



From Bench to Bedside: Anticipating Ethical Challenges in the Clinical Translation of the HMP

Richard R. Sharp, PhD

Director of Research

Staff, Department of Bioethics

Ruth M. Farrell, MD, MA

Assistant Professor of Surgery

Staff, Department of Bioethics



Cleveland Clinic



Roadmap Initiative Goals for the Human Microbiome Project

One part of the NIH Roadmap

- Develop a reference set of microbial genome sequences & preliminary characterization of the human microbiome
- Describe relationships between human disease & changes in the human microbiome
- Develop new tools for computational analysis
- Support a Data Analysis and Coordinating Center
- Create a publicly available resource repository

6. Examine ethical, legal and social implications (ELSI) of HMP research

The Role of ELSI Research and HMP

- **A unique forum in which to examine this new model of medical innovation**
 - **Call to examine and address the ethical, legal and social implications of emerging technologies from the Human Microbiome Project**
 - At the level of the bench
 - Translation from the bench to bedside
 - Bedside and beyond to community
 - **There are multiple facets of this line of inquiry**
 - Decision-making and informed consent
 - Understanding patients' perceptions about the HMP and its clinical applications
 - **Help to develop mechanisms to assist in the translation process**
 - *End products of your scientific work deliverable to patients*
 - *Anticipate and address road blocks and detours along the way*
-

Bringing the HMP to the Bedside

- Focus on the downstream clinical impact and implications for technology users
- **Multiple potential applications**
- **Adult, Pediatric, Neonatal**
- **GI, Urology, Dermatology, OB/GYN**



What do these conditions mean for patients?

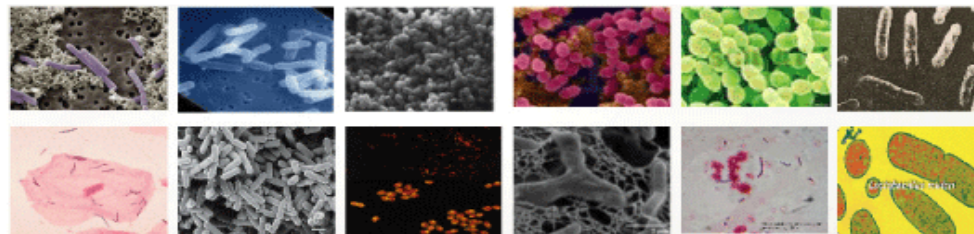
How can HMP knowledge and technology be used to help patients?

Ask these questions at the same time as advances in scientific knowledge

Develop a framework for anticipating the ethical challenges that arise with the clinical translation of novel technologies

Translational Genomic Research from the HMP

- **Using genomic science to develop specific interventions that can be used in clinical and public health settings to benefit human health**
- **Applied to the Human Microbiome Project**
 - Improve our understanding of the role of bacteria in human physiology and disease
 - Use this knowledge and resulting technology to address a diversity of medical problems
- **Diagnostic tools and individualized probiotic therapies**
 - Address microbial imbalances that can lead to disease
 - Use genetically modified bacteria as a new way of delivering therapeutics



From In Utero to the World Around Us

- Ecosystem of bacteria allow our bodies to function
 - Where do the microflora come from?
 - When do we acquire them?
 - How do we acquire them?
 - What role do they play in health and disease?
 - Do they change over time?
 - These questions play an important role in how we define health and illness in the context of the HMP
 - Equally important for bench, clinical, and ELSI researchers
 - We all have a common interest in answering these questions



HMP is Changing Paradigms of Health and Disease

- **A dimension of personalized healthcare**
- **Shifts the ways we think about human health and illness**
- **Conceptualizing human health**
 - Normal functioning based on bacteria providing functions which we have not yet evolved for
 - Comprehending the sheer volume of microflora and “foreign” DNA
 - Defining individuals
 - Defining groups and communities
- **Conceptualizing human disease**
 - Understanding the role of microflora in human dysfunction and disease
 - Changes in the human microbiome correlate with changes in human health

Defining Health and Disease in the Age of Genetics and Genomics

- **Genetics**

- **Genotype—phenotype dilemma**

- Complexity of genetic expression
- Role of environment and behavior

- **Therapeutic gap**

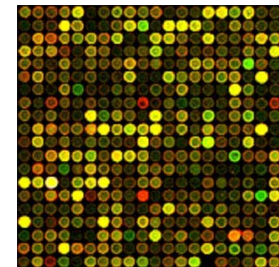
- Gap between the ability to sequence genomes and ability to offer effective remedies
- Making *meaningful* clinical decisions

- **Living with the knowledge and quality of life**

- **Disclosure, privacy and confidentiality**

- **Diversity and tolerance of difference**

- **Genomic level information amplifies these existing challenges and dilemmas**



Challenges Superimposed by Scientific Knowledge from the HMP

- **Scientific community already is facing a host of challenges from genetics and genomics**
- **Relatively uncharted territory**
 - Working within the paradigm of the microbiome
 - Undersanding the interplay between human genetics/genomics and microbial DNA
- **Finding the right balance**
 - Avoiding harm while delivering the benefits of technological innovation
 - Phenotypic uncertainty
 - Therapeutic gaps
 - Quality of life
 - Disclosure, privacy, and confidentiality
 - Identity and diversity



Probiotics: A Clinical Application of the HMP



- **Probiotic therapies present an important context in which to examine the types of novel therapeutics that will evolve from the HMP**
- **Ingestion of bacteria and the expression of that bacteria's genome within the human host**
- **Activation of bacteria DNA leads altered physiological function**
 - Affecting existing bacterial microflora and their genetic functions
 - Inducing the host (human) genome to produce endogenous proteins to restore normal function
- **Potential therapeutic platforms**
 - Patient-matched probiotics containing genetically-*specific* microorganisms
 - Patient-matched probiotics containing genetically-*modified* microorganisms

Informed Decision-Making about Clinical Applications of HMP Findings



- **Challenges for informed consent given understandings of the human microbiome**
- **Initial perceptions, attitudes and concerns set the stage about the translation of new therapies**
 - Treatment efficacy
 - Mechanism of action
 - Safety
 - Acceptability

What to patients already know about probiotics?

What should they know to make an informed decision?

What do patients want/need/expect from the HMP and its researchers?

What does the General Population Know about Probiotics?



Unexpected Interactions

- **Unexpected interactions of bacteria within the environment of the human host**
 - Both in relation to other bacteria and human host cells
 - Development of unexpected changes to the microbial ecosystem could result in adverse microbe-host interactions
 - Development of a severe host immune response to probiotic bacteria

How to stop treatment once started?

Unpredictable Behavior

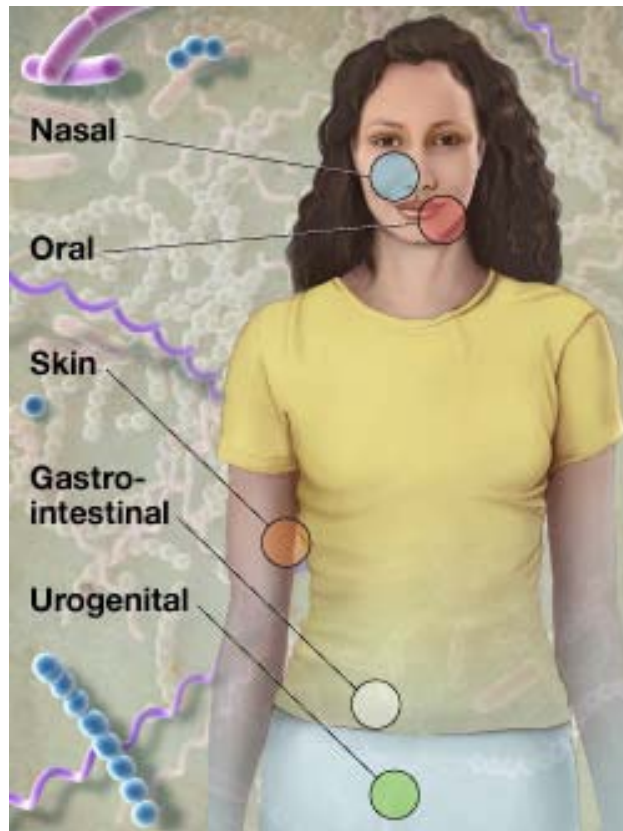
Naturally Occurring Microorganisms

- **Probiotic agents may behave much differently than predicted**
 - Unanticipated gene expression in host environments
 - Acquired mutations occurring spontaneously via bacterial DNA-transfer mechanisms.
 - Example: Bacteria that develop drug resistance through DNA exchange with other bacterial genomes

Genetically Altered Microorganisms

- **Engineering of new bacterial genomes that express a desired set of proteins**
 - Genetically modified organisms may take on the same inherent DNA-exchanging and mutating behaviors
 - Leading to erratic or unexpected behavior
- **Expression of these genomic products has the potential for even greater deviation from expected results**

HMP Outside of the Individual



They begin in the individual patient.

Where do they all go?



Release into the Environment

- **Unexpected release of novel bacteria into the environment**
- **Probiotic bacteria are ultimately eliminated from the body by natural mechanisms**
 - Possibility of environmental contamination
 - Third-party exposure to bioengineered probiotics
 - Considerations of human, plant and other animal ecosystems
 - “In properly functioning septic systems, groundwater contamination from viruses, bacteria, nutrients, and other organic wastewater pollutants has been well documented”
 - Standord and Weinbberg, “Evaluation of On-Site Wastewater Treatment Technology to Remove Estrogens, Nonylphenols, and Estrogenic Activity from Wastewater.” *Environ. Sci. Technol.* 2010, *44*, 2994–3001

How do we control the effect probiotics on a community once they are introduced into the individual?

Clinical applications of HMP require ELSI research at the level of individual and public health concerns

Translation to the Bedside and Beyond

- **Like all medical interventions, patients must be able to make informed decisions about their use, including weighing potential benefits against risks prior to use**
 - Clinical research
 - Patient care arena
- **Evidence-based and effective physician-patient communication strategies facilitate the successful translation of metagenomic technologies**



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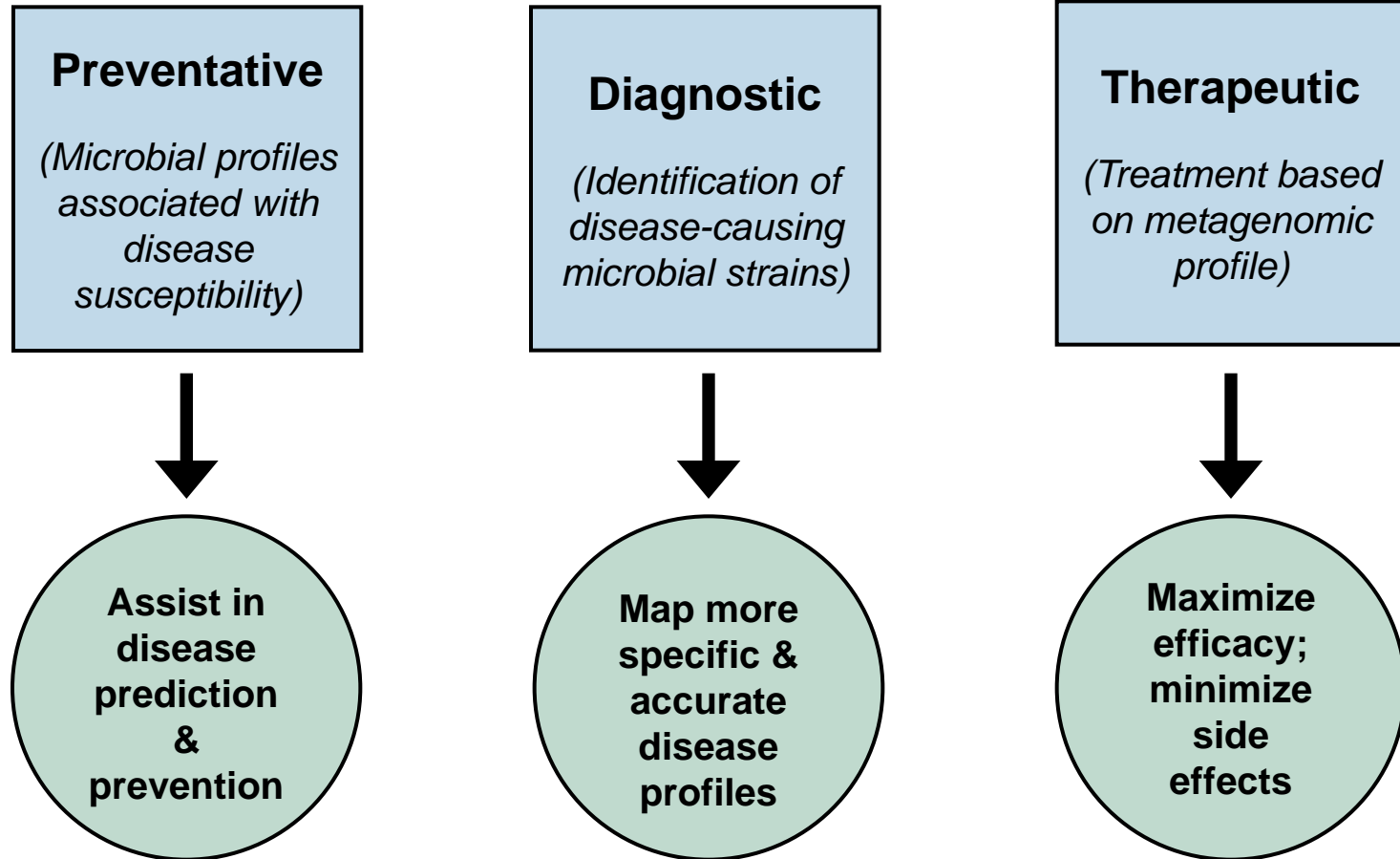
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Why do ELSI research within HMP?

Conduct studies that anticipate challenges in the introduction of new technologies into patient care:

- How do patients' values and moral beliefs impact the transition from bench to bedside?*
- How should clinicians present potential benefits and risks of promising but still unproven therapies?*
- What ethical challenges are associated with clinical innovation?*

Applying HMP research to patient care: GI sampling & metagenomic analysis



Translational bioethics and the HMP

Q: Suppose HMP researchers are successful and generate new therapeutic options based on metagenomic technologies and the capacity to manipulate the human microbiome. Will patients welcome these developments?

A: We don't know.

- Concerns about genetic discrimination?
- Concerns about GM foods?
- Concerns about gene therapy?

Case study: clinical translation and HMP

Aims:

1. To characterize patient understandings of genetically modified (GM) probiotics, including willingness to use and beliefs about potential benefits and risks.
2. To develop recommendations on how to discuss probiotics and metagenomic technologies with patients in a manner that is informed by widely held patient values and beliefs.

Summary of Methods

Design

- Multi-site focus group study
- Cleveland Clinic, Mayo Clinic, JHU

Sample

- Patients with chronic GI diseases
- Primarily IBD, IBS, pouchitis

Data Collection

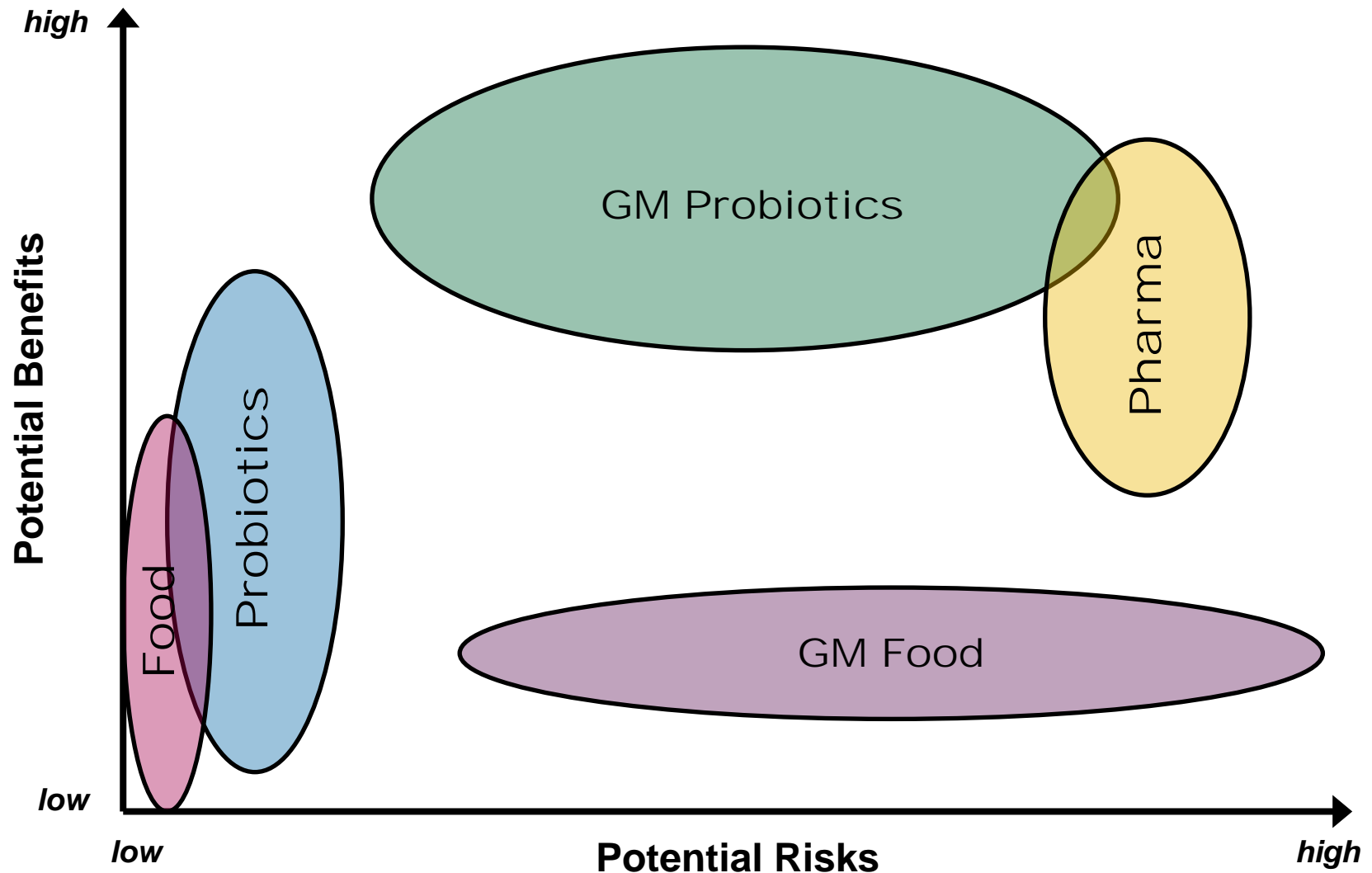
- Structured moderator guide
- Demographic questionnaire

Data Analysis

- Focus group transcripts; independently coded by 2 analysts using NVivo
- Inductive analytic methods and descriptive analysis



Patient Understandings of Therapeutic Options



Patients distinguish GM food and GM probiotics

GM Food vs. GM Therapeutics

“If I saw genetically altered corn in the store I would steer away from it but now we are talking about something that I could have a health benefit from. ... I would jump ship!”

What information will first users want?

Skepticism and scientific data

“I’d need to see a whole workup of like, say, a thousand patients, a control and all that kind of stuff to make a decent decision about it, you know...until I see hard data in front of me, I don’t want to stick anything in my body that I don’t know, for sure, is gonna either not harm me or help.”

Communication with physicians

“I’d rather the information come from either government studies or my doctor or some credible source instead of...what I happen to see at a shelf or commercials.”

Cautious Optimism

“We live in a time when human science can make big mistakes with big repercussions ... your mistakes can be broad-reaching. ... We have to be really careful... .”

Conclusions

1. GI patients are unlikely to express major concerns about targeted probiotic therapies, GM probiotics, and clinical applications of metagenomics.
2. GI patients have limited familiarity with HMP-related research and feel overwhelmed by the volume of information available about probiotics.
 - Patients often feel that they cannot discuss their interests in probiotics openly with their clinicians.
 - Patients would welcome the availability of a trusted Internet resource describing new scientific developments (HMP-supported activity?)
3. Patients with chronic GI diseases often view their clinical situation as unique and will be particularly enthusiastic about therapeutic options that they view as new forms of “personalized medicine”.
 - Vulnerable to aggressive marketing of HMP-derived therapies?
 - Exercise restraint in how we, as a community of researchers involved in the HMP, frame its clinical promise.

SPECIAL REPORT

JANUARY 17, 1994 \$2.95

TIME



Genetics THE FUTURE IS NOW

New breakthroughs can cure diseases and save lives,
but how much should nature be engineered?



 Cleveland Clinic

LIFE

Research Team

Cleveland Clinic:

- Richard Sharp
- Ruth Farrell
- Patty Marshall
- MaryBeth Mercer
- Margaret Brinich
- Janelle Highland
- J.P Achkar

Johns Hopkins University

- Gail Geller
- Krista Harrison
- Gerard Mullins

Mayo Clinic

- Jennifer McCormack
- Jon Tilburt
- Katherine James
- Edward Loftus

Acknowledgments

This work was supported in part by NIH grant R01 HG004877;
Patient Perceptions of Bioengineered Probiotics and Clinical
Metagenomics.

Sharp RR, et al. Helping patients make informed choices about
probiotics: a need for research. Am J Gastroenterol.
2009;104:809-13.



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Richard R. Sharp, PhD¹ and Ruth Farrell, MD, MA²

**Director of Research and Staff, Department of
Bioethics¹; Staff, Department of Bioethics²**



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