Abstracts

Session 1 - Introduction to COMETS and COMETS Analytics Tutorial

The Consortium of Metabolomics Studies (COMETS) is an NCI-led international consortium that aims to provide a collaborative framework for evaluating associations between metabolomic profiles and disease or health outcomes. From these efforts, COMETS Analytics (CA) was developed to efficiently conduct statistical and meta-analyses of metabolomics data using standardized input and output formats as well as automated data and model integrity checks. CA also mitigates challenges in metabolomics analyses across cohorts by centralizing metabolite name and covariable harmonization. CA does not require specialized expertise to use and can be run on the cloud or locally, thereby addressing data sharing and protection concerns. Currently, CA supports many different types of models, including generalized regression, conditional logistic regression, survival, and correlation models.

This portion of the workshop is interactive and participants will learn how to utilize CA primarily through the R package (with the option to follow along on the web interface). Participants are encouraged to visit https://github.com/CBIIT/R-cometsAnalytics/tree/master/RPackageSource and download CA locally prior to the workshop. Specifically, this session will cover 1) an introduction to COMETS; 2) a description of the framework of CA; 3) standardized input sheets, including metabolite name harmonization and covariable harmonization; 4) analyzing single cohorts; and 5) meta-analyses. Step-by-step guidance will be provided and participants will be able to engage in real time with workshop leads to test CA and understand its applicability in their own research.

Session 2 - Latest Developments in Prospective Analyses of Metabolomic Epidemiology Studies

Talk 1: Rachel Kelly (Harvard University)

The Metabolome of BMI: A COnsortium of METabolomics Studies (COMETS) Meta-analysis of 46 diverse cohorts

Metabolomics is ideally suited to explore the drivers and consequences of body mass index (BMI) on a mechanistic and metabolic level. Here, we present the largest meta-analysis to date of BMI~metabolite associations including >125,000 adults from 46 cohorts worldwide within the context of the COnsortium of METabolomics Studies (COMETS). Of 1183 plasma metabolites which could be harmonized across at least six cohorts; a random- effects meta-analysis identified 421 (35.6%) metabolites as significantly associated with BMI after adjustment for age, sex, race, education category, smoking status, alcohol consumption level, fasting status and nested case-control status and applying Bonferroni correction. The metabolite most strongly positively correlated with BMI after adjustment for covariates was the lipid cortolone glucuronide (r: 0.396, 95% CI 0.367, 0.425, p=4.11x10-125). The strongest inverse association was with Concentration of large HDL particles (r: -0.296, 95% CI -0.354, -0.236, p=2.59x10-19). Comprehensive assessment of interactions by sex, region, race, profiling platform, fasting

status, diabetes and age found that although results were largely consistent across strata, there was some evidence of significant interactions by region for certain subclasses such as sterols. Importantly, although the crossover in measured metabolites across platforms was low, there was high consistency in results where metabolites were common. Similarly, there was little evidence of heterogeneity across cohorts. In addition to their biological implications, which both confirm previous work and identify novel BMI associated metabolites, the findings of this study demonstrate the feasibility of large-scale metabolomics meta-analyses across a diverse range of populations.

Talk 2: Waylon Hastings (Tulane University)

Leveraging COMETS to Explore Impacts of Caloric Restriction on Metabolomic Aging

One of the most promising geroprotective interventions is caloric restriction (CR). The foremost data for effects of CR in humans comes from the NIA-supported Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy (CALERIE™) randomized clinical trial. Using data from CALERIE™, researchers have provided evidence for significant reduction in rates of biological aging estimated using epigenetic clocks and blood chemistry biomarkers. Predominate mechanisms theorized to mediate CR impacts on aging include attenuation of oxidative damage, alterations to glucose-insulin signaling, and reduced inflammation, each of which may provide independent and interactive contributions. One appealing avenue to explore these processes simultaneously is metabolomics.

Metabolomic data from cohorts within the Consortium of Metabolomics Studies (COMETS) was linked using shared measurement IDs (Metabolon) to form a robust reference population. Two metabolomic indices of biological aging were constructed using elastic net regression: one trained to predict chronological age associated metabolomic dysregulation (MetaboAge1), and a second predicting metabolomic-mediated risk for mortality (MetaboAge2).

Preliminary analyses provide mixed results for CR intervention impacts on metabolomic aging. Although CR was associated with increased age-associated metabolomic dysregulation (MetaboAge1), there were trends toward decreased metabolomic-mediated risk for mortality (MetaboAge2) across the same duration. Functional characterization of metabolites comprising metabolomic age scores reveal mineral absorption and glycine metabolism as key pathways mediating metabolomic aging. Discussion highlights important caveats related to reference population construction and parameterization of metabolomic aging. Addressing these factors will be a key consideration as the COMETS referent is further compiled and metabolomic training methodology is increasingly refined.

Talk 3: Demetrius Albanes (National Cancer Institute)

A Multi-Cohort Prospective Analysis of Blood Metabolites and Glioma Risk in COMETS

COMETS offers tremendous potential scientific collaboration with ~80 cohorts worldwide which is especially advantageous for studies of less common health outcomes such as gliomas, which are both rare and lethal. To this end, we conducted a de novo pooled analysis of nested case-control studies from 9 COMETS cohorts. Cancer-free controls were individually matched to 803 glioma cases based on age, sex, self-identified race/ethnicity, and blood collection date. An ultrahigh-performance LC-MS/MS platform (Metabolon, Inc.) identified 874 known metabolites in

pre-diagnostic serum/plasma, and logistic regression models estimated odds ratios (ORs) and 95% confidence intervals for associations between 1-SD increases in circulating metabolites and glioma risk. Fifty-eight metabolites were associated with glioma overall, including 3-methylglutarylcarnitine (OR=1.19; P=0.001), cholate (OR=0.85; P=0.001) and a sphingomyelin (SM) (d18:2/21:0, d16:2/23:0, OR=1.19; P=0.002). Analysis restricted to cases diagnosed >5 years after blood collection showed 51 metabolites associated with risk, including SM d18:2/23:1 (OR=1.32; P=5.2×10-5), and two other SMs (d18:2/21:0, d16:2/23:0 and d17:1/24:1(15Z)) (ORs=1.27 and 1.26, respectively; P<5.6×10-4). High-grade glioma (n=595) or glioblastoma (n=485) showed similar positive risk estimates, including for 3-methylglutarylcarnitine, which achieved Bonferroni significance (OR=1.35; P=3×10-5), and several sphingomyelins. Gene-set and principal components analyses confirmed that the sub-pathways of SM, dihydro-SM, fatty acid, and dihydroceramide metabolism were significantly associated with overall glioma risk, and dihydro-SM, dihydroceramide, SM, lactosylceramide, glutathione, and purine metabolism were associated with high-grade glioma (all P values <0.05). Our findings regarding altered metabolic pathways/dysregulation occurring years before glioma diagnoses may be related to etiologic factors or subclinical disease.