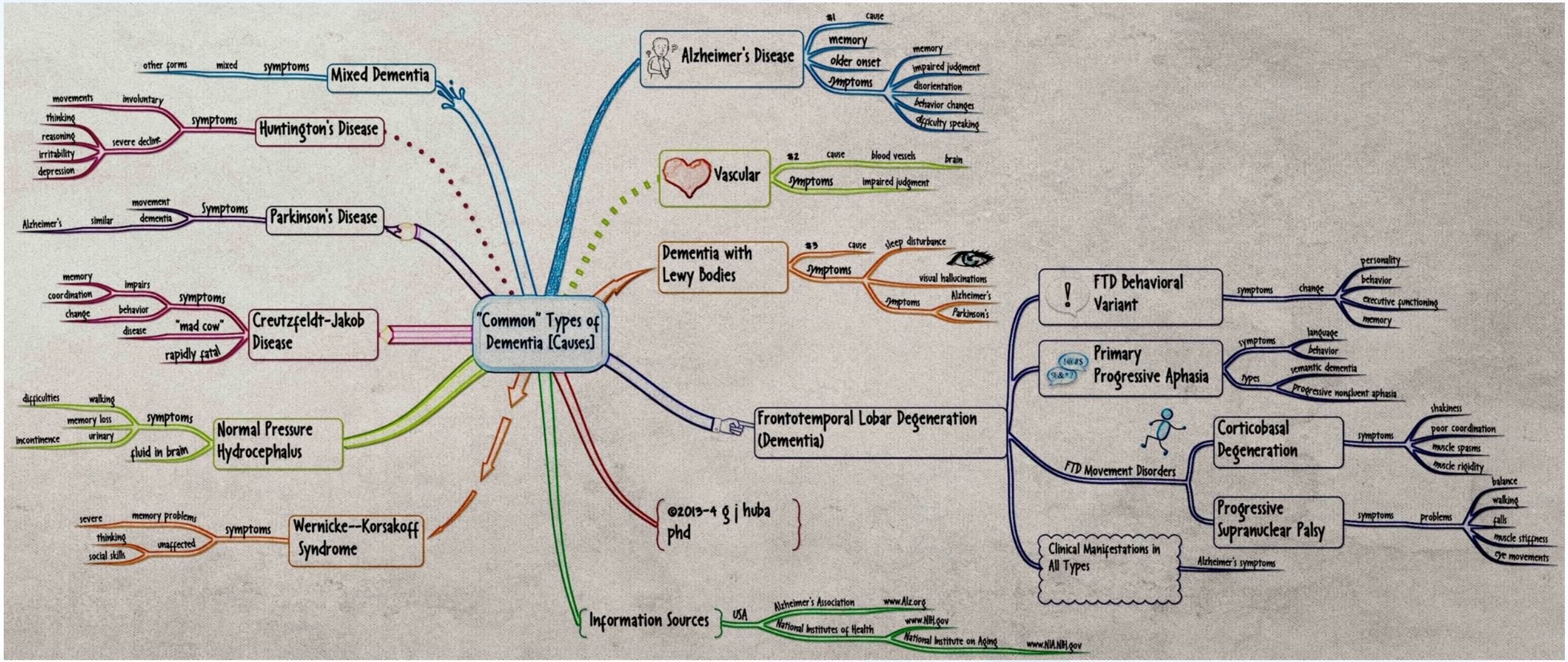
# What's in a name?

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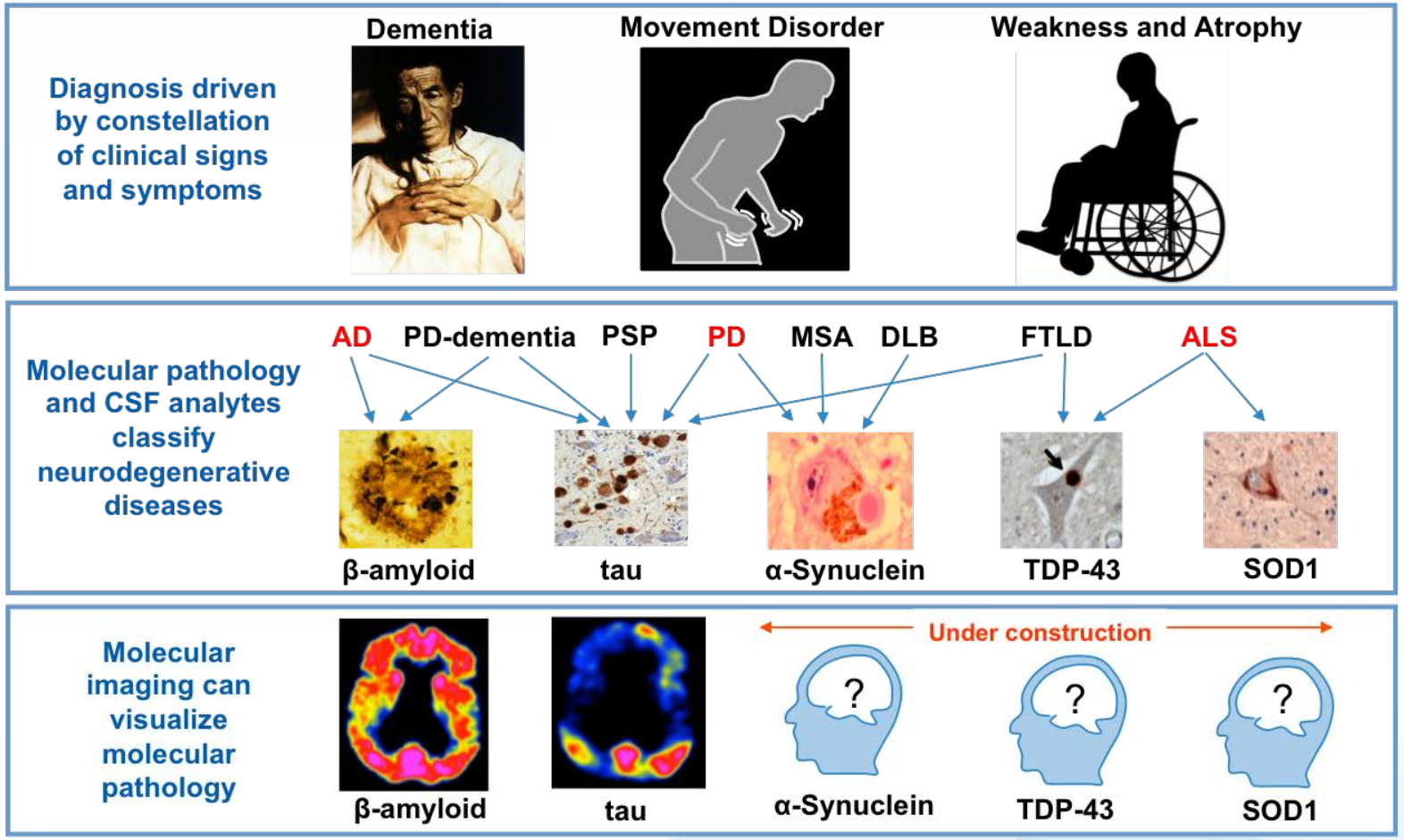
# We are pioneering a pathology targeting approach using biomarkers




AD Alzheimer's disease: PD Parkinson's disease: PSP Progressive supranuclear palsy: MSA multisystem atrophy: DLB Dementia with Lewy bodies: FTLD Fronto temporal dementia: ALS Amyotrophic lateral sclerosis

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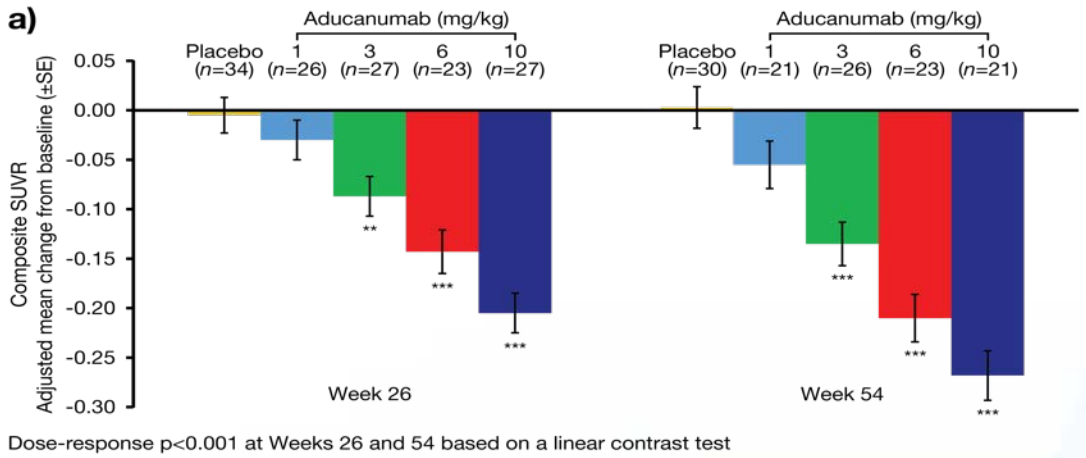
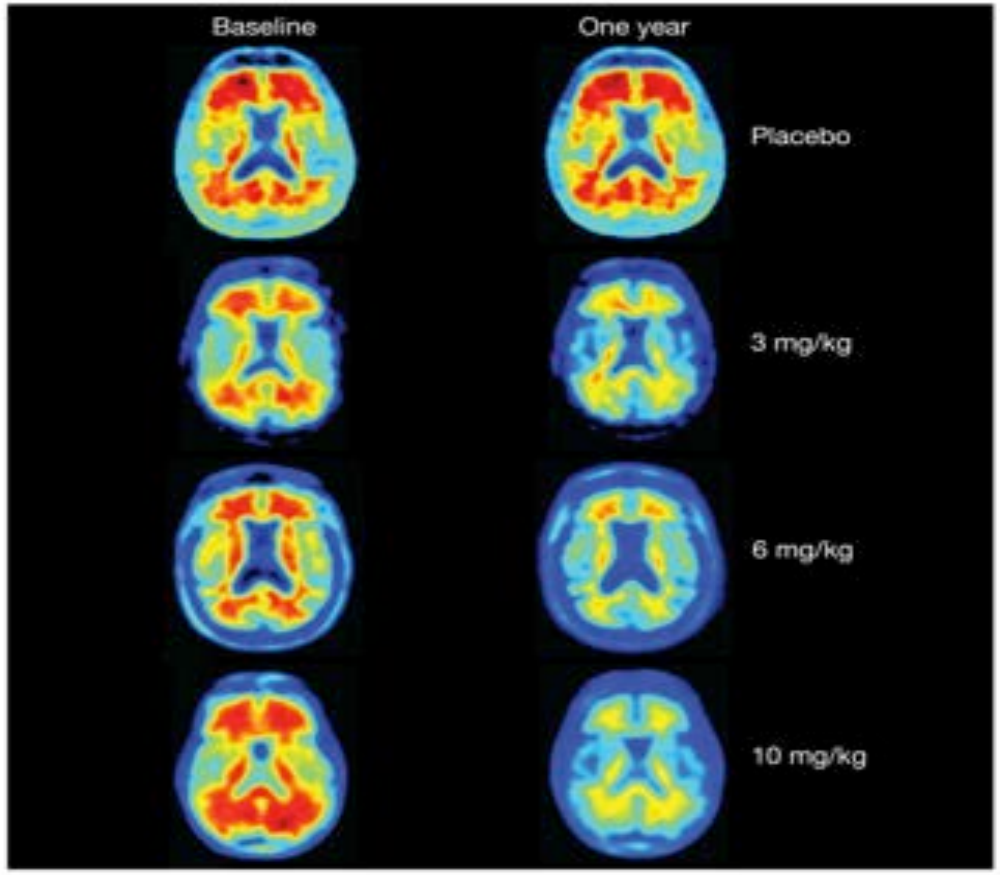
# A PRIME example: Its all about the pathology

| | Amyloid PET Negative % | | |
|---|---|---|---|
| | ε4 non-carrier | ε4 carrier | All |
| PRIME[1] (prodromal – mild; mean MMSE ~25) | 57% | 20% | 39% |



Dose-response p<0.001 at Weeks 26 and 54 based on a linear contrast test

[$^{18}$F]Florbetapir (Amyvid™ ) positron emission tomography (PET) at baseline and following 54 weeks aducanumab treatment

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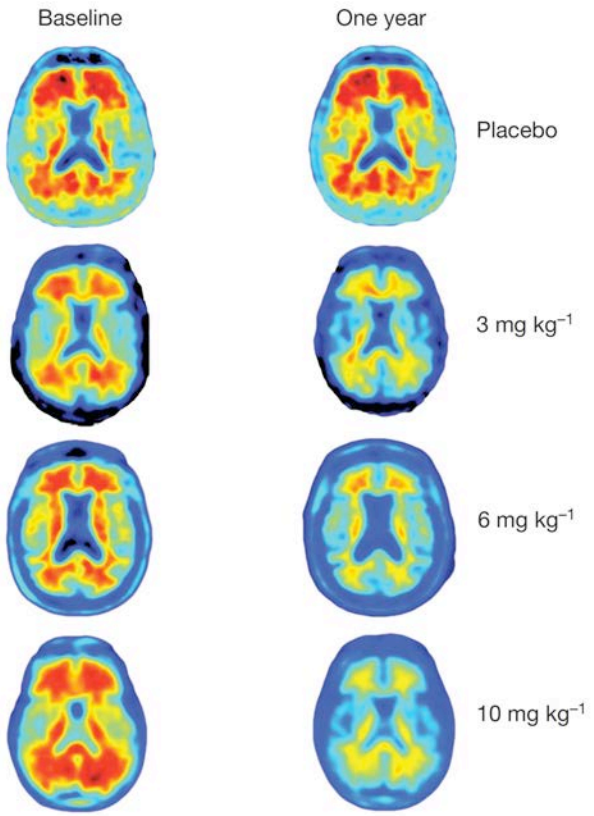
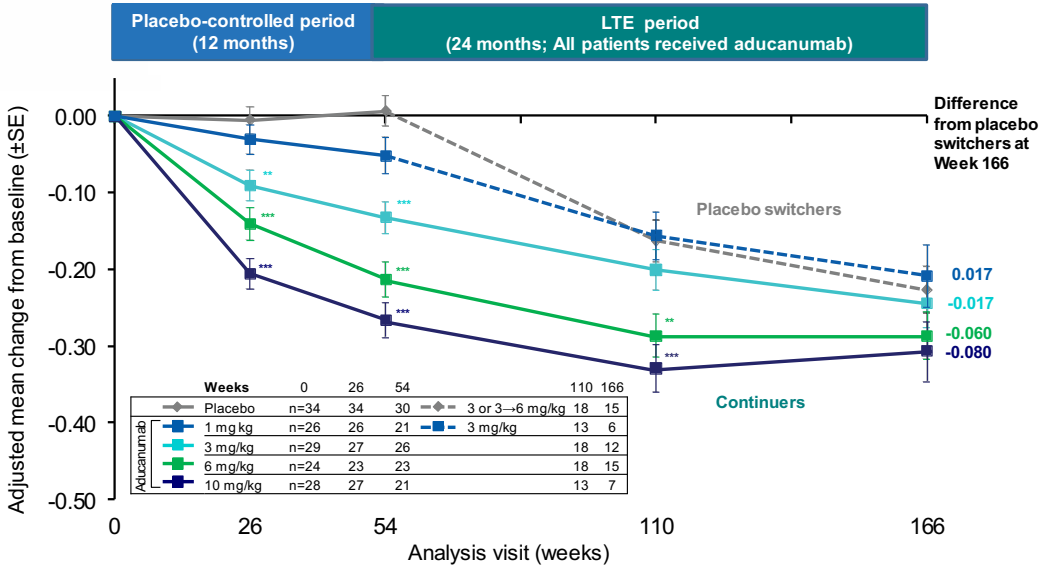
Sevigny et al. (2016) Nature 2016

# Implementation of Amyloid PET Imaging In Aducanumab PRIME Clinical Trial

Amyloid PET approved by FDA for diagnosis of the presence of amyloid pathology and is used to enroll patients in clinical trials




*Sevigny et al, Nature, 2016*




*Nominal * P<0.05; Nominal ** P<0.01; Nominal *** P<0.001 vs placebo in the placebo-controlled period and vs placebo switchers in the LTE period*

*Haeberlein et al, CTAD 2017*

- Evidence of target engagement and of dose- and time-dependent reduction in plaque load in the aducanumab treated patients

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# Thank you!

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