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Subtotal Direct Costs (excludes consortium F&A) Year 7: 389,636 Year 8: 390,661 Year 9: 405,534 Year 10: 416,349	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
<i>Senior/Key Personnel:</i>		
	<i>Organization:</i>	<i>Role Category:</i>
Eric Juengst Ph.D.	Case Western Reserve University	PD/PI
Jennifer Fishman PhD	McGill University	Other (Specify)-Co-PI
Richard Settersten PhD	Oregon State University	Other (Specify)-Co-PI
Robert Binstock PhD	Case Western Reserve University	Faculty
Michelle McGowan PhD	Case Western Reserve University	Faculty

Appendices

Juengst-appendice

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Appendix

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Project Summary

“Personalized genomic medicine” (PGM) is being promoted as a “new paradigm for health care” and a major goal for translational genomic research (TGR). In addition to overcoming TGR’s remaining scientific hurdles, achieving that goal will involve addressing a number of ethical, legal, and social challenges. Some of those challenges reflect the ways that different social policies and health care economies will complicate TGR’s ability to realize PGM as a viable health care paradigm. But other challenges might emerge from the goal itself, depending upon how PGM is interpreted by those who shape it as a social practice. This project explores this suggestion by documenting how PGM and its most attractive virtues are interpreted by those involved in defining them for TGR and society, and the challenges and choices they are encountering in the process.

PGM is a goal that unites a wide array of biomedical initiatives, from medical sequencing, gene expression, and pharmacogenomics research to public health, clinical, and commercial services. Its promissory virtues are precision diagnosis and risk prediction, individualized therapy, prevention, health promotion, and patient empowerment. Different proponents of PGM interpret and rank these promises differently, with different implications for the realization of PGM as a health care paradigm. We focus on four sets of interpreters that will have particularly important roles in shaping the way PGM emerges as a social practice: (1) the scientists, research sponsors, companies, and policy organizations that promote PGM as a biomedical paradigm; (2) the journals, public review bodies and educational institutions that mediate the implementation of this paradigm; (3) the health care institutions and professionals that pioneer the paradigm by providing PGM services in practice; (4) the patient-based organizations that increasingly help shape its public reception. Our empirical studies of the views of these social co-producers of PGM will then be used to generate an analytic map of their different visions, designed to draw out their ethical, legal, and social implications for TGR and health policy. The “translational pipeline” of genomic research will have many branches towards its distal end. This project is designed to anticipate the directional choices that these branches will require, so that the PGM that TGR finally delivers into the complicated plumbing of our society is as clean and safe as possible.

A major goal of genomic research is to develop health care tools that can achieve more precise diagnoses and risk predictions, individualized therapy, prevention, health promotion, and greater patient empowerment. The proponents of these advances call their goal “personalized genomic medicine.” But many different parties are involved in shaping this vision for health care, and their different interpretations of its virtues carry different ethical, social, and legal implications. The purpose of this project is to study how some of the most influential parties who are promoting, implementing, providing, and using “personalized genomic medicine” understand its promises and potential pitfalls. This understanding will allow us to define the policy choices that lie ahead for researchers, health care providers, and the public as translational genomic research moves closer to its goal.

Resources

Laboratory:

N/A

Clinical:

N/A

Animal:

N/A

Computer:

All investigators and research assistants will use computers that are attached to the CWRU network for Internet and e-mail purposes. High-speed network printers will be available. All CWRU faculty and staff have access to the latest software at no charge—e.g., Microsoft Office, Adobe Acrobat, etc.

Office:

The project will be based in the Department of Bioethics at the CWRU School of Medicine. The Department has over 7,000 square feet of office/library/conference room space. Since many of the investigators are members of the Department, they already have offices. Additional space will be available to house research assistants.

Other:

N/A

Major Equipment: N/A

Budget Justification:

Personnel:

Dr. Juengst (Co-Principal Investigator, [EFFORT] and funding for all years) is Professor of Bioethics and Director of the Center for Genetic Research Ethics and Law in the School of Medicine at Case Western Reserve University. Dr. Juengst will co-direct the proposed project with Drs. Jennifer Fishman and Richard Settersten. Dr. Juengst will be responsible for the overall coordination of the grant and all personnel on site. He will take primary leadership for the Specific Aim 5, which is focused on the ethical, legal and social implications anticipated by architects of personalized genomic medicine. These analyses will build directly on the findings from the extensive empirical work that will be conducted for the first four aims, in which he will also participate.

Robert Binstock, Ph.D. (Co-Investigator, [EFFORT] and funding for all years) is Professor of Aging, Health, and Society in the School of Medicine at Case. As a public policy expert, Dr. Binstock will work contribute to the empirical research and work closely with Dr. Juengst to address the ethical, legal and social implications anticipated by architects of personalized genomic medicine. They will describe and analyze the results of our empirical findings, as well as the published works and presentations of scientists, bioethicists, and policy makers to better contextualize the field of PGM. As a team member, Dr. Binstock will regularly attend all project meetings as an active collaborator on the ongoing empirical research.

Michelle McGowan, Ph.D. (Co-Investigator, [EFFORT] and funding for all years). Dr. McGowan is Assistant Professor of Bioethics in the School of Medicine at Case. Dr. McGowan will work closely with the three co-PIs on the data collection and analyses for the empirical projects associated with Aims 1 through 4. With Dr. Fishman, she will have primary responsibility for data collection and analyses for Aim 4. For Aim 3, she will also conduct the observational field work at the Cleveland Clinic. As a womens' studies scholar, Dr. McGowan will also serve as an important colleague in the discussion of the ethical, legal and social implications of personalized medicine discussed in Aim 5.

Marcie Lambrix, M.A. (Project Manager, [EFFORT] and funding for all years). Ms. Lambrix, a doctoral candidate in Sociology at Case, will be responsible for the daily management of the empirical studies conducted for Aims 1 through 4, including all administrative tasks related to Case Western Reserve University's Institutional Review Board, the recruitment of project participants, the development, dissemination and collection of interview instruments, and the coordination of data analysis.

Michael Flatt, M.A. (Research Assistant, [EFFORT] and funding for all years). Mr. Flatt, who is also a doctoral candidate in Sociology at Case, will work closely with the Project Manager in planning and implementing the research tasks of the team. He will work on developing interview guides for all aims, interviewing participants, attending scientific and medical conferences, and coding data.

Roselle Ponsaran, M.A. (Research Assistant, [EFFORT] and funding for all years) Ms. Ponsaran will work closely with the other research staff to ensure that the daily empirical tasks of the project are completed efficiently. Ms. Ponsaran will play a special role in providing regular updates on new published research and on newsworthy items in the media that pertain to PGM.

TBA (Research Assistant 2, 6 months effort and funding for all years). This position will help the research staff to collect data for Aims 1-4 by performing administrative tasks, such as scheduling interview appointments and making follow-up recruitment calls. The RA will also conduct interviews and code data.

Fringe benefits are calculated at 23.5% for Year 1 and increased .5% for each year thereafter.

Consultants:

There will be 10 consultants in Year 1. Each consultant will be paid \$1,000 and will be responsible for providing expert ongoing advice on questions related to the field of personalized medicine. Consultants will be engaged strategically for assistance with developing the samples of participants for the empirical research associated with the first four aims, and especially in efforts to oversample minorities and women to ensure our targeted

enrollments. Consultants will also provide advice on the development and publication of manuscripts, including reviewing manuscripts when appropriate.

Supplies:

General Research Computer Supplies: \$1,000 is requested to cover the costs of audiotapes, batteries, stationary, padded envelopes, computer supplies, file folders, pocket file folders, pens, pencils, paper, etc. in Year 1. This amount is increased 3% per year.

\$1,000 is requested in Year 1 to cover the costs of books and journal subscriptions necessary for the project. This amount is increased 3% per year.

Travel:

Data Collection: \$6000 is requested in Year 1 to cover expenses related to attendance at medical conferences (2 investigators x 2 meetings @ \$1,500/meeting). These conferences will be data collection sites as indicated in Aim 3. This amount is increased 3% per year.

Professional: \$8,000 is requested for Year 1 to cover expenses related to attendance at professional meetings (2 investigators x 2 meetings @ \$2,000/meeting). This amount is increased 3% per year.

Funds are requested for biannual meetings of the research team. Once per year, Drs. Fishman and Settersten will come to Cleveland to meet with the research team. \$2,400 is requested in Year 1 to cover the travel costs (1 trip x 2 persons x \$1,200/trip). This amount is increased 3% per year. There will be another annual meeting of the research team, rotating locations between Montreal, QC and Corvallis, OR. \$8,000 is requested for Year 1 to cover expenses for travel to this meeting (1 trip x 4 persons x \$2,000/trip). This amount is increased 3% per year.

Other Expenses:

Transcription. Tracey Baker, a professional transcriber who works as an independent contractor, will transcribe the audiotapes from the interviews. The cost will be \$2,500 (100 hours x \$25/hr) per year in Years 1-3.

Postage: \$100 is requested for postage in Year 01. We have increased costs by 3% for subsequent years.

Telephone: \$1,000/year is requested to help pay for telephone costs. We have increased costs by 3% in subsequent years.

Oregon State University Sub-Contract:

Richard Settersten, Ph.D. (Co-PI, EFFORT and funding requested for all years) is Professor of Human Development and Family Sciences in the College of Health and Human Sciences at Oregon State University. Dr. Settersten is an expert on human development, the life course, and social policy. Dr. Settersten will co-direct the proposed project. Because the empirical research associated with the first four research aims is so extensive and intertwined, Dr. Settersten will share primary leadership with Dr. Fishman on the responsibilities for Aims 1 through 3, have secondary responsibility on Aim 4, and in analyzing data, presenting papers, and publishing articles that result from the empirical projects associated with them. Drs. Settersten and Fishman have a strong track record of joint leadership and collaboration on our research team. They also have methodological and theoretical skills that are complementary, and synergistic. Drs. Settersten will also be involved in the final aim (on the ethical, legal and social implications of personalized genomic medicine) because these culminating analyses will build directly on the results of their extensive empirical research in the first four aims. No special research assistance is being requested for Dr. Settersten.

Indirect costs are requested each year at the rate 46.2%.

McGill University Sub-Contract

Jennifer Fishman, Ph.D. (Co-Principal Investigator, EFFORT and no funding for all years) is Assistant Professor in the Biomedical Ethics Unit and Department of the Social Studies of Medicine at McGill University in Canada. Dr. Fishman will co-direct the proposed project. Dr. Fishman will share leadership with Dr. Settersten on the responsibilities for Aims 1 through 3, and she will share leadership responsibilities with Dr. McGowan on Aim 4. She will also analyze data, present papers, and lead the publication of articles that result from the projects associated with Aims 1 through 4.. Drs. Fishman will also be involved in the culminating projects associated with Aim 5, which build directly on the results of their extensive empirical research in the first four aims.

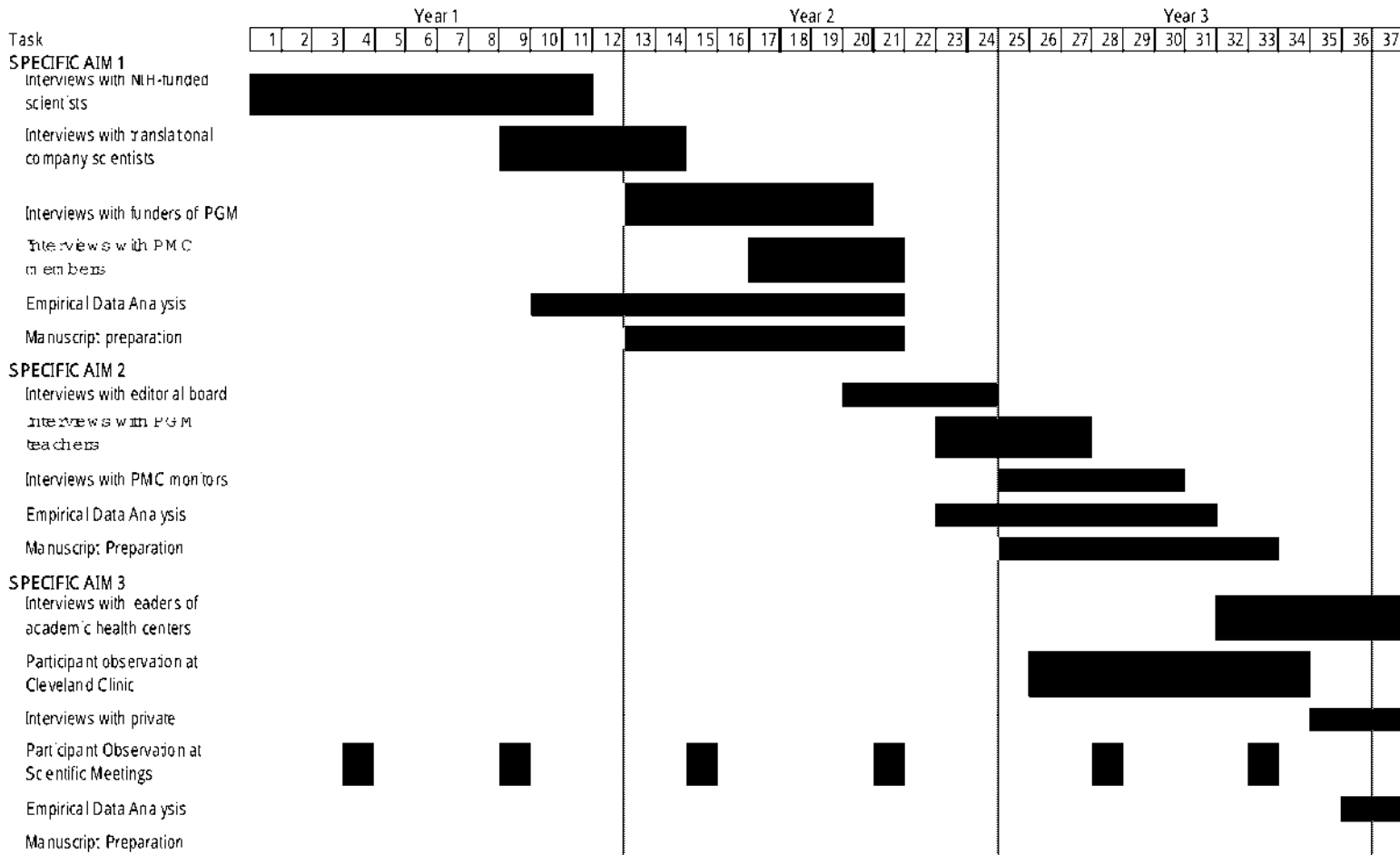
TBA Research Assistant (50% effort and funding for all years). This position will report to Dr. Fishman and will be responsible for assisting the team with interviewing participants and coding data. No fringe benefits are charged as this is a graduate student position.

Supplies: \$2,400 is requested in Year 1 to cover the cost of a computer and printer for the graduate assistant as well as research supplies. \$300 per year is requested in Years 2-4 to cover the cost of research supplies.

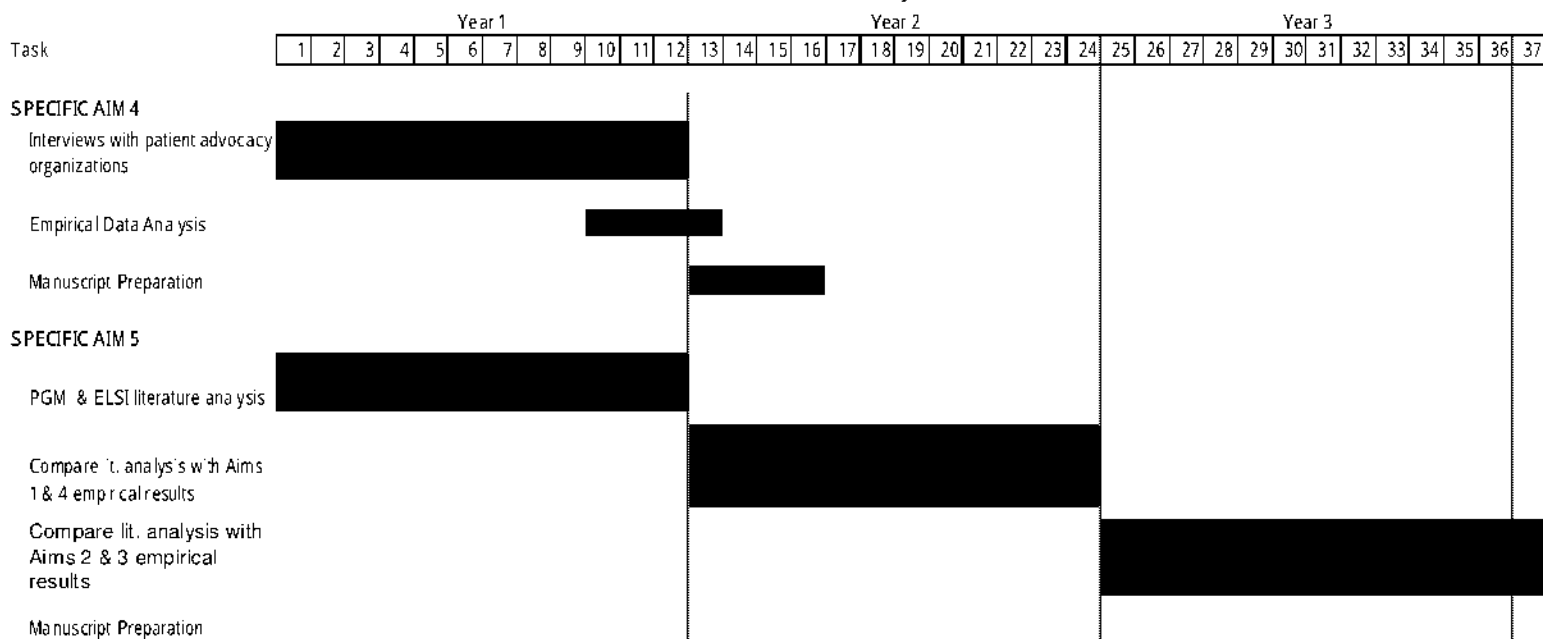
\$600 is requested in Year 1 to cover the cost of copying and telephone calls. This amount is increased 3% per year.

Indirect costs are requested in each year at the rate of 8%.

Project Timeline



Project Timeline



Program Director/Principal Investigator (Last, First, Middle): Fishman, Jennifer, Renee

PERSONNEL:

Jennifer Fishman, PhD (Co-Principal Investigator,) Dr. Fishman will provide major leadership on all phases of the empirical projects associated with Aims 1 through 4. She will work closely with the research team and direct the staff in their data collection efforts and be primarily responsible for the data analysis of Aims 1 through 4. Together with Dr. Settersten, Dr. Fishman will continue to oversee interviewing and field work, the development of interview guides, the coding and analysis data, and the presentation and publication of research papers from the project.

Because the bulk of the infrastructure, including research staff, for our ongoing project exists at Case Western Reserve University, Dr. Fishman is only requesting grant support for a Graduate Research Assistant who will assist the project locally at McGill University.

TBA- (Graduate Research Assistant,) and funding is requested for years 1-4). This position will provide support for Dr. Fishman in conducting interviews and fieldwork under Aim 3. In later years, the research assistant will assist in coding and analyzing interview data.

SUPPLIES:

Non-Recurring Supply Costs:

One laptop computer @ \$1600 is requested for use by the research assistant.

One printer @ \$500 is requested for use by Dr. Fishman and the research assistant.

Recurring Supply Costs:

General and Computer Supplies: \$300 is requested to cover the costs of computer supplies, file folders, paper, pens, etc. This amount is requested each year of funding.

OTHER EXPENSES:

Copying/Printing: To cover the expense of duplication charges, we have budgeted \$300 in Year 01. We have increased costs by 3% for subsequent years.

Telephone: \$300/year is requested to help pay for telephone costs. We have increased costs by 3% in subsequent years.

Oregon State University Sub-Contract
Budget Justification

Co-PI Richard Settersten, Ph.D., is budgeted at [redacted] % Effort for academic year salary support, and [redacted] months of summer support, for all four years of the project. As Co-PI, Dr. Settersten will provide major leadership on all phases of the empirical projects associated with Aims 1 through 3, and secondary leadership roles on Aims 4 and 5. Because the infrastructure, including research staff, for our ongoing project exists at Case Western Reserve University, Settersten is only requesting salary support as part of his sub-contract. This is consistent with our current arrangements, which have been highly effective. Settersten will lead weekly conference calls with Co-PI Jennifer Fishman and the research team. Settersten will oversee interviewing and field work, the development of interview guides, the coding and data analysis, and the presentation and publication of research papers from the project. The [redacted] % Effort support reflects the minimum effort necessary to lead these empirical projects and reduces Settersten's teaching load each year by 2 courses, which will ensure the necessary time for the project. Salary is increased [redacted] % Effort fringe rate is increased by 2% each year. Fringe rates for academic year support are [redacted] % Effort Year 1, [redacted] % Effort Year 2, 54% in Year 3, and [redacted] % Effort Year 4. Fringe rates for summer support are [redacted] % Effort in Year 1, [redacted] % Effort Year 2, [redacted] % in Year 3, and [redacted] % Effort Year 4. Indirect costs are calculated at 46.2% of direct costs.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix: * First Name:
 Middle Name:
 * Last Name:
 Suffix:

* New Investigator? No Yes

Degrees:

2. Human Subjects

Clinical Trial? No Yes

* Agency-Defined Phase III Clinical Trial? No Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix: * First Name:
 Middle Name:
 * Last Name:
 Suffix:

* Phone Number: Fax Number:

Email:

* Title:

* Street1:

Street2:

* City:

County:

* State:

Province:

* Country: * Zip / Postal Code:

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? No Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: <http://stemcells.nih.gov/registry/index.asp>. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page and PHS398 Checklist. The responses provided on these pages, regarding the type of application being submitted, are repeated for your reference, as you attach the appropriate sections of the research plan.

*Type of Application:

New Resubmission Renewal Continuation Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application	<input type="text" value="1246-Juengst-Intro.pdf"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
<small>(for RESUBMISSION or REVISION only)</small>			
2. Specific Aims	<input type="text" value="1247 Juengst specific aims.p"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
3. Background and Significance	<input type="text" value="1248 Juengst Background.pdf"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
4. Preliminary Studies / Progress Report	<input type="text" value="1249-Juengst-Preliminary.pdf"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
5. Research Design and Methods	<input type="text" value="1250-Juengst-researchdesign"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
6. Inclusion Enrollment Report	<input type="text" value="1251-Juengst-enrollment rep"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
7. Progress Report Publication List	<input type="text" value="1252-Juengst-publications.p"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>

Human Subjects Sections

Attachments 8-11 apply only when you have answered "yes" to the question "are human subjects involved" on the R&R Other Project Information Form. In this case, attachments 8-11 may be required, and you are encouraged to consult the Application guide instructions and/or the specific Funding Opportunity Announcement to determine which sections must be submitted with this application.

8. Protection of Human Subjects	<input type="text" value="1253-Juengst-human subjects"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
9. Inclusion of Women and Minorities	<input type="text" value="1254 Juengst women and mino"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
10. Targeted/Planned Enrollment	<input type="text" value="1255-Juengst-targeted enrol"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
11. Inclusion of Children	<input type="text" value="1256-Juengst-children.pdf"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>

Other Research Plan Sections

12. Vertebrate Animals	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="text"/>	<input type="text"/>
13. Select Agent Research	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="text"/>	<input type="text"/>
14. Multiple PI Leadership Plan	<input type="text" value="1257-Juengst-Multiple PI.pdf"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>	
15. Consortium/Contractual Arrangements	<input type="text" value="1258-Juengst-Consortium.pdf"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>	
16. Letters of Support	<input type="text" value="1259 Juengst Letters of Supp"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>	
17. Resource Sharing Plan(s)	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="text"/>	<input type="text"/>

18. Appendix

reviewers' comments

reviewers' comments

Specific Aims

What would it mean for society to have genomic research successfully translated into “personalized genomic medicine” (PGM)? PGM and its cognates (such as “individualized therapy”) are labels that have emerged over the last twenty years to refer to the promise of using molecular genetic information from patients to develop more individually effective, predictive, and preventive health care interventions. Realizing this promise has become a major goal for translational genomic research (TGR), and its manifest virtues have attracted a wide range of subscribers within biomedicine. It is not yet clear, however, what PGM might look like as a social practice, since different interpretations of those virtues could take TGR and health care in quite different directions. As TGR moves towards this goal, it will become increasingly urgent to understand these interpretations and the social policy choices they create. **The goal of this project is to help meet that need by documenting the ways in which the principal stakeholders of PGM interpret its promise, and extrapolating an analytic map of the ethical and social challenges these interpretations could provoke in practice.** Our preliminary studies have identified four sets of stakeholders with influential roles in shaping PGM as a social practice: (1) initial “**promoters**” of PGM as a biomedical goal; (2) “**mediators**” who validate, edit, and operationalize PGM as a health care paradigm; (3) “**providers**” who pioneer the paradigm in practice; (4) the patient-based organizations that represent the “**users**” who first experience PGM’s practical effects. Since these stakeholders act simultaneously and in dialogue with each other, we do not expect their co-production of PGM to be an entirely linear or sequential process. Nevertheless, the conceptual cascade between their different roles provides a logic for organizing our research against the following five specific aims:

Aim 1. To describe how the primary promoters of PGM as a biomedical research goal envision PGM as a social practice and assess its potential benefits and risks.

The first aim of our project is to analyze the interpretations that genomic scientists and their sponsors and agents give to PGM, in order to describe how they understand its promises. Although they develop their interpretations in negotiation with each other and other stakeholders, these are the social actors who promote PGM as a biomedical research goal by recruiting other scientists to its banner and soliciting its subsidy from taxpayers and investors. The cases that the promoters make to their audiences for embracing PGM are important to understand because they will shape TGR’s scientific priorities, the allocation of research funds, and the research practices of scientists. To accomplish this aim, we will conduct semi-structured, in-depth interviews with active TGR scientists and thought leaders, their sponsors in government and the private sector, and the leadership of their primary advocacy organization, the Personalized Medicine Coalition.

Aim 2. To describe how those who mediate the development and diffusion of new health care practices interpret PGM and its promise as a health care paradigm.

In order to realize PGM as a social practice, TGR must do more than develop new clinical tools from basic research findings. It must also negotiate the acceptance of those tools by biomedicine’s internal gatekeepers and public monitors, and sell its vision to the medical educators who manage the canon of normative medical thinking. We call these three kinds of middlemen the “mediators” of PGM’s progress, since their judgments about its products will be influential in shaping the suite of tools and services that become the socially legitimized core of what PGM offers to health care providers. The mediators’ assessments of the benefits promised by PGM’s promoters are critical in those judgments. To capture these assessments, we will conduct interviews with representatives from three kinds of mediators relevant to PGM: the journals most relevant to the scientific self-policing of PGM; the public committees most active in overseeing the emergence of PGM; the educational programs charged with the responsibility of translating knowledge about PGM to health professionals and medical students. We will be interested in seeing how each of these groups’ interpretations of the virtues of PGM might influence their judgments about the possibilities of PGM in the clinical setting.

Aim 3. To describe how health care providers both interpret and shape PGM in the clinical setting, and experience its relative strengths and weaknesses in practice.

The third aim of the project will assess the ways in which health care institutions and clinicians experience PGM’s benefits and challenges in actual practice. Few clinical settings currently offer actual genomic-based

medicine to patients, but those that do will be instrumental in defining PGM as it moves towards mainstream practice. In order to anticipate the directions in which these pioneers might take the enterprise, it will be important to document the experiences of those who are in the vanguard of providing PGM in the clinical setting, and their perspectives on its promises and pitfalls. We will conduct semi-structured in-depth interviews with representatives of the leading academic medical programs and private practices that identify themselves as providers of PGM to achieve this aim. In one these centers (the Cleveland Clinic's Genomic Medicine Institute), we will also conduct intensive ethnographic fieldwork, including observations during clinical appointments, in order to analyze daily practices.

Aim 4. To examine how PGM is being interpreted by patient advocacy organizations and their members.

Over the last two decades, patient advocacy organizations have become influential stakeholders in disease-specific translational research, and those concerned with genetic health problems have been active constituents in the support of TGR. As the “voice” of the consumers, patients, and beneficiaries at the end of the translational research pipeline, these groups have a role in shaping the trajectory of TGR to PGM. In many interpretations, however, PGM is not primarily focused on the rare hereditary conditions that motivate these groups' special interest in TGR; rather, it is framed and promoted as helping the general population prevent and treat common complex diseases. This makes these groups' perspectives on PGM and its virtues very important for us to explore in this project. We will interview leaders and members of patient advocacy organizations representing a spectrum of genetic health problems about their visions of PGM as a social practice, and what they understand to be the benefits and risks of a personalized genomic approach to medicine for individual patients, patient groups, and society.

Aim 5. To develop an analytic map of the ethical challenges and policy choices that different interpretations of PGM could generate for TGR and health care.

The final aim of our project is to elucidate the ethical, social, and policy implications of the results of our stakeholder studies, and construct a guide to the choices they will present as TGR approaches its goal. Our previous research suggests that examining the interests and concerns of PGM's promoters, mediators, providers, and users will allow us to abstract a rich array of potential decision points in the evolution of PGM and to identify considerations that might be used in their resolution. Achieving this aim will involve an iterative process of classifying and comparing our qualitative data analyses as they emerge; we will extrapolate from the taxonomy of the virtues that different co-producers attribute to PGM and the stakeholder interests that animate them to the ethical and social risks they entail. Since all of PGM's co-producers will still be involved in negotiating the use of this map from different positions of power, its development will not guarantee that PGM develops along any particular route – or even whether it will emerge as an ethically acceptable social practice. Having a clear guide to the issues and options from multiple perspectives can, however, help level the playing field for those negotiations, and help all the negotiators anticipate the potential challenges in the road(s) ahead.

Background and Significance

“Personalized Genomic Medicine” is a concept that has emerged in tandem with the human genome research that is providing its tools – and for which it provides a crucial justification. At the dawn of the Human Genome Project in 1990, for example, Patricia Baird called for a genetic “paradigm shift” in health care, arguing that:

Rather than ignore the internal genetic component to disease cause, we should evaluate the genetic input and then attempt to tailor preventive or therapeutic programs to take it into account. We will then be able to focus our prevention of disease where it will have most effect -- to those who are predisposed, and before they start down the pathogenic pathway. ...We need to see our own genetic individuality as a potential origin of disease. We are all different --we are all genetically unique -- which means our risk for disease is different one from another. Progress depends on realizing this and applying the knowledge to prevention.¹

Over the course of the Human Genome Project, its leadership followed suit, by consistently predicting that:

Ultimately, the results of the HGP ... will profoundly alter our approach to medical care, from treating disease that is already advanced to a preventative mode focused on identification of individual risk. This should permit early initiation of changes in lifestyle and medical surveillance, preventing individuals from becoming ill in the first place.²

As genomic research has moved on from the successful completion of the Human Genome Project into its “translational” phase over the last decade, “PGM” has become the label for this vision of health care, and serves as a banner that unites many of biomedicine’s leading research enterprises in their efforts to shape the future of medicine. Within the federal government, former Department of Health and Human Services Secretary Michael Leavitt produced reports promoting the vision,^{3,4} former National Institutes of Health Director Elias Zerhouni elaborated ambitious “roadmap” initiatives to show biomedical researchers the way,⁵⁻⁷ the Center for Disease Control scrambled to find a place for PGM in public health⁸ and the National Institute for Human Genome Research reframed its mission against this vision’s “grand challenges.”⁹ In the UK in 2003, health secretary John Reid proclaimed that “we are standing on the threshold of a revolution in health care,” in which “genetics promises a more personalized, approach to health care, with interventions tailored to each person’s own genetic profile.”¹⁰ The leaders of academic and commercial biomedical research institutions followed suit, creating a national wave of new institutes and programs devoted to realizing PGM.¹¹ This activity produced its own advocacy organization in 2004, the Personalized Medicine Coalition. Federal legislation was introduced in the U.S. in 2006 by Senators Barack Obama and Edward Kennedy to help propel the movement.¹²

At the rhetorical level, there is no mystery about the virtues of this “tectonic shift in medicine”¹³: every exposition of PGM repeats them as a *mantra*, as in this passage from a recent manifesto in the movement’s new journal, *Personalized Medicine*:

“Personalized healthcare is envisioned as a comprehensive approach, incorporating gene-biological information to understand each person’s unique requirements for health maintenance, disease prevention and therapy tailored to genetic or molecular profiles. In addition, it includes consideration of each individual’s environment, health-related behavior, culture and values. *Thus, personalized healthcare promises to be predictive, preventive, and pre-emptive, with the potential to transform current healthcare into a value-based, patient-centric healthcare system*.”¹¹

Despite all this enthusiasm, moving from the completion of the Human Genome Project to the realization of PGM has not been an automatic or instantaneous process. In part, the difficulties are scientific. But economic, regulatory, and political barriers to progress have also slowed translation.¹⁴⁻¹⁷ The U.S. still lacks a clear system for ensuring the utility of new genetic tests before they are introduced,^{18,19} and it is not clear how “individualized” their complementary therapies can become if they are to be commercially viable.²⁰⁻²² Despite the passage of federal legislation barring genetic discrimination in employment, worries about the exclusionary use of genetic information in life and long-term care insurance persist.²³ Even the current US remedies for

protecting patients' privacy and the interests of human research subjects have been charged with retarding TGR's progress.^{24- 25}

These regulatory concerns only grew when direct-to-consumer (DTC) personalized genome services became available for purchase on the Internet in 2007. While advertisements for DTC genetic testing first appeared on the Internet in the early 2000s,^{26,27} the recent expansion of the market to include multiplex genetic tests and personal genome scanning services has attracted a great deal of attention within biomedical, scientific, and political sectors^{14,28} These "recreational genetics" companies are not required to ensure that their services are accurate, clinically validated, or reliable^{29,30} and clinicians are not yet prepared to counsel their patients about the implications of the DNA profiles they might buy.^{31,32} Against that backdrop, the risks of premature diffusion of PGM are thrown into relief, generating more calls for regulation regardless of their impact on the pace of translation.³³

Moreover, most of these regulatory gaps and hurdles also provoke ethical concerns. If the costs of personalized genomic risk assessments and individually tailored therapies are high enough to limit PGM to "concierge medicine" and other forms of elite health care, it will become harder for the poor to enjoy its benefits, raising social justice challenges to TGR's priorities.³⁴ On the other hand, if PGM amounts to no more than patient risk stratification along ethnic, racial, or socioeconomic lines, it risks exacerbating the social problems that already exploit these categories.³⁵⁻³⁷ If PGM's services are unreliable and clinicians remain ill-equipped to interpret them, the risks to patients' best interests and the public's welfare increase.^{38,39} And, if enthusiasm for PGM threatens the protections afforded biomedical research volunteers, important questions of human rights and scientific integrity are provoked.

The literature that addresses these ethical, social, and policy challenges often frames them as issues imposed on PGM by the structural constraints of our society and regrettable constrictions in the translational pipeline. Our interest is in whether the PGM paradigm is itself a contributing factor to those well-studied ELSI challenges, and, if so, in what ways. For example, the early detection and prevention of risky gene-environment interactions are often cited as key virtues of PGM, and when the environmental side of the equation cannot be manipulated, "primary prevention" in this context is sometimes interpreted as preventing the transmission of the risky genotype -- reintroducing all the ethical issues involved in intervening in people's reproductive decision making that complicate traditional medical genetics.⁴⁰ Most proponents of PGM resist this slide by concentrating on multi-factorial adult problems such as drug dosing, rather than on deterministic genetic diseases and reproductive risk testing.⁴¹ PGM's claim to "individualize" these medical interventions reflects an awareness and appreciation of human genetic diversity, which has both medical and political appeal. It can both increase the safety and efficacy of therapeutic interventions, and suggest that care is being customized to patient's needs and identities. Of course, to the extent that PGM's "personalization" is limited to a patient's genetic profile, this focus also risks exacerbating any background inclinations to reduce the patient's individuality and identity to his/her genes.⁴²

To explore these ideas, we will cast a wide net across the contemporary PGM landscape. Most ELSI research on the topic has focused on two practices that PGM's early proponents used to illustrate its benefits: DNA-based health risk assessments and genotype-dependent drug prescribing. Over the last decade, however, PGM has attracted an array of subscribers that go well beyond genomic profiling and pharmacogenomics. Today the label is used for activities as disparate as traditional reproductive genetic testing and counseling, gastrointestinal bacterial profiling, wellness and health promotion behavioral modifications, nutritional regimes, family history taking, and public health screening programs. This variety generates a wide range of interpretations of "personalized, predictive, preventive and participatory" medicine and how genetic tools become involved. For the purpose of our study, this interpretive diffusion can function like an electrophoretic gel, exaggerating the differences between possible accounts so that they are easier to isolate and compare. This diversity also creates the need for "boundary work" within the PGM community to police the use of its label, which often provokes more reflective attempts at normative self definition that can be illuminating.⁴³ As the subscribers to PGM move further away from its core practices, their attempts to adapt the model force its reinterpretation, exposing logical extensions of its precepts that can highlight the issues at stake.

Since the inception of the Human Genome Project, it has been popular in some quarters to cast the ethical, legal, and social issues in TGR as essentially time-limited problems, caused by the “therapeutic gap” between our abilities to read people’s genomes and offer effective remedies to any identified deficits.⁴⁴ As genomic medicine catches up with genome science, it is argued that the issues caused by this awkward interim should evaporate because it will no longer be in anyone’s interests to discriminate on the basis of genotype—i.e., our “personalized” diagnoses and risk assessments will make actuarial gambles unnecessary and the availability of individualized treatments will undercut their stigmatizing potential within our health care system. If, in fact, there are important potential issues embedded in the aspirational frame of PGM itself, closing the “therapeutic gap” may not provide relief from these concerns. This will be frustrating, unless these challenges have been anticipated well in advance. This project is designed to help address this need.

Preliminary Studies/Progress Report

Our plans for this study represent the convergence of three lines of scholarship within the CWRU Center for Genetic Research Ethics and Law (CGREAL): (a) Dr. Juengst's previous conceptual and ethical analyses of interpretations of prevention, prediction, and personal identity in genetic testing contexts; (b) our empirical pilot studies of the commercialization of genomic research and the "translational" rhetoric that informs it, led by Dr. Fishman; (c) the professional stakeholder analyses that Drs. Settersten and Fishman have developed within our ongoing National Institute of Aging R01 study of social challenges in the clinical translation of scientific efforts to understand and control the biology of aging. The study we are now proposing draws on results, concepts, and methods from each of these efforts, and to that extent represents a next logical step for each line of inquiry. Bringing them together, however, also opens up the new set of research aims we now propose to address, and has provoked significant innovations in our theoretical approach. In this section, we describe the key contributions that these three lines of previous research bring to unlocking our new questions, thereby setting the stage for the new research design that their synergies have inspired.

a. Prediction, Prevention, Personal Identity, and Genomics.

Dr. Juengst's philosophical contributions to ELSI research have all been attempts to help clarify the goals and assumptions of human genetics in order to anticipate its implications for different spheres of policy and practice. Over the last five years, his work has been increasingly focused on the ideas that drive biomedicine's efforts to "translate" basic genomic science into tangible health care benefits, both in the design and conduct of TGR (through CGREAL's P50 supported studies) and in the evolution of molecular genetic medicine as a social practice (through our NIA R01 case study of translational biogerontology and "anti-aging medicine"). For Juengst, our current proposal represents a particularly exciting stage in this research program because of the way the concept of PGM promises to reflect on and be illuminated by his program's most robust themes to date. This project draws on three themes that promise to be useful in exploring the possibility that PGM's virtues could also raise ethical and social challenges: **the limits of prediction, the logic of prevention, and the dangers of essentialistic interpretations of human identity.** These themes help generate our motivating hunch that PGM's virtues might also be the source of ethical and social challenges, stand behind our interest in turning to PGM's proponents and users in exploring that hunch, and help provoke the questions we will ask of them.

The limits of prediction. Its promise to introduce an era of more predictive medicine stands out among all of PGM's putative virtues as the one most easily understood as double-edged, since the clinical limitations and social risks of predictive genetic information have been a central topic of ELSI research for two decades. Juengst's contributions to this discussion have concentrated on the ethical tensions that predictive uncertainty can raise for clinicians,^{45,46} families,^{47,48} genetic researchers,^{40,49} and customers of commercial genetic services,⁴² and the conceptual implications of predictive genetic information for the understanding of health and disease.⁴⁹ Even where complementary preventive interventions are available, this work helps show that the medicalization of probabilistic health risks can raise important issues by reifying risk groups, stigmatizing the vulnerable, and foreclosing opportunities unnecessarily. To the extent that PGM is grounded in the identification of such health risks and frames them as personal flaws within individual patients ("poor drug metabolism," "low environmental threshold," "mismatched mutation repair" etc.), these issues will continue to deserve attention by its architects and users. Moreover, since the diagnostic definition of these risk categories often flows "upstream" into TGR from the clinical setting, health care providers who invent and use these foundational definitions are not just passive recipients at the end of the TGR pipeline.⁴⁹ By defining the terms in which PGM is conceptualized, they become important actors amongst the "co-producers" of PGM – and, therefore, a key set of potential informants for our study.

The logic of prevention. PGM's promise to shift healthcare's focus from disease treatment to disease prevention is its intuitively most attractive virtue for many stakeholders. For patient advocacy groups, prevention promises to spare families and communities the suffering that inspires their activism. For clinicians, health care institutions, and commercial service providers, pre-emptive interventions promise better outcomes – and the expansion of their services to asymptomatic at-risk patients seeking "health maintenance." For health policy makers and public health agencies, prevention promises lower health care costs and better population

health measures. Philosophically, however, as Juengst's research on this topic suggests, prevention in genetic medicine must always guard against two sets of moral mistakes: a return to the coercive ethos of collective eugenics or a slide into an unjust ethos of personal enhancement.

On one hand, this work underscores the ease with which the logic of prevention can lead to an equivocation between PGM as an approach for preventing the expression of a genetic disease in an individual ("phenotypic prevention"); and PGM as a strategy for preventing the intergenerational transmission of disease genes (genotypic prevention). For example, to explain how PGM might contribute to public health, some authors point to its preventive mission, and appeal to the public health field's traditional, lexically-ordered scheme of primary, secondary, and tertiary "levels of prevention." "Primary prevention" has traditionally been considered the ultimate goal of public health interventions, and for genetics primary prevention is often defined in terms of reproductive interventions that allow families and communities to avoid the birth of children with genetic diseases. As a result, equivocating between these two senses of prevention in discussions of genetic risk testing generates the deeper questions of public authority, social justice, and professional allegiance that invoke the shadow of eugenics and animate ethical concerns.^{40,45} To date, PGM has largely avoided these questions by focusing resolutely on phenotypic prevention. As reproductive genetic testing and population screening programs take up the mantle of PGM, it will become important to test that resolve by examining the logic of prevention that PGM employs.⁵⁰

On the other hand, as our previous studies of genetic enhancement issues have shown, the concept of prevention can also provide a useful cover for the manipulation of traditional constants of the human condition, such as aging, in potentially unjust ways. Juengst's collaborations with Mehlman, Murray, and Parens on a range of existing "enhancement" practices (including cosmetic surgery, the use of performance-enhancing drugs in sport, the use of biosynthetic growth hormone to increase stature, and the use of psychopharmaceuticals to improve cognitive performance) underscore two important social planning problems regarding the use of genetic and genomic tools for enhancement purposes.^{51,52} The first was the recognition that most potential genetic enhancement interventions will be initially developed as therapies for frank diseases, and then applied to healthy individuals for enhancement purposes after they have become medically established. This creates regulatory and professional issues of "off-label use," and shifts the focus of ethical responsibility for any potentially unjust uses of enhancement from the researchers who develop the interventions to the health professionals and users who would "abuse them." The second problem is that, in many cases, even the off-label use of these enhancing interventions can be medically justified as efforts to *prevent* the same diseases they were initially developed to treat.

In studying these problems, we focused on the ongoing debate over the emergence of "anti-aging medicine" and the provocative scientific claims of the biogerontologists about the prospects for controlling human aging. This work revealed patterns and questions that took our analyses of the ethics of genetic enhancement in several unexpected directions. With NHGRI/NIA support, and the addition of Robert Binstock, Stephen Post, and Peter Whitehouse as collaborators, we observed that the ethical debate over the moral merits of attempting to control human aging is not two-sided but is tripartite, pitting "life cycle traditionalists" against both "prolongevists" seeking to extend the life span and "meliorists" seeking to prevent late life disease.⁵³ Further, the debate was driven as much by the need for professional "boundary work" between different professional stakeholders – e.g., researchers and their sponsors, journals and legitimizing organizations, clinicians and entrepreneurs, as by bioethical argument. These patterns overlap and interact in interesting ways in scientific and scholarly debates over controlling aging.⁵⁴ We, however, were most interested in the apparent power of the preventive frame, especially within the biomedical community.⁵⁵ In person, many biogerontologists admire the prospect of extending the human life span, reject the concerns of the "life cycle traditionalists," and express ambivalence over the question of whether senescence itself should be considered pathological. In public and in print, however, the meliorist view dominates their discourse—i.e., interventions aimed at controlling aging are defended in terms of their abilities to prevent or forestall late-life disease.⁵⁶ What the example of biogerontology suggests, of course, is that the prevention of diseases through early interventions into normal processes will, in some cases, also involve the re-engineering of the traditional constants of the human life cycle.

For our current project, this research on the logic of prevention suggests several important elements: First, to the extent that reproductive genetic services and public health programs are accepted as forms of PGM, the shadow of eugenics will need to be addressed. Similarly, to the extent that PGM embraces the preventive strengthening of human phenotypes it does not want to pathologize, such as normal aging, susceptibility to poisons, or muscle repair, its proponents and users will need to position themselves within the debates over the ethics of human enhancement. For example, some PGM advocates urge a turn to the “genetics of health” to identify modifier genes and protective alleles that promote health and longevity, “despite presence of genetic and environmental risks”.⁵⁷ This gives PGM an attractive emphasis on individual health promotion, which appeals to the strong meliorist approach that is current within biomedicine. Of course, as this quote suggests, this also opens the model to a wide range of interests that would otherwise be marginalized as suspect forms of biomedical “enhancements.”

The dangers of essentialism. A third philosophical theme that informs our current project is also a familiar one for ELSI researchers: it concerns the risks of over interpreting genetic information as meaningful to personal identity. Given the last twenty years of efforts by the scientific community and ELSI researchers to discourage the public from investing too much personal meaning in the results of DNA tests, it may seem surprising – and perhaps disheartening—that the signature mark of the recent wave of companies to provide “personalized” genetic profiles to customers has been the inclusion of first-person pronouns in company names: “23andMe,” “deCODEme,” “Knome,” “Mycellf,” and “Mygenome.” While the rhetoric of these commercial enterprises is more flamboyantly essentialistic than that of other stakeholders in PGM, it does flag a broader concern. In fact, Juengst and Nordgren’s preliminary analysis of this rhetoric suggests that this appeal to genetic essentialism – the view that our genomes do intrinsically define our personal identities as secular substitutes for the soul – does play a tacit role in many stakeholders’ visions of PGM. For the DTC services, our work traces this appeal to the confluence of three philosophical currents in Euro-American culture: the distinctly pre-modern search for a naturalistic understanding of individual identity; the thoroughly modern cachet of genomics as a science; the post-modern emphasis on radical individual self-determination in a pluralistic world.^{42,58} By suggesting that “personal genomics” can help consumers understand socially potent aspects of their identities these services naturalize identity categories that we usually embrace when they work in our favor but resist when they count against us socially.⁴⁹ By trading on the cachet of genomic science to legitimize these identities, consumer genomics can powerfully reinforce the importance of these socially ascribed identities for both the customer’s self identification and identification by others. Far from providing startling insights that can liberate customers from the constraints of old social labels, genomic testing may simply reinscribe those labels into their genes.

To the extent that these commercial services influence the shape of PGM as a social practice by being incorporated into mainstream health care, this risk will underscore the need to think clearly about the senses in which PGM is “personalized.” This will be particularly important for the parts of PGM that “personalize” interventions only by assigning individual patients to different population-based genetic risk groups.⁵⁸ Here, we can draw on the four kinds of risk group classifications that Juengst suggests can have potent consequences for their members’ social ascribed identities: family affiliation; ancestral origin; clinical risk cohort; ethnicity.⁴⁹ This work suggests that the conceptual connections between “individualizing” therapeutic interventions and essentialistic interpretations of personal identity will be another important tension to explore with those co-producing PGM, and particularly supports our interest in hearing from genetic advocacy groups and ethnic minorities.

b. PGM and personal responsibility for health

In addition to Juengst’s conceptual and rhetorical analyses, our interests in using the commercialization of genomic services as a lens on TGR have been explored from social scientific perspectives as well, under the leadership of Dr. Fishman. Over the last year, Fishman, McGowan, and Lambrix have conducted participant observation research at professional conferences to assess the emergence of DTC personal genome scanning services. As part of this research, they have examined the cultural meaning of DTC genomics for various stakeholders (e.g., bioinformaticists, genome scientists, ELSI researchers, scientists, and entrepreneurs) and the social values that contribute to their understandings of the commercialization of these new services.⁵⁹ The explicit move to providing genetic information directly to consumers outside of a clinical setting exemplifies the

virtue that PGM sees in placing more responsibility for health care and health knowledge squarely onto the shoulders of patients/consumers themselves. As the Personalized Medicine Coalition stresses in describing PGM, “it is proactive and participatory, engaging patients in lifestyle choices and active health maintenance to compensate for genetic susceptibilities”.¹³ Whether or not PGM emerges primarily as a commercial consumer service in the future, the early arrival of DTC companies under its banner shows the power of “patient empowerment” as a virtue, and hints at the issues of exploitation it can provoke.⁶⁰

In a related pilot study, McGowan, Fishman, and Lambrix also began collecting data early in 2009 for an empirical study of the impact and implications of the promise of PGM for “early adopters” of DTC personal genome scanning services. The objective of this study is to assess individuals’ reasons for purchasing personal genome scanning on the Internet. In addition, it seeks to find out how they interpret the results and apply them in making health-related decisions, and what these users of genomic services understand to be the potential benefits and detriments of personalized medicine. While companies offering DTC genome scanning tout the personal empowerment of consumer access to their own genomic information, we argue that it will be important to assess whether increasing patient or consumer empowerment in this context also has the effect of increasing individual responsibility for one’s own genomic health.^{59, 61} More recently, Dr. McGowan was awarded an NRSA postdoctoral fellowship to explore primary care physicians’ familiarity with DTC genetic testing and personalized genome services, how they interpret the complex information presented in whole genome scanning reports; and describe the implications they see for the health care care provider-patient relationship. The interview guide and results of this study will be instrumental in the development of materials for our current study of genomic medicine clinicians’ perspectives on PGM (Specific Aim 3).

We do not think that DTC genomic services are driving the emergence of PGM, or that they necessarily reflect what it might grow to be as a social practice. However, these services do represent one of the first social expressions of PGM’s vision, leapfrogging the traditional translational pipeline to offer services in the name of PGM before the mainstream of health care is prepared to do so. To that extent, it has served as a useful laboratory for pilot studies that can help generate questions to ask about PGM as a social practice. For our current project, these pilot studies suggest that it will be important to ask stakeholders about the extent to which PGM can live up to its promise to empower patients to take responsibility for their own health care, and what the correlative risks of that might be for the provider-patient relationship. For example, one company says:

At DNA Direct, we believe that testing is about empowerment – your body and your health are ultimately your responsibility, and your genes offer tremendous insight into personal, medical and lifestyle choices. . . . Genes are a valuable part of the equation, and they must be interpreted in context and in privacy. We have set a unique service that does just that – while providing individuals with knowledge and insight to take control of their personal health”.⁶²

Of course, taken to extremes, the notion that health is a matter of individual responsibility can serve to exculpate those social actors who ordinarily share that responsibility, such as health care institutions, health care funders, and health professionals. At the same time, it can impose undue burdens of responsibility on individuals to police their “environment, health-related behaviors, culture and values” in ways that prevent disease.⁶³

c. Social stakeholders and the “co-production” of translational biogerontology.

Finally, our current project builds on our ongoing study of the evolution of translational biogerontology and the emergence of “anti-aging medicine.” This project is an empirical study of three sets of stakeholders—biogerontological scientists, anti-aging clinicians, and anti-aging patients, in order to document the interpretations they give to efforts to control human aging and to uncover the social, commercial, political, and ethical considerations that influence those choices. Having previously observed that, like PGM, *prediction* and *preemptive intervention* were the benefits that biogerontologists and their research sponsors use to explain and justify their interest in controlling human aging, we are seeking to know more about the emergence of anti-aging medicine and its relationship to the preventive paradigm.^{64, 65} How do the translators and users of this

paradigm explain and justify their interests, and where do their interpretations cohere or conflict with the norms of the preventive interpretation? To accomplish this goal, we mounted a more formal empirical study of how anti-aging interventions are interpreted by those who use, provide, and debate them, shifting the composition of the team again to include our sociological colleagues Dr. Fishman and Dr. Settersten, and two medical sociology doctoral candidates, Ms. Lambrix and Mr. Flatt. We are now finishing the final year of this study.

To date, we have completed in-depth interviews with 43 prominent biogerontologists and 32 anti-aging clinicians. We have finished our participant observation activities by attending nine (both scientific and medical) anti-aging/biogerontology conferences. By August, 2009, we will have completed interviews of what will likely be 35 patients of anti-aging medicine as well. In addition, we have begun the normative analysis of the implications of our findings for policy and regulatory concerns. All interview transcripts and field notes pertaining to the first two sets of stakeholders—biogerontologists and anti-aging clinicians—have been transcribed and coded. Our publications from these projects are listed in Appendix C.

From Anti-Aging to PGM

Because biogerontology has already seen its science “translated” (prematurely) into clinical practice on the strength of the preventive frame, it offers a useful example to examine in anticipating the future of PGM. Four elements in the arguments over anti-aging science and medicine elements of that picture provide particularly provocative starting points for our current study.

Translational pathways. Anti-aging science has been translated into applications in a myriad of ways. While there are no FDA-approved innovations or interventions for anti-aging purposes, aside from those for cosmetic purposes (e.g., botox), products and techniques are made available to patients via anti-aging clinicians and directly to consumers in drugstores and elsewhere. The traditional linear translational pathway from science to clinical practice, in which a scientific development makes its way from basic research to human clinical trials to FDA approval, has been by-passed for many of these applications. Clinicians “translate” scientific data themselves and then provide personalized products and techniques to their patients. For example, human growth hormone (HGH) and other hormones are often used to prevent senescence, although they are not approved by the FDA for anti-aging purposes. At professional meetings, such as those of the American Academy of Anti-Aging Medicine, clinicians are taught how to use lab tests to look for each patient’s individual hormone “deficiencies” and then create personal HGH prescriptions. Other pharmacotherapies touted to consumers for their anti-aging properties are also ubiquitously available on-line or over the counter. For example, David Sinclair of Harvard University is recognized as having discovered resveratrol, the compound in grapes (and other plants) thought to have life-extending and disease preventing properties. Sinclair’s work on resveratrol is on the traditional translational pathway to a pharmaceutical through the company Sirtris Pharmaceuticals (which Sinclair recently sold to GlaxoSmithKline). Meanwhile, resveratrol is already available in various over-the-counter forms for interested consumers, having bypassed the traditional channels.

These alternative translational pathways and the increasing availability of innovations by clinicians create complex conflicts between biogerontologists and anti-aging clinicians. This tension seems to be amplified by the fact that efforts to control human aging are seen by some as morally suspect endeavors, exacerbating concern that the availability of applications before they are properly tested threatens the legitimacy of biogerontology as a scientific field.^{66,67}

PGM seems to be embroiled in similar circumstances. While numerous researchers are pursuing pharmacogenomic and other therapies through traditional translational pathways, others are creating applications of genetic and genomic research and offering them directly to consumers. These range from nutrigenomic products to whole genome scans to genetic susceptibility testing available for purchase without regulatory approval. Genetic and genomic research, like anti-aging research, is the subject of ethical debate as well. In fact, the relationships between constituencies is likely to be even more complicated in the emergence of PGM as new partnerships are created between for-profit companies, academic institutions, and governmental parties. We are eager to uncover the nature of these relationships and explore how the controversies play out in this emergent arena.

Disease prevention. Our analysis of the rhetoric that anti-aging scientists and clinicians use to describe their research and practice led us to examine the use of individualized disease prevention as a way of framing the goals of the respective projects. Their emphasis on disease prevention keeps both researchers and clinicians. keeps them in harmony with laudable medical goals, and shields them from potential ethical criticism for attempting to manipulate one of the constants of the human condition.⁶⁹ However, one of the consequences of invoking prevention as a goal is the medicalization of aging itself. As many biogerontologists have expressed it, “aging is the single biggest risk factor for disease in late life.” This leads to the definition of new diagnostic categories within senescence, such as “mild cognitive impairment,” on the grounds that “the identification of people at potential risk of dementia with a view to early therapeutic intervention is important, because it may lessen distress for both patient and family, minimize the risk of accidents, prolong autonomy, and perhaps even ultimately prevent the onset of the dementing process itself”.⁷⁰ While this medicalization helps legitimize early intervention, it also has the potential to place large numbers of people in the “at risk” role, with its attendant risks of stigmatization and heightened responsibilities.⁶⁵ Much the same seems to be happening in PGM, as genetic variations and susceptibilities are reconceptualized as “vulnerabilities” in order to be targeted for medical detection and intervention.⁷¹ We would like to study the impact of that shift on the thoughts and work of those involved in the development of PGM.

Making medicine personal. One unexpected finding that emerged clearly from our interviews with anti-aging clinicians was the extent to which they emphasized that their practices were “personalized and individualized” to their patients’ needs,⁶⁸ While they count themselves as part of medicine’s new personalized paradigm, their clinical modalities were not genetically or genomically-based. What they meant by “personalized care” were the more traditional practices of taking extensive medical histories, increasing physician time with patients, and attempting to go beyond treating symptoms to uncovering the underlying pathology. Moreover, they overwhelmingly felt that individualized care is precisely what their patients were seeking when they turned away from more conventional biomedicine. Anti-aging physicians’ impetus to move into this new field was driven by the sense that physician interactions in the United States today have generally become routinized and impersonal, with the quality of care and decisions determined by insurance and managed care companies rather than being “patient-centered.”⁶⁸ This is very similar to the advocates of PGM, who warn that “Healthcare today is in crisis: it is expensive, reactive, inefficient, and focused largely on one size fits all treatments for events of late stage disease. *The answer is personalized, predictive, preventive and participatory medicine.*”¹³ The strong desire on the part of both physicians and patients to return to an earlier era of more personalized health care, coupled with the emergent technological developments of personalized medicine emerging in genomics, led us to wonder how PGM will frame this multi-dimensional concept of “personal” and how it will be realized in practice.

Research Design and Methods

This project involves the description of professional attitudes and beliefs, the analysis of the evolution of biomedical concepts, and the extrapolation and critical assessment of ethical and policy concerns. Methods appropriate to each of these forms of scholarship will be employed under the leadership of co-PIs with expertise in their use. The different lines of research will be conducted in a staggered, iterative fashion (see timeline at end of budget justification) so that they may each benefit from the others' findings. Regular team meetings will serve as the principal forum for integrating the lines of inquiry. At these meetings, we will review our progress, hammer out our collective analyses, and discuss the new literature our research staff brings to our attention. This approach has proven fruitful in the past because of the overlap between the spheres addressed by the different project aims.

This section will explain the project's theoretical framework, and details the research that will be conducted for each aim. We will also describe the four-year timetable for accomplishing the research, the protocol for developing interview guides and conducting interviews, and key strategies for analyzing resulting data.

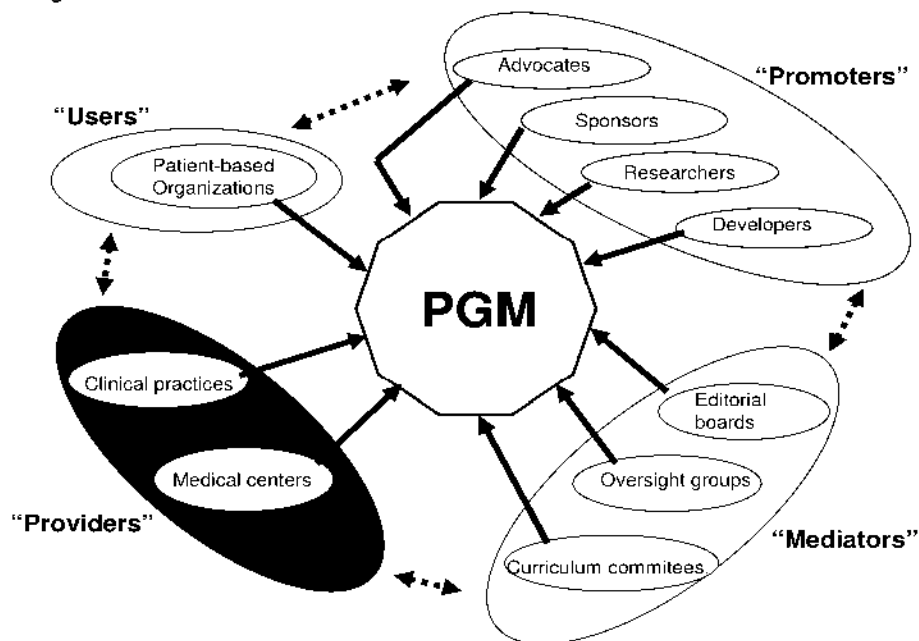
Theoretical Framework

Our approach to this project is grounded in the idea that widely-shared concepts such as PGM develop under the influence of multiple social actors with reasons to care about how the concepts are understood and acted upon within a society. Within political science, this process is often described as a negotiation between stakeholders whose different interests will be affected by a final policy outcome. For historians and philosophers interested in the evolution of scientific concepts, it can be framed as the interplay of different methodological perspectives and theoretical commitments within a scientific community and the effects of those interactions on the scientific claims that result.⁷² In sociology, both interpretations of this idea have been combined for use in guiding empirical studies of emerging social practices, in "social worlds and arenas theory".^{73,74} This is the theoretical framework we have used in designing this research, and to which we will return in conducting our analyses.

Social worlds and arenas theory suggests that we imagine a social phenomenon we are interested in understanding—whether it is a concept, a practice, or policy or a problem—as an object under construction in hypothetical space. The space is society, and the object's location—the "social space" it occupies, or its "social arena"—is determined by its function. For example, the social arena of PGM would be the specific social space where "goals for TGR" are hammered out, within the successively larger social spheres dedicated to determining the direction of biomedical research and the future of health care. Moreover, the social universe is also populated by numerous "social worlds," such as "the scientific community" or "the legal system" or "the patient advocacy world," which are integrated networks of people and social institutions with their own special interests, perspectives, and trajectories through social space. When their trajectories intersect particular social arenas, these social worlds become involved in the design and development of the projects in those arenas, negotiating as stakeholders for their special interests and contributing their special "situated" or "positional" perspectives as collaborators.⁷⁵ While the extent and influence of this involvement varies with the nature of the project and relative power of the worlds involved, the resulting "co-production" of social projects such as PGM is shaped by multiple agendas, cultures, and values. In this sense, PGM is what sociologists call a "boundary object"—i.e., a concept, policy, or practice that "is both plastic enough to adapt to local needs and constraints of the several parties employing them, yet robust enough to maintain a common identity across sites".⁷⁶ This model has been particularly useful in studying emergent arenas in science and medicine. Because contemporary scientific and medical developments are "multi-sited," involving numerous actors in various social organizations, social worlds theory is especially helpful for keeping account of the relevant actors without assuming that the developmental process is linear.⁷⁷

Figure 1 (below) diagrams this model for our project. From the leads in our past work, we have identified ten of the (many) social worlds involved in the co-production of PGM as a biomedical paradigm that will be potentially useful to study. For organizational purposes, we have grouped these ten worlds into four constellations

Figure 1



according to their role in the project of designing and implementing PGM: the “promoters” who are its architects and builders; the “mediators” who are its inspectors; the “providers” who will operate it; the “users” who it is designed to benefit. Our interest is in identifying the special interests and perspectives that color the ways in which those assigned to the PGM project from each of these worlds interpret their mission. For example, journal editorial boards, given their “positionality” as gatekeepers in their social world of authors, peer reviewers, competing journals, etc., may be mostly concerned about ensuring the scientific validity and integrity of PGM. Thus, they are more likely to prize the epistemic virtues of PGM—precision diagnosis, reliable predictions, etc.—over whether or not it empowers patients or promotes health. Health care providers, given their position in their social world of patients, payors, and malpractice suits, may be interested in the prospect that PGM can pre-empt clinically difficult critical care situations and help improve the safety and efficacy of drug dosing. Public health agencies, likewise, may focus on the promise of PGM to help promote personal responsibility in life style and nutritional choices, in order to improve population health measures.

Two other features of this diagram are important to note as well. As the dotted arrows between the sets of co-producers suggest, the social worlds involved in the development of PGM do not act in isolation. The constellations interact as the arrows indicate, and there are natural overlaps and interactions between the individual worlds as well. As social worlds theory suggests, most individuals, for example, will be citizens of multiple social worlds simultaneously, and many worlds are mutually interdependent in various ways. Untangling these influences requires nuanced and open-textured inquiry, and thus qualitative rather than quantitative empirical research methods, such as the in-depth, semi-structured key informant interviews we propose below.

Secondly, notice that the force lines indicating how these social worlds shape PGM also tether them in orbit around it. One measure of the social importance of “boundary objects” such as PGM is how far into social space their gravitational field extends. Clearly, some proponents would like PGM to dominate the whole biomedical sector, bringing the sector’s many other boundary objects—like the practice of medicine, concepts of health and disease, health policies, etc. – and the social worlds involved in their co-production into orbit around it. Whether this ambition will make PGM the lodestar of biomedicine or its black hole is the question that ultimately motivates our research.

In sum, social worlds theory provides a rich and appropriate framework for our project. By emphasizing that important social practices such as PGM are always “co-produced” by multiple social actors, social worlds theory opens up a range of stakeholder perspectives on what constitutes PGM. This variety is what will allow us to isolate the most influential of PGM’s virtues, and triangulate among them to develop a map of the policy

choices they might create for TGR.⁷⁸ Moreover, social worlds theory is a method for studying institutional and organizational actors, as well as individuals. With the exception of a few thought leaders, most individual participants in a given social world contribute collectively to its social projects through the institutions and organizations it supports. This means that institutional and organizational perspectives are more important than most individual views for understanding the boundary objects in question, allowing us to interview our respondents as key informants for the social worlds they inhabit rather than simply individuals with personal opinions.⁷⁴

Our interviews of these key informants will be guided by a common set of interview questions that will be developed according to the protocol described below. In general, these questions will be designed to document:

- How our respondents understand the goals and scope of PGM as a goal for TGR and a paradigm for health care, given their positions in the social worlds from which they are recruited;
- How, from their world's point of view, they would rank TGR's scientific priorities, in terms of the allocation of research funds and the research practices of scientists;
- How they envision the public and private sector will collaborate or compete with one another in terms of translating genomic research into personalized medicine;
- How they understand the role of their social world in the design and development of PGM;
- From the vantage point of their role in its co-production, how they interpret PGM's principal virtues or promises as a goal for TGR and a paradigm for health care;
- What they see as the key risks or challenges that realizing PGM as a goal for TGR and a paradigm for health care might raise for their social world and society at large;
- How they think their social world's perspectives on and contributions to TGR and the development of PGM compare with those of other co-producers;

Aim-specific Research Plans

Aim 1. To describe how the primary promoters of PGM as a biomedical research goal envision PGM as a social practice and assess its potential benefits and risks.

The first aim of our project is to analyze the interpretations that genomic scientists and their sponsors and agents give to PGM, in order to describe how they understand its promises. Although they develop their interpretations in negotiation with each other and other stakeholders, these are the social actors who promote PGM as a biomedical research goal by recruiting other scientists to its banner and soliciting its subsidy from taxpayers and investors. The cases that the promoters make to their audiences for embracing PGM are important to understand because they will shape TGR's scientific priorities, the allocation of research funds, and the research practices of scientists. To accomplish this aim, we will conduct semi-structured, in-depth interviews with active TGR scientists and thought leaders, their sponsors in government and the private sector, the organizations and companies that develop their work for medical application, and the leadership of their primary advocacy organization, the Personalized Medicine Coalition.

Dr. Settersten's role in our ongoing study of the evolution of translational biogerontology and Dr. Binstock's expertise in the political science of biomedicine make them the natural leaders for our team's efforts in this aim. They will develop the interview guide with co-investigators Fishman and McGowan, supervise the interviews, oversee the data analysis process, and collaborate with Juengst and our consultants in identifying the implications of our data. The project's research staff will be involved throughout the process in piloting the interview guide, conducting the interviews, and coding the interview transcripts. The whole team will collaborate on co-authoring papers from our analysis.

We will interview leading recipients of NIH funding related to PGM (15 cases) as key informants from the basic scientific research community. We will interview representatives from prominent translational genomic research companies and institutes (10 cases) as representatives from translational organizations. We will interview leaders or former leaders of the National Human Genome Research Institute (NHGRI), National Institutes of Health (NIH), and Centers for Disease Control and Prevention (CDC) (10 cases) as representative of public

sponsors. We will interview leaders of the Personalized Medicine Coalition and its member organizations (10 cases) as representatives of advocacy organizations.

1A. Researchers: Recipients of NIH Funding for Research Related to PGM

The world of TGR itself is one of the social worlds that has the biggest stake in the definition of PGM as a goal for TGR. The scientific community that conducts TGR, and the laboratories and institutions that its funding sustains, are most influentially positioned and most directly benefit from biomedicine's adoption and support of this goal. Conversely, they have the most to lose if PGM's promises turn out to hollow or double-edged. Those biomedical scientists whose research gambles with public funds, such as those who receive NIH funding for their work, are the most invested individuals. These grants symbolize the hopes of both the broader biomedical community and the taxpayers for PGM's promises. The published work that stems from these projects creates the scientific foundation for the future of the field. This puts a high premium on this constituency to be as clear as possible about its goals and promises, which makes it a promising source of data for our study. We will interview 15 key informants from this constituency.

To generate a sample of 15 key informants from the world of NIH-funded TGR, we will use the NIH "CRISP" (Computer Retrieval of Information on Scientific Projects) database to extract information on projects that have been funded in the past five years (2004-2009) by the NIH. We will use three different keyword search terms: "personalized medicine," "pharmacogenetics," and "pharmacogenomics." Examples of funded projects found in a preliminary search include: clinical studies related to making better medication and dosage choices; drug development studies to clarify relations between genotypes and drug response phenotypes (both safety and efficacy); studies that evaluate genetic variations and predict individual responses to particular medications; research to educate health care professionals and other groups about the potential benefits of new genomics and proteomics technologies. The duplicate results from these searches will be eliminated to generate a final list of grants to serve as a source of potential informants. In collaboration with our scientific consultants, our research team will review this list and select up to 15 investigators to be interviewed, based on their roles within the world of TGR. This strategy is not intended to yield a representative sample of all NIH-funded TGR researchers; rather, its explicit goal is to allow us to identify this group's most important thought leaders. Given the NIH's increasing appreciation of the perspectives of women and minority scientists in this world, we will be particularly keen to identify and include their projects on our interview schedule.

Expert Consultants for Building Basic Scientist Sample

To ensure that our samples capture the depth, breadth, and diversity of the emerging field of PGM, we have arranged to consult with two individuals who are leaders in TGR areas aimed at the two canonical forms of PGM--DNA-based diagnostics and pharmacogenomics: Dr. Joseph Nadeau, James H. Jewel Professor and Chair of the Genetics Department at the Case Western Reserve University School of Medicine and Co-Director of the Center for Computational Genomics; Dr. Howard McLeod, Fred N. Eshelman Distinguished Professor and Director of the University of North Carolina Institute for Pharmacogenomics and Individualized Therapy. Both have agreed to collaborate with us in this project (see letters of support, Appendix A). Dr. Nadeau and McLeod will review the list of researchers from the CRISP database to identify those who are most influential in their field, as well as those who are considered "up and coming." We will also use their knowledge of the field to identify women and minority researchers so that we can oversample from these groups.

1B. Developers: Key Translational Enterprises

The world of institutions and people engaged in the business of developing practical healthcare tools from the scientific results of TGR is a second social world with a role in promoting PGM. The ways in which PGM is defined as a social practice will become direct benchmarks for the success of those from this world because they are the enterprises that are charged with making the tools that can realize that definition. For private sector enterprises, this success means inventing products and services that make profits for their investors. For non-profit enterprises, it means discovering applications of TGR that elevate their social standing and secure their continued financial support. In both cases, developers have strong interests in interpreting PGM's promises in terms of their own capacities to fulfill them, and promoting that vision of PGM as the true holy grail of TGR. This social world is important to study because the companies are an "obligatory passage point" for

the implementation of PGM. The translation to clinical practice cannot happen without their skills. Their vision of PGM will, therefore, be influential for its future.

Our first sample from this world will be comprised of 10 informants from four of the leading translational research organizations that embrace PGM as their aspirational goal. In-depth interviews with these informants will yield critical insights from the vantage points of individuals who are directly involved in translational efforts in spheres outside of academia. This initial group will also provide information about both the larger organizations and start-up ventures that appear to be particularly influential in framing PGM as a goal for TGR. We will sample strategically from this list to ensure that we are capturing the full range of commercial and non-profit enterprises involved in this social world. As we proceed, we will continue to solicit nominations from those we interview. We have identified four organizations as initial venues from which we will conduct 10 key informant interviews. Two of these organizations are non-profit research institutes developing clinical applications of genomic information, and two are commercial companies that sell the technologies required for those applications:

- Translational Genomics Research Institute (TGen), is a not-for-profit genomics research institute. Scientists at TGen conduct research on the human genome to assess how genomic variation can be used on a personalized level to make medical diagnoses and prognoses, and to target treatment for a wide range of complex diseases.
- Coriell Institute for Medical Research is a non-profit biomedical research institute that is equipped for extensive biobanking and genotyping. Its Personalized Medicine Collaborative is currently collecting samples from 10,000 volunteers for whole genome analysis. They plan to use these genome samples to assess the clinical utility of genome-informed medical decision making and to assess genotypic variation in responses to medical treatments for complex diseases.
- Affymetrix is a leader in the field of DNA microarray technologies used in TGR. Both TGen and Coriell use the DNA-analysis platform called GeneChip, which is manufactured and marketed by the for-profit corporation Affymetrix. Affymetrix also sells its products to academic, governmental, pharmaceutical, biotech, diagnostic, and consumer-product companies.
- Illumina, another important player in the SNP chip industry, is focused on improving technologies for analyzing genomic variation. The company's products are used in the academic, biotechnology, pharmaceutical, and government sectors for research on diseases and for the development of drugs and clinical genetic tests.

Expert Consultants for Building Translational Enterprise Sample

To ensure that our sample reflects the full range of private-sector companies and non-profit enterprises involved in translation, we will consult with two industry experts: (1) Dr. Geoffrey Duyk, Managing Director of TPG Ventures, a venture capital affiliate of Texas Pacific Group. (Dr. Duyk was formerly the President of Research and Development at the drug development company Exelixis and the Vice President of Genomics at Millennium Pharmaceuticals. (2) Dr. Jeffrey Trent, president and scientific director of the Translational Genomics Research Institute (TGen) and the former scientific director of NHGRI (see letters of support, Appendix A).

1C. Sponsors: Public Funders of PGM-Related Research

The third social world that is active in the co-production of PGM is the world of governmental agencies and officers who manage the public sponsorship for TGR on the taxpayers' behalf. Governmental programs have been instrumental in promoting PGM as a rationale for TGR in ways that are similar to their role in other campaigns designed to garner public support for biomedical research—such as the “war on cancer” or “the decade of the brain.” Moreover, since they hold TGR's purse-strings, these programs are positioned to wield significant influence over TGR's directions and priorities as it attempts to realize PGM as a social practice. Thus, while it is unusual and potentially risky to turn one's research lens on the sources of one's own funding, the failure to do so in this project would be a serious omission. Moreover, our experience to date with the National Institute of Aging is that the NIH promotes transparency and is willing to support this kind of self-reflective research by its own grantees. We plan to conduct approximately 10 interviews for this project with

thought leaders associated with the National Human Genomic Research Institute (NHGRI), NIH at large, the Department of Health and Human Services (DHSS), and the Centers for Disease Control and Prevention (CDC). Our interests in these interviews are to document how these institutions understand PGM as a goal for TGR, and why they advocate this goal as a vision for health care in the U.S.

Since the completion of the Human Genome Project in April 2003, NHGRI's mission has evolved to encompass a broad range of studies aimed at understanding the structure and function of the human genome and its role in health and disease. The Institute's guidance in developing genomics research as a powerful tool in an era that seeks to transform medical care is a key part of this goal.

Following the organizational structure of NHGRI, we have identified 6 key leaders to interview. These include current and former officials from the Director's Office, the Divisions of Extramural and Intramural Research, the Intramural Center for Genomics and Global Health (which concentrates on applying TGR to international and minority health concerns), and current and former members of the National Advisory Council for Human Genome Research. In order to avoid entangling NHGRI in a conflict of interest with respect to the review of this project, we have not yet approached these potential interviewees to secure their willingness to participate. Given the NHGRI's history of public self-reflection on the ethical, legal, and social implications of its work, we anticipate a positive reception to our overtures.

Moving outward to NIH, we will seek to interview current and former officials from the NIH Director's Office and its Office of Science Policy, key advisers from the Director's Advisory Committee, and officials from other NIH Institutes that publicly promote initiatives aimed at realizing PGM, such as the National Cancer Institute, the National Heart Lung and Blood Institute, the National Institute for Child Health and Human Development and the National Institute of Aging. We will seek to interview former NIH Director Dr. Elias A. Zerhouni because of his particularly active role in promoting PGM as part of his "Roadmap Initiative."⁶ Similarly, we will also seek to interview former Secretary of the U.S. Department of Health and Human Services Dr. Michael Leavitt because of the priority his Secretariat gave to realizing personalized health care through its "Personalized Health Care Initiative," a vision that relies on TGR as the route to enabling "medicine to be tailored to each person's needs".^{3,4}

Finally, another player that has become increasingly active the world of TGR sponsorship has been the CDC, through its Office of Public Health Genomics. This office, together with NHGRI and the NCI, has recently launched the Genomic Applications in Practice and Prevention Network (GAPPNet), a "collaborative initiative to realize the promise of genomics in healthcare and disease prevention," which sponsors TGR in the context of state health departments.⁸⁰ Since the focus of that agency is on population and public health concerns, it will be particularly interesting to explore its positioning with respect to PGM and how it understands PGM's promises for its institutional mission. Our former CGREAL colleague Dr. Katrina Goddard, who recently completed a research fellowship with the OPHG, has agreed to assist us in identifying key actors from that program at the GAPPNet to approach for interviews (see letters of support, Appendix A).

1D. Advocacy Organizations

Finally, the social world with the most explicit mandate to promote PGM is the world of the constituencies that advocate for more governmental support of TGR and champion the vision of PGM as "a tectonic shift in medicine".¹³ With the collaboration of the Personalized Medicine Coalition (see letters of support, Appendix A), we will interview 10 thought leaders from its advisory committees and member organizations. The PMC is an organization that seeks to promote sound public policy development on matters that will affect the realization of the promise of personalized medicine. PMC membership encompasses a broad spectrum of academic, industrial, patient, and health care provider constituencies. The PMC works with member organizations to both minimize the duplication of efforts and collaborate to improve leverage. It also allows federal and state policy makers to participate in this educational process with private sector health care leaders, helping all to better understand the science and the policy issues. This makes its interpretations of PGM particularly important to understand for our purposes.

We will begin by consulting with the two primary leaders of the PMC: Dr. Edward Abrahams, Executive Director, and Dr. Wayne A. Rosenkrans, Jr., President and Chairman (see letters of support, Appendix A). These consultations will provide a birds-eye view of the field from the vantage point of a large coalition with an explicit policy mission. We will then ask each PMC leader to nominate up to 5 additional member organizations of the Coalition that they view as particularly influential in advocacy efforts related to personalized medicine. We will interview the leaders of up to 8 organizations. To oversample minorities, we will also ask the leaders of PMC to help us identify racial and ethnic groups with which they have alliances and to whom we could turn for interviews (e.g., the patient advocacy group, National Alliance for Hispanic Health, is a member of PMC).

Aim 2. To describe how those who mediate the development and diffusion of new health care practices interpret PGM and its promise as a health care paradigm.

In order to realize PGM as a social practice, TGR must do more than develop new clinical tools from basic research findings. It must also negotiate the acceptance of those tools by biomedicine's internal gatekeepers and public monitors, and sell its vision to the medical educators who manage the canon of normative medical thinking. We call these three social worlds the "mediators" of PGM's progress, since their judgments about its products will be influential in shaping the suite of tools and services that become the socially legitimized core of what PGM offers to health care providers. Those judgments will take into account the assessments of the benefits promised by co-producers of PGM, including promoters, which will depend in turn on the mediators' interpretations of those virtues.

We will conduct interviews with three sets of social actors who mediate PGM: scientific gatekeepers, medical educators, and public monitors. The scientific gatekeeper interviews will be conducted with members of the editorial boards of the two journals most relevant to the scientific self-policing of PGM: *Personalized Medicine and Pharmacogenomics* (12 cases). Health professional educators will be drawn from the group of social actors who are charged with the responsibility of translating knowledge about PGM to health professionals and medical students at the National Coalition for Health Professional Education in Genetics and selected medical schools (18 cases). In each case, we will be interested in seeing how their interpretations of the virtues of PGM might influence their judgments of the possibilities for the realization of PGM in the clinic. Public monitors will be drawn from the Department of Health and Human Services Secretary's Advisory Committee on Genetics, Health and Society and the CDC's EGAPP program, which together have provided the most active public oversight for PGM to date (6 cases).

Dr. Settersten's leadership in studying the role of professional gatekeepers in our ongoing study of the evolution of translational biogerontology and Dr. Fishman's work on the co-production of medical knowledge enable them to take the leadership responsibility for this aim. They will develop the interview guide with co-investigators Binstock and McGowan, supervise the interviews, oversee the data analysis process, and collaborate with Juengst and our consultants in identifying the implications of our data. The project's research staff will be involved throughout the process in piloting the interview guide, conducting the interviews and coding the interview transcripts. The whole team will collaborate on co-authoring papers from our analysis.

2A. Scientific Gatekeepers

The scientific media, as a central locus of scientific peer review, plays an important role in legitimizing the claims of TGR and policing the ideological boundaries of PGM. We will sample 12 members of the editorial boards of two journals that have positioned themselves as flagship venues for research related to PGM, *Personalized Medicine and Pharmacogenomics*, both of which are international in scope (6 members of each). Unlike more established journals of more general scope that publish TGR reports, such as *Genetics in Medicine*, *Nature Genetics*, or the *American Journal of Human Genetics*, these two journals are likely to rise or fall with the fate of PGM. For that reason, they have large investments in ensuring that its promises are realistic and well grounded. *Personalized Medicine*, founded in 2004, is the official journal of the Personalized Medicine Coalition (PMC). The editorial board of *Personalized Medicine* is comprised of leading experts within the areas of pharmacogenomics, pharmacogenetics, and pharmacoproteomics. Similarly, *Pharmacogenomics*, first published in February 2000, publishes peer-reviewed articles on the emergence of new pharmacogenomic initiatives and their impact on research and development and regulatory strategies,

newly-developed technologies for accessing and exploiting genomic information, and reviews of genotyping and clinical data in particular therapeutic areas.

Each journal has an editorial board of approximately 60 members, which will therefore allow us to systematically sample from among 120 scientists and thought leaders. Members of journal editorial boards make judgments about the scientific work that will (and will not) be published and given attention. As a result, they are also setting research standards for the field and establishing a foundation on which future research and clinical work will be built. In this way, their work helps define the canonical forms of PGM, and that makes their interpretations of its mission and virtues important for our inquiry. We will interview 6 members of each board by contacting every tenth name as listed and cycling back through the list in the same way with the remaining names as needed. Scientists will first be invited to participate via an e-mail message, which will also provide important details about the study. If there is no reply within four days, we will place a phone call. If there is still no response, we will send another e-mail with information presented in a fresh way that emphasizes the importance of their participation in the study. If there is still no response, we will return to our sampling list and continue with name selection criteria.

2B. Teachers: Translation to Medical Professionals and Students

The education of the health professionals that might practice it is another important way in which the precepts of PGM are mediated. The introduction of PGM to new professionals entering medicine will be an integral aspect of the successful translation of PGM to the clinic. Educational organizations, training programs, and health sciences curricula are powerful vehicles for legitimizing concepts such as PGM for health professionals, and for disseminating the tools and clinical strategies developed to realize its promises. As Thomas Kuhn suggested in introducing the concept of a “paradigm shift,” scientific revolutions are rarely complete until the next generation of scientists, trained under the new paradigm, gains control of their field.⁷⁹ To anticipate the ways in which PGM might unfold as a social practice, it will, therefore, be important for our project to know what health science educators are teaching the next generation of health care providers about its promises and pitfalls. We will turn to two important kinds of thought leaders to gather this information: the National Coalition for Health Professional Education in Genetics (NCHPEG), and the committees charged with overseeing the treatment of genetics in medical school curricula.

The National Coalition for Health Professional Education in Genetics (NCHPEG) bills itself as an “organization of organizations” committed to a national effort to promote health professional education and access to information about advances in human genetics. It was established in 1996 by the American Medical Association, the American Nurses Association, and the National Human Genome Research Institute. Members of NCHPEG represent an interdisciplinary group of leaders from more than 140 health professional organizations, consumer and volunteer groups, government agencies, private industry, managed care organizations, and genetics professional societies. The stated mission of NCHPEG is to “promote health professional education and access to information about advances in human genetics to improve the health care of the nation.” As such, it is positioned to be a primary influence on the conceptualization of PGM for health science educators, and a major voice for the social world of health professional education in policy making for TGR. Since NCHPEG acts as a broker between scientific advances and medical education, it will be valuable to examine how it conceptualizes itself as a co-producer of PGM as social practice.

We will interview the three staff members responsible for giving lectures to individuals, organizations, and students. We have already made contact with NCHPEG and have enlisted the assistance of its founding Executive Director, Joseph McInerney, as a guide to its constituencies and thought-leaders (see letters of support, Appendix A). McInerney has been involved in genetics education for 30 years, developing educational programs for audiences ranging from K-16 students and teachers to health professionals. We will also interview the current staff of NCHPEG, paying particular attention to its efforts to develop Diversity and Cultural Competency Objectives for health professional education. This initiative is intended to increase diversity in NCHPEG’s membership, ensure that NCHPEG’s programs and activities are culturally sensitive, and increase minority and underserved communities’ access to genetics education materials and resources

Our interviews will assess how the staff operates in order to fulfill the stated mission of NCHPEG. The interviews will cover a range of topics, including the manner in which NCHPEG tailors its message to a variety of audiences that includes K-12 students, medical students, and health professionals within and outside the field of genetics. We will ask these staff members what the obstacles are to educating medical professionals about PGM, and what they think are the possibilities that PGM has to offer. Additionally, we will ask about the relationship between genetics and race, particularly with respect to personalized health care. We plan to analyze the specific content of their lectures through conference attendance. Additionally, we hope to analyze the curriculum content that NCHPEG produces and distributes through its individual projects to member organizations.

The Genetics Curriculum in Medical Schools. Another route to understanding how the concepts and promises of PGM will be interpreted to health professionals is to examine current trends in medical school curricula. These existing curricula are important because, unlike NCHPEG's efforts, they are not necessarily developed in collaboration with stakeholders in TGR or PGM. In fact, these curricula are notoriously conservative in what they incorporate as important received wisdom, and slow to embrace new ideas. As a result, the extent to which they discuss the prospect of PGM at all will be an important measure of the level to which that concept has filtered into the biomedical world. To assess this activity, we will conduct interviews with the social actors charged with overseeing the treatment of genetics in 15 medical schools.

The Accreditation Council for Graduate Medical Education (ACGME), a private, non-profit council that evaluates and accredits medical residency programs in the United States, identifies forty-nine graduate studies programs that offer a specialization in Medical Genetics in the United States. The eight medical schools associated with the academic health centers that will be studied in Aim 3A described below are included in this list of 49 programs with Medical Genetics specializations. To capitalize on that synergy, those eight schools are a top priority in this aim. Beyond these, we will randomly sample from the ACGME list of schools to expand our sample to 15 programs. Directors of each program will be contacted by phone and/or e-mail in order to identify the appropriate contact person who oversees the genetics program curricula.

In order to ensure minority representation in our sample, we will broaden our sample to include three schools from the White House Initiative on Historically Black Colleges and Universities (HBCUs). Two HBCU medical schools, Meharry Medicine College and Morehouse School of Medicine, will be included. Since 1970, Meharry has conferred more than 10 percent of the Ph.D. degrees awarded nationally to African Americans in all of the biomedical sciences. While it does not have a Medical Genetics specialization, the school provides residency training in Preventative Medicine. We will request an interview with both the Director of this training program and the Director of Medical Education. We will also request an interview with the Associate Dean for Medical Education Course Sequence Director for Fundamentals of Medicine at Morehouse. Finally, we will request an interview with the Director of the Human Genome Center (NHGC) at Howard University. The goal of the NHGC is to bring multicultural perspectives and resources to an understanding of human genome variation and its implications for human health.

2C. Monitors: Public Oversight Bodies

Finally, a third set of stakeholders who will govern the eventual shape of PGM as a social practice is composed of the institutions that have been established to monitor the emergence of PGM on behalf of the public. The dominant institution in this world might be the FDA for much of biomedicine. But one famous feature of the social arena in which PGM is developing is that many of TGR's potential applications fall beyond its current regulatory purview. In its place, two other committees have become important social actors in helping to ensure that PGM's promises are evidence based and well validated before they are disseminated in practice: the DHHS Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) and Evaluation of Genomic Applications in Practice and Prevention (EGAPP). Since the procedures and policies they recommend will both shape the evolution of PGM and reflect how they understand the enterprise and its virtues, it will be important for our study to put our questions to both of these groups.

The DHHS SACGHS is a 17-member executive branch advisory committee that was chartered in 2002 and charged with making policy recommendations to the Secretary regarding the integration of genetic and genomic information into health care. The SACGHS has been influential in setting standards for clinical genetic

testing and working with the FDA to regulate commercial laboratory services. We will request an interview with the Chair of SACGHS to probe its views on the opportunities and challenges ahead for the development of PGM. In addition, Dr. Kevin Fitzgerald, a current member of the SACGHS, has agreed to serve as consultant to our project to help identify two other particularly influential leaders on the committee (see letters of support, Appendix A).

The CDC's EGAPP working group supports a "coordinated, systematic process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice in the United States." They are especially focused on evaluating available evidence related to the "validity and utility of rapidly emerging genetic tests for clinical practice." This independent, multidisciplinary panel prioritizes and selects tests, reviews CDC-commissioned evidence reports and other contextual factors, highlights critical knowledge gaps, and provides guidance on appropriate use of genetic tests in specific clinical scenarios." We know several members of the EGAPP Working Group through CGREAL's network in the ELSI research community, and we can approach them for advice in identifying key informants from this monitoring body.

Aim 3. To examine how health care providers both interpret and shape PGM in the clinical setting.

The third aim of the project will be to assess the ways in which health care institutions and clinicians experience PGM's benefits and challenges in actual practice. Few clinical settings currently offer actual genomic-based medicine to patients, but those that do will be instrumental in defining PGM as it moves towards mainstream practice. Because their concerns center on how to develop the field in order to make PGM clinically viable, it will be important to document their perspectives on its promises and pitfalls, in order to anticipate the directions in which these pioneers might take the enterprise. We have identified 8 leading academic clinics that are currently, or will soon be, providers of PGM in the United States. We will conduct interviews with the leaders of those centers (about 16 cases). We will also conduct intensive ethnographic fieldwork in one of these centers (the Cleveland Clinic's Genomic Medicine Institute), including observations during 20 clinical appointments in order to analyze daily practices. In addition, we will interview 4 physicians in a single private practice that bills itself as one of the first in the country to provide PGM. Finally, we will enhance our interview data by gathering observations at conferences dedicated to PGM. Each of these components is further described below.

Dr. Fishman's previous experience conducting research in health care settings makes her the natural leader for the team's efforts in this aim. She and co-investigators Settersten and McGowan will develop the interview guides, supervise the interviews, develop the clinic observation guidelines, and oversee the data analysis process. Dr. Fishman will collaborate with Juengst in identifying the implications of the data. The observations will be conducted by McGowan and Lambrix. The project's research staff, Lambrix, Flatt, and a third research assistant, will be involved throughout the process in developing and piloting the interview guide, conducting the interviews, and analyzing the data.

3A. Interviews with Leaders of Academic Health Centers

We have identified eight key academic centers within the social world of providers of PGM that are currently in the vanguard of delivering PGM: Institute of Genomic Medicine at New Jersey Medical School; Ohio State's Center for Personalized Health Care; Emory University and Georgia Tech's Center for Health Discovery and Well Being; Harvard Medical School and Partners HealthCare System Center for Genetics and Genomics; the Charles R. Bronfman Institute for Personalized Medicine, Mount Sinai Medical Center; Duke Center for Genomic Medicine; the Mayo Clinic Genomics Research Center; Baylor College of Medicine's current undertaking, Baylor Clinic and Hospital, which is slated to open in 2010. Information about each of these sites can be found in Appendix B. We compiled this list from a web and literature search by looking for mentions of the most prominent centers promoting their interest in personalized medicine. We also used lists that others who have been tracking the field have compiled, most notably Steven Murphy's weblog⁸¹ and the list compiled by Xu, et al.¹¹ The organizational structures of each of these centers vary, but in general we will conduct at least two interviews at each center with the executive director, medical director, director of communications,

and/or genetic counseling director. Other centers may emerge through our research process, and we will keep the door open for exploring those new institutions through further interviews.

3B. In-Depth Case Study of a Clinic: Cleveland Center for Personalized Genetic Health Care

The Cleveland Center for Personalized Genetic Health Care, which is part of the Genomic Medicine Institute (GMI) of the Cleveland Clinic Foundation, is one example of the kind of PGM provider we would like to study.. Dr. Charis Eng, the Director of both the Center and the Institute, has already given us permission to be interviewed and to conduct ethnographic fieldwork there (see letters of support, Appendix A). The Genomic Medicine Institute is an ideal location for this fieldwork, not only because its internationally recognized facility is literally a mile from Case Western Reserve University, but because of the uniqueness of the newly-established Center for Personalized Genetic Health Care. The Center specializes in genomic risk education, diagnostic evaluation, genetic testing, and counseling to help individuals determine their personal risk for diseases that may run in their families or their risk for passing on a heritable genetic condition to their children.

Past research has shown ethnographic observation to be particularly useful in studying health care settings because the observations that result will perfectly augment data from our interviews. In addition to our observations, we will interview multiple staff members at the Center, including Dr. Eng herself, clinical geneticists, nurses, and other instrumental personnel that we identify in our observations. We will be certain that the privacy and confidentiality of all participants is protected. We will carefully review our observations and de-identify all notes so that they will not compromise the identity of the clinician or patient.. Although this study is not focused on patients' perspectives but on understanding clinical practice, we will ensure compliance with national standards related to research ethics. In particular, we will be properly introduced to each patient by a member of GMI staff. Each patient will be given the choice as to whether a member of our research team has their permission to observe their clinical appointment. If permission is granted, we will administer informed consent process at that time.

Our methods will include gathering observations and interviewing. A member of the research team will observe clinician-patient sessions, paying careful attention to the following domains: (1) content of the information given to patients; (2) how the patient interprets and uses that information; (3) the language used to describe genetic testing; (4) how these sessions invoke the ideas of "personalized medicine." The research assistant will be as unobtrusive as possible during the appointment, and will not interrupt or speak. Although some notes will be taken during the appointment, most of the notations will occur immediately after the appointment in order to minimize intrusiveness and while the encounter is still fresh in the research assistant's mind. We plan to observe 20 appointments, being mindful of the need to maximize the range of appointment types. We will attempt to observe at least one session for each type of personalized medicine appointment that the Institute provides, including cancer pharmacogenetics, predictive genetic testing, and prenatal/pre-conception genetic screening. We will also represent the ethnic and racial population of the Cleveland Clinic's patient population in our observations, working towards oversampling for African-American patient encounters if necessary. Field notes will be transcribed and analyzed along with the other data using a set of common analytic strategies employed by our team that is described below.

3C. Interviews with Private Practitioners of Personalized Medicine

One of the first private medical practices to devote itself to PGM is the New York-based Helix Health. According to its founder, Dr. Steve Murphy, Helix Health is currently a one-of-a-kind clinic that works in concert with traditional medical providers to provide ongoing advice to patients undergoing genetic/genomic testing and interpreting complex results. In addition to his practice, Dr. Murphy devotes significant time to disseminating the latest developments in the field of PGM, through his popular web blog, the *Gene Sherpa*. As a vocal proponent of PGM, he is one of the first of his kind to have an articulated vision and position on how PGM should look for physicians who wish to implement PGM into their daily practice.. For this reason, we have made arrangements to interview him., along with three other Helix Health physicians. (see letters of support, Appendix A). According to Dr. Murphy,

3D. Enhancement through Observations at Professional Conferences

We will enhance the robustness of our interview and ethnographic data for this aim by conducting participant observations at ongoing conferences devoted to PGM. Scientific and medical conferences are critical enactments of a scientific social arena, bringing together key social worlds in one physical location. A good example of these types of conferences is the annual Harvard Medical School-Partners HealthCare Personalized Medicine Conference. This conference brings together many social worlds in PGM to discuss the growing importance of the field and the political, economic, and scientific aspects of implementation. Another good example is the annual conference on Personalized Health Care, sponsored by the Ohio State University Center for Personalized Health Care. It brings together many of the co-producers of PGM: academic experts, industry leaders, government policy makers, and consumer advocates from around the nation, to discuss breakthroughs in personalized medicine research and the challenges of translating findings to clinical practice. We will send two members of our research team to each meeting whenever possible in order to capture the rich data collection opportunities that these conferences represent. Field notes will be independently generated by each observer. These notes will be transcribed each evening while events are fresh in the researcher's mind. While capturing conference content is important, it is more important to capture those elements of the conference not represented by Powerpoint slides—that is, the ways in which social actors at the conference talk in formal and informal settings about PGM, its future, and the ways they think it is currently shaped and constituted. All field notes will be transcribed and analyzed along with the other data using a set of common analytic strategies employed by our team that is described below.

Aim 4. To examine how PGM is being interpreted by patient advocacy organizations and their members.

Over the last two decades, patient advocacy organizations have become influential co-producers of disease-specific translational research; those concerned with genetic health problems have been active constituents in the support of TGR.⁸²⁻⁸⁴ As the “voice” of the consumers, patients, and beneficiaries at the end of the translational research pipeline, the social worlds inhabited by patient groups can be expected to have a role in shaping the trajectory of TGR to PGM. In many interpretations, however, PGM is not primarily focused on the rare hereditary conditions that motivate their special interest: it is framed and promoted as helping the general population prevent and treat common complex diseases. This makes these social actors' perspectives on PGM and its virtues very important for us to explore in this project. For this aim, we will interview leaders and members of four patient advocacy organizations representing a spectrum of genetic health problems about their visions of PGM as a social practice, and what they understand to be the benefits and risks of a personalized genomic approach to medicine for individual patients, patient groups and society.

Dr. Fishman and Dr. McGowan's ongoing study of early users of DTC personal genome scanning, positions them well to lead our team's efforts in this specific aim. McGowan and Fishman will develop the interview guide, supervise the interviews, oversee the data analysis process, and collaborate with Juengst and our consultants in identifying the implications of our data. The project's research staff, Lambrich, Flatt and Ponsaran, will be involved throughout the process in piloting the interview guide, conducting the interviews and coding the interview transcripts.

Under this aim, we will interview the leaders and board members of four patient advocacy organizations that represent a spectrum of genetic health problems: Mendelian diseases; diseases with low-frequency genetic variants with intermediate penetrance; and common diseases with low-penetrance genetic links, such as those that are the object of GWAS research.⁸⁵ We will conduct 40 interviews, ten with each patient advocacy organization, regarding their social world's orientation toward the promises of TGR and PGM. We are interested in assessing their social world's attitudes and receptiveness towards TGR and PGM, their level of interest and receptiveness to the co-production of TGR, how they interpret the goals of PGM in health- and treatment-related decisions, the future roles they envision for patient advocacy organizations in TGR, and what they understand to be the benefits and risks of a personalized genomic approach to medicine for individual patients, patient groups, and society. We are also interested in asking representatives of this social world about their visions of PGM as a social practice, how the frames of “proactive” and “preventive” health care inform patient advocacy organizations' perspectives, how the goal of PGM may shape the future of biomedical

research and health care delivery, and how patient advocacy organizations envision themselves as co-producers of TGR and PGM.

Mendelian disease: Alpha-1 antitrypsin disorder.. We have already identified and secured a letter of support from the Alpha-1 Foundation to participate in this effort (see letters of support, Appendix A). The Alpha-1 Foundation is a patient advocacy organization dedicated to promoting research and support for alpha-1 antitrypsin deficiency, a Mendelian condition linked to chronic lung and liver disorders. The Foundation has dedicated over \$35 million to research towards curing Alpha-1, both externally and through an internal research mechanism. We anticipate that this organization's leadership and members' involvement with research on rare hereditary disease will provide important insight into the ways in which this social world conceptualizes the prospect of a personalized genomic approach to medicine.

Complex disease: Tourette's Syndrome.. We have also secured an agreement to collaborate from the leadership of the Tourette's Syndrome Association (verbal exchange/agreement with Sue Levi-Pearl, Vice President, Medical and Scientific Programs). Tourette's Syndrome is a complex disorder that typically appears in childhood, manifesting in the form of involuntary physical and vocal tics. The cause of Tourette's Syndrome is unknown and inheritance patterns are unclear, although it is currently believed that a combination of genetic and environmental factors contribute to the expression of the disease. The Tourette's Syndrome Association is dedicated to supporting and funding research to identify the cause, and to treat and to cure this syndrome. The participation of the Tourette's Syndrome Association will be particularly valuable for assessing attitudes toward PGM when the genetic origin of a disease is complex or unclear.

Chronic disease: Parkinson's Disease. We will build on preliminary research that we have conducted in this arena to recruit additional other patient advocacy organizations. In our pilot research involving early adopters of personal genome scanning services, we learned of partnerships that have been formed between patient advocacy organizations and the commercial entity 23andMe to conduct research on the genomic basis of the complex disorder of Parkinson's disease. The purpose of this partnership is to establish a biobank of Parkinson's patient genomes that can be used for TGR. Our preliminary research has indicated both interest and skepticism towards this endeavor amongst Parkinson's patients, and has pointed us towards voluntary health organizations for Parkinson's Disease that are participating in the 23andMe Parkinson's Disease Community. These organizations are currently recruiting 10,000 Parkinson's patients to donate DNA samples for genome scanning and genomic research. For this specific aim, we will be targeting the social world of Parkinson's disease voluntary health organizations that have partnered with 23andMe to conduct disease-specific genomic research. For example, The Michael J. Fox Foundation for Parkinson's Research has already expressed an interest in learning more about participating in our study.

To round out our sample of patient advocacy organizations we will also conduct targeted recruitment from the organizations affiliated with the Personalized Medicine Coalition, Genetic Alliance, and the National Organization of Rare Diseases. These umbrella organizations serve as clearinghouses for hundreds of patient advocacy organizations in the United States that represent a range of genetic health problems. Our consultant Dr. Richard R. Sharp (Cleveland Clinic) collaborated with the Genetic Alliance to survey patient organizations about their involvement in biomedical research, and this recruitment strategy yielded a high level of responsiveness to participate. We are hopeful that, with Dr. Sharp's assistance, a similar strategy will generate a similar level of enthusiasm to participate. We will be particularly mindful of equitable participation of women and minorities, both in the leadership and the membership of patient groups. The membership of patient advocacy organizations is often heterogeneous, so we will employ strategic theoretical sampling strategies [see further explanation in Inclusion of Minorities and Women sections] from these groups to increase inclusion of diverse populations in our study.

Aim 5. To develop an analytic map of the ethical challenges and policy choices that different interpretations of PGM could generate for TGR and health care

Our research on this specific aim will involve searching for, describing, and analyzing arguments, rather than observing and reporting on social phenomena. This mode of "data collection" continues the methods we have

used in our previous work—that is, analyzing the results of our empirical findings, as well as the published works and presentations of scientists, bioethicists, and policy makers about PGM, criticizing and reconstructing their arguments, and probing the limits of their conclusions. Scholars from humanities disciplines will recognize the typical patterns of their work behind this approach. Our methods differ from those of traditional humanities scholarship only in our team approach, the interdisciplinary breadth of our collaboration, and the steps we will take to ensure the robustness of our conclusions.

Achieving this aim will involve an iterative process of classifying and comparing our qualitative data analyses and the PGM literature to produce a taxonomy of the virtues that different co-producers attribute to PGM and the ways in which they might lead to correlative vices. It is premature to propose the interpretations of PGM's virtues that will be most important to examine under this aim in advance of the data from our empirical work, or the issues that will emerge from that examination. We can, however, anticipate the rhythm of our work on the basis of our previous experience.

1. We will be able to start our work concurrently with the empirical research by turning to two bodies of existing literature: the biomedical and health policy literature that promotes PGM, and the ELSI literature that discusses the contextual challenges that face its two canonical manifestations, predictive genetic risk assessments and pharmacogenomic profiling. With the former, we will be looking for explicit expositions and defenses of PGM's virtues, and the ways they are prioritized and interpreted by these proponents, much as we will do in our interviews. With the latter, our goal will be to work backward from the existing discussions of the “external” ELSI challenges that TGR faces in realizing PGM to identify which theoretical virtues are implicated in those challenges. This will give us a reflection of how ELSI researchers, at least, view the terrain and the interpretations of PGM that seem to inform their discussions of its issues.
2. Then, as our empirical data are analyzed, we will be able to gauge the concordance between the views of those who discuss PGM theoretically in the literature and the various stakeholders immersed in its pursuit. This should help throw into relief the relative salience and weight of different values in the practical evolution of PGM, which will then help us to anticipate where the major axiological decision points will come within the TGR translational pipeline.
3. In the final stage, we will return to those parts of the ELSI literature that frame PGM as our respondents do, in order to draw on the arguments used in elaborating and discussing the ethical, legal, and social implications of the ways they make the case for PGM. This will allow us to annotate our analytic map of the ethical challenges with decision-making considerations.

Dr. Juengst will lead our analyses under this aim, in collaboration with Dr. Binstock. During this process, we will also consult the scientists who served as key informants for the empirical studies, to whom we will circulate our findings for insights and critique. In addition, we will consult with Richard Sharp and Anders Nordgren, two philosophical colleagues who hold diametrically-opposed views on many of the issues raised by PGM (see letters of support, Appendix A). These consultants will be specifically charged with making sure that our focus on the interpretive categories we bring from our previous work does not blind us to other interesting findings in the empirical explorations and ethical analyses of the proposed project. As our inquiries generate results, we will pool our efforts to produce integrated analyses of our major findings under this aim. In addition, we will vet our work with the larger interdisciplinary faculty of the CWRU Center for Genetic Research Ethics and Law.

Protocol for Developing Interview Guides and Conducting Interviews (All Aims)

Qualitative in-depth interviews have been shown to provide a valuable foundation for a broader understanding of contextual matters relevant to study issues being explored. In-depth interview guides include a series of semi-structured questions and probes to facilitate discussion. Initial draft interview guides will be developed by the team based on specific research questions being addressed and a systematic review of the literature. After a draft is developed, Fishman and Settersten will independently review the guide, carefully examining the phrasing and order of questions, follow-up probes, overlooked issues, and the like. They will then make detailed recommendations for revisions, together with input from members of the team. This iterative process will continue over the course of several meetings. The interview guides will then be pilot tested. The

interviewers will report back in detail about how well the questions worked in the field, and we will continue to refine core questions and a range of effective probes.

When the interview guide is complete, the interviewers will begin recruiting participants and conducting interviews. After each interviewer has conducted a few interviews, we will revisit the guide one last time for any improvements. The proposed project relies on a variety of samples, and each one will have its own specific protocol with respect to how, when, and at what intervals we will contact potential participants. Written consent will be obtained from all individuals. All interviews will be digitally recorded. The digital file will then be sent through a secured network site (a paid service to which we subscribe) to the highly-skilled transcriptionist with whom we regularly work. The transcripts reflect the interview conversation verbatim. The transcriptionist destroys the file once the transcription is complete. Once we receive the transcript, the interviewer who conducted that particular interview carefully reviews and edits the transcript for accuracy and returns to the recorded conversation to clarify or fill in any questionable or incomplete text. The interviewer also simultaneously “de-identifies” the transcript, eliminating any information that would compromise the confidentiality of the participant.

Key Strategies for Analyzing Data (All Aims)

All data—including interview transcripts, field notes, and other materials (e.g., images and text from websites and printed matter), will be analyzed using the general principles of grounded theory.^{86,87} Grounded theory approaches seek to uncover the social processes and conditions that lie behind the phenomena in question and unravel their consequences. It is a method that is especially suited to a study such as the one we are proposing, in which the general phenomenon and its processes have not been fully articulated, and in which constant comparisons between data from multiple samples and sources are a critical part of the research agenda.⁸⁸ These systematic procedures move beyond description, and enable theories to be developed in an inductive fashion.

All data will be entered into Atlas.ti, a software package for organizing and analyzing qualitative data. Transcripts and field notes will be imported into the program as text. These primary documents are easily retrieved, segmented into passages, and marked as “quotations,” which are then coded, indexed, sorted, and annotated with commentary from members of the team. Atlas also contains a sophisticated search system that allows us to find complex combinations of phrases, words, characters, and symbols. Standard procedures for analyzing qualitative data will be employed, based on successive coding passes. We will begin with open coding of content at the level closest to the content of the text and continue through broader and more analytic codes. We will begin the coding process once we have a handful of transcripts and interviews are ongoing. We start with open coding, in which large sections of text are coded (for example, an entire section of the interview guide, or a handful of targeted questions). Specific codes will be developed using both deductive strategies (built on existing scholarship and then applied to the transcripts) as well as inductive strategies (built directly from the transcript text). A coding manual will then be developed in collaboration with the investigative team. The manual will include definitions for each code, illustrative quotes, and special instructions for applying them. To enhance construct validity and reliability of the conceptual domains identified, qualitative data will then be coded by two independent reviewers, who were also interviewers. This strategy—having core team members conduct the interviews, do the coding, and develop our analyses, — creates tremendous advantages in ensuring the integrity and top quality of the resulting data and analyses.

Research Plan and Timetable

We have outlined a timetable for implementing the central tasks associated with each of the specific aims across the four years of the project (see timetable in Budget Justification). To launch the project, we will begin with Specific Aim 1, developing our sample population of the “promoters” of PGM. Simultaneously, we will begin our recruitment for the interviewees outlined in Specific Aim 4, members of patient advocacy organizations. We begin our inquiry with these two groups for several reasons. First, given their traditional roles at the “front end” of TGR’s pipeline, our interviews with the promoters of PGM, will be instrumental in setting the stage for the rest of the project. Meanwhile, the patient advocacy organizations provide an important counterpoint to the promoters and their increasing role in priority-setting for TGR will also be important to appreciate from the start. In the next phase of the project, we will turn to the mediators and

providers, because their influences in the practical realization of PGM are so heavily interdependent. We will continue to move our way through our groups of interviewees in each specific aim in a progressive fashion, aiming to conduct around 50 interviews/year. While our work on Aim 5 will proceed throughout the project, the full elaboration of our analytic map of challenges and choices, and their relevant ethical, social and policy considerations, will, of course, rest on the empirical foundation built in Aims 1 through 4. As such, the completion of Aim 5 is slotted for the final year of the project.

Principal Investigator/Program Director (Last, First, Middle): Juengst, Eric T.

Inclusion Enrollment Report**This report format should NOT be used for data collection from study participants.****Study Title:** Controlling Human Aging: Alternative Rationales and Implications**Total Enrollment:** 88**Protocol Number:** _____**Grant Number:** 5 R01 AG020916-05**PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative)
by Ethnicity and Race**

Ethnic Category	Sex/Gender			Total
	Females	Males	Unknown or Not Reported	
Hispanic or Latino	1	0	0	1 **
Not Hispanic or Latino	30	55	0	85
Unknown (individuals not reporting ethnicity)	0	2	0	2
Ethnic Category: Total of All Subjects*	31	57	0	88 *

Racial Categories

American Indian/Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	1	1	0	2
White	30	54	0	84
More Than One Race	0	0	0	0
Unknown or Not Reported	0	2	0	2
Racial Categories: Total of All Subjects*	31	57	0	88 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

Racial Categories	Females	Males	Unknown or Not Reported	Total
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	1	0	0	1
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of Hispanics or Latinos**	1	0	0	1 **

* These totals must agree.

** These totals must agree.

Progress Report Publications and Presentations

R01-AG/HG020916 Publications: 2006-2008

- Binstock, R.H, Fishman, J.R. and Johnson, T.E. (2006). Anti-Aging Medicine and Science: Social Implications. In: Binstock, R.H and George, L.K. (Eds.). *Handbook of Aging and the Social Sciences*, 6th ed. (pp. 436-455). San Diego, CA: Academic Press.
- Binstock, R.H, Fishman, J. R. and Juengst, E.T. (2006). Boundaries and Labels: Anti-Aging Medicine and Science. *Rejuvenation Research*, 9(4), 433-435.
- Binstock, R.H. (2007). Our Aging Societies: Ethical, Moral, and Policy Challenges. *Journal of Alzheimer's Disease*, 12, 3-9.
- Binstock, R.H, Fishman, J.R. and Juengst, E.T. (In press). The Ethics, Sociology, and Politics of Anti-Aging Medicine and Science. In: Runkel, T. (Ed.). *Beyond Therapy*. Bonn, Germany: Institut für Wissenschaft und Ethik.
- Binstock, R.H. and Fishman, J.R. (In press). Social Dimensions of Anti-Aging Science and Medicine, In: Dannefer,D. and Phillipson,D (Eds.). *International Handbook of Social Gerontology*. Thousand Oaks, CA: Sage.
- Fishman, J.R., Binstock, R.H. and Lambrix, M.A. (2008). Anti-Aging Science: The Emergence, Maintenance, and Enhancement of a Discipline. *Journal of Aging Studies*, 22(4), 295-303.

In Press

- Settersten, Jr., R.A., Flatt, M.A. and Ponsaron, R. (2008). From the lab to the front line: How individual biogerontologists navigate their contested field. *Journal of Aging Studies*, 22(4), 304-312.

Presentations

- Binstock, R.H. (2006, January 24). Anti-Aging Medicine and Science: An Arena of Conflict and Profound Implications. Distinguished Lecture for the Institute on Aging, University of North Carolina, Chapel Hill, North Carolina.
- Binstock, R. H. (2006, April 1). The Politics of Presentation: The Case of Anti-Aging Medicine and Science. Lecture at a conference on Ethics sponsored by the Institute of Science and Ethics, Bonn, Germany.
- Binstock, R. H. (2006, April 20). Anti-Aging Medicine and Science: Hype, Hope, and Implications. Armin Grams Memorial Lecture, University of Vermont, Burlington, Vermont.

Binstock, R. H. (2006, June 5). Aging Well: Anti-Aging Medicine and Science. Lecture at a symposium on Aging Well, at Harvard University, Cambridge, Massachusetts.

Binstock, R. H. (2006, November 3). The Challenges of a Long-Lived Society. Keynote speech for a conference on Living Longer: The Medical, Social, and Ethical Consequences, at Xavier University, Cincinnati, Ohio.

Binstock, R. H. (2006, November 19). Anti-Aging Research: The Status Quo. Chaired symposium at the 49th annual meeting of the Gerontological Society of America, Dallas, Texas.

Binstock, R. H. (2006, November 19). The Societal Implications of Anti-Aging Research. Chaired symposium at the 49th annual meeting of the Gerontological Society of America, Dallas, Texas.

Binstock, R. H. (2008, March 28). Anti-Aging Science and Medicine. Special Lecture at the Joint meeting of the American Society on Aging and the National Council on Aging, Washington, D.C.

Binstock, R. H. (2007, November 17). Anti-Aging Interventions: How Likely? How Soon? What Societal Implications? Chaired symposium at the 60th annual meeting of the Gerontological Society of America, San Francisco, CA.

Binstock, R.H. and Fishman, J.R. (2007, September 6). Biogerontology as an Emerging Discipline. Presentation at the 36th annual meeting of the British Society for Gerontology, Sheffield, England.

Binstock, R. H. and Settersten, Jr., R.A. (2007, November 17). Anti-Aging Science and Medicine: The Making of a Field and Its Professionals. Chaired symposium at the 60th annual meeting of the Gerontological Society of America, San Francisco, CA.

Binstock, R. H. and Settersten, Jr., R.A. (2008, November 22). Anti-Aging Medicine: Perspectives on Providers and Users. Chaired symposium at the 61st annual meeting of the Gerontological Society of America, Washington, D.C.

Binstock, R. H. and Settersten, Jr., R.A. (2008, November 22). Anti-Aging As a Medical Specialty: The Relationships Between Marketing and Clinical Practice. Presentation for the symposium, Anti-Aging Medicine: Perspectives on Providers and Users, at the 61st annual meeting of the Gerontological Society of America, Washington, D.C.

Fishman, J. R., Binstock, R.H., and Lambrix, M.A. (2007, November 17). The Objectives of Anti-Aging Science: Implications for Legitimacy, Funding, and the Future. Presentation for the symposium, Anti-Aging Science and Medicine: The Making of a Field and Its Professionals, at the 60th annual meeting of the Gerontological Society of America, San Francisco, CA.

Fishman, J.R. and Lambrix, M.A. (2007, October 20). How Anti-Aging Researchers Make Epistemological Claims: Legitimizing a Scientific Discipline. Presentation at the 9th annual meeting of the American Society for Bioethics and Humanities, Washington, D.C.

Fishman, J.R. and Lambrix, M.A. (2008, October 24). Anti-Aging Medicine in the Clinic: The Ethics of a New Medical Specialty. Presentation at the 10th annual meeting of the American Society for Bioethics and Humanities, Cleveland, OH.

Fishman, J.R. (2008, September 13). Anti-Aging Science and Medicine: Where Forbidden Knowledge Meets Desire in the Laboratory. Presentation at the Brain, Mind, and Society Conference. McGill University. Montreal, QC.

Lambrix, M.A., Flatt, M.A. and Fishman J.R. (2008, August 15). The General Public Has No Idea What's Coming...Presentation at the Annual Meeting of the Society for the Social Studies of Science. Rotterdam, Netherlands.

Lambrix, M.A., Flatt, M.A, and Fishman, J.R. (2008, September 2). Extending the Human Lifespan: Achievements and Challenges of Genetic Research on Aging. Round table discussion at the 103rd annual meeting of the American Sociological Association, Boston, MA.

Settersten, Jr., R.A., Flatt, M.A., and Ponsaran, R. (2007, November 17). Navigating Careers in Anti-Aging Science: The Risks and Rewards of Research in an Emerging and Contested Field, Presentation for the symposium, Anti-Aging Science and Medicine: The Making of a Field and Its Professionals, at the 60th annual meeting of the Gerontological Society of America, San Francisco, CA.

Human Subjects Protection

A. Description of proposed involvement of human subjects: Most of our work will involve the recruitment of human subjects for in-depth interviews. These interviews will largely take place by telephone; some will occur in person. We will also conduct ethnographic fieldwork in a clinical setting (the Center for Personalized Genetic Healthcare).

B. Research material obtained from human subjects: Interviews will be digitally audio recorded and then transcribed. We will also take field notes at public scientific conferences and as part of our ethnographic research, noted above.

C. Plans for recruitment of subjects and consent procedures: Potential interview subjects will be identified through our use of online databases, membership lists, organization websites, and public documents. We will introduce our study via email and/or a mailed letter. If a potential subject is interested in participating, s/he will call or email a member of the research team to learn more about the study. The study will be explained and, if the subject is still interested in participating, s/he will schedule an interview time and will be sent an informed consent document. At the scheduled interview time, the appropriate member of the research team will phone the subject. They will review the informed consent document together and the researcher will obtain recorded verbal consent. All participants will provide informed consent to participate in the study before the interview commences. Once an individual has provided consent, the interview will begin and be audio recorded.

All interview subjects will be assigned a numeric identification number and a permanent record of identifiers will be kept on a password protected computer, separate from the folders with interview transcripts and digital audio files. All subject information will be kept in coded form on computers. To ensure participant confidentiality, there will be no identifying information in the transcripts. We will obtain basic background information from participants (gender, ethnicity, age, education, occupation). Identifying keys will be kept in a separate, locked location. Only the study investigators and appropriate research staff will have access to the transcripts and audio digital files. The audio files will be destroyed once transcription, coding, and reliability work are complete. All computers and databases will be password-protected, and all paper copies of informed consent, data, and other sensitive documents will be kept in a locked file cabinet in a secure location.

Before beginning our fieldwork at the Cleveland Center for Personalized Genetic Healthcare, we will obtain human subjects approval from the Cleveland Clinic Foundation, as well as from our home institutions. Each member of the clinic staff will be provided with a description of the study and an IRB-approved informed consent document that will be explained by the researcher seeking their consent to participate. The informed consent document will inform them that no identifying information will be collected about them and that their employer will not have access to any of the data collected. When a patient comes in for an appointment, the clinic staff will ask them if a member of our research team can sit in on their appointment. They will also be provided with a description of the study and given an informed consent document that will be explained to them by that researcher. If they agree to participate, they will sign the consent document. No identifying information will be collected about the patients and no audio or video recording will be made of the appointment. Handwritten field notes will be destroyed after transcription to computer file. The computer files will protect the identity of the clinic staff and patients and will not include any identifiers. A numeric identification code will be used to identify clinic staff.

D. Potential risks: The risks of this study are minimal. The majority of our interviews will be conducted with professionals working in various parts of the field of PGM. The study description and informed consent documents will indicate that we will ask them about the nature of their work and the orienting goals of the organization for which they work. All prospective participants will be reminded in the informed consent process that their participation will remain confidential, that they need not answer any questions that make them uncomfortable, and that they have the right to discontinue their participation at any time. In the case of our ethnographic fieldwork at the Center for Personalized Genetic Healthcare, members of the staff may be concerned about members of our research team observing them as they work. We will assure them, and ensure, that their colleagues and superiors will not have access to, or knowledge of, these observations and that they will in no way be connected to evaluations of their job performance.

E. Provisions for protecting against potential risks: To maintain participant confidentiality of all of our interviewees, we will not allow any employer of our human subjects to access to data. Subjects will be told that they are free to refuse to answer any question that makes them uncomfortable and to stop their participation at any time. In the case of our ethnographic fieldwork at the Cleveland Center for Personalized Genetic Healthcare, we will disguise the identity of the Center so as to protect employee confidentiality. There will be no way to identify patients based on our data. The researcher will remain as unobtrusive as possible when observing clinic appointments. Individuals will be given option to go on the record or be unidentified.

F. Why risks to subjects are reasonable in relation to potential benefits: The potential risks of participation are minimal. We are primarily interested in institutional analysis of the goal of PGM. Thus, participants will be characterizing their professional institution's orientation to this goal. The subject matter is not particularly sensitive or socially undesirable. Furthermore, only those participants who are interested in discussing these matters will choose to participate—and, as noted earlier, participation will remain confidential and participants will be free to refuse any questions and discontinue their participation at any time. Given how little is known about the emergence of PGM, the benefits of obtaining information about the use of personalized medicine are large. The possible concerns of Cleveland Clinic employees are understandable, given that the observations occur within their setting. As described above, we will make every effort to minimize any risks associated with these observations.

Inclusion of Women and Minorities

Our primary interests throughout the project lie in explicating the various social worlds of PGM and the stakeholders who make up those groups. What matters most for our inquiry, and therefore for our sampling, are the unique *positions* that individuals hold in the emergent field of PGM, rather than their individual characteristics. Participants essentially serve as reporters on their particular institutional location or position (e.g., those who hold specific leadership roles in organizations such as NIH, NCHPEG, and PMC; those who direct academic health centers or oversee the genetics curriculum in medical schools; those who are members of editorial boards or recipients of NIH funding). We have no control over the characteristics of the people who hold those positions, and in some cases there is a known imbalance by gender and race.

To the extent that we can identify women and minorities in advance—and in many cases we can, we will intentionally oversample members of both groups. And to the extent that these characteristics are not readily apparent, we will work closely with our key contacts at collaborating institutions and organizations to ensure that women and minorities are well-represented in all of our samples. Moreover, we will also use consultants who are well-positioned in each of the stakeholder groups to build sampling lists that intentionally oversample women and minorities for each and every sample and to ensure that we successfully reach our targeted enrollments. Below, we highlight a few specific points related to the inclusion of women and minorities.

Inclusion of women: We estimate that about half of interviewees will be women. As described above, in some cases we are sampling on the basis of positions in organizations, or from pre-established lists of people, not on the basis of individuals and their characteristics. The pool will include approximately 40% women across the various components of the study. If the presence of women is more limited in some subsamples, we will, to ensure their full inclusion, oversample women until we reach 40% female representation. We will examine all pre-established lists beforehand to identify potential female participants in each group and explicitly target them in our recruiting.

In sampling clinic patients we will also develop a recruitment strategy that intentionally oversamples female interviewees. For example, with our hosts at the Cleveland Clinic, we will arrange our observations in the Personalized Medicine program to ensure that equal numbers of male and female patients are observed. Patient advocacy organizations are often made-up of members of both genders who experience the same genetic disease, thus we will also oversample women who are leaders and members of patient advocacy organizations to ensure adequate representation of women in our sample overall.

Race and especially gender may be known and actively accounted for in oversampling with respect to many of the pre-established lists of professionals. In cases where there is a known imbalance of men over women (for example, in seeking NIH-funded scientists or scientists who hold positions in medical sequencing companies or start-up ventures), analysis of the sampling lists and initial round of interviews will help us actively monitor the inclusion of women and intentionally oversample women with targeted recruiting until we reach 40% female representation.

Again, we will work closely with our key contacts at collaborating institutions and organizations to ensure that women are well-represented in all of our samples. We will also use consultants who are well-positioned in each of these stakeholder groups to build sampling lists that intentionally oversample women and ensure that we successfully reach our targeted enrollments.

Inclusion of minorities: We estimate that we will be able to obtain at least 20% minority representation in our overall participant sample—i.e., 36% overall, 20% African American.

We will ensure that each and every sample is as diverse as possible when it comes to the representation of women and minorities. We have developed several steps that will ensure adequate inclusion. To the extent that it is possible to determine the presence of minorities in these lists, we will examine the lists will be beforehand to identify potential participants from these groups for targeted recruiting. The race of the person may be known or ascertained in some of the pre-established lists of members of professional organizations.

In addition, analysis of the initial round of interviews will help us to schedule additional interviews to ensure adequate inclusion of minorities. Following the techniques of theoretical sampling, a type of qualitative methodology, individuals in areas underrepresented in the initial sample will be contacted after the first round of interviews has been conducted and analyzed in order to obtain an inclusive range of responses. This sampling technique relies on an iterative selection process in which data are coded and analyzed conjointly with data collection; the emergent analysis determines what data to collect next and from whom. Theoretical sampling and conjoint analysis and collection of data will also allow me to achieve theoretical saturation, whereby we purposely sample to the point of redundancy in terms of the themes emerging from the interviews. Using targeted recruiting and theoretical sampling, we will oversample minorities from the individuals available to interview until we reach approximately 20% African-American representation from the sample.

We have also thought carefully about how to oversample members of minority groups for each of our aims, and there are several instances in which we will have further opportunities to ensure the adequate inclusion of minorities. In our studies of the translation of PGM to medical professionals and students, for example, we will intentionally and strategically sample three schools from the White House Initiative on Historically Black Colleges and Universities (HBCUs). We will both interview and consult with the director of NCHPEG's Diversity and Cultural Competency Objectives, which seeks to create training programs and activities that are culturally sensitive and to increase minority and underserved communities' access to genetics-education materials and resources.

As another example, we will also consider race-linked genetic health disorders in selecting patient advocacy organizations, and ask the leaders of PMC to help us identify racial and ethnic groups with which they have alliances and to whom we could turn for interviews (e.g., the patient advocacy group, National Alliance for Hispanic Health, is a member of PMC).

In addition, we will work closely with our collaborating institutions and organizations to ensure that minority groups are well represented in all of our samples. For example, we will arrange our observations in the Personalized Medicine program at the Cleveland Clinic to ensure all minority patients coming through are approached about our study, so that among clinic patients we will intentionally oversample minority interviewees.

We will also use consultants who are well-positioned in each of these stakeholder groups to build sampling lists that intentionally oversample women and ensure that we successfully reach our targeted enrollments.

Program Director/Principal Investigator (Last, First, Middle): Juengst, Eric T.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Anticipating Personalized Genomic Medicine: Impact and ImplicationsTotal Planned Enrollment: 150

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	11	14	25
Not Hispanic or Latino	60	65	125
Ethnic Category: Total of All Subjects *	71	79	150
Racial Categories			
American Indian/Alaska Native	0	0	
Asian	10	15	25
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	15	15	30
White	45	50	95
Racial Categories: Total of All Subjects *	70	80	150

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

Inclusion of Children

While the issues of PGM that we are trying to understand are clearly relevant to children, our research plan does not include children as research subjects. The purpose of our project is to explicate the perspectives of the professionals and other actors who are playing primary roles in architecting the emergent field of PGM. These architects are adults, though their work has implications for children and youth. We acknowledge that PGM is certainly related to and has implications for the delivery of pediatric medicine and pediatric populations. Given our primary aims and the already large scope of the project, the inclusion of children would be better suited for future extensions of the project.

Multiple PD/PI Leadership Plan

This research project will be led by an interdisciplinary team of three Co-Principal Investigators at three institutions: Jennifer Fishman (McGill University), a sociologist of medicine and bioethics; Richard Settersten, a specialist in human development and the life course, with expertise in social policy, health, and inequality (Oregon State University); and Eric Juengst, a philosopher with interests in genetic research ethics and law (Case Western Reserve University).

Our decision to take advantage of the new NIH Co-PI option reflects the interdisciplinary nature of our collaboration, and its evolution over the course of our current research. Juengst has been the PI of record for our current project, and he oversees its administrative aspects as well as our efforts to reflect on the ethical and policy implications of our findings. The project's empirical research, however, has been led entirely by Fishman and Settersten, who each bring unique and complementary methodological and theoretical strengths to the work. They designed the study when they were both Juengst's colleagues at CWRU, and they have continued to manage the research team, data collection, and analyses since their respective moves to McGill and Oregon State. If not for the benefits that come to the project because of the infrastructure of CGREAL, Fishman and Settersten could have taken over as PIs of record for our work during its empirical phase—and they played that role in practice. Because the same division of labor will characterize the project proposed here, we will now proceed as Co-PIs because it gives credit where it is due by recognizing the roles that the three of us have shared so far.

Thus, in the proposed project, Juengst will assume overall responsibility for administering the grant, integrating it within CGREAL, and leading our collaborative work on Aim 5. Fishman and Settersten will share primary responsibility for leading all of the research proposed as part of Aims 1 through 4.

This arrangement does, of course, call for a very clear plan for allocating responsibilities and making decisions within the project. If we were just starting out together, any such plan would face the inevitable bumps of being tested in practice. Fortunately, we have already been traveling down this road for three years, and now know its challenges quite well. In the process, we have developed three sets of practices that ground our collaboration and will continue to provide the leadership plan for this project.

Communication. E-mail communication is efficient and ubiquitous, but has been insufficient for our needs. We have instead established a practice of weekly “lab meetings” by conference call, to which we devote up to two hours for planning, ongoing empirical work, and discussing findings. In particularly busy periods, we hold two such meetings per week. For the next project, we will continue this practice and once a quarter we will convene a face-to-face meeting for the whole research team, hosted in turn by each of the Co-PIs. These quarterly meetings will be especially important occasions to meet with our consultants, and handle any managerial challenges that require more in-depth discussion.

Decision Making. Our decision making is decentralized and consensual, but braced by personal assumptions of responsibility. Thus, under the supervision of our Project Manager, Marcie Lambrix, members of the research staff are expected to take initiative on many of the daily decisions related to prioritizing and implementing research tasks, and to report on these issues at our weekly lab meetings. At that level, decisions about next steps, analytic directions, and publications are made by the co-investigators and staff together, under the direction of the Co-PIs. Thus, for our empirical studies, Fishman and Settersten are responsible for establishing a division of labor for all tasks, for securing collective agreement on publication plans, and the like, while Juengst assumes that role for our ethical and policy analyses. For overarching administrative matters, the three Co-PIs will make joint decisions, with Juengst assuming ultimate responsibility for seeing them through.

Credit Sharing. Our practice is to reserve co-authorship on conference presentations and research publications to those team members actively involved in the research being reported or discussed. In most instances, all members of the research team, including the research staff and trainees, are extended opportunities to participate. First and last authorships similarly depend on the initiative and involvement of the co-authors in a particular report, although careful attention is paid to developing publication plans that ensure an equitable distribution of premium authorships across the team. Official overarching project reports are to be co-authored

by the Co-PIs, in whichever order seems appropriate. Most importantly, authorship plans will be discussed and established in advance for particular publications. Any disagreements over professional credit within the team will be openly addressed at our weekly lab meetings and adjudicated by the Co-PIs. In the event of any disagreements between the Co-PIs concerning credit, we are fortunate to have a wise senior colleague on our team, Professor Binstock, and we agree to abide by his judgment as our "Supreme Solomon."

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Consortium/Contractual Agreements

Consortium agreements will be established with Oregon State University (Dr. Settersten) and McGill University (Dr. Fishman). These agreements are detailed in the budget justification.

The following letter of support was included as part of the original application and is provided with the permission of Dr. Eng. An additional 12 letters were included in the original application but have been redacted to protect the privacy of individuals providing letters of support.

October 15, 2008

Eric T. Juengst, Ph.D.
Professor of Bioethics
Director, Center for Genetic Research Ethics and Law
Department of Bioethics
Case Western Reserve University
10900 Euclid Avenue
Cleveland, OH 44160-4997

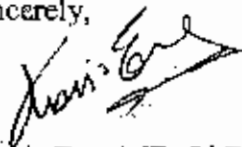
VIA FAX: 216-368-8713

Dear Eric,

Thank you for inviting me to collaborate on your proposed project, "Personalized Genomic Medicine: Impact and Implication," to study the ethical, legal and social issues in translational genomic research from the perspectives of those involved in pursuing the goal of personalized genomic medicine. Individualized preventive healthcare does serve as an important goal for our work at the Cleveland Clinic Center for Personalized Genetic Healthcare (CPGH) and I would be happy to work with your team to create opportunities to explore the impact and implications of that idea as a framework for our clinical work with our clinicians and researchers.

The research questions you are proposing to address about the dynamics of, and constraints on, the process of translating genomic research into individualized healthcare benefits are important to all of us in the genomics community. Given the many ways this idea is being used, a careful study of how "personalized genomic medicine" is interpreted by those involved in the translational process and the implications of that paradigm for clinical care within our society's healthcare system is clearly needed. I look forward to our collaboration.

Sincerely,



Charis Eng, MD, PhD

PHS 398 Checklist

OMB Number: 0925-0001

Expiration Date: 9/30/2007

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:

New Resubmission Renewal Continuation Revision

Federal Identifier:

2. Change of Investigator / Change of Institution Questions

Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

* First Name:

Middle Name:

* Last Name:

Suffix:

Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes No

If the answer is "Yes" then please answer the following:

* Previously Reported: Yes No

4. * Program Income

Is program income anticipated during the periods for which the grant support is requested?

Yes No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount (\$)	*Source(s)
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>
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5. Assurances/Certifications (see instructions)

In agreeing to the assurances/certification section 18 on the SF424 (R&R) form, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the agency's application guide, when applicable. Descriptions of individual assurances/certifications are provided at: <http://grants.nih.gov/grants/funding/424>

If unable to certify compliance , where applicable, provide an explanation and attach below.

Explanation: