Differences in a biomarker's predictive ability across racial groups

Steve Lewitzky, Novartis Pharmaceuticals

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Overview

- Introduction: Differences in biomarker predictivity across racial groups
- Possible explanations for observed differences
- Resulting challenges
  - Determining the actual reason(s) for observed differences
  - Estimating predictive performance of a biomarker in specific racial groups
  - Classifying prospective drug recipients by racial group
- Key questions to consider

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Introduction: differences in strength of genetic associations across racial groups

- Not uncommon for strength of genetic associations to vary across racial groups
  - Disease risk
  - Dose level
  - Risk of ADR
- Differences across racial groups can exhibit different patterns
  - Strong association in group A, weaker in group B
  - Association exists in group A, non-existent in group B
  - Association in group A in one direction, association in group B in opposite direction
- Hence, if intent is to use the associated allele as a predictor of a subject's outcome, predictions may be more accurate in one racial group than in another

Possible explanations for differences in marker predictivity across racial groups

- Existence of other unknown risk factors (genes, environmental factors), with frequencies that differ across racial groups
  - May act independently of the identified biomarker, or may interact with it
    - Biomarker may not be found at all in certain racial groups
    - Substantial evidence that HLA alleles interact with other factors to increase risk of ADR or disease
- Identified biomarker does not cause the outcome, but is in linkage disequilibrium (LD) with the actual causal allele
  - Hence, identified allele acts as proxy for the actual causal allele
  - Strength of LD is known to vary across racial groups due to different evolutionary histories
- Combination of the above

Highly challenging to determine the source of racial differences in marker predictivity (1/2)

- Are there additional risk factors, with frequencies that differ between racial groups?
  - Need specific hypotheses re: additional factors
    - Factors must be measured/measurable
  - May be many factors with small individual effects
  - Need for multiple testing adjustment across all factors evaluated
  - Hence, substantial sample size needed within each racial group considered

Highly challenging to determine the source of racial differences in marker predictivity (2/2)

- Is the identified allele in LD with a different, non-genotyped allele that actually causes the outcome?
  - Due to extensive LD throughout the genome, may be thousands of other alleles in LD with the identified allele
    - May be a combination of several less common alleles
  - Restricting search to potentially functional variants generally still results in an excessive number of candidate alleles
    - Lack of knowledge of mechanism
    - Recent publication suggests that most regions of genome could be functional
  - If association is linked to an HLA allele, more likely to be causal
    - Hence, racial difference more likely caused by additional unknown risk factors

Exacerbating the problem: in clinical development, often not possible to compare marker predictivity across racial groups

- Typical clinical trial is predominantly comprised of one or only a few racial groups
  - Other groups may be included but usually in small numbers
- Even if White, Black, and Asian are well represented, many smaller groups/subgroups are unlikely to be
- Difficult to define which populations are truly “distinct”
  - Likely to differ by compound, indication, outcome, biomarker

Summary of the problem

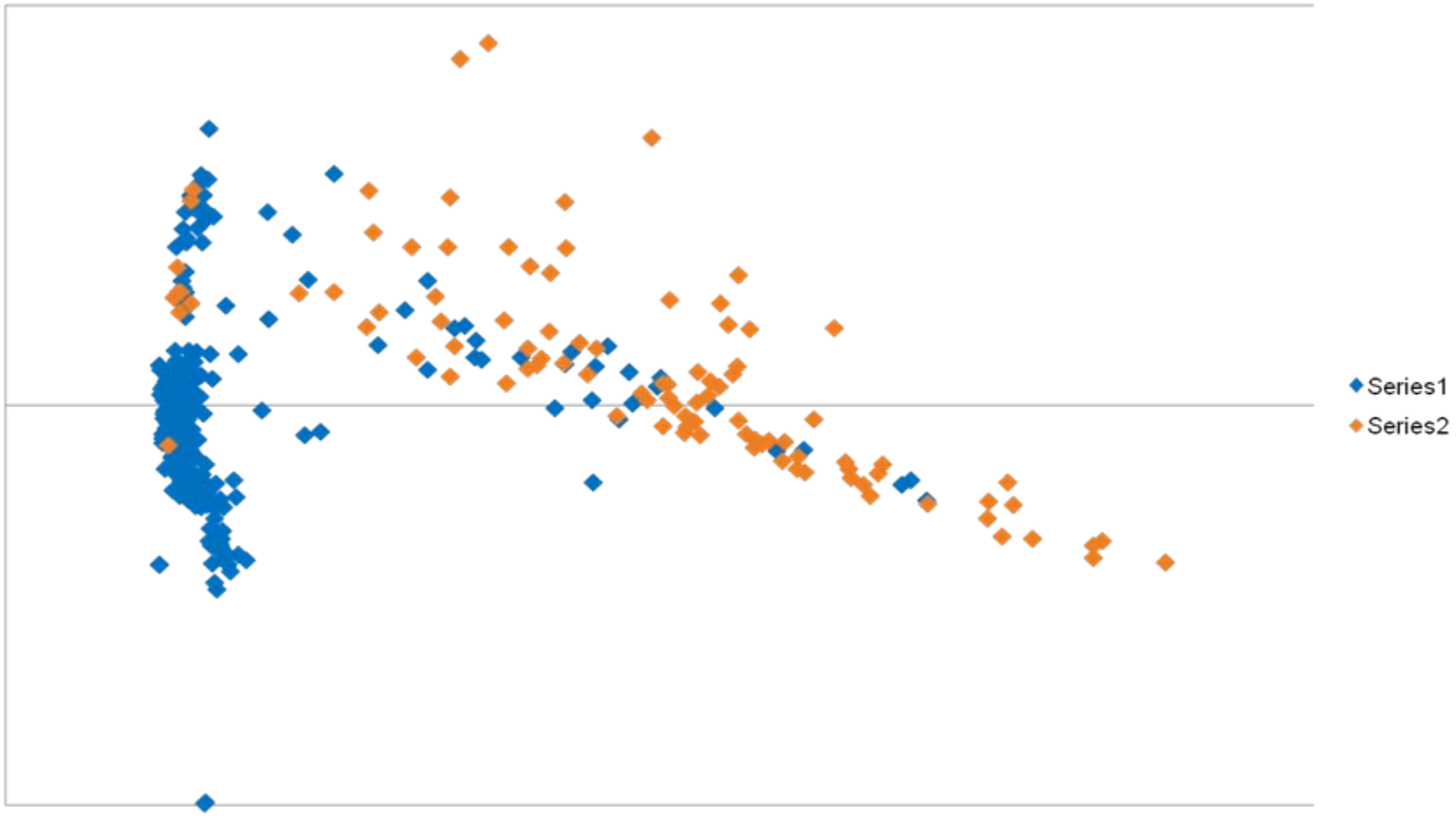
1. If the factors causing an outcome were known in their entirety, our ability to predict outcome should be similar across racial groups
2. In reality, the causal factors are usually only partially known
3. Generally, therefore, any identified biomarker is an imperfect correlate of the true causal factor(s)
4. In the absence of complete causal information, predictive ability of an identified biomarker may differ across racial groups
5. Not possible to reliably characterize a biomarker's predictive ability in undersampled racial groups

- All of the above are likely true of drug safety, drug efficacy, and disease biomarkers

Considerations for approvability of a drug when a biomarker's ability to screen out patients at elevated risk for an ADR is substantially greater in racial group A than in group B (or is unknown in group B)

- Deny approval for all patients
  - Denies group A access to a product that could fill important unmet need
- Grant approval for all patients, subject to biomarker test
  - May place group B at elevated risk for ADR
- Grant approval only for patients in racial group A, subject to biomarker test
  - Ethical concerns
  - Practical concern: To which racial group does a patient belong?
    - Self-reported race often inconsistent with genetic background
    - Patients may not feel comfortable undergoing genetic test to assess racial background
    - How to evaluate drug safety for patients of mixed racial background?

Principal components graph of 2 racial groups and self-reported race



Singer et al., Nature Genetics 42(8): 711-716 (2010)

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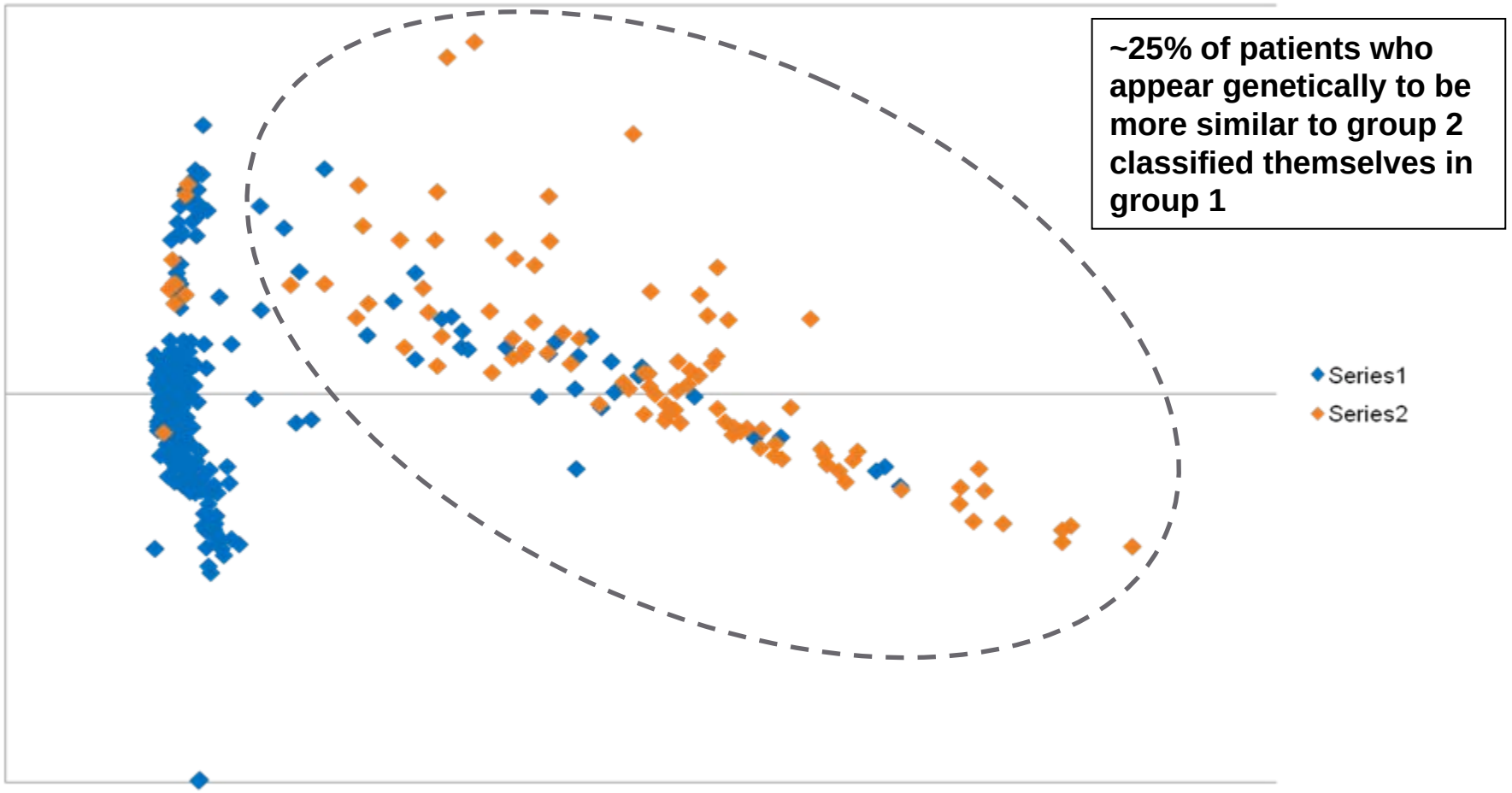

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Key questions to consider

Hypothetical scenario

- Drug X is found to clearly have greater efficacy than alternative therapies currently available
- However, Drug X is not approvable in the broad population due to unacceptably high incidence of a certain ADR
  - Alternative therapies have lower incidence of this ADR
- Retrospective pharmacogenetic study identifies biomarker predicting risk of this ADR
  - Confirmed in prospective study
  - Restricting drug access to biomarker-negative patients (all races analyzed together) would reduce risk of ADR to level comparable to competitors
  - Subgroup analysis reveals that screening would reduce ADR risk sharply in racial group A (incidence would become lower than that of competitors), but only slightly in racial group B (incidence would remain considerably higher than competitors)
  - No other biomarker available to further reduce risk in group B

Key questions (1/2)

- Question #1: What factors could affect approvability and labeling for a drug in the following scenarios?
  - A biomarker reduces risk of ADR to an acceptable level in racial group A but not in racial group B
  - A biomarker reduces risk of ADR to an acceptable level in racial group A, but there are insufficient data in other racial groups to estimate the predictive ability of the biomarker
  - The biomarker is intended to be used to predict drug efficacy rather than risk of ADR

Key questions (2/2)

- Question #2: Are there circumstances under which a drug could be approvable for a specific racial group, or non-approvable for a specific racial group – with or without a biomarker? If so:
  - Under what circumstances?
  - How would a subject's race be determined in practice?
  - How would patients of mixed racial background be evaluated?

Backup slides

FDA guidance on racial and ethnic groupings for clinical assessment

- Racial groups
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino