Setting the Stage

Digital Medicine and the Brain

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IMI Stakeholder Forum 2019

Brain health and disease in the digital era – 2020 & beyond

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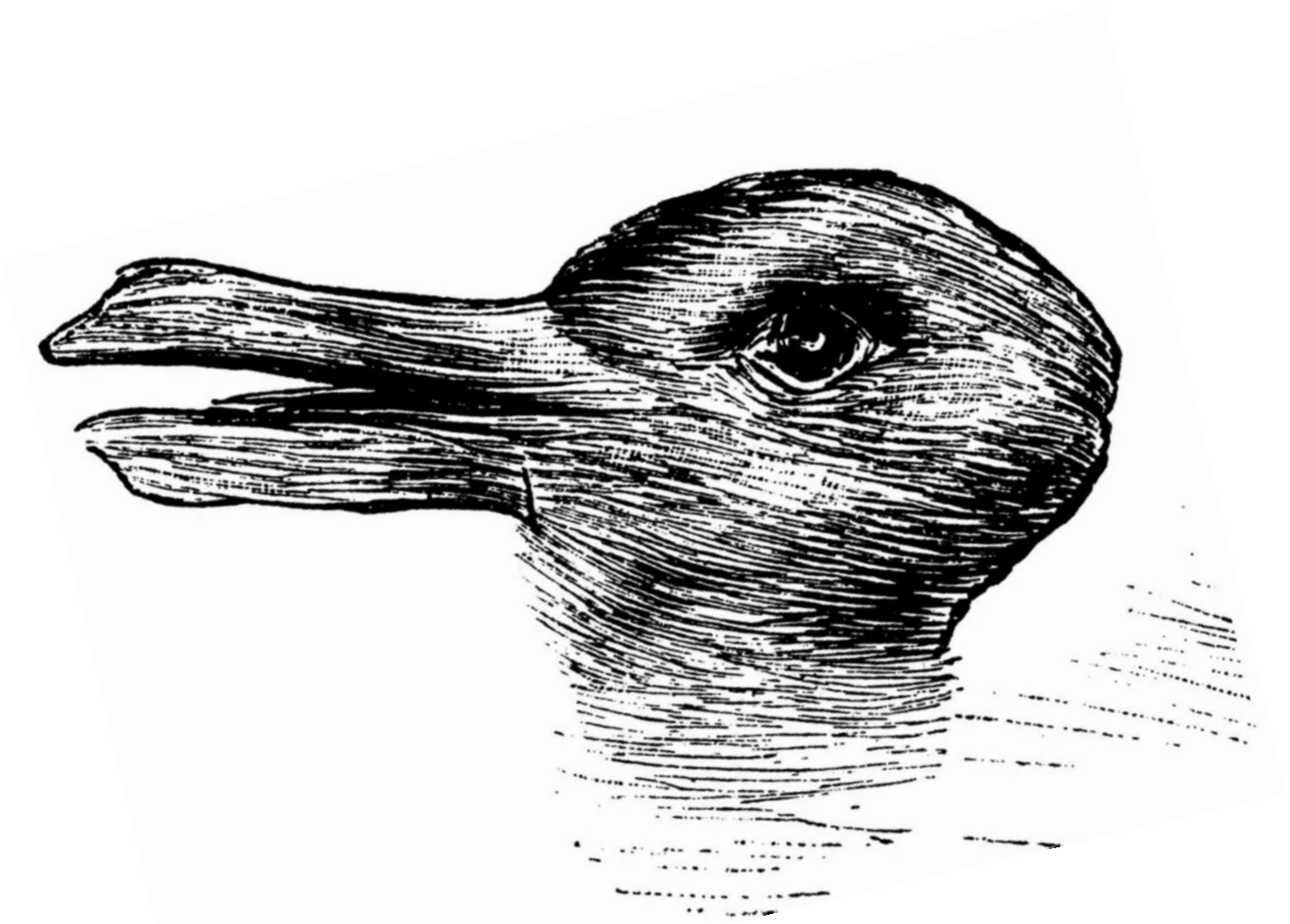
The Birth of a Scientific Revolution



Khun, T. The Structure of Scientific Revolutions, 1962

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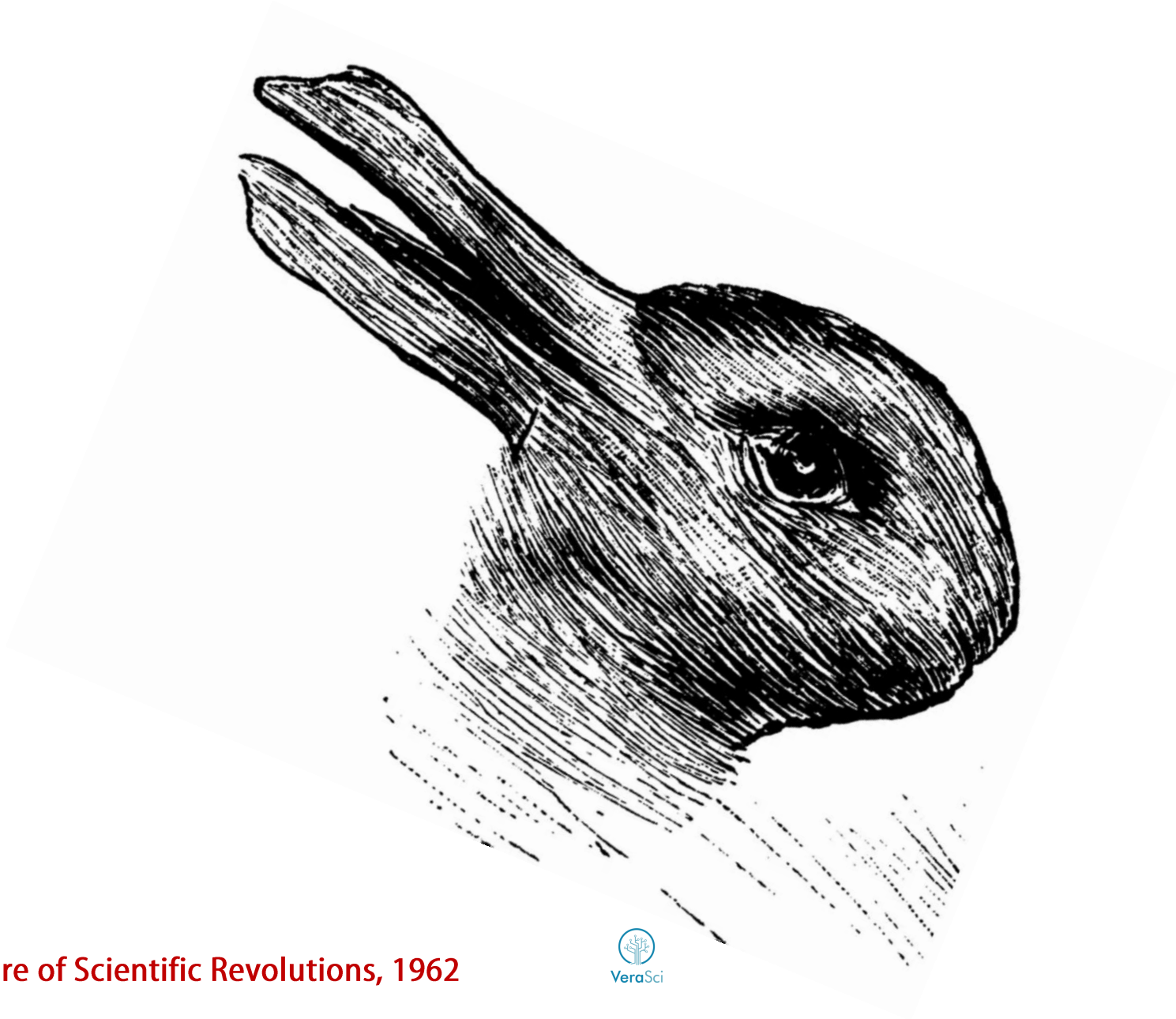

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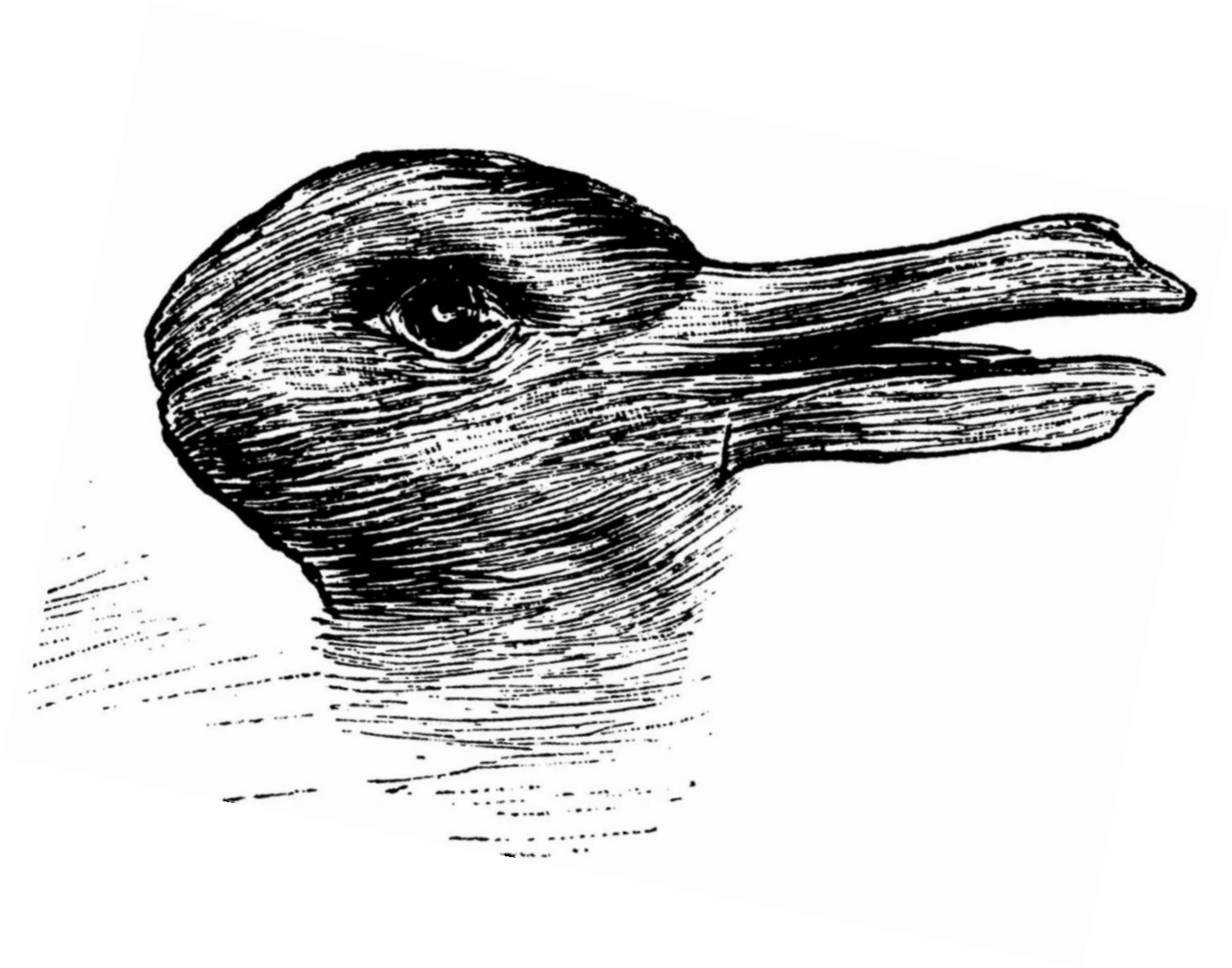

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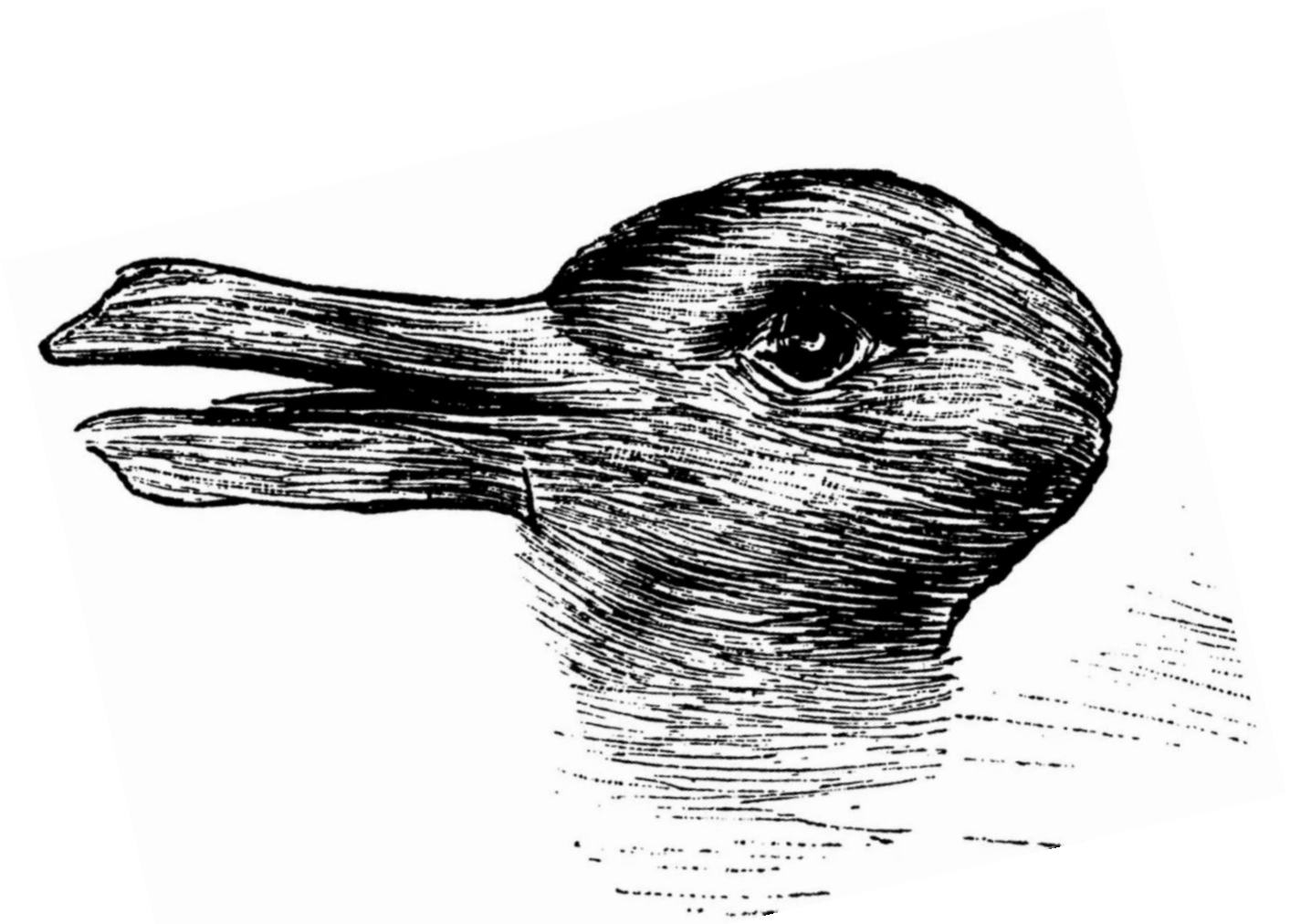

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Biology and Medicine are now dead Sciences, they have become Information Sciences

Toward Precision Medicine

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

2011

Committee on A Framework for Developing a New Taxonomy of Disease

Board on Life Sciences

Division on Earth and Life Studies

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

The four Ps of Precision Medicine: predictive, preventative, personalized and participatory.

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

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Statement of Principals: Digital products and CNS disorders

- The field of research and development in CNS disorders will see an **intensification of digital products** used as biomarkers, tools for population stratification, outcome assessment and medicinal products.
- The precision medicine paradigm applied to CNS disorders, will be realized primarily through digital products mostly because there is **still limited knowledge of the molecular mechanisms of CNS diseases**.
- Digitalization allows a **precise characterization** of the behavioral variability and can handle the big and complex datasets generated.

CNS = Central Nervous System

Fact: Population Growth, Life Expectancy and Health

Earth's population = **7.6 billion people**

Exponential growth started only **200 years ago**

Between year 1000 and 2000 it grew **3 times faster**

In the last 100 years it increased **from 1.5 billion to >7.5**

Life expectancy increased **by more than 35 years**

Mental issues range from **16.5 to 27%** of the total population*

All ailments connected to aging will escalate

* The Global Burden of Diseases, WHO Geneva, 2017

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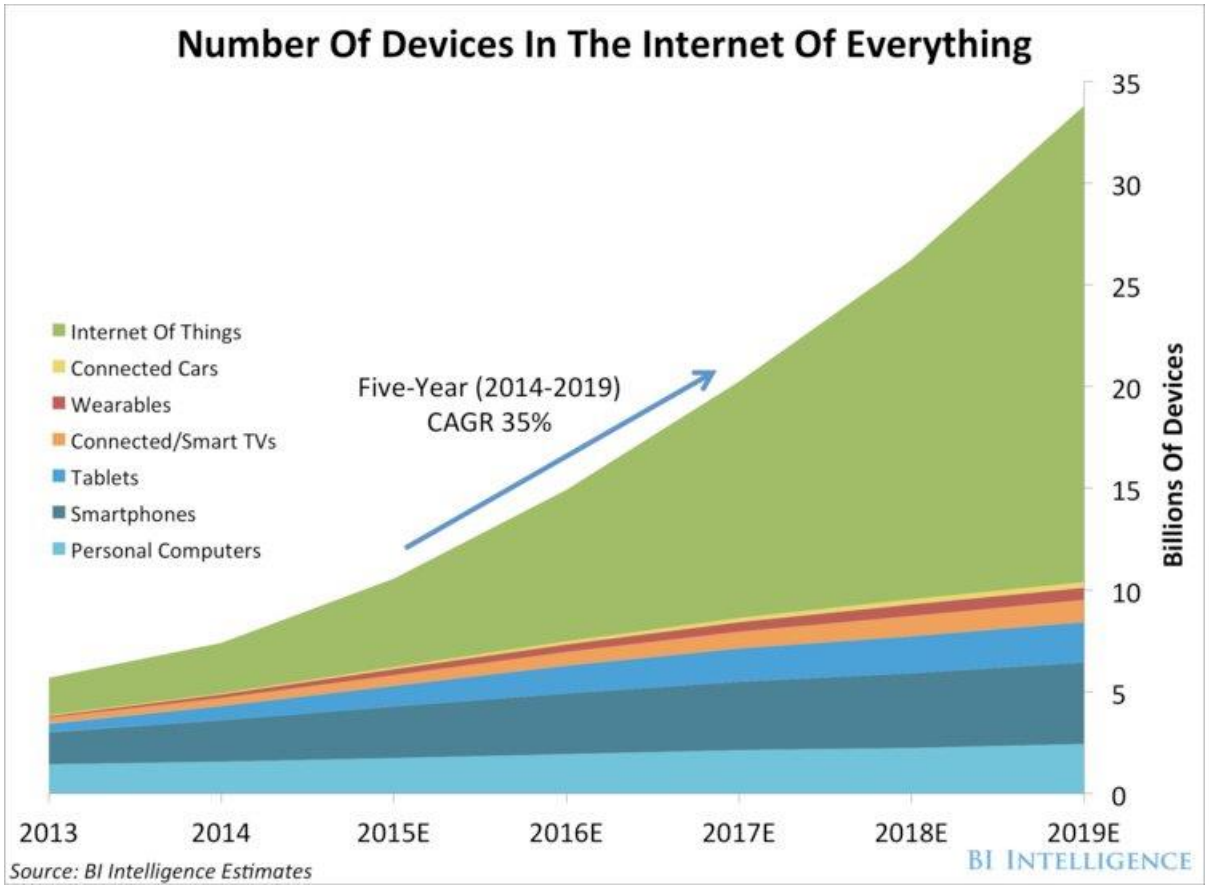
Fact: number and types of devices



Pope's inauguration 2005 vs. 2013.

http://www.businessinsider.com/internet-of-everything-2015-bi-2014-12?r=UK&IR=T

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Numbers of the Big(health)-Data (R)evolution

- This availability of both qualitative and quantitative **data is unprecedented** in the history of mankind (*i.e.* today it equals 2.5 quintillion bytes/day and by 2020 will equal **1,7 Mb per person / per second** from 200 Billion connected devices)*;

Technology-computing, connectivity and storage capacity will enable availability of health data **exponentially** in two ways: increasing **computerization** and quantifying **self and mobile-health:**

- **Increasing computerization** of medical processes and procedures **should** link all data to information and to knowledge in a virtuous interexchange
- **Quantifying self and mobile-health**, *i.e.* the possibility for each person, healthy or not, to measure their medical condition through smartphones and wearable sensors, will become the primary source of health data **with a special emphasis on mental health.**

***Source: Intel Corporation; Mb = a unit of information ≅ 1 million bytes; Exabyte = one quintillion ≅ 1 billion gigabytes**

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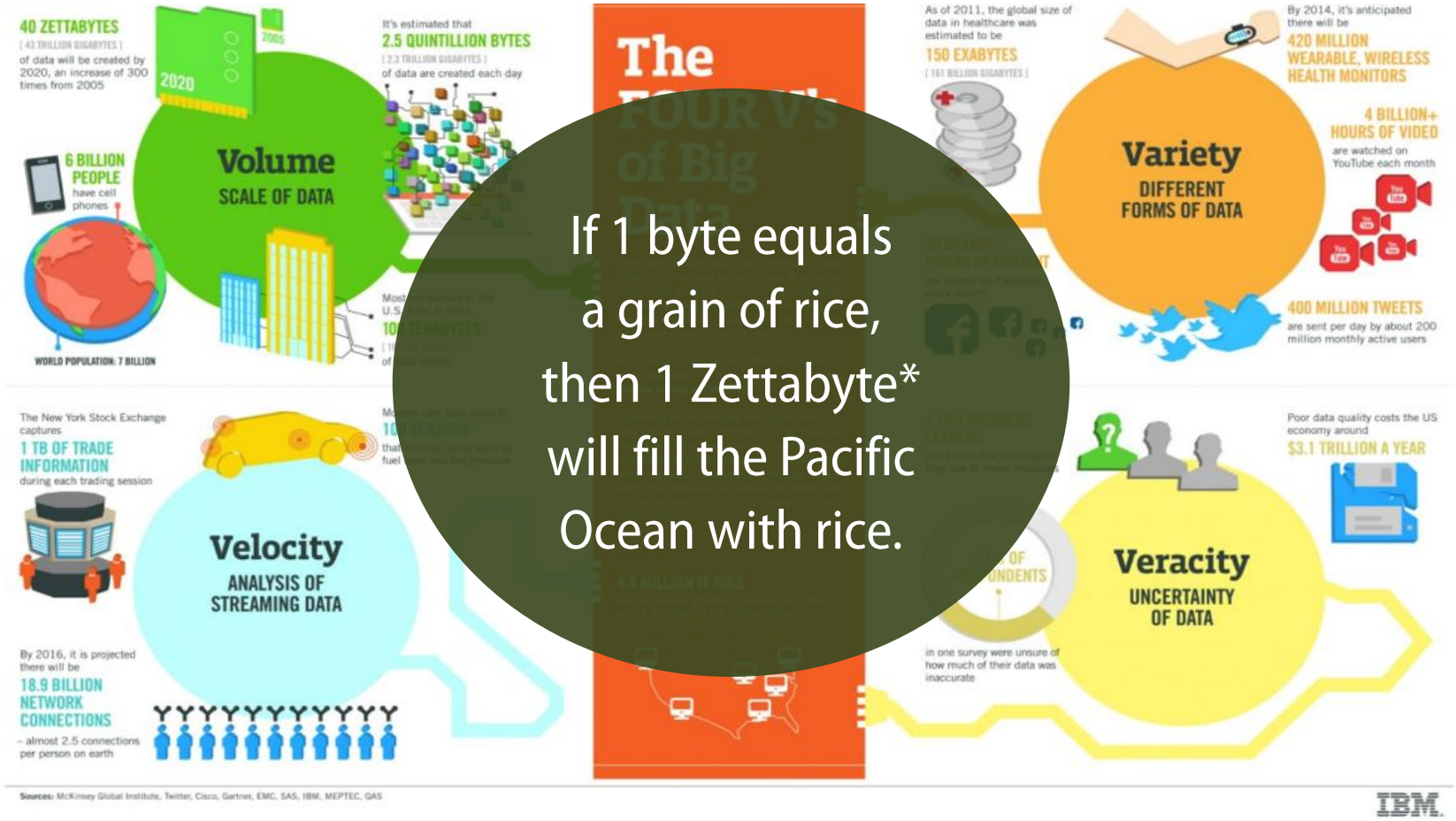
We will have 40 ZettaBytes of Healthdata by 2020

What are we really saying here?



*A unit of information equal to 1 sextillion (10^{21}) bytes.

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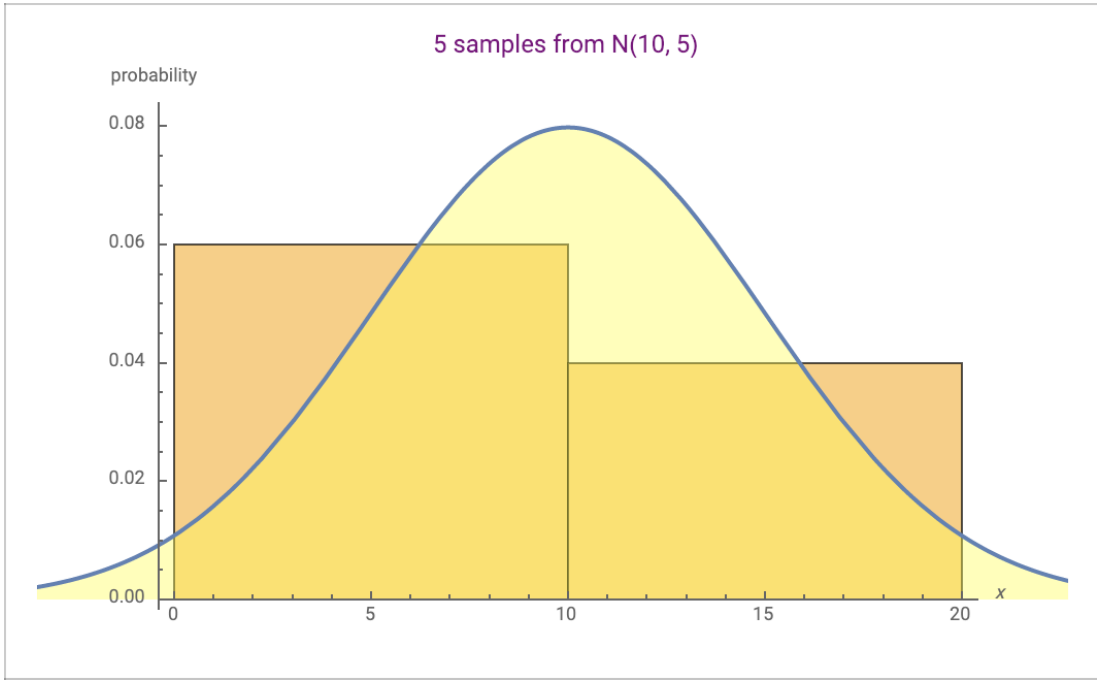
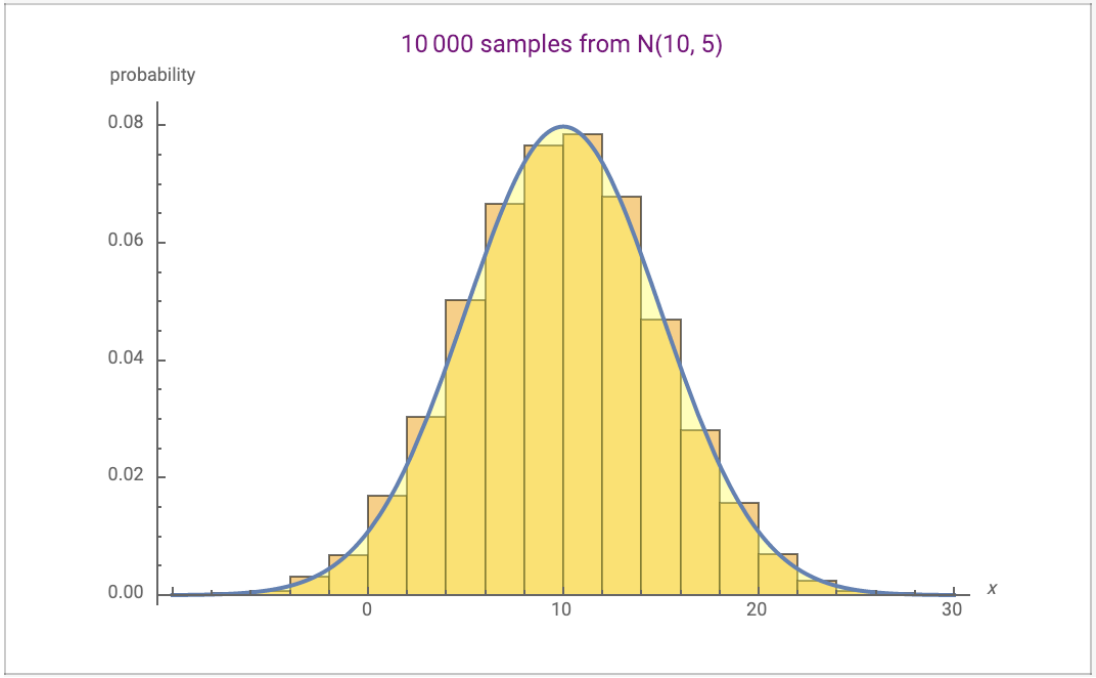
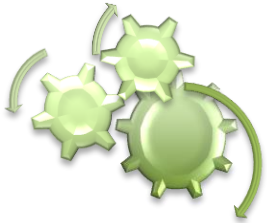
Impact of Sample Size on Approximating Normal Distribution







As sample sizes increase, the sampling distributions approach a normal distribution.
With "infinite" numbers of successive random samples, the mean of the sampling distribution is equal to the population mean (μ).

https://demonstrations.wolfram.com/ImpactOfSampleSizeOnApproximatingTheNormalDistribution/

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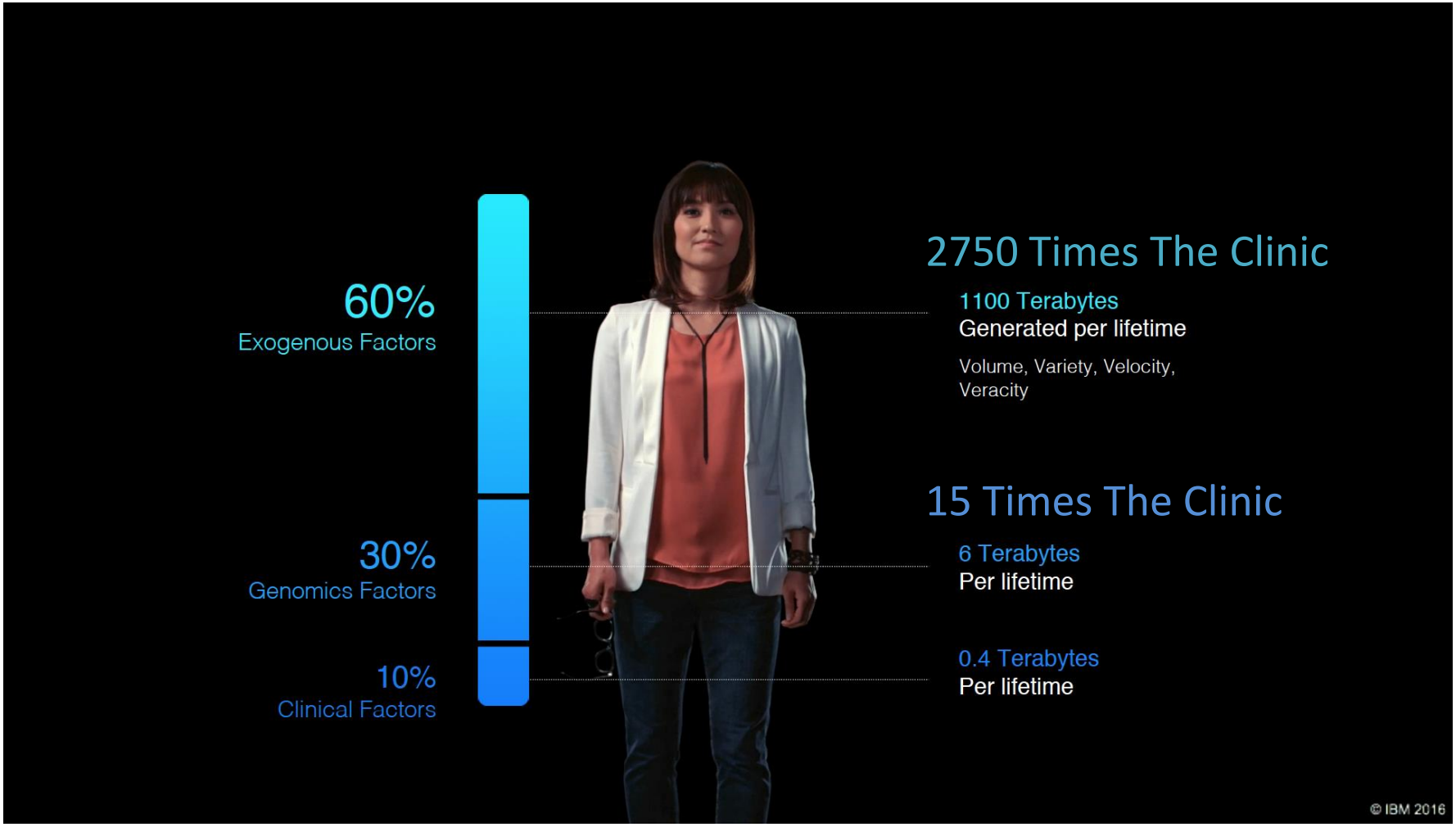
Source, type and size of data



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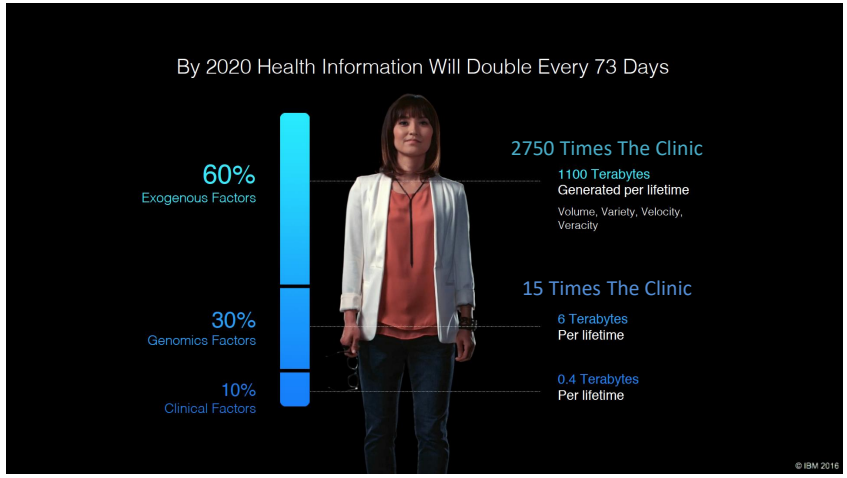
Research and Clinical Implications of Big Data

- New organizational model (healthcare)



- Innovation in life sciences and biotech
  - Selective drug discovery by Artificial Intelligence (A.I.)
  - Population definition (Big Data, digital phenotyping)
  - Digital measures of outcome (wearables, apps, sensors)
  - Siteless clinical trials

- Preventive and participatory medicine aimed at **healthy individuals at risk** (digital and non-digital biomarkers)
- Digital Therapeutics (Dtx) as an integral part of treatment

arXiv:1510.02855v1 [cs.LG] 10 Oct 2015

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How do you capture and elaborate data from a device?

Use this kind of "stuff"

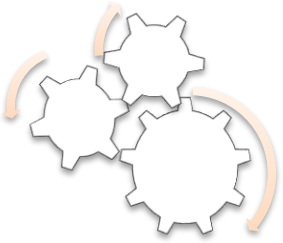
- Application of an iterative approaches
- Employ real life certified database (when possible)
- Massive adoption of A.I.
- Machine Learning
- Integrate structured and unstructured data

Potential Pitfalls

- Junk in / Junk out
- Missing data
- Unrealistic values
- Not preparing the data for further elaboration / submission

What we have vs. what is coming

- Sensors for "activity" monitor
- Pattern recognition
- Human to machine interface



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Pattern recognition

European Journal of Cancer 113 (2019) 47–54

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Deep learning outperformed 136 of 157 dermatologists in a head-to-head dermoscopic melanoma image classification task

Titus J. Brinker [a,b,*], Achim Hekler [a], Alexander H. Enk [b], Joachim Klode [c], Axel Hauschild [d], Carola Berking [e], Bastian Schilling [f], Sebastian Haferkamp [g], Dirk Schadendorf [c], Tim Holland-Letz [h], Jochen S. Utikal [i,j,l], Christof von Kalle [a,l], Collaborators[2]

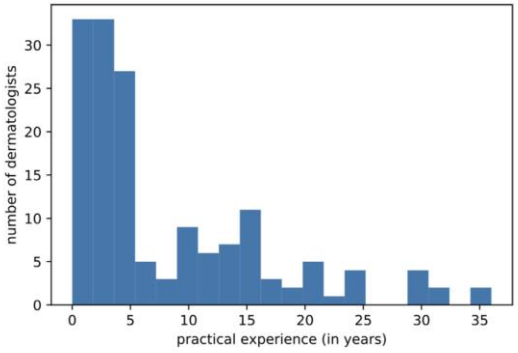


Fig. 1. Distribution of years of experience for participating dermatologists.

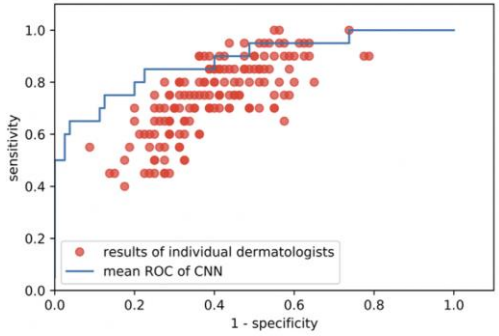
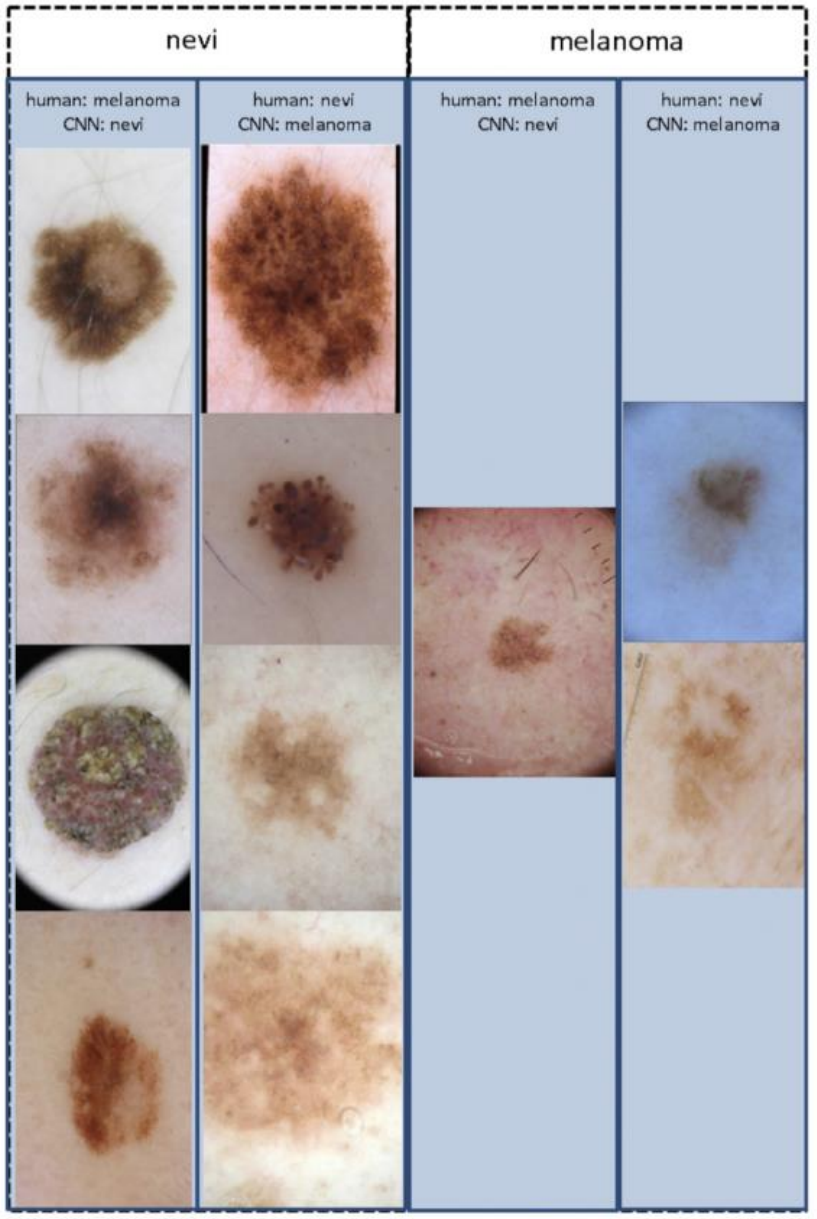


Fig. 2. The mean receiver operating characteristic (ROC) curve over all 10 runs. CNN, convolutional neural network.



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Trained Humans are able to rule-out psychosis

DSM5 has included APS as a condition for further study

Across **SIPS** samples (20, 46, 48–50), Se was 0.96 (95% CI: 0.88–0.99) and Sp was 0.39 (95% CI: 0.32–0.46)

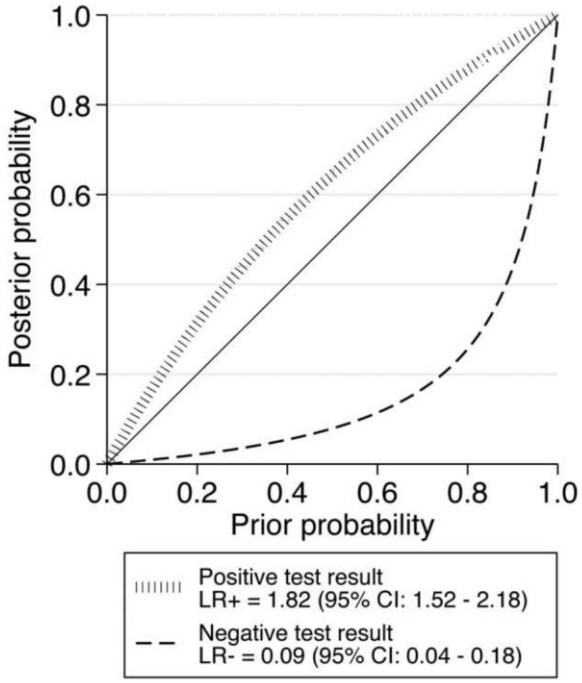
Across **CAARMS** samples (44, 45, 47, 51), Se was 0.96 (95% CI:0.82–0.99) and Sp was 0.56 (95% CI: 0.38–0.73).

The risk of developing psychosis is 26% in 38-month follow-up

Interviews showed an outstanding ability of the instruments to **rule out** psychosis at an expense of their ability to **rule in** psychosis

At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction

Paolo Fusar-Poli[1,2], Marco Cappucciati[1], Grazia Rutigliano[1], Frauke Schultze-Lutter[3], Ilaria Bonoldi[1], Stefan Borgwardt[4], Anita Riecher-Rössler[4], Jean Addington[5], Diana Perkins[6], Scott W. Woods[7], Thomas H. McGlashan[7], Jimmy Lee[8], Joachim Klosterkötter[9], Alison R. Yung[10], Philip McGuire[1,2]



CAARMS, Comprehensive Assessment of At Risk Mental State; CI, confidence interval; SIPS, Structured Interview for Psychosis-Risk Syndrome; APS Attenuated Psychosis Syndrome; Fusar-Poli P, *et al. World Psychiatry* 2015;14:322–332

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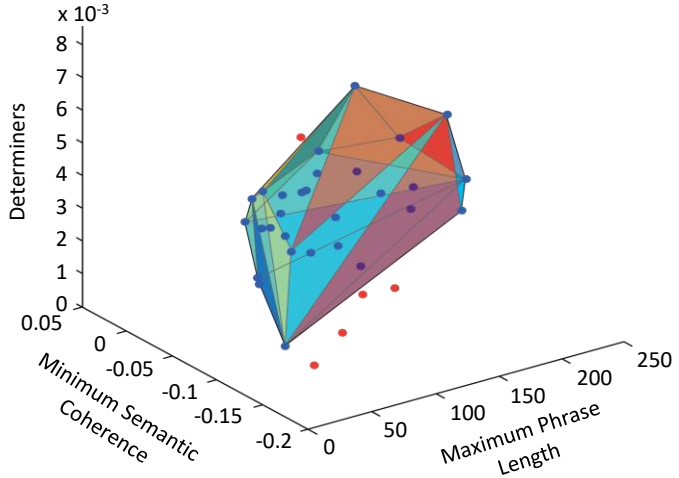
Machines are able to rule-out and rule-in psychosis

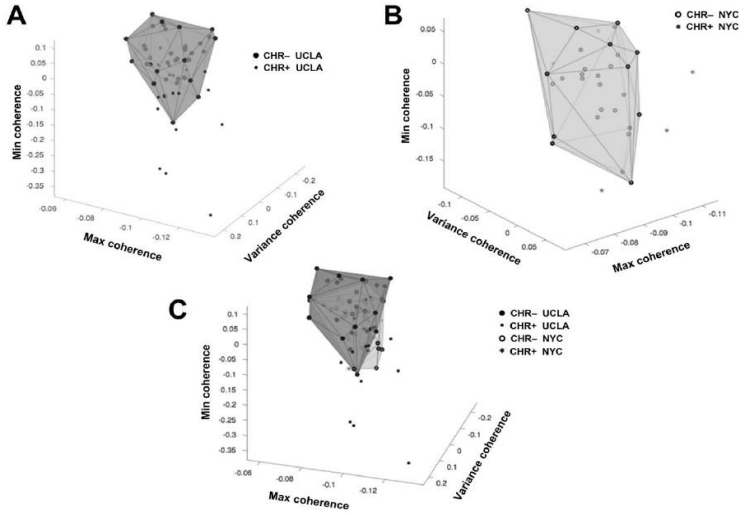
Automated analysis of free speech predicts psychosis onset in high-risk youths

Gillinder Bedi[1,2,9], Facundo Carrillo[3,9], Guillermo A Cecchi[4], Diego Fernández Slezak[3], Mariano Sigman[5], Natália B Mota[6], Sidarta Ribeiro[6], Daniel C Javitt[1,7], Mauro Copelli[8] and Cheryl M Corcoran[1,7]

BACKGROUND/OBJECTIVES: Psychiatry lacks the objective clinical tests routinely used in other specializations. Novel computerized methods to characterize complex behaviors such as speech could be used to identify and predict psychiatric illness in individuals.
AIMS: In this proof-of-principle study, our aim was to test automated speech analyses combined with Machine Learning to predict later psychosis onset in youths at clinical high-risk (CHR) for psychosis.
METHODS: Thirty-four CHR youths (11 females) had baseline interviews and were assessed quarterly for up to 2.5 years; five transitioned to psychosis. Using automated analysis, transcripts of interviews were evaluated for semantic and syntactic features predicting later psychosis onset. Speech features were fed into a convex hull classification algorithm with leave-one-subject-out cross-validation to assess their predictive value for psychosis outcome. The canonical correlation between the speech features and prodromal symptom ratings was computed.
RESULTS: Derived speech features included a Latent Semantic Analysis measure of semantic coherence and two syntactic markers of speech complexity: maximum phrase length and use of determiners (e.g., *which*). These speech features predicted later psychosis development with 100% accuracy, outperforming classification from clinical interviews. Speech features were significantly correlated with prodromal symptoms.
CONCLUSIONS: Findings support the utility of automated speech analysis to measure subtle, clinically relevant mental state changes in emergent psychosis. Recent developments in computer science, including natural language processing, could provide the foundation for future development of objective clinical tests for psychiatry.

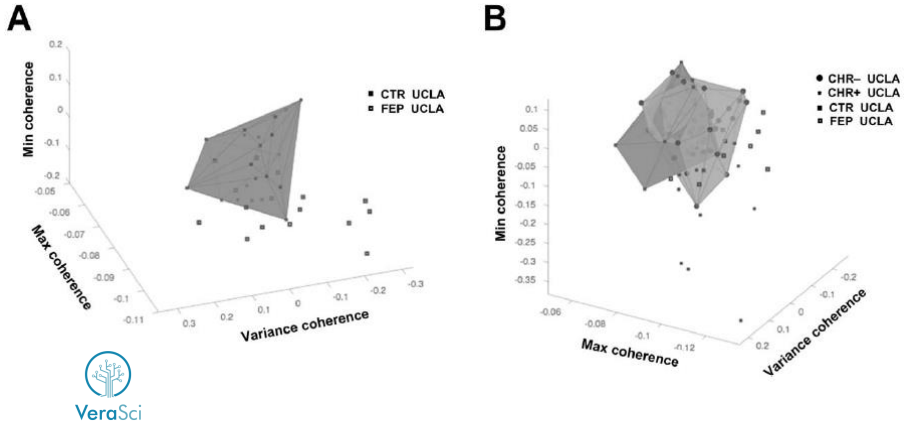
npj Schizophrenia (2015) **1,** Article number: 15030; doi:10.1038/npjschz.2015.30; published online 26 August 2015





Prediction of psychosis across protocols and risk cohorts using automated language analysis

Cheryl M. Corcoran[1,2], Facundo Carrillo[3,4], Diego Fernández-Slezak[3,4], Gillinder Bedi[2,5,6], Casimir Klim[2,5], Daniel C. Javitt[2,5], Carrie E. Bearden[7], Guillermo A. Cecchi[8]



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Opportunities: digital biomarker tools

At-home use in measuring cognitive/functional/behavioural sub-domains in clinical trials

- Memory, executive function- Passive
- Movement, GPS (actigraphy, location)- Active

Active vs passive measures

- Certain domains of cognitive function require more active testing (SDMT on a phone or tablet)
  - Active measures require a reward system
  - Reminders so patients don't forget to do them
- Others like movement and social functioning can be more passively monitored
  - Passive measures may require sharing data with subject (*e.g.* Fitbit) to encourage adherence
  - Patients need to wear the devices and keep them charged

SDMT, Symbol Digit Modalities Test

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Issues: digital biomarker tools

Some of the digital biomarker issues with regards to validation and product labelling?

- Like any measure, basic psychometrics and testing considerations such as
  - **Reliability**
  - **Validity**
  - **Practicality**
- **Data analytics, extraction** and **integrity** processes namely:
- Is the device measuring the construct that you think it is measuring?
- Consider translational (does it fit with animal models?)
- Validation and certification of measures will be necessary for regulators/payers
  - Regulators could request to issue a qualification opinion and then use your biomarker to enrich a population
  - These surrogate and secondary endpoint measures should be linked with primary or co-primary

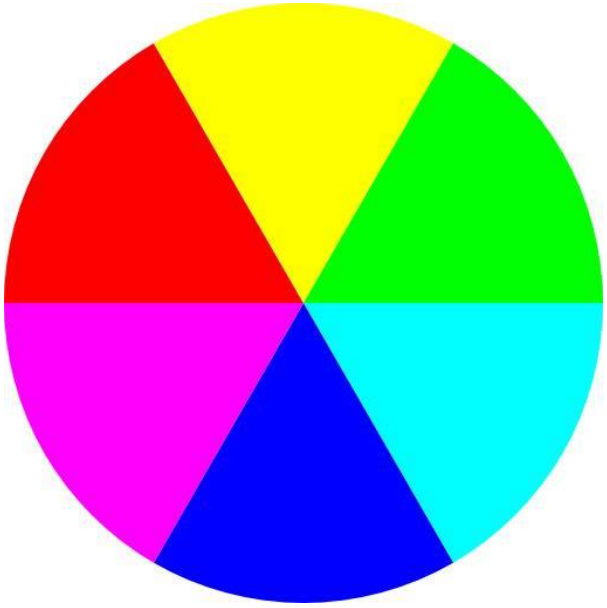
Product labelling consideration

- Potential to replace Phase IV studies with patient-centred outcomes (see regulatory/payer considerations above)
  - Example: Improves social activity in people with depression
  - Example: **Identify healthy person at risk for a mental disorder (spectrum and/or prodromes)**

Keefe RSE and Pani L., Biol Psychiatry Cogn Neurosci Neuroimaging. 2018 Nov;3(11):900-902.

The Spectrum and the Prodromal States Concept Construct

From this



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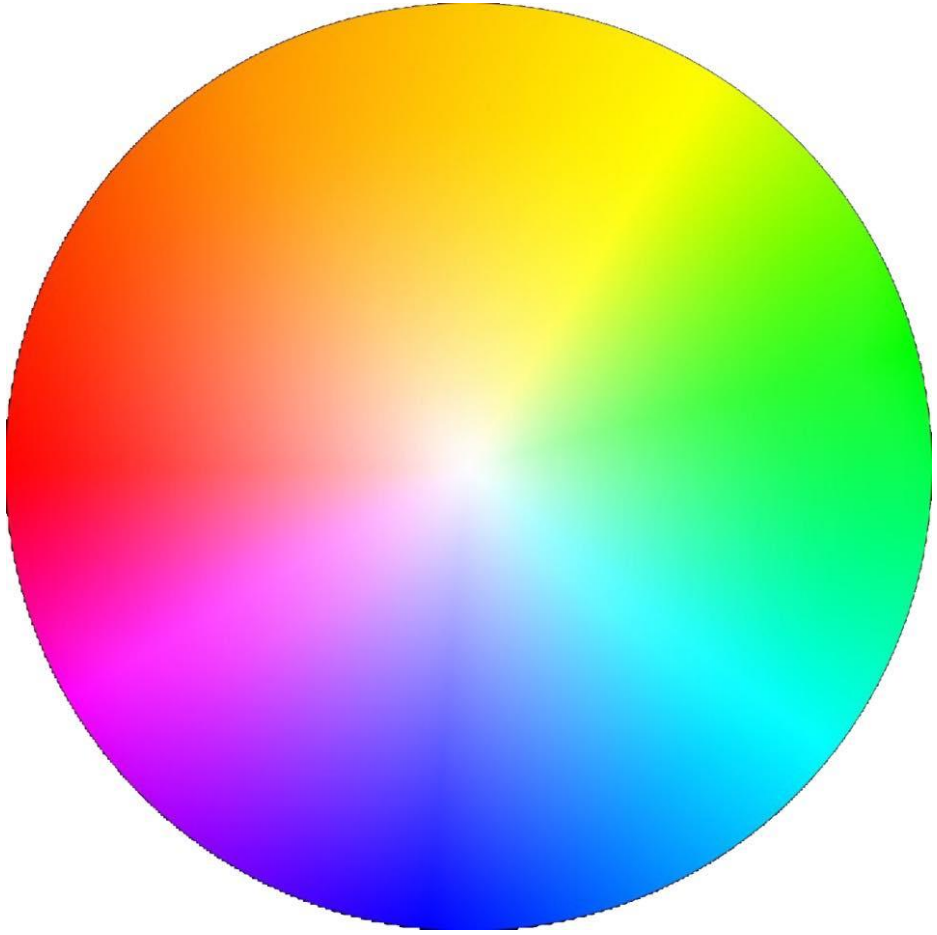

Images after Pietro Zanarini, CRS4, 2018

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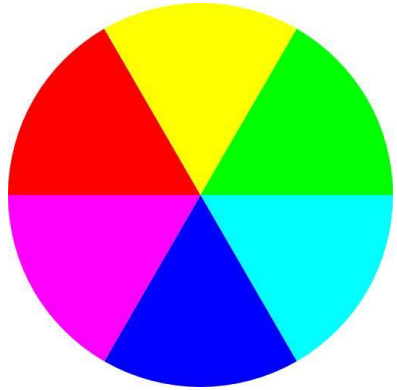
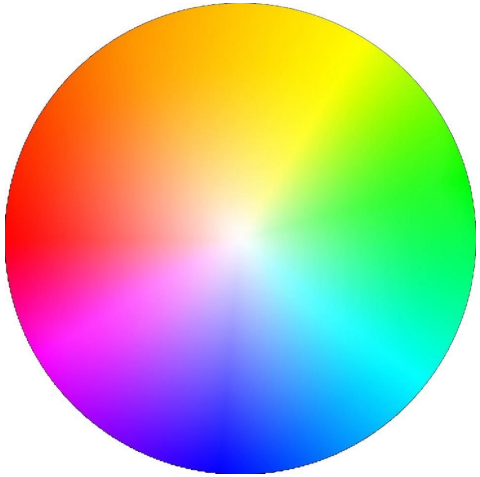
Biomarkers and Early Treatment

- Spectrum disorders with no clear neurodegenerative patterns are regulatory (and clinically) challenging
- Attenuated psychotic syndrome could be an early manifestation of a more severe state or an attenuated state that does not evolve and may be found also in the general population
- Early (and evolving) stages and transitory psychotic states may be difficult to differentiate solely on the basis of clinical observation
- Biomarkers **(especially digital)** could be found and used as biological characteristics of behavioural patterns





Pani L. and Keefe RSE, (2019, in press) Schizophrenia Research: Cognition

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Continuum vs. Spectrum Concept Construct

- AD for example is a continuum that follows an increasing severity pattern up to the diagnosis of dementia (neurodegenerative disease). A similar paradigm can be applied for instance to Parkinson's disease or Schizophrenia where a shift towards early treatment is triggering a vast amount of research into biomarkers with high PPV for early population identification
- The EMA considers pharmacological interventions directed to suspected pathophysiological mechanisms underlying AD at a pre-symptomatic stage a reasonable approach for prevention strategies.
- The FDA considers patients with Stage 1 of AD and no symptom a valid target because intervention should start as early as possible, an effect biomarkers could be the basis for an accelerated assessment
- Is Schizophrenia, for instance, a degenerative disease that develops in a continuum or a spectrum of clinical manifestations? Does cognition in Schizophrenia follow the spectrum concept construct?

AD, Alzheimer's disease; EMA, European Medicines Agency; FDA, US Food and Drug Administration; PPV, Positive Predictive Value

Digital shift towards early treatment of prodromal states

R&D follows this paradigm as precision products target molecular mechanisms in population with or without clinical symptoms

When the molecular mechanism is well known population identification is relatively easier (gene therapy and monogenic diseases)

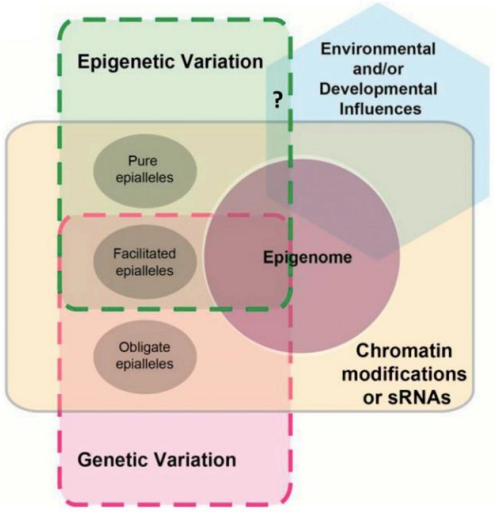
In multifactorial diseases such as mental disorders preventative strategies are very challenging because:

- There are multiple molecular pathways that contribute to the disease
- Environmental factors interact with endogenous factors
- Phenotypes are complex and population identification cannot be based solely on symptoms but on GxE interactions (hence the 'problem' of phenocopies)

R&D = research and development

- Where Genes (G) and Environment (E) interact (GxE) like in

the case of any multifactorial disorders such as mental disorders then following continuously any brain produced behaviour in the environment could provide essential information on brain's health (*e.g.* ecological measures).



Epigenetic variation: Heritable differences that are independent of changes in DNA sequence

Chromatin modifications: Differences in the presence or types of histones (variants) and modifications of DNA (methylation) or histones (methylation, acetylation, etc) and small RNAs that are often associated with epigenetic variation but can be influenced by genetic variation or development / environment

Epigenome: The genome-wide distribution of chromatin modifications or DNA methylation patterns that may include non-heritable changes or genetically influenced patterns

Epialleles: Meiotically heritable allelic differences in chromatin state
Pure epialleles: Epialleles that have differences in chromatin state that are independent of any genetic information
Facilitated epialleles: Epialleles for which a genetic difference (i.e. transposon insertion) leads to the potential to adopt alternate chromatin states
Obligate epialleles: Epialleles with altered chromatin state that is fully dependent upon genetic variants (either cis or trans-acting changes)

Topical Review on Epigenetics and Chromatin Modifications

Epigenetics: Beyond Chromatin Modifications and Complex Genetic Regulation[1]

Steven R. Eichten, Robert J. Schmitz*, and Nathan M. Springer*

Pani L. and Keefe RSE, (2019, in press) Schizophrenia Research: Cognition

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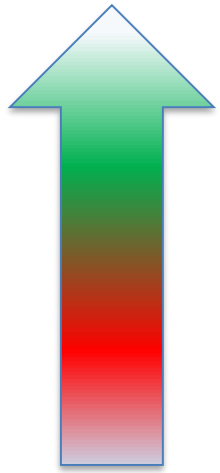
Digital Phenotyping In Autism

Examples of sensors, phenotypes, and evidence

Sensor / Technology	Clinical Phenotype Assessed (examples)	Progress in Biomarker Development
Mobile / Web Apps	Digital phenotyping, behavior, remote video assess., etc.	More
EEG	Brain electrical activity/networks, spectral power, etc.	
Eye-tracking	Attention, social gaze, visual tracking, pupillary response,	
Actigraphy (+)	Activity level, RRBs, sleep	
Face emotion proc.	Measures / quantifies affect, dynamic range /complexity	
Speech/Voice (+)	Speech duration/quality/turns, prosody, tone, vocabulary	
Skin Conductance	Emotional reactivity/dysregulation, anxiety, etc.	Less
Automated Beh. Ax.	Lab-based behavior pattern assessment	



- Multiple studies are increasing our understanding of the potential utility of measures as disease / stratification / change 'biomarkers'
- Confirmatory studies, analyses ongoing to confirm first candidate biomarkers to be used in clinical trials
- Continuing to link to theories, symptoms, known Autism Spectrum Disorder causes

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Digital Therapeutics (DTx)

- Digital therapeutics (DTx) deliver evidence-based therapeutic interventions to patients that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease.
- They are used **independently or in concert with medications**, devices, or other therapies to optimize patient care and health outcomes.
- DTx products incorporate advanced technology best practices relating to design, clinical validation, usability, and data security.
- They are **validated by regulatory bodies** as required to support product claims regarding risk, efficacy, and intended use.
- Digital therapeutics **empower patients**, healthcare providers, and payers with intelligent and accessible tools for addressing a wide range of conditions through high quality, safe, and effective data-driven interventions.

Drug Device Combination: Proteus

Ingestible event maker + Ingestible sensor co-formulated with active pharmaceuticals

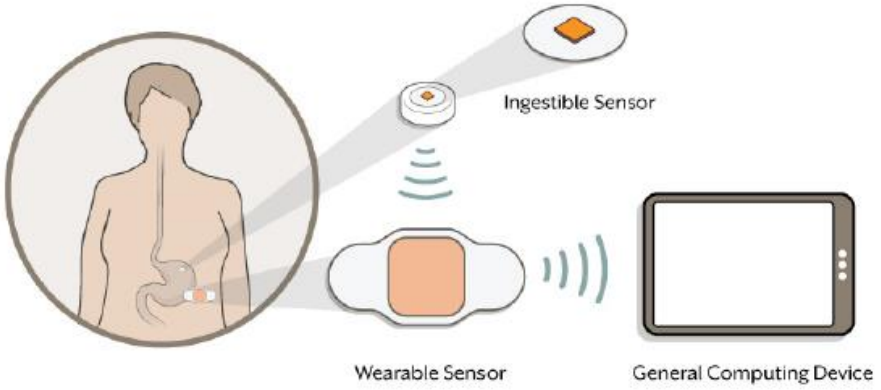
Proteus + Aripiprazole approved by the FDA as **Abilify MyCite**

The company announced that 31 other products are currently in development

EMA qualification opinion request:

- Measure adherence (positive)
- Physiologic and behavioral parameters

as indications of therapeutic response.



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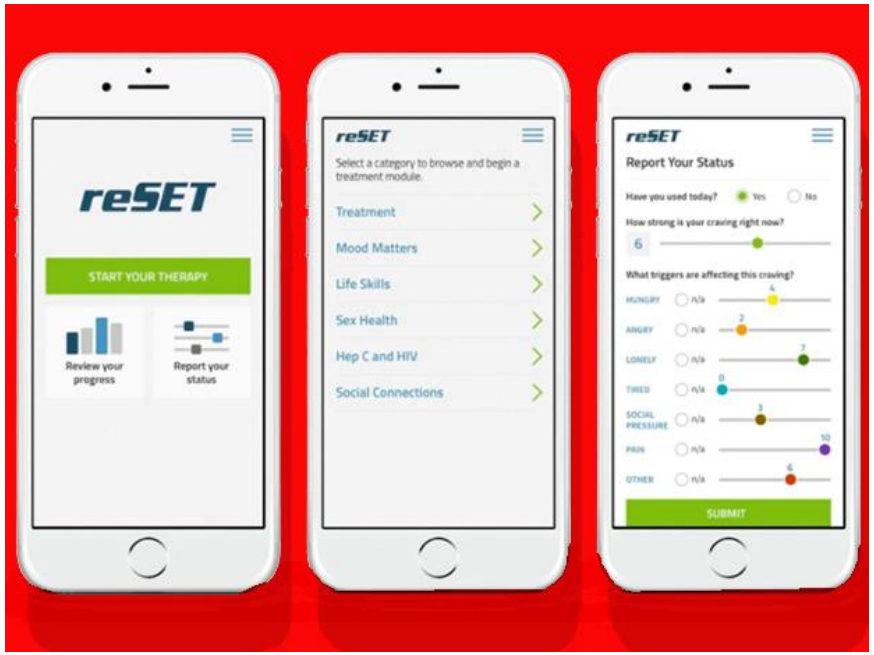
Proteus: Possible Regulatory Challenges

- Quality assessment of medical devices embedded in medicinal products
- Clinical relevance of the proposed claim (*e.g.* adherence)
- Interpretation of data and statistical significance for indications different from diagnostic categories
- Adequacy of the outcome to measure the construct of interest
- Advantages/comparison with other devices

Shift toward Digital Tx: The Software is the MoA



FDA permits marketing of mobile medical application for substance use disorder

Multi-site, unblinded 12-week clinical trial of 399 patients who received either standard treatment or standard treatment with the addition of a desktop-based version of Reset which could be accessed at the clinic or at home.

The data showed a statistically significant increase in adherence to abstinence for the patients with alcohol, cocaine, marijuana and stimulant Substance Use Disorder (SUD) in those who used Reset, 40.3 percent, compared to the patients who did not, 17.6 percent.

The clinical trial did not demonstrate the effectiveness of using the Reset device in patients reporting opioids as their substance of abuse.

The Reset device is indicated as a prescription-only adjunct treatment for patients with SUD who are not currently on opioid replacement therapy, who do not abuse alcohol solely, or whose primary substance of abuse is not opioids.

Data from the clinical studies did not indicate any side effects associated with the device.

PEAR THERAPEUTICS

Tx = Therapeutics; MoA = Mechanism of Action

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Digital Therapeutics (DTx): Project EVO™ - MoA

Project: EVO™ is an investigational digital treatment developed by Akili Interactive Labs.

- It uses the Selective Stimulus Management Engine (SSME ™) engine, designed to improve attention and inhibitory control through a video game-like interface. The SSME ™ engine involves simultaneous engagement in visual targeting and continuous motor tasks in an adaptive, autonomous algorithm that continuously pushes an individual's cognitive control performance within the context of multi-tasking interference.
- This enables the administration of a personalized treatment experience specific to the needs of each individual patient.

AKL-T01 for ADHD – Phase 2

In a randomized, controlled trial of 348 children and adolescents diagnosed with ADHD, AKL-T01 showed a statistically significant improvement (p=0.006) compared to an active control (sham videogame) on the predefined primary endpoint, a change in the Attention Performance Index (API), a composite score from the Test of Variables of Attention (T.O.V.A.®).

The T.O.V.A.® is an objective measure of sustained attention and inhibitory control.

AKL-T01 was shown to be safe in this study, with no serious adverse events observed.

AKILI

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EVO™: Possible Regulatory Challenges

The EVO™ technology platform enables selective targeting and activation of specific cognitive neural systems in the brain that exhibit deficiencies from various medical conditions.

- Quality assessment of medical devices used as therapeutics
- Potential multiple indications, specificity of the intervention
- Lack of Guidelines for products like AKL-T01 to advice on trial design, appropriate comparators, endpoints, duration/persistency of treatment effect
- Videogames if assessed like medicines are safe, but do they have specific safety issues we do not know yet?
- How to assess personalized delivery of stimuli and software that learn?

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Digital Tools for outcome assessment in CNS

- Building a regulatory framework for validation (and eventually qualification) of digital tools for outcome assessment.
- This includes for instance the statistical understanding of complex data beyond psychometrics such as speech analytics
- Use of digital products for population stratification and identification.
- Could a population eligible for a regulatory claim be identified with big data analytics?
- Could a population be considered eligible for treatment if found at risk for the development of a disorder by means of an A.I. algorithm?

A.I. = Artificial Intelligence

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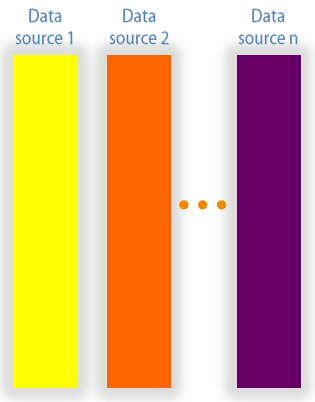
Code and use innovative data analytics as a game changer

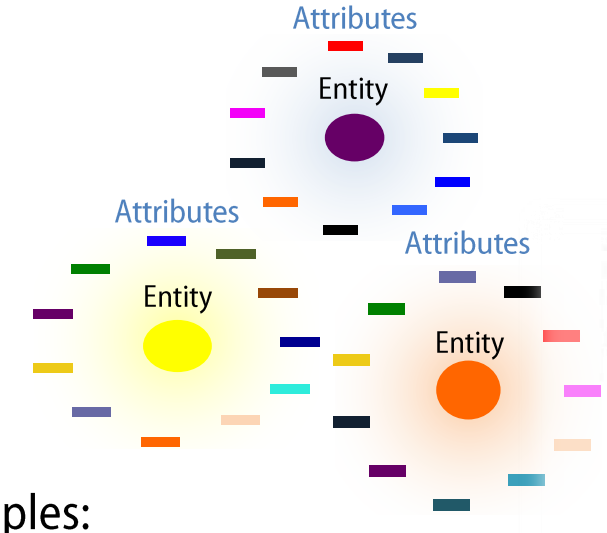
Traditional, relational model



Examples:

- ID x Cholesterol
- ID x Glycemia
- Cholesterol x Glycemia
- **Structured x Structured**

Entity centric model



Programmatic and Predictive data transformation:

Deep Learning

Examples:

- ID x All blood tests
- Each blood test vs. others
- All correlations possible
- **Structured x Unstructured (is this really possible?)**

Courtesy of William King, Zephyr Health (modified)

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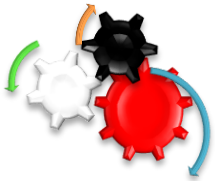
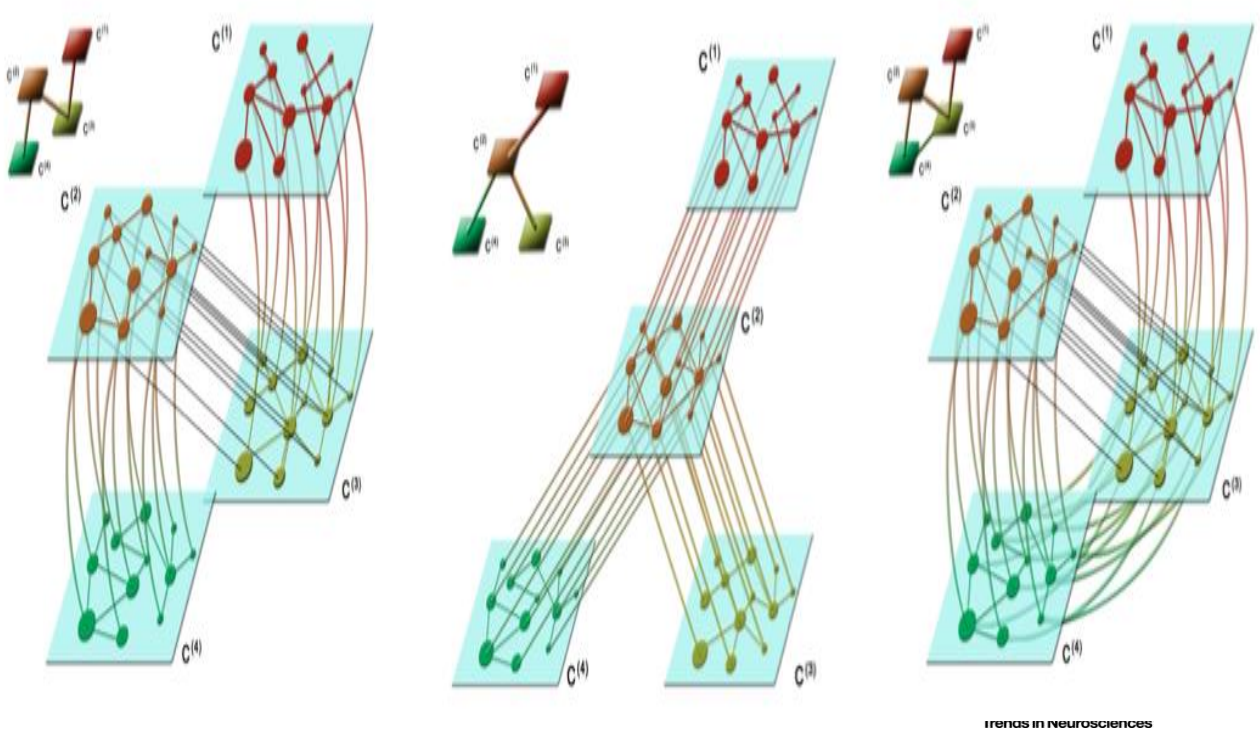
Then, challenge the structured to unstructured relationship

A multiple data level cluster complexity problem



a) Heterogenous Sources
b) Heterogenous Formats
c) Heterogenous Knowledge
d) Heterogenous Scales
e) Integrated into weighted and oriented multilayers networks



Trends in Neurosciences

Pani L. and Chessa A., unpublished

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How to reconcile Big Data and Privacy

Could good faith legal safeguards make *de facto* Europe non competitive?

- The new EU General Data Protection Regulation has been implemented on May 25th, 2018
  - Driven by the principle of data minimisation
  - Privacy by design and default
  - Right to opt out
  - Informed consent
  - Data ownership – personal / public / private
  - Need access to a sufficient amount of "good quality data"

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How to reconcile Big Data and Privacy

May good faith legal safeguards make *de facto* Europe non competitive?

- The new EU General Data Protection Regulation has been implemented on May 25th, 2018 **but…**
  - Driven by the principle of data minimisation **(it will preclude machine learning)**
  - Privacy by design and default **(it will preclude predictive analytics)**
  - Right to opt out **(but how?)**
  - Informed **(really informed?)** consent **(impossible to predict to what I am giving consent to)**
  - Data ownership – personal / public / private **(issue is not on ownership but on access)**
  - Need access to a sufficient amount of "good quality data" **(indeed impossible with limits above)**

- **EU Regulators / Payers will have these additional problems**
- **Not enough (sometime none) competence with in-house and hands-on skills**
- **Education of new types of assessors with very broad data science and life science knowledge.**
- **Inability to certify and validate different data sources to be integrated among them.**
- **Rule the emerging strong engagement by patients as data generators.**

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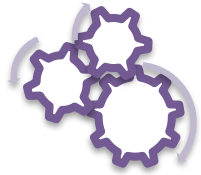
Final considerations

- The most important innovation disrupter: *i.e.* the ICT impact on an expanding set of end-user devices is here now. Business models will evolve (fast) thanks to smart machine technologies
- This will challenge and force all of us to rethink how data-information-knowledge transitions are being created and used. The difference, if any, between patients and consumers will fade away
- The bigger the data the bigger the biology and we will move from inferential to representative knowledge but in doing so we must augment perimeter defense for privacy and rule-based security detection with user and entity behavior analytics
- To date pharma companies have wasted a lot of time and effort on digital gimmicks, gadgets and gurus, but are now organizing themselves better and are even starting to collaborate in shaping the future digital healthcare landscape
- The immediate opportunity areas for pharmaceuticals are: digital clinical trials, customer/patient engagement and operational efficiency
- The question arises: are we ready for all of the above?



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