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APPLICATION OF GENOMICS DATA FOR INNOVATIVE DRUG DEVELOPMENT

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INTRODUCTION/AGENDA

- Historical and current uses of genetics data
- Recent advances in the utilization of genetics data in drug development
- What we can learn from genetics data and some ideas on how such information might be used
  - This presentation will focus on efficacy
- “Brainstorm” next steps on collaborative approaches to advance our collective knowledge and recommendations for the utilization of genetics data in regulatory decision making and product labeling

KEY MESSAGE

Genomic information should be more broadly utilized by FDA as a component of the efficacy and safety evaluation of new drugs.

HISTORICAL APPLICATIONS OF GENOMICS TO TARGET DISCOVERY AND DRUG DEVELOPMENT

- Identification of disease associated genetic mutations or variants
  - Genome-wide association studies: cases vs controls
  - Mendelian studies: families
- Predicting increased risk for adverse drug reactions
  - Absorption, distribution, metabolism and excretion: *e.g. CYP2C19* for clopidogrel (Sanofi/BMS)
  - Hypersensitivity: *e.g. HLA-B* for abacavir (GSK)
- Selection of patients most likely to respond
  - Genetic targets: *e.g. BCR-ABL* for nilotinib in chronic myelogenous leukemia
  - Variants in other genes associated with response: *e.g. RAS* for the use of panitumumab for the treatment of metastatic colorectal cancer (patients with *RAS* mutations do not respond to treatment; Amgen)

RECENT INNOVATIONS IN MOLECULAR TECHNOLOGIES HAVE PAVED THE WAY FOR NOVEL APPLICATIONS OF GENOMICS DATA TO DRUG DEVELOPMENT

Large databases of human genomic information

Link data to understand genetic variants with increased or decreased risk for a particular disease

High Quality, Curated Clinical data from electronic health records (EHRs)

Goes beyond the days of family studies

Facilitates identification of genetic causes of disease(s)

NEW

Predict long-term effects of target inhibition (efficacy and safety)

Study the long term EHR data of persons who have a non-functioning variants of target gene

Current State: Large genetic and medical information databases

GSK (23andme) | Amgen (deCODE) | Regeneron Genetics Center (Geisinger Healthcare System)

REGENERON GENETICS CENTER (RGC) COLLABORATION WITH UK BIOBANK AND BIOPHARMA CONSORTIUM

RGC WILL SEQUENCE 500,000 PARTICIPANTS BY THE END OF 2019

- Regeneron and other pharma companies are partnering to sequence the 500,000 participants
- UK Biobank recruited 500,000 people aged between 40-69 years in 2006-2010
- Provided blood, urine and saliva samples for future analysis
- UK Biobank is linking to a wide range of electronic health record and is collecting detailed health information on participants
- Subsets of participants underwent more-comprehensive examinations, including extensive imaging and lung-function studies

HYPOTHESIS: GENOMICS CAN QUALITATIVELY PREDICT LONG-TERM, TARGET-RELATED EFFICACY AND SAFETY OUTCOMES

Clinical Trials to Demonstrate Effects on Biologic Phenotype

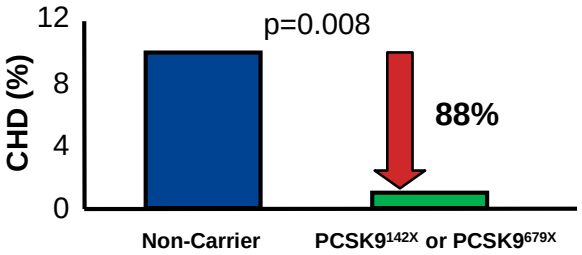
- A pharmacologic intervention that truly mimics the clinical phenotype identified in human genomic studies will recapitulate the clinical benefit observed in genetics studies
- Approval based on biomarker endpoints
- Large clinical outcome studies may not be necessary

Genetics Inform Product Labeling about Clinical Outcome Directionality

- As breadth/reliability of genetics data increase, so do the opportunities for FDA to make use of these data to inform providers and patients of relevant findings
- Precedent with labeling changes over time (e.g., addition of Pharmacogenomics subsection – FDA Guidance for Industry, 2013)

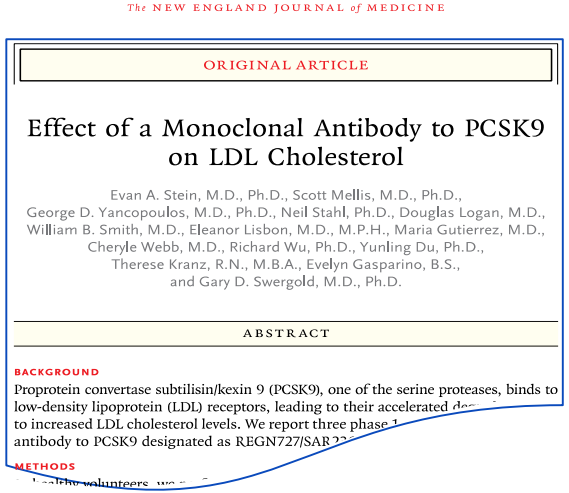
ANTI-PCSK9 ANTIBODIES MIMIC THE CLINICAL LIPID PHENOTYPE ASSOCIATED WITH PCSK9 LOSS-OF-FUNCTION GENETIC VARIANTS AND CORROBORATED THE CLINICAL OUTCOMES OBSERVED IN GENETIC STUDIES

PSCK9 variants linked to decreased coronary heart disease



Adapted from Cohen JC, et al. New Engl J Med 2006; 354: 1264–72.

Substantiation of lipid phenotype associated with genotype



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol

Evan A. Stein, M.D., Ph.D., Scott Mellis, M.D., Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Stahl, Ph.D., Douglas Logan, M.D., William B. Smith, M.D., Eleanor Lisbon, M.D., M.P.H., Maria Gutierrez, M.D., Cheryle Webb, M.D., Richard Wu, Ph.D., Yunling Du, Ph.D., Therese Kranz, R.N., M.B.A., Evelyn Gasparino, B.S., and Gary D. Swergold, M.D., Ph.D.

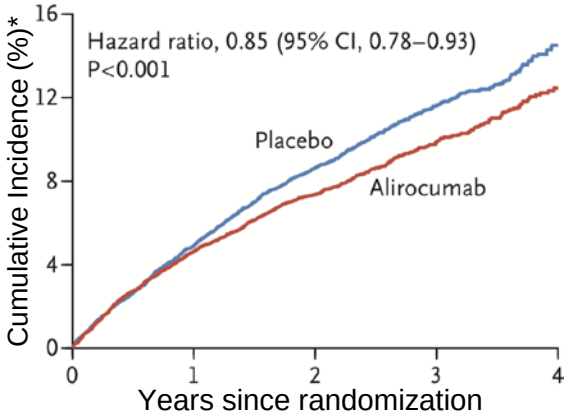
ABSTRACT

BACKGROUND

Proprotein convertase subtilisin/kexin 9 (PCSK9), one of the serine proteases, binds to low-density lipoprotein (LDL) receptors, leading to their accelerated d… to increased LDL cholesterol levels. We report three phase 1… antibody to PCSK9 designated as REGN727/SAR2…

METHODS

Clinical outcomes predicted by genetics



* Primary composite endpoint: death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, unstable angina requiring hospitalization

MAKING SMARTER DRUG DEVELOPMENT A REALITY THROUGH GENOMICS DATA

- Industry/FDA collaboration needed to establish data and regulatory standards
- Stakeholder engagement
  - Public Workshops led by FDA or in collaboration with Industry Groups (e.g., BIO, PhRMA)
  - Formation of Expert Working Group (EWG)
  - Development of white paper led by FDA in collaboration with EWG
  - Solicitation of comments (e.g.,via Federal Register) to questions that can inform the development of draft guidance(s)
  - Identify opportunities for additional stakeholder engagement initiatives, pilot projects
- Guidance for industry
  - Develop formal recommendations to Sponsors and manufacturers to level-set approaches and expectations on data quality and potential use in support of regulatory applications
    - Can data standards be established for genetic or transcriptome data for use in regulatory decision-making and labeling?
- Harmonize approaches in concert with other global agencies (e.g., EMA, ICH, HC)