A Novel Precision Medicine Approach To Improve The Outcome Of Clinical Trials

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ABSTRACT

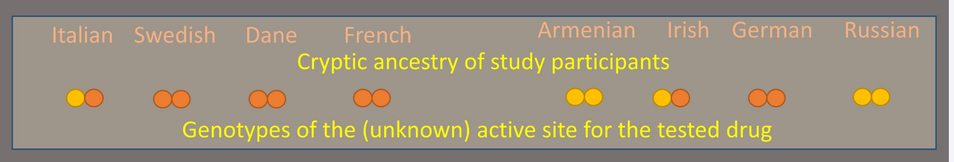
Clinical trials are necessary to determine the drug performance on a small cohort of individuals. The result of these trials determine whether the drug should progress for larger scale clinical evaluation. The pairing of cohort individuals is usually done at random after matching their demographic criteria (e.g., age, sex, and ethnicity). In a trial setting, one member of each pair is administered the treatment, and the other (control) is administered a placebo. **It is well established that randomized trials can lead to a stratification bias resulting in biased and non-reproducible results**. Multiple factors may cause geographic variation in the results of randomized controlled trials: genetic background (ancestry/biogeography), natural immunity that develops at different rates in different places, variation in complementary treatments between sites, variation in hospitalization practices and patient reports, and chance. These problems become worse with the rapid growth of multi-national trials where each site contributes a small number of individuals. These and other problems hamper clinical trials, limit their accuracy, mask the beneficial effects of drugs, and consequently increase the developmental costs. **We propose solutions to all these problems.**
First, we developed Pairwise Matcher (***PAM***), the first tool that optimizes individual matches based on demographic and genetic criteria (http://www.elhaik-lab.group.shef.ac.uk/ElhaikLab/index.php). **Second**, we designed *DREAM* a novel microarray dedicated to precision medicine. **Finally**, we can identify subgroups of respondents and determine whether the drug has therapeutic benefits for specific groups.

A CHRONIC PROBLEM WITH CLINICAL STUDY DESIGNS

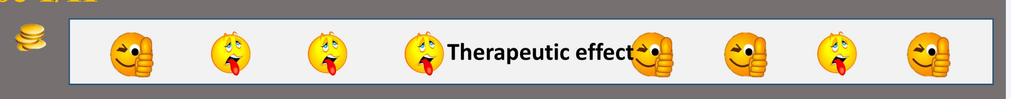
Study design

We know

We don't know

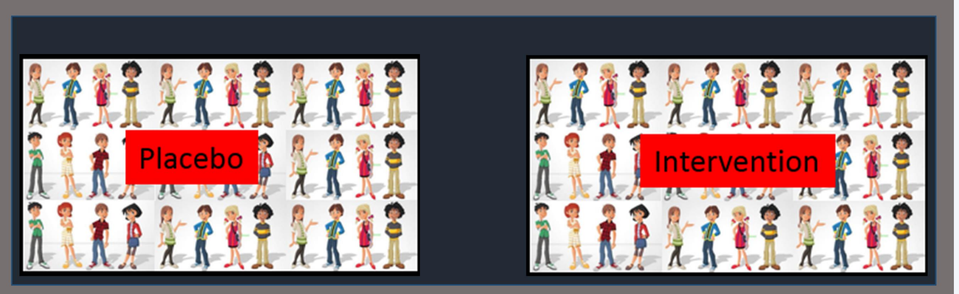


Phase I/II



The Drug performs best for people with the 🟡 allele, common in East Eurasia.
Based on this initial trials we can conclude that the drug is **effective**

Phase III



The therapeutic effect is now **gone.**
The drug is effective for people with the 🟡 allele
but **we don't know that.**

What happened here?

We invested a lot of resources on developing and testing a drug.
In the pilot phase the drug showed a premise,
but the effect disappeared in the larger trial.
We thereby concluded that the drug was ineffective.

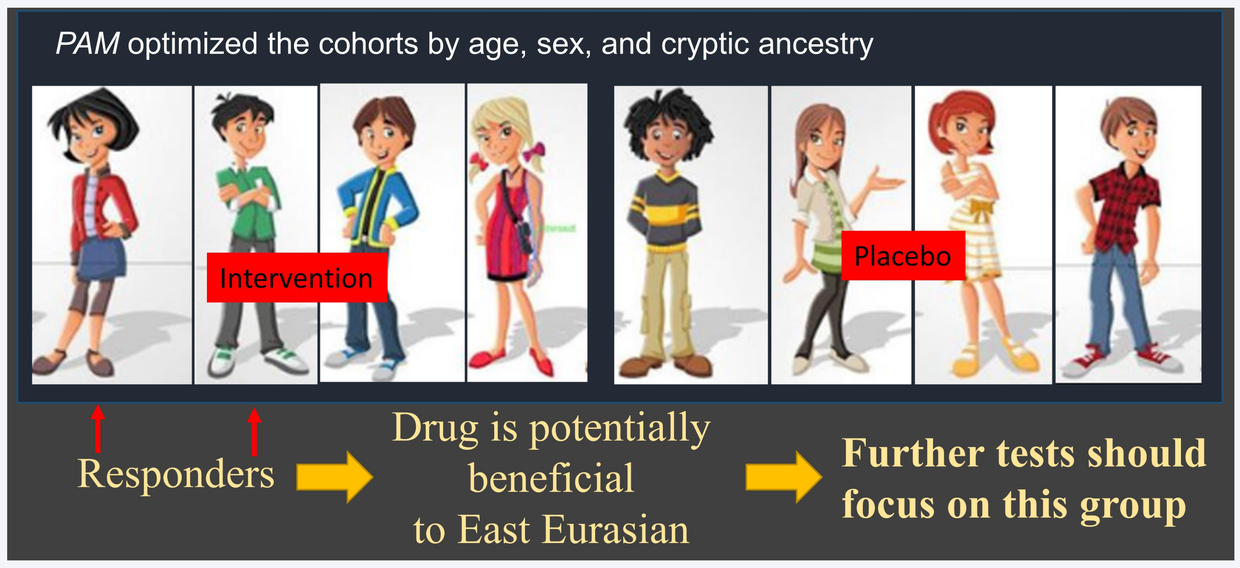
In reality,
the drug has beneficial effects for a significant population group.
But we don't know that.
The conclusion that the drug is ineffective was incorrect.

WHY DID WE REACH THE WRONG CONCLUSIONS?

1. Allocating people based on self defined ethnicity/race.
2. Ignoring or misunderstanding their genetic population structure.
3. Failing to identify subgroups of respondents

OUR SOLUTIONS

- *PAM* matches participants based on demographic and genetic similarity. It allows researchers to optimize the sets and make informed decisions about their trial design.
- *DREAM* can uncover cryptic population structure and has all genes/regions known to affect drug metabolism to support clinical trials.
- PAM+ would be able to identify which population group/s responded to the drug even if the cohort effect was insignificant.



PRIOR ART

PCA and PCA-like methods are commonly used to match cases with controls. These methods are highly inaccurate (<5% of the samples were correctly predicted to countries), require human intervention (i.e., biased), and are inaccurate for samples of mixed ancestries. PAM is supported by the Geographic Population Structure (GPS) engine, which yields accurate biogeographical predictions. GPS was shown to predict the country, island, and village of origin of worldwide individuals from their DNA (Elhaik et al. 2014; Nature Communications).

CONCLUSIONS

We developed a set of solutions to improve the accuracy of randomized control trials: PAM, is the first and only tool that optimizes individual matches based on demographic and genetic criteria; and DREAM, a microarray dedicated to precision medicine that supports PAM. Finally, we can identify subgroups of respondents, even in a failed trials, and determine whether the drug has therapeutic benefits for specific population groups.

CONTACT

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