The M.U.R.D.O.C.K. Study: Reclassifying disease using molecular biomarkers

Jessica D. Tenenbaum[1], Colette Blach[2], Swati Chakraborty[3], Ashley Dunham[1], Sheng Feng[5], Matthew Gardner[3], Carol Haynes[2], David Lobach[4], Joseph Lucas[6], Brian McCourt[3], Meredith Nahm[1], Jeanette J McCarthy[4], Robert M Califf[1]

[1] Duke Translational Medicine Institute, [2] Duke Center for Human Genetics, [3] Duke Clinical Research Institute, [4] Department of Community and Family Medicine, [5] Department of Biostatistics and Bioinformatics, [6] Institute for Genome Sciences and Policy

Contact Information:
Jessica D. Tenenbaum, PhD
jessie.tenenbaum@duke.edu
919-668-8811

Abstract

Introduction: The MURDOCK Study (Measurement to Understand the Reclassification of Disease Of Cabarrus/Kannapolis) is a long-term epidemiological study aimed at improving disease classification and population health. Researchers at Duke University, in partnership with the citizens and health care providers of Cabarrus County in North Carolina, are applying post-genomic era technologies to major chronic diseases. In doing so, we will identify underlying linkages across some of today's leading causes of illness and death, aid in redefining healthcare practices, and enable improved preventive practices among patients.

Background: Throughout the history of medical practice, the classification of disease has relied primarily upon macroscopic observation, with diagnoses based on symptoms at the systemic or, at best, the cellular level. However, recent advances in high throughput biomolecular assays have enabled both sub-classification of disease and the detection of previously unrecognized similarities between seemingly unrelated diseases. These new insights can have important implications for decisions regarding therapeutic intervention.

Methods: The MURDOCK study consists of three project "horizons." Horizon 1 (H1) involves the generation and analysis of molecular data for existing large, clinically well-annotated cohorts of four distinct diseases. Biological assays have been performed across these different cohorts, including genomic, proteomic, metabolomic, and imaging techniques. The objective for this horizon is to *establish biosignatures that can help predict disease progression and response to treatment*. Horizon 1.5 (H1.5) consists of the creation and population of a subject registry for prospective studies. Horizon 2 will validate the H1 hypotheses using the volunteers enrolled in H1.5. Horizon 3 and beyond will extend the study to additional diseases of interest.

MURDOCK Horizons

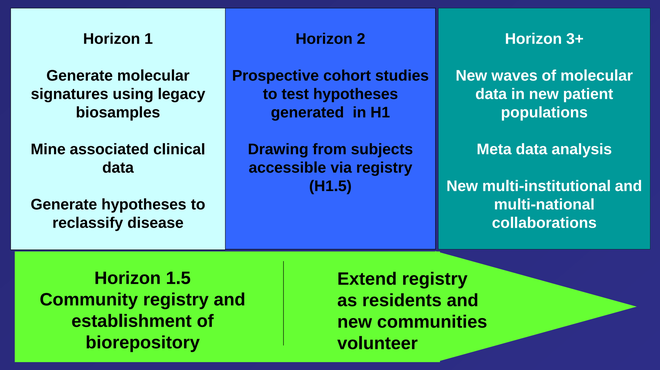


Figure 1: MURDOCK Horizons. Horizon 1 began at Duke in October, 2007, with existing clinical cohorts. In parallel, beginning in January, 2008, a team based at the North Carolina Research campus in Kannapolis, North Carolina (see box at right) has made continuous progress on Horizon 1.5 through community engagement, specimen storage logistics, and infrastructure for subject registration. The first volunteer was entered into the registry February 16th, 2009. Horizon 2 will begin following completion of data analysis from Horizon 1 using the subject enrolled through Horizon 1.5.

Horizon 1

Cardiovascular disease, n ≈ 6700	1. What baseline clinical features best stratify risk for coronary disease events? 2. What -omic profiles best stratify risk for coronary disease events and how do they contribute incrementally to clinical characteristics?
Hepatitis C Virus, n ≈ 1000	1. What protein biomarkers (host or viral) predict response to IFN therapy? 2. Are there protein biomarkers (host or viral) associated with different HCV genotypes?
Osteoarthritis, n ≈ 1900	1. What imaging biomarkers predict OA progression? 2. What molecular biomarkers predict OA progression?
Obesity/ Weight loss, n ≈ 1000	1. What metabolomic biomarkers predict response to weight loss? 2. What metabolomic biomarkers help stratify who is able to keep off weight lost?

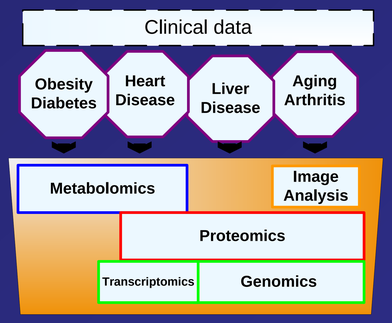


Figure 2: Methodologies used in Horizon 1 cohorts. Octagons represent the 4 diseases in H1. Highlighted boxes under the diseases show what data types have been generated for which cohorts. A finite set of overlapping clinical data is available across all cohorts. Preliminary molecular and imaging data analysis has yielded promising biosignatures to predict disease progression in osteoarthritis and response to therapy in Hepatitis C.

MURDOCK Integrated Database

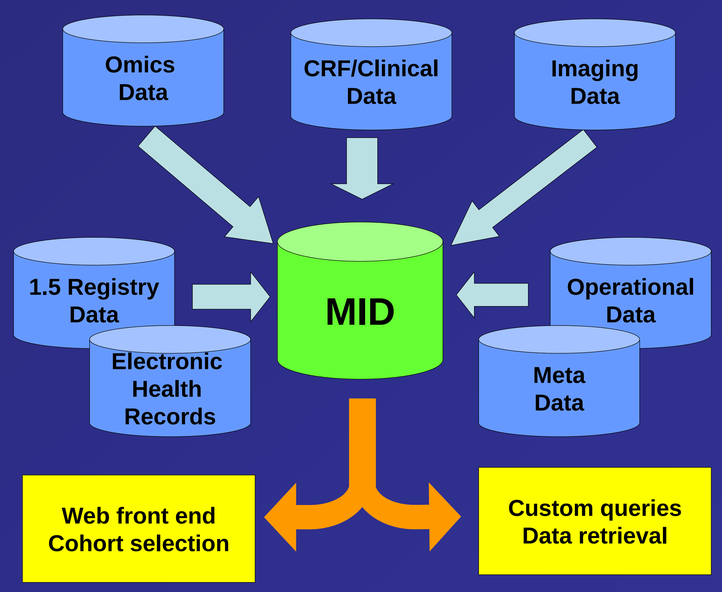
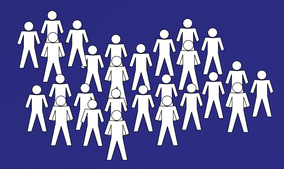


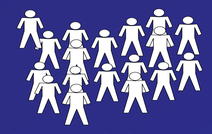
Figure 3: The MURDOCK Integrated Database. This database will contain all types of MURDOCK data, including clinical and molecular data, as well as sample and study metadata. Clinical data collected through the case report forms for the four individual studies has been mapped to overlapping common data elements, where possible. Preset data queries will be available through a web interface, and comprehensive datasets will be obtainable through customized queries after IRB approval.

Horizon 1.5



Additional Cabarrus County volunteers

N = 35,000

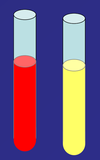


Random population sample of Cabarrus County, NC

N = 15,000

Subjects:

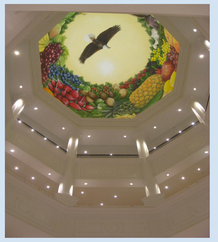
- Volunteers identified through community outreach
- Random population sample will be identified by addresses and recruited through mailings, follow-up phone calls, and door-to-door visits.



Collect:

- Blood, Urine
- Clinical data, family history
- Electronic Health Record, when available, through partnerships with local health providers

North Carolina Research Campus



- Private-public venture between David H Murdock, state of North Carolina, several NC universities.
- Home of the MURDOCK Study
- Located in Kannapolis, NC (Cabarrus County)
- Foster collaboration and further advancements in the fields of biotechnology, nutrition and health.
- 90,000 sq ft core lab, including state-of-the-art technology in genomics, proteomics and metabolomics.

Discussion

The MURDOCK study represents a new model of collaborative translational investigation, a whole much greater than the sum of its parts. Multiple teams have formed to handle data management and analysis for both molecular and clinical data. The MURDOCK study illustrates how, as biological assays improve and expand, and well-defined standards are agreed upon for common data elements, new approaches to biomedical research are now feasible where they would have been impossible only a decade ago.

Acknowledgements

David H Murdock

NIH/NCRR UL1-RR-024128

Horizon 1 Investigators: Virginia Kraus, John McHutchison, Kristin Newby, Laura Svetkey