Biological Psychiatry

Brainwide Risk Scores: an example of psychiatric risk prediction from resting-state fMRI

--Manuscript Draft--

Manuscript Number:	
Full Title:	Brainwide Risk Scores: an example of psychiatric risk prediction from resting-state fMRI
Article Type:	Early Career Investigator Commentary
Author Comments:	Thanks for the opportunity to write this commentary!
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Order of Authors:	Charles H. Schleifer
Additional Information:	
Question	**Response**
Please provide the name of the person who served as your Senior Mentor for this commentary.	Carrie Bearden
Number of words in the main text	1487
Number of tables (main-text only)	0
Number of figures (main-text only)	1

Title: Brainwide Risk Scores: an example of psychiatric risk prediction from resting-state fMRI

Author: Charles H. Schleifer

Refers to: A Brainwide Risk Score for Psychiatric Disorder Evaluated in a Large Adolescent Population Reveals Increased Divergence Among Higher-Risk Groups Relative to Control Participants
https://pubmed.ncbi.nlm.nih.gov/37769983/

Main Text:

Mental illness represents a significant and growing source of morbidity and mortality worldwide (1). The impacts of inadequate diagnosis and treatment are felt through countless lived experiences as well as the global economic burden of years of life lost to disability and early death. Intervening early in the time course of someone's emerging mental illness is critical for improving outcomes. To this end, there is a major need for the development of improved tools for sensitive and specific psychiatric risk prediction. Over the last century, the fields of psychiatry and neuroscience have made significant progress in our understanding of the neurobiological substrates of mental illness. Much of this progress has been fueled by technological advancements in the tools we have to measure relevant biological signals. However, this has not yet translated to widespread and effective use of biomarker-based screening and risk assessment for the vast majority of psychiatric conditions (2).

In the current issue of Biological Psychiatry, Yan et al. (3) develop a Brainwide Risk Score (BRS) to quantify an individual's phenotypic similarity to multiple psychiatric disorder reference groups based on functional network connectivity (FNC) derived from resting-state functional magnetic resonance imaging (rs-fMRI). These BRSs reveal a gradient of low-risk to high-risk FNC patterns in youth from the Adolescent Brain Cognitive Development (ABCD) study, and were found to be predictive of psychosis status in individuals from the Human Connectome Project Early Psychosis (HCP-EP) data set. This BRS framework bears some conceptual resemblance to a polygenic score (PGS), which applies summary statistics from large genome-wide association studies to calculate someone's overall risk score for a trait from a large set of genomic features (4). Neuroimaging risk score approaches are compelling for multiple reasons. They can advance our understanding of psychiatric disorders and psychiatric risk by characterizing the associated system-level brain alterations, while also providing a framework for making individual-level

predictions from neuroimaging data. This is crucial if we hope to move beyond case-control group-level analyses to derive clinically actionable information from neuroimaging in psychiatry.

To calculate BRSs, reference FNC maps were first generated for schizophrenia (SCZ), autism spectrum disorder (ASD), major depressive disorder (MDD) and bipolar disorder (BPD), and matched control groups for each clinical group, from a total of 5,231 rs-fMRI scans from 7 studies. FNC was calculated using NeuroMark (5), an open-source tool for group-information guided independent components analysis (ICA). This is a “hybrid [functional connectivity] approach, in between fully data driven ICA and fixed region of interest approaches” (3) in that the same 53 ICA networks are derived from each scan while also accounting for inter-individual variability in the networks. Patient and control reference maps were created by averaging FNC matrices within groups.

Next, comparable FNC matrices were generated for each individual from the ABCD and HCP-EP datasets, and a BRS was calculated to index similarity to each psychiatric disorder. For each connectivity feature, they calculated the Euclidean distance between an individual and each reference group map. An individual’s BRS for a given psychiatric disorder was computed as the summed distances to the map for that psychiatric reference group subtracted from the summed distances to the corresponding control group map, producing a single numeric value. A larger BRS indicates a greater overall similarity to the psychiatric disorder reference map, which is hypothesized to represent greater risk of developing that disorder.

In the ABCD sample, BRSs illustrated a continuum of low-risk to high-risk fMRI patterns across individuals. Those in the lowest percentiles of risk (i.e., lowest BRS) were similar regardless of which reference group was used, and tended to show a robust and potentially protective FNC pattern involving sensorimotor, subcortical, and cerebellar regions. Specifically, low-risk individuals on average showed positive sensorimotor-visual and cerebellar-subcortical connectivity, and negative sensorimotor-subcortical and cerebellar-visual connectivity. Individuals with high BRSs showed more “patient-like” FNC profiles and tended to differentiate more towards a specific patient group. However, the BRSs did suggest a notable amount of phenotypic comorbidity, with 7.7% of people overlapping in the top 25th percentile for all 4 disorders. Some connectivity phenotypes were particularly related to certain psychiatric groups, e.g., decreased connectivity in a sensorimotor network and increased sensorimotor-subcortical connectivity was related to high-risk FNC profiles in all disorders, whereas increased cerebellar-visual connectivity was related to SCZ and ASD but not MDD or BPD.

These BRSs highlight specific brain networks that may be involved in risk for general psychopathology or specific disorders, but to what extent do they enable clinically useful

predictions? From the total n=8191 baseline ABCD scans, within the subsample of n=82 with the top 1% of BRS scores, the schizophrenia BRS, but no other BRSs, was significantly related to psychosis-risk symptoms. In the HCP-EP sample, a binary classifier was able to predict psychosis status from the vector of four BRSs with 73% accuracy, which was comparable to the accuracy achieved when using the full FNC matrix.

In the manuscript introduction, Yan et al. propose some qualities of “an ideal metric for longitudinally assessing psychiatric risk in adolescents [which] should be: 1) reproducible and adaptable to environmental factors, 2) related to the underlying mechanisms of psychiatric disorders, 3) consistent with clinical symptoms, and 4) able to distinguish patients with mental disorders from healthy control participants.” I would add that a metric for clinical use should also be: 5) scalable, in terms of financial and logistical burdens, and 6) equitable, ensuring that the tool or its implementation does not harm vulnerable or minoritized groups or disproportionately benefit those with power in society. These 6 qualities are important to consider for any tool that will be used for medical or psychiatric risk prediction. The landscape of potential tools includes various brain imaging modalities, genomics, and a wide range of behavioral assessment methods ranging from clinical interviews to passive data collection from mobile phones or wearable devices.

Neuroimaging risk scores, such as the BRS described here, have several key strengths. However, obstacles remain for the field to grapple with. With high-quality scan acquisition and standard preprocessing workflows, neuroimaging can generate reproducible biomarkers which have the unique benefit of measuring aspects of brain structure and function at a specific moment in time (2). For this reason, brain imaging risk scores can capture relevant influences of a broad range of environmental factors that are inaccessible to genomic methods like PGSs which rely on inherited single nucleotide polymorphisms. Both PGSs and approaches like BRSs have the benefit of measuring important sources of biologically relevant information that relate to the underlying mechanisms of psychiatric disease. In this sense, these methods have an advantage over behavior-based measures. However, behavior remains the gold standard for psychiatric diagnosis via clinical interview.

Even for behavioral measures, scalability can be a barrier to widespread clinical implementation, especially as a screening tool when the pre-test probability is low or unknown. Risk calculators based on demographic and clinical scores have proven effective in contexts such as clinical high risk for psychosis, but often still require trained personnel to administer specific clinical interviews and neurocognitive tests (6). Collection of blood or saliva for genomic testing includes additional costs, risks, and challenges, though in some cases can be scaled with fewer

trained personnel. All neuroimaging modalities, and especially MRI, require significant infrastructure and personnel resources, with high capital and operational expenses. Costlier measures like MRI may eventually be most effective if targeted towards high-risk individuals identified in a multi-modal screening approach.

MRI-based screening measures are also particularly impacted by image preprocessing choices and constrained by computational resources (7). Risk scores from structural neuroimaging such as T1-weighted MRI summarized to standardized sets of brain regions are one option to increase scalability of the approach (8,9). With fMRI data, the preprocessing issue can be solved by applying the same data pipelines to the reference/training data and the new testing data, as Yan et al. did here, but this requires voxel-level image data and resources to store and process thousands of scans. As well-resourced institutions become increasingly able to conduct these types of analyses, it will be of central importance to fund and facilitate effective data sharing and open-source software which will allow for expedient and equitable access to the means of scientific progress.

For any screening tool, increasing access through lowering costs and logistical barriers will support the goal of creating an equitable benefit to society. Beyond that, we also must consider the specific challenges of each technology. PGSs, for example, currently have unsatisfying predictive utility for people of non-European or mixed ancestry due to the unequal representation of European ancestry in large genome-wide studies (10). Neuroimaging risk scores may avoid some of these concerns while also avoiding biases in language or clinical judgment inherent in behavior-based metrics. On the other hand, PGSs present a clear example of the importance of diverse and representative training sets, which also applies to neuroimaging-based risk score approaches. In the modern era of increasingly large and accessible neuroimaging datasets, brain biomarkers will hopefully become a valuable tool for psychiatric risk prediction.

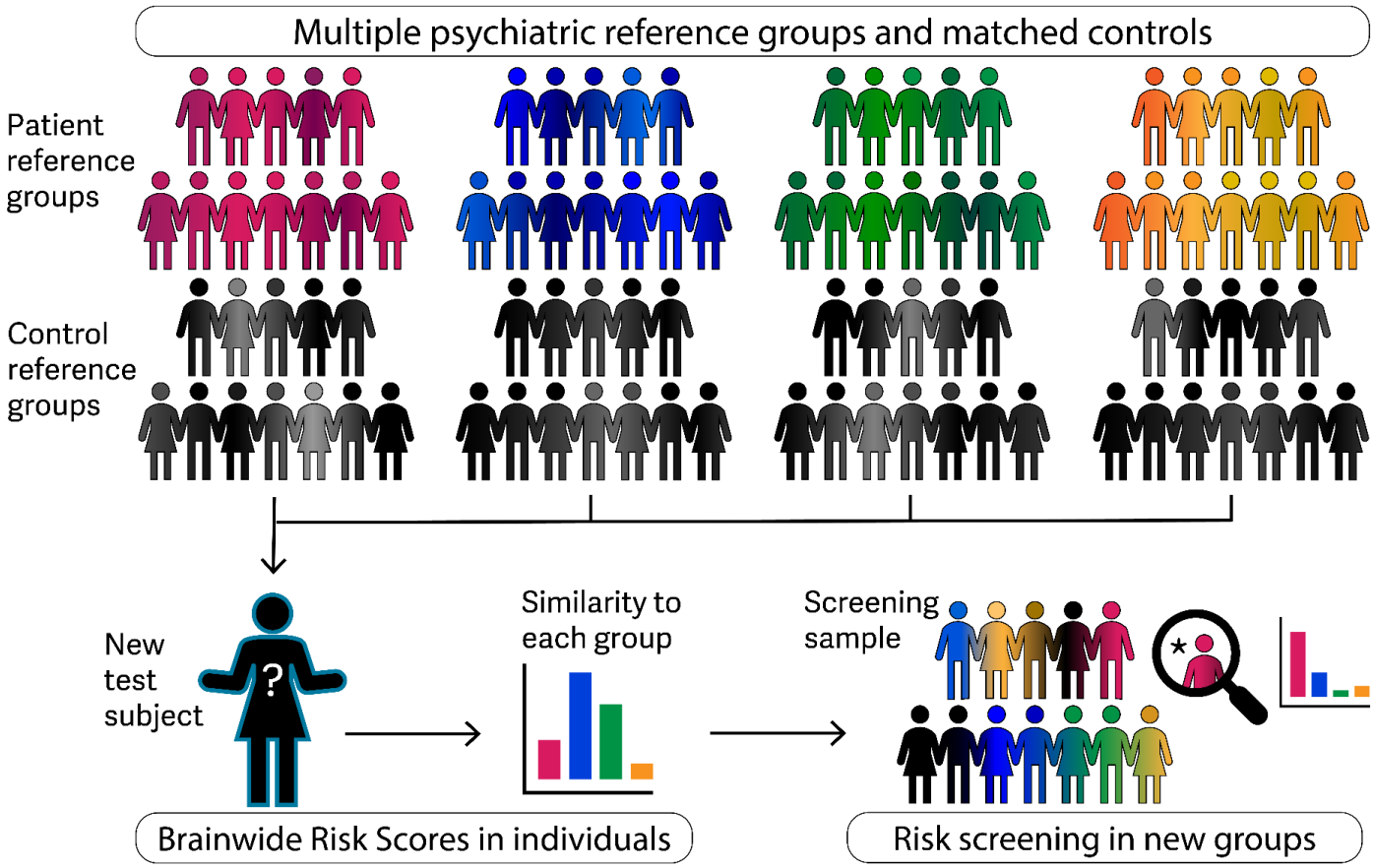

Figure 1. Brainwide Risk Score conceptual visualization. Reference brain maps are built from large samples of MRI scans representing multiple psychiatric disorders and matched neurotypical controls. A scan from a new individual can be compared to these references to calculate a risk score for each disorder. This can be applied to new samples to screen for people with high-risk brain phenotypes.

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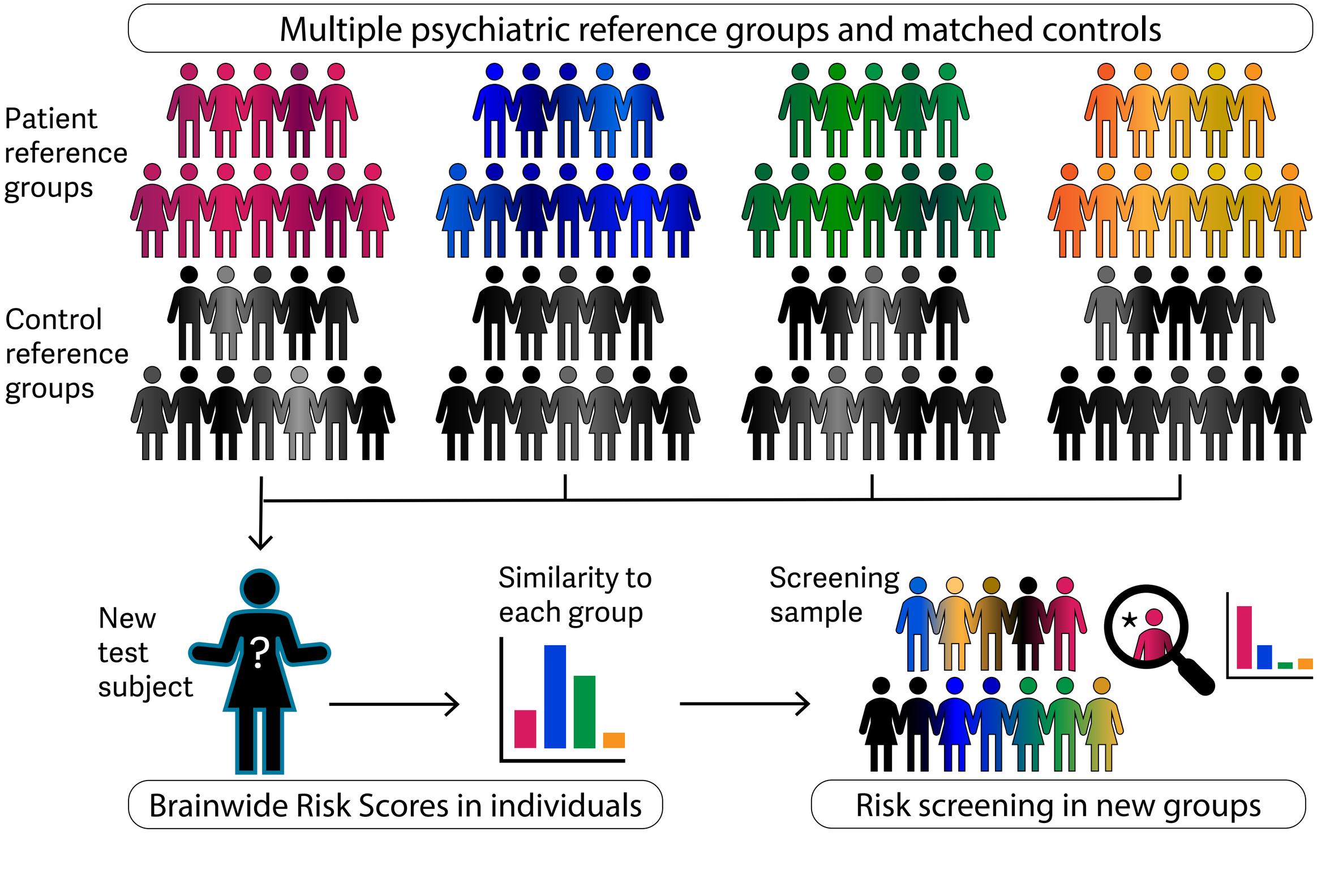
Figure1


Multiple psychiatric reference groups and matched controls
Patient reference groups
Control reference groups
New test subject
?
Similarity to each group
Screening sample
Brainwide Risk Scores in individuals
Risk screening in new groups