Möglichkeiten und Grenzen von individuellen Verhaltensprognosen auf der Basis von genomweiten polygenen Werten

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Swiss Assessment
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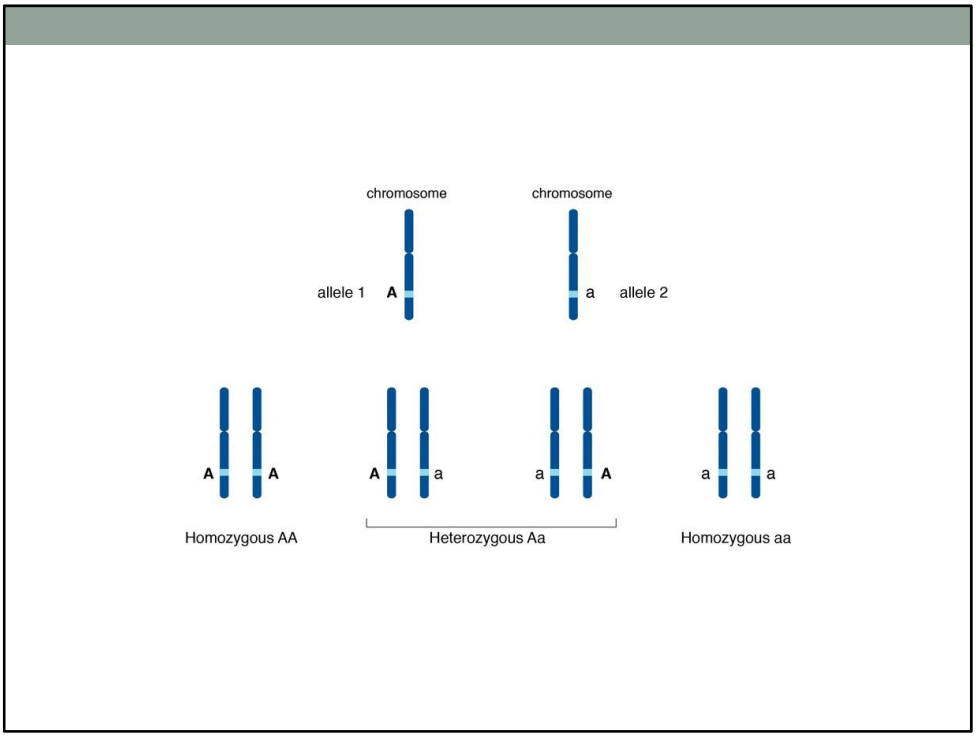
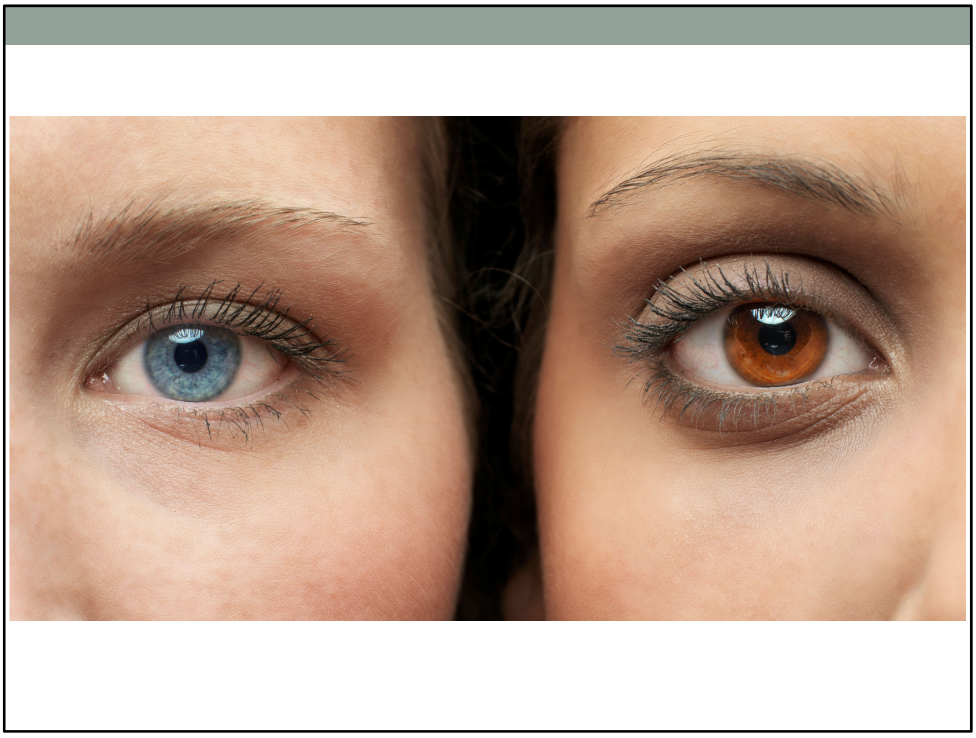
Window: 1h 15; talk for 45 min

Verstaendnis von genetischen Einfluessen auf phenotypische Auspraegung im Allgemeinen von Mendel's Erbsen gepraegt.
Experimente zur Verbung von Farbe – gelbe und gruene Erbsen. Mendel beobachtet zum ersten Mal systematische Muster in Vererbung ueber 28,000 Erbsenpflanzengenerationen.

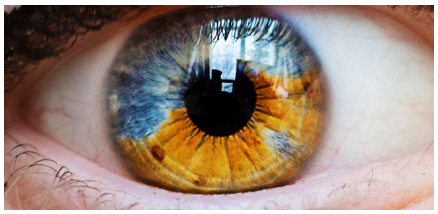


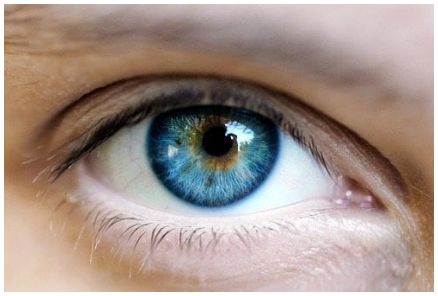
Was uns allen davon am meisten in Erinnerung geblieben ist, ist das wir ein Allel von unserem Vater und eins von unsere Mutter geerbt haben

Von jedem ein Allel per Chromosom, Kombination bestimmt phenotypische Auspraegung.



Blau oder braun. Nur das diese Logik fuer die meissten Phenotypen nicht stimmt.





Eye colour ist eine komplexe Eigenschaft: viele genetische Varianten beeinflussen diesen Phenotypen.

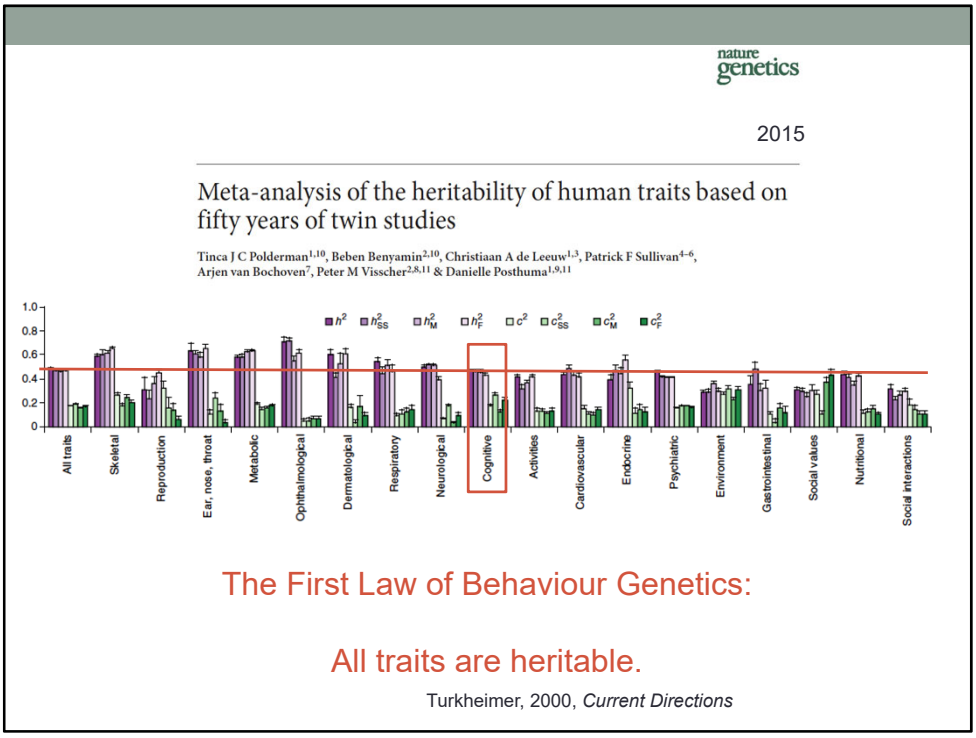
Genauso wie psychologische Eigenschaften von vielen genetischen Varianten beeinflusst sind, die wir heute identifizieren und messen koennen.

Einzelne Geneffekte gibt es auch, zum Beispiel Chorea Huntington, so genannte autosomal-dominant vererbte Krankheit. Es gibt eine ganze Reihe sognenannter Single-Gene Disorders, aber die sind selten (1 in tausend), und erklaeren nicht ‘normale’ Unterschiede in psychologischen Eigenschaften oder Verhalten zwischen Menschen

Eineiige und zweiige Zwillinge, die zusammen aufwachsen: Wenn die eineiigen sich aehnlicher sind in einer Eigenschaft als die zweieiigen, dann muss die Eigenschaft genetisch beeinflusst sein.

Eineiige gene = 100%; eineiiges Aufwachsen = 100%.
Zweiig gene = 50%; Aufwachsen = 100%

Alice and Ellen



Sprung von Augenfarbe zu Verhalten.

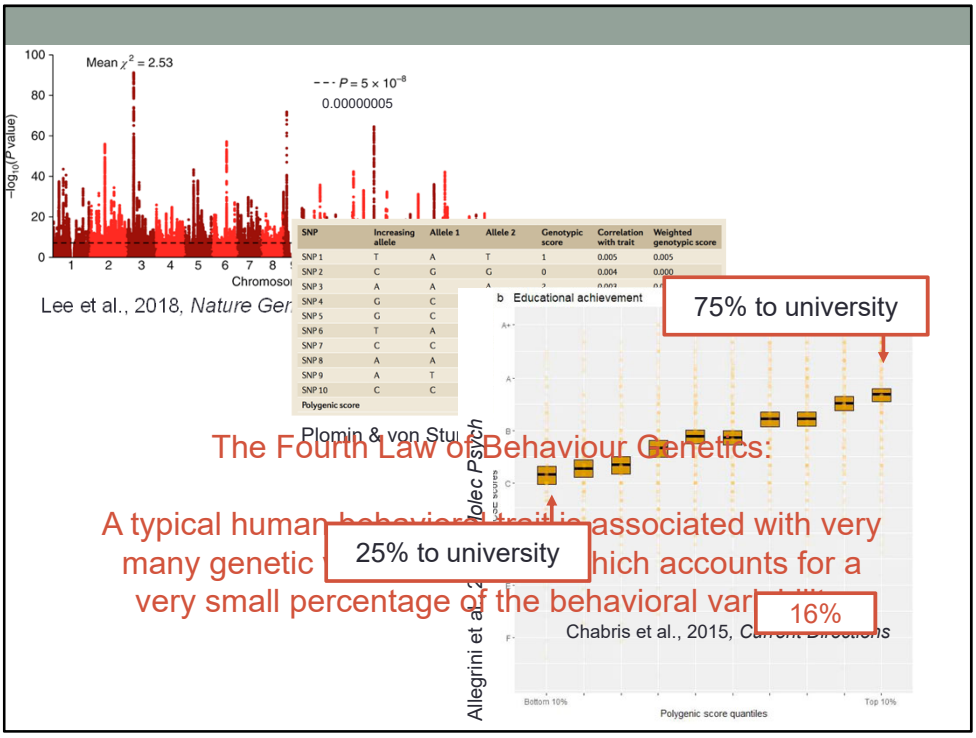
h2 means % attributable to genetic influences

More than 3000 studies; across trait domains; purple bars = h2; y axis.

A meta-analysis of twin correlations for 17,804 traits from 2,748 publications including 14,558,903 partly dependent twin pairs. Estimates of heritability across all traits 49%. For a majority (69%) of traits, the observed twin correlations are consistent with a simple and parsimonious model where twin resemblance is solely due to additive genetic variation.

Ich interessiere mich fuer kognitive Faehigkeiten insbesondere und werde im Folgenden hauptsaechlich Forschung zu den kognitive Faehigkeiten zitieren. Kog Faeh sind auch 50% erblich, also muessten wir Gene dafuer finden koennen.

Gegensatz normatives und ID – overview on perspectives – all fields benefit from DNA revoltion but Evolution seems to be surprisingly aussen vor



Let's find the genes. Genome-wide association study of 'years spent in education'

Associations between DNA variants across genome and phenotype of interest → years spent in education (available; large sample with genotype data); 1.1. million (Lee et al, 2018)
Large sample to reliably identify DNA variants associated with phenotype
DNA variants are SNPs
Y axis: genome
x axis: p-values → dotted line significant
1000s with small effect size
Apply summary statistics to independent sample

Figure: The *P* value and mean χ^2 value are based on inflation-adjusted test statistics. The *x* axis is chromosomal position and the *y* axis is the significance on a –log10 scale. The dashed line marks the threshold for genome-wide significance ($P = 5 \times 10^{-8}$) (n = 1,131,881).

Associations of SNPs across genome with phenotype. Multiple comparisons, so very low p-value, few genome-wide significant.

1,271 hits; Loci average effect sizes of .05%; average effect size of SNP .005%

Focus on hits and pathways vs using summary statistics to apply to independent samples & create aggregates of DNA variants to predict phenotypes and study Gx E

Build GPS, test association in other samples with grades

Heritable ≠ Innate
- Children have to be taught to read

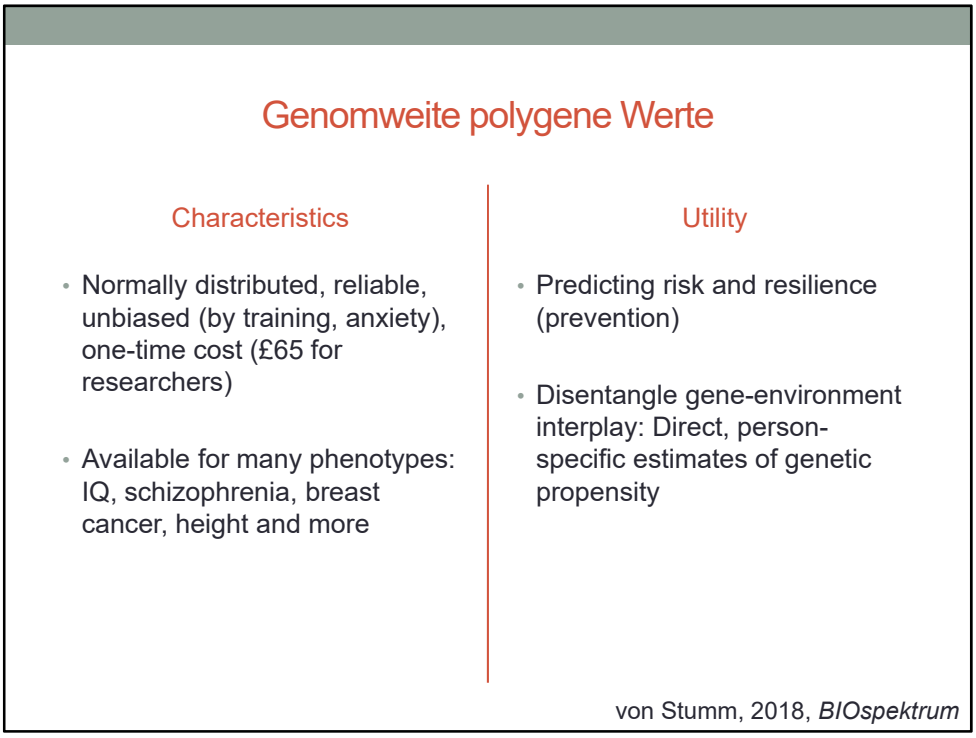
Heritable ≠ Immutable
- Probabilistic propensities

Heritable ≠ Policy
- Values x ethics x science

Vorbehalte

Wahrscheinlichkeit / Neigung

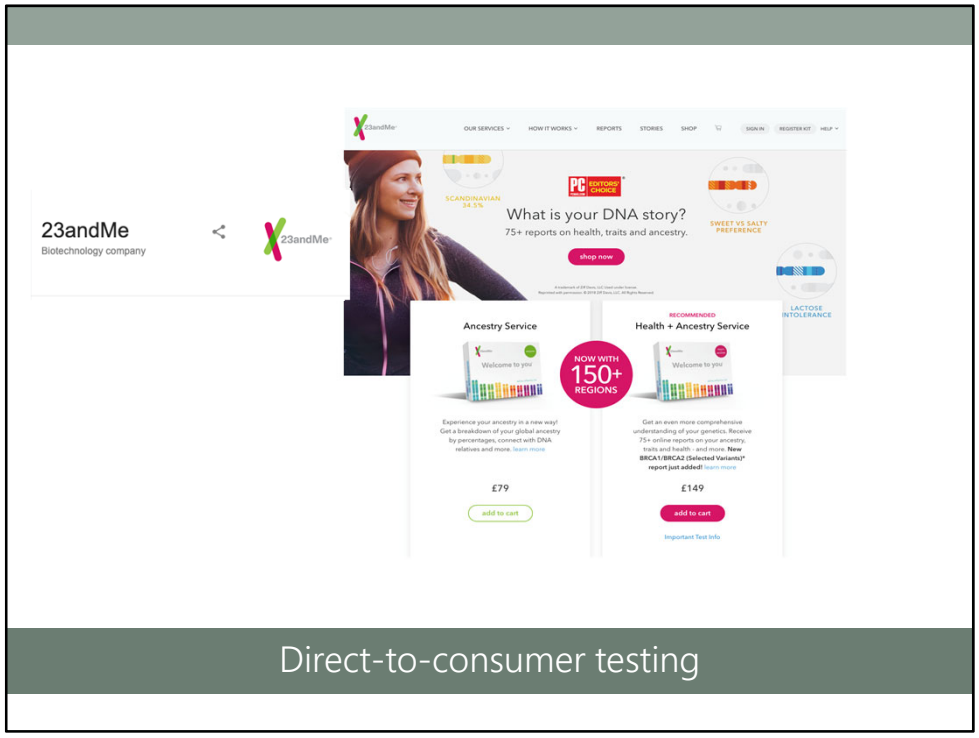
Politische Richtlinie



Anthropometrisch

Drei Beispiele, die die Vorteile von GPS demonstrieren um das Zwischenspiel von genetischen und sozialen Einfluesse zu untersuchen, weil sie alle mit dem klassischen Zwillingstudiendesign und seinen Erweiterungen – also Adoption etc – nicht moeglich waeren.

Groesstes potential: Prevention. Beispiel Brustkrebs: top 3% haben 70% risk to get BC, average woman 15%
Alzheimers: The APOE4 allele, present in approximately 10-15% of people, increases the risk for Alzheimer's and lowers the age of onset. Having one copy of E4 (E3/E4) can increase your risk by 2 to 3 times while two copies (E4/E4) can increase the risk by 12 times. Only 1% of people with Alzheimer carry 2 x E4. Increased risk by about 75%



Direct-to-consumer testing

What good is it to find such tiny effects? For common disorders like heart disease or schizophrenia or complex traits like weight and schizophrenia, the final advance of the DNA revolution was the realisation that we can add up the thousands of SNPs that are associated with a trait. These aggregated SNP scores, called polygenic scores, can be calculated for each individual based on the information obtained from genome-wide association studies. In this way, your SNP chip results can be used to create your polygenic scores for thousands of traits.

Although the first wave of polygenic scores explains only 5 to 15 per cent of the risk, they are already among the best predictors we have for some common diseases such as Alzheimer's, obesity, heart disease, diabetes and inflammatory bowel disease. The risks are stark at the extremes of polygenic scores. For example, nearly forty percent of men in the top three per cent of the polygenic score for coronary artery disease will develop heart disease, whereas fewer than five per cent of men in the lowest three per cent of the polygenic score will succumb. Bigger and better studies are ongoing which will produce more powerful polygenic scores.

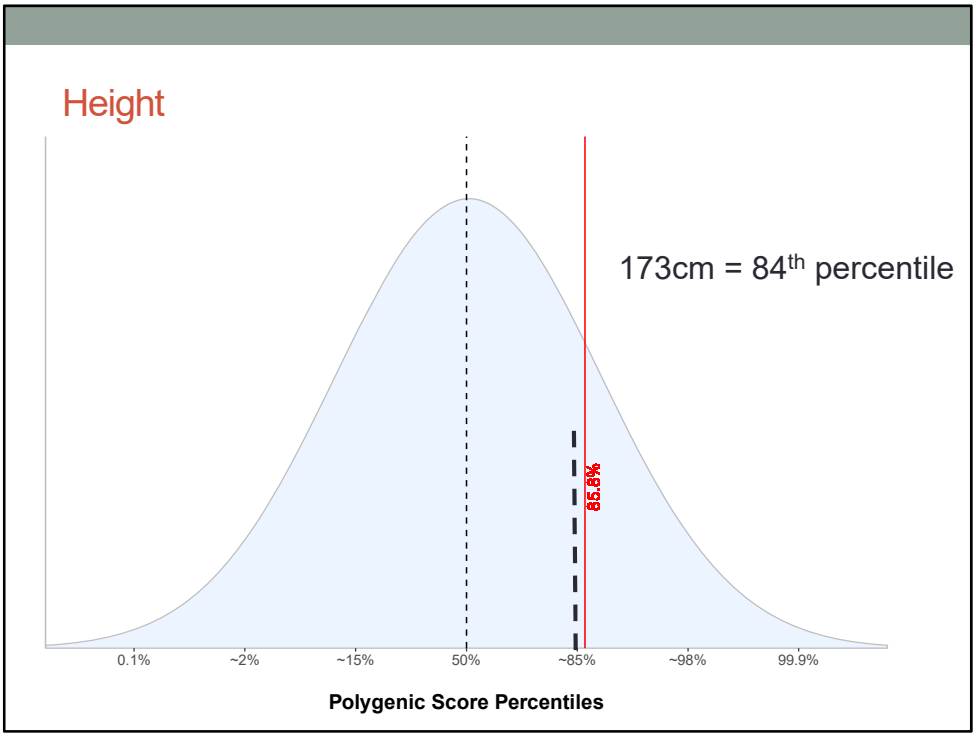
Polygenic scores are what I used to make DNA predictions about my height and weight and the other traits. However, 23andMe provide only a few polygenic scores, for example, for weight. What you get from 23andMe is detailed reports about your ancestry, information about relatives who have used 23andMe, detection of single mutations that cause or contribute to rare disorders and some mutations that contribute to common disorders and complex traits. These reports come with user-friendly tutorials that allow you to drill down as deep as you would like into the science behind these findings. The actionable results are summarised in a health action plan that includes suggestions, for example, about diet, exercise and seeking advice from your GP. They also enable participation in research at your own pace, answering a few questions at a time, for example about lifestyle and psychological traits. About eighty percent of participations answer some research questions.

For historical reasons of US governmental regulations, 23andMe does not create polygenic scores for the major psychological domains of personality, psychopathology or cognitive abilities. However, 23andMe makes it easy to download your SNP chip genotypes once you search their website for 'download raw data'. This is a text file showing your A's, T's, C's and G's for half a million SNPs. The file is about 20 megabytes, which is not too large to be received as an email attachment for most people.

By itself, this text file with your child's genotypes would not be of much use to you unless you wanted to see what your child's genotype is for a particular SNP. Polygenic scores require totting up your genotypes for thousands of SNPs after each SNP is weighted by its effect size in the genome-wise association study of the target trait. What's more, to get good polygenic scores, you need to use your SNPs to impute your genotypes for millions of other SNPs from a resource panel of a thousand individuals with whole-genome sequence data.

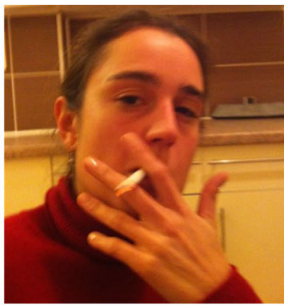
I analysed my DNA in our lab and created my polygenic scores using the latest methods. I also compared my results to those from several major companies. The way for you to get polygenic scores for you or your child is to upload your DNA data from 23andMe to one of several companies that have sprung up that will create your polygenic scores for hundreds of traits. Most of these services are free because the companies want to use genotype data for research (and perhaps other) purposes. Caution is warranted at present because companies vary a lot in the quality of polygenic scores they provide. Compare results from several companies. A not-for-profit academic good Samaritan creates state-of-the-art polygenic scores for free (www.impute.me). Impute.me will not use your DNA data for other purposes – they delete your DNA data after sending you your report. Although the reports that you get from impute.me are not as user-friendly or glitzy as those provided by most companies, they are high quality and include

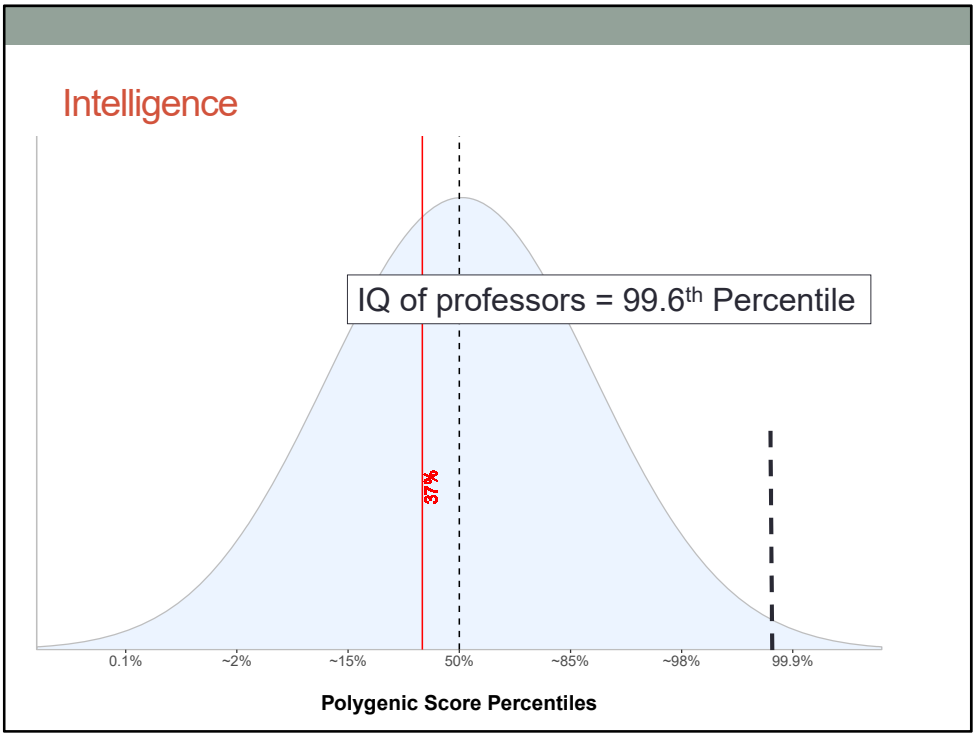
polygenic scores for more than one hundred complex medical disorders and more than a dozen psychological disorders, including alcohol dependence, bipolar, depression, obsessive-compulsive, post-traumatic stress and schizophrenia.



Research is me-search

Ever smoked

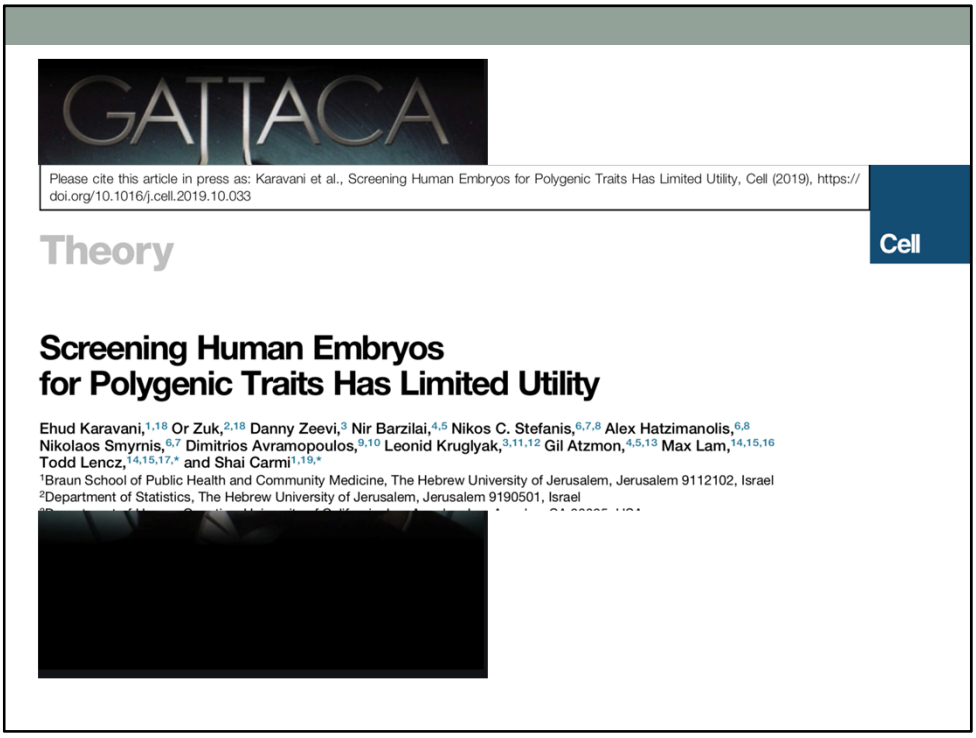




Is this all a big mistake?

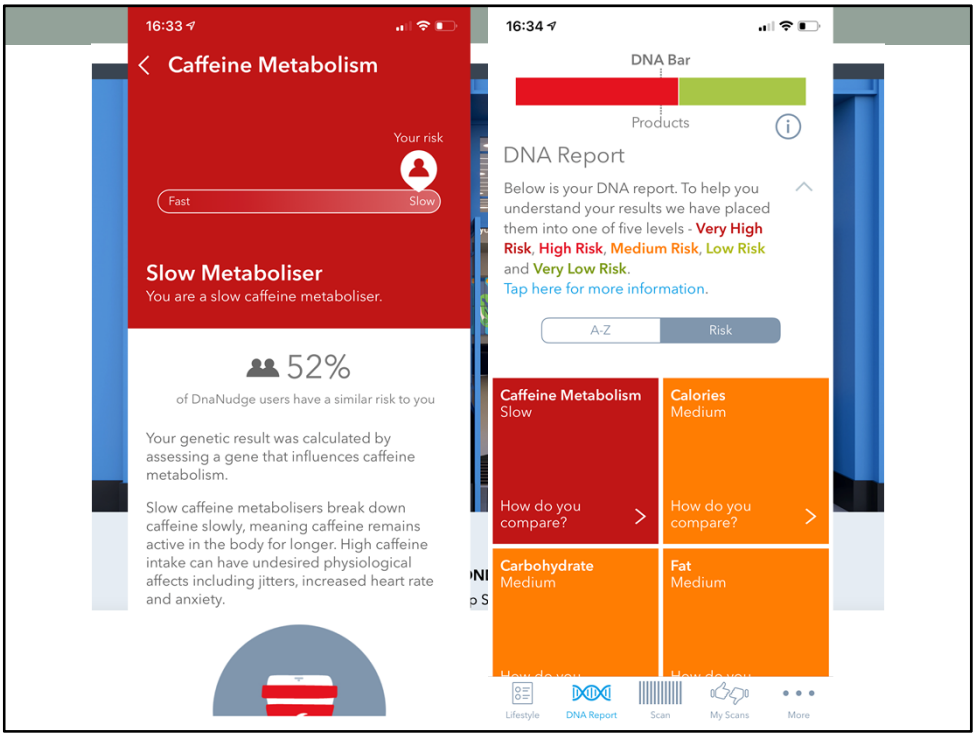
No, it just took a lot to carry me over to the finishing line.

Institute for dyscalculia



Erleben wir gerade den Abend bevor das genetische Zeitalter erwacht, wo Kinder kriegen und Zugang zu Unis eine Frage der ‘richtgen’ DNA sind? Nicht ganz, aber es ist auch nicht voellig unrealistisch.

Wir muessen uns vorbereiten auf eine Zeit, wenn DNA Information zugaenglich und aussagekraeftig sind. Wie wollen wir das regulieren,


16:33
Caffeine Metabolism
Your risk
Fast
Slow
Slow Metaboliser
You are a slow caffeine metaboliser.
52%
of DnaNudge users have a similar risk to you
Your genetic result was calculated by assessing a gene that influences caffeine metabolism.
Slow caffeine metabolisers break down caffeine slowly, meaning caffeine remains active in the body for longer. High caffeine intake can have undesired physiological affects including jitters, increased heart rate and anxiety.
16:34
DNA Bar
Products
DNA Report
Below is your DNA report. To help you understand your results we have placed them into one of five levels - Very High Risk, High Risk, Medium Risk, Low Risk and Very Low Risk.
Tap here for more information.
A-Z
Risk
Caffeine Metabolism
Slow
How do you compare?
Calories
Medium
How do you compare?
Carbohydrate
Medium
Fat
Medium
Lifestyle
DNA Report
Scan
My Scans
More

Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.

Marie Curie (1867-1934)

Wir muessen mehr verstehen um am besten auf DNA Unterschiede einzugehen. Und wir muessen uns ueberlegen, wie wir als Gesellschaft mit DNA Informationnen umgehen wollen.

Genetic Counselling oder besser genetische lehre in der Schule, so wie es IT Kurse und Sexualkunde gibt

Thank you

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