**** Working Draft – "White Paper" on Informed Consent Protocols ****

Introductory Note to this Document:

This "White Paper" evaluates several informed consent protocols for use in ongoing and future MGIC research. In August 2006 a version of this document was distributed to colleagues at NIH/NHGRI, as well as in the broader ELSI community for feedback and commentary.

Due to several requests for a distributable version of this document, and in keeping with our commitment to openness, we are making the paper available with only a handful of redactions, removing only personal communications and the names of specific individuals and the references to privileged conversations. This version is substantively identical to that which was distributed in August 2006.

This document was not intended for formal publication and, therefore, it is still in a "working draft" form. However, we hope that even this rough version may prove useful in stimulating further discussion on the issues that it addresses, and it may be freely distributed and cited provided appropriate attribution.

George Church, Jeantine Lunshof, and Daniel Vorhaus
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Clarification and Discussion of Proposed MGIC Informed Consent Protocol

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NIH Center for Excellence in Genome Science (CEGS)
Molecular and Genomic Imaging Center (MGIC)
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In the nearly two years since the Molecular and Genomic Imaging Center (MGIC) began its research, technical innovations and successful research endeavors have propelled the Center forward in pursuit of its goals at unanticipated speeds. These rapid developments have generated a host of questions and issues for both MGIC and NIH/NHGRI to consider.

Over the course of four months this past spring, collaborators at MGIC and at NIH/NHGRI conducted an extended correspondence which addressed many of these emerging issues. That informal discussion has lead to this document on the proposed research plan, drafted in conjunction with relevant ELSI scholars and professionals.

This document is designed to alleviate recent confusion and miscommunication between MGIC and NIH/NHGRI, and to elicit NIH/NHGRI's response to a narrowly framed issue of crucial relevance to future and ongoing MGIC research. It is presented in the following three parts:

1) MGIC General Summary and Project Overview: Using verbatim language from the original MGIC grant proposal, approved by NIH/NHGRI on March 10, 2004,[1] this section summarizes the ongoing research strategies and goals of MGIC for the reader unfamiliar with the original grant.

2) Active Issues in MGIC Research: This second section of the document outlines several potential areas of concern or confusion for NIH/NHGRI, and concludes by isolating a single key question for NIH/NHGRI consideration: "what is the most appropriate informed consent protocol for use in MGIC research, and why?"

3) The MGIC Proposal: An "Open" Informed Consent Protocol: The final section of the document investigates alternative informed consent protocols for ongoing and future MGIC research, including the widely used HapMap protocol and a proposed open informed consent protocol. After a thorough ELSI analysis of these approaches, we conclude that the appropriate protocol for MGIC research is one which adopts "openness" as its core principle, and as a means to fully informed consent.

[1] MOLECULAR AND GENOMIC IMAGING CENTER, *Specialized Center of Excellence in Genomic Science (CEGS) P50 Proposal*, (Jun. 1, 2003) (available at http://arep.med.harvard.edu/P50_03/Church03.doc) (accessed 28 April 2007)

It is our hope and belief that this scholarship represents a document that poses a narrowly focused question for NIH/NHGRI consideration, and that explains and defends MGIC's preferred response to that question. We believe, and we are confident that NIH/NHGRI will agree, that this response is clearly and conclusively supported by the existing CEGS grant, as well as by the thorough supplemental ELSI investigation and scholarship MGIC has undertaken.

I. MGIC General Summary and Project Overview

With the exception of this opening paragraph the language of this section is drawn entirely and *verbatim* from the NHGRI-approved MGIC proposal.[2] This section is designed to revisit the approved purpose and goals of the MGIC and to provide sufficient background for readers to evaluate the informed consent proposal, including the compatibility of that proposal with the approved mission of MGIC, without assuming familiarity with prior NHGRI materials or conversations on the part of the reader.

Introduction. We propose here the **Molecular and Genomic Imaging Center (MGIC)** in response to a biomedical-community-wide need for flexible, cost-effective, high-resolution technology to identify and characterize variation in biological systems at the level of genomes and transcriptomes. We plan to help meet this need by developing the *pol*ymerase col*ony*, or *polony*, technology. Polony technology is realistic, close-at-hand, modular, and versatile. The MGIC will efficiently integrate contributions from technologists and biologists to develop a robust platform for high-throughput nucleic acid analysis.

Technology. Our goal is to simultaneously address a broad spectrum of important challenges in nucleic acid analysis: ultra-low-cost/high-precision (1) DNA sequencing; (2) comprehensive quantitation of mRNA abundances; (3) profiling combinations of alternatively spliced exons within individual mRNA transcripts; (4) direct and unambiguous molecular haplotyping over long genomic distances; (5) determination of DNA sequences and gene expression profiles of single cells and *in situ*. We believe that all of these objectives can be achieved in a realistic time-frame by developing a unified platform, the polony technology. […] In their current state, the polony technologies offer a balanced risk-portfolio, ranging from protocols in their infancy to immediate deliverables validated through successful proof-of-concept experiments and with which we are ready to begin high-throughput collection of primary biological data. What remains in common is that each is "high payoff", as success in any one of our technical objectives would in itself represent a substantial contribution to the community.

Biology. A key measure of the value of a biomedical technology is the sum of its direct and indirect contributions to patient care (i.e. diagnostics, prognostics, and therapeutics). Our interests fall along two tracks. The first track is to characterize and understand stem

[2] *See Id.* The language in this section comes from pages 62, 63 and 102 of the proposal. Quotations and pinpoint citations are omitted.

cells. […] The second track is to apply measurements of nucleic acids to survey genotypic and phenotypic variation in the human population with the eventual aim of applying the technologies in diagnostics and prognostics. Realizing the "genomics-to-bedside" vision will require nucleic acid technologies that are compatible with clinical considerations, e.g. in terms of acceptable costs, acceptable error rates, etc. Much of the technology proposed here was designed with those considerations in mind.

Synergy. The primary mission of the MGIC is to efficiently integrate a diverse set of technical advances into a robust platform that can be applied to answer specific, critical biological questions that are poorly addressed by existing methods. We are pursuing *highly* multidisciplinary goals, and feel that this requires a talented, highly multidisciplinary team that (i) works well together and (ii) is capable of communicating across academic and geographic boundaries.

Open Source Biology. Our proposed CEGS will have a strong commitment to making the polony technology accessible to the full biomedical community. We are inspired by GNU and Linux, open-source projects that have proven to be effective models for software development, as well as the success of our own open collaborations. […] We have developed, and will continue to develop, our protocols using off-the-shelf instrumentation and reagents. We have also made up-to-date protocols and software publicly available on our website […]We are committed to exporting the polony technology into as many hands as possible so that it can be rapidly improved and modified in parallel.

ELSI

Privacy of genetic information is a key ELSI concern. The potential for genetic discrimination in insurance coverage and in the workplace are the central issues around which debates, legislation, and lawsuits concerned with privacy have focused […]. However, ongoing efforts of the research community, in part supported by the Human Genome Project, have made it increasingly easy and inexpensive to gather large amounts of sequence and expression data, and technologies to gather large amounts of other kinds of data (protein, interaction, single cell …) are in various stages of development. In addition, a key direction of recent research has been to demonstrate how diverse kinds of data may be integrated—indeed, *must* be integrated—in order to understand biological processes. Finally, as an ultimate goal of nearly all such efforts is to apply these technologies and data to clinical diagnosis and therapeutics, these techniques will eventually be applied to human beings on a wide scale. Through its development of polony technology, the MGIC is part of this research direction, and shares this interest in clinical application.

The core question is: How may the gathering of increasing amounts of genetic information be made compatible with ethical and legal requirements for privacy? Anything approaching a comprehensive genotype or phenotype (including molecular phenotypes) ultimately reveals subjects' identity in our increasingly wired world as surely as conventional identifiers like name and social security number. We call this

"comprehensive identifying" genetic information. This raises numerous specific questions:

- Are current informed consent practices sufficient to give human subjects adequate understanding of the potential that their identity may be discernible in large genetic data sets obtained from them?
- Is enough protection afforded by allowing researchers open access to such data sets so long as they agree not to take the analytical steps that would link these data to a specific person, or is this inadequate and impractical?
- Is there a kind and level of genetic information for which it would be virtually impossible for a researcher *not* to link it with a specific person?

Yet at the same time, the course of recent research shows ever more convincingly that availability of large, correlated sets of genetic data by the research community is required to understand and manage human health and disease. As scientists dedicated to such projects, we must therefore ask about the other side of the issue: How can comprehensive identifying genetic information be gathered and made available to the research community?

II. Active Issues in MGIC Research

In attempting to address these crucially important ELSI issues it is clear that our analysis must now extend beyond the original MGIC proposal and seek a concrete answer to a difficult question: "How may the gathering of increasing amounts of genetic information be made compatible with ethical and legal requirements for privacy?"[3]

However, before we address this question directly we believe that it is useful to carefully and precisely identify the specific issue placed before NIH/NHGRI for review. In particular, a review of past correspondence between NHGRI and MGIC members has revealed several distinct areas of concern which, while potentially relevant to ongoing MGIC research, are effectively distinguished from the issue at hand. We hope to dispel confusion by identifying each of these potential areas of concern, and by clearly delineating which issue we hope to resolve at this point in time.

Since the beginning of 2006, NHGRI has articulated three distinct concerns with respect to continuing MGIC research.

1) Scope: What is the anticipated scope of MGIC research? Specifically, does the MGIC grant envision the resequencing of an entire individual genome?

2) Confidentiality: Does the MGIC proposal contemplate the public release of human genome sequence information, whether complete or partial, when it is *intentionally* associated with identifying biographical and phenotypic information?

[3] *Id* at 102.

While both of these are important ELSI questions raised by NHGRI, neither need be answered at this time, and neither is addressed in this space. Rather, this document poses a third, narrowly conceived, question that is of immediate importance to MGIC:

> 3) Informed Consent: What is the most appropriate informed consent protocol for use in ongoing MGIC research, and why?

This is the *single question* presented in this document, and NHGRI's answer is of vital importance to the progress of ongoing MGIC research. Whether or not MGIC conducts any further or future genome resequencing (scope), or releases research data into the public sphere in any form (confidentiality), an appropriate informed consent protocol must be identified for MGIC research to proceed.

III. The MGIC Proposal: An "Open" Informed Consent Protocol

In order to ensure that the gathering of increasing amounts of genetic information is compatible with ethical and legal requirements for privacy, and to provide complete and valid informed consent for its research participants, MGIC has proposed a unique open informed consent protocol to govern ongoing research involving potentially identifying genetic information.

A. Why Promising Privacy is Dangerous

Initially, and at the request of NHGRI, MGIC carefully considered an informed consent protocol which presupposes the privacy and confidentiality of identifying genetic information except in carefully controlled circumstances which have been disclosed in advance to research participants. This approach is exemplified by the informed consent protocol employed by the International HapMap Project (HapMap). The well-known HapMap consent protocol effectively promises research participants almost perfect genetic privacy:

> Because the database will be public, people who do identity testing, such as for paternity testing or law enforcement, may also use the samples, the database, and the HapMap, to do general research. *However, it will be very hard for anyone to learn anything about you personally from any of this research because none of the samples, the database, or the HapMap will include your name or any other information that could identify you or your family*.[4]

By assiduously protecting the integrity of the database, anonymizing genetic information and decoupling it wherever possible from other identifying information, HapMap aims to protect the genetic privacy of all participants, including those whose well-being might be compromised by its release.

[4] INTERNATIONAL HAPMAP PROJECT, *Consent Form*, and *HapMap CEPH Reconsent Form*, http://www.hapmap.org/consent.html.en (accessed April 28, 2007) (emphasis in original).

However, in the same consent document, the paragraph discussing the risks of participation does contain a clear reservation:

> If your sample is used, lots of genetic information from your sample will be put in the database, and lots of people will be able to look at it for any purpose. However, there are only (sic!) a couple of ways anybody could trace the information back to you. One is if they thought your information might be in the database, got another sample from you, did many tests on that sample, and then compared the genetic information from those tests with the information in the database. The other way is if somebody compared the information in the database with genetic information known to be from you that was in another database and figured out who you were. The risk of either of these things happening is very small, but it may grow in the future.

Though it does not unambiguously guarantee the privacy or anonymity of participants' genetic information, the HapMap informed consent protocol suggests that the risk of re-identification is a vanishingly small one; a suggestion upon which at least some potential research participants are certain to rely.

Undoubtedly, there are research participants, whether of HapMap or other similarly consented projects, who would choose to withhold their consent but for the implicit promise of complete genetic privacy and anonymity.[5] And this reluctance to participate without full privacy guarantees may be particularly advisable if, as some scholars have suggested, research participants tend to "give up more than they realize when they hand over their DNA."[6]

Unfortunately, increasing evidence provided by specialists from the field of bioinformatics strongly suggests that absolute confidentiality is not a promise that medical and scientific researchers can deliver upon.[7,8] Researchers should actively strive to make research participants aware of the fact that even otherwise unidentified DNA can act as such an identifier. Indeed, as early as 1996 the American Society of Human Genetics warned researchers against creating an overly robust privacy expectation, suggesting that "investigators should indicate to the subject that they cannot guarantee absolute confidentiality."[9] In a recent statement concerning genome-wide association studies they put the risk clearly:

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[5] *See e.g.*, Anita L. Allen, *Genetic Privacy: Emerging Concepts and Values*. In: Mark A. Rothstein (ed.) GENETIC SECRETS: PROTECTING PRIVACY AND CONFIDENTIALITY IN THE GENETIC ERA . Yale University Press, New Haven, London, 1997, p. 31-59.

[6] Patricia A. Roche & George J. Annas, *DNA Testing, Banking, and Genetic Privacy*. (2006) NEW ENGLAND JOURNAL OF MEDICINE 355: 545-546.

[7] Bradley A Malin & Latanya Sweeney, *How (not) to protect genomic data privacy in a distributed network: using trail re-identification to evaluate and design anonymity protection systems*. (2004) JOURNAL OF BIOMEDICAL INFORMATICS 37: 179-192.

[8] Zhen Lin, Art B. Owen, & Russ B. Altman, *Genomic Research and Human Subject Privacy*. (2004) 305 SCIENCE 305:183.

[9] THE AMERICAN SOCIETY OF HUMAN GENETICS. (1996) *ASHG Report: Statement on informed consent for genetic research*. AMERICAN JOURNAL OF HUMAN GENETICS 59:471.

> "The ASHG is acutely aware that the most accurate individual identifier is the DNA sequence itself or its surrogate here, genotypes across the genome. It is clear that these available genotypes alone, available on tens to hundreds of thousands of individuals in the repository, are more accurate identifiers than demographic variables alone; the combination is an accurate and unique identifier.[10]

That the confidentiality of genetic data cannot and should not be guaranteed suggests that a research participant's consent may not be valid when it depends on an assurance, or even an unchallenged expectation, of complete genetic privacy and anonymity.

Balanced against these concerns is a body of ever more convincing evidence, supported by recent research at MGIC and throughout the scientific community, which suggests that the availability of large, correlated sets of genetic data is imperative to our understanding and management of human health and disease. It is imperative that such comprehensive identifying genetic information be gathered, and be made available to the research community, without violating basic moral, legal, and ethical principles or harming the individuals and the communities whose continuing participation is vital to the long-term success of human genetic research.

B. A Description of the open Consent Protocol

In light of this emerging dilemma MGIC has carefully considered, and now proposes to adopt, an alternative to the traditional informed consent protocol; one which openly acknowledges the possibility of the complete and public disclosure of an individual's genetic information, and makes the acceptance of this hypothetical a prerequisite to research participation.

The proposed study protocol, which has received continuous approval by the Harvard Medical School Institutional Review Board (HMS-IRB) as the Personal Genome Project (PGP) protocol,[11] seeks fully informed consent by positing a full and public disclosure of all genetic information as the starting point for consent; implicit and explicit guarantees of anonymity, confidentiality, and privacy are uniformly removed. Thus, the open PGP protocol permits, but does not require,[12] the resequencing of a participant's entire genome and the full and public disclosure of genetic information linked to identifying biographical and phenotypic information. The potentially broad sweep of the PGP protocol guarantees that consenting subjects think deeply about their participation, and that the risks associated with a disclosure of identifying genetic information, whether that occurs intentionally or otherwise, are transparent and fully understood.

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[10] http://www.ashg.org/genetics/ashg/news/gwas.shtml , 30 November 2006 (accessed 28 April 2007)

[11] The "Personal Genome Project" protocol was originally approved on August 31, 2005, and the most recent iteration was re-approved on July 27, 2006. The protocol is available for review on request.

[12] It is important to reemphasize that although the HMS-IRB has approved the study protocol to resequence entire genomes (scope), and to intentionally publicize participants' genetic information in association with identifying biographical and phenotypic information (confidentiality), neither of these steps are required of the PGP, and neither of these issues should detract from the single specific issue now before NIH/NHGRI: What is the most appropriate informed consent protocol for use in ongoing MGIC research?

To satisfy these goals the open consent protocol is structured to:

> [R]ecruit individuals who, in consultation with their family and health care providers, feel that they can give well-informed consent, accepting the risks of revealing whatever medical conditions they might have.[13]

In order to satisfy this goal, that participants in ongoing MGIC research be able to give truly well-informed consent, potential participants are limited at present to individuals with a master's degree in genetics or equivalent,[14] and are presented from the outset with a straightforward description of the risks of participation and, in particular, of public disclosure or identification:

> The risks of public disclosure of your genotype and phenotype information could affect employment, insurance, and social interactions for you and your immediate family. For example, data such as facial images can be used to identify you which could result in higher than normal levels of contacts from the press and other members of the public motivated by positive or negative feelings about the study. This could mean a significant loss of privacy and personal time.[15]

The protocol purposefully avoids any guarantee of genetic privacy or anonymity, and it thereby assures that research participation is restricted to those individuals who are comfortable with the publication of their identifying genetic information, regardless of its content. Whether or not an individual's genetic information ultimately enters the public domain, and whether or not it could be used to identify her, we believe it is imperative that an informed consent protocol openly acknowledge both of these possibilities.

C. ELSI Analysis of the open Consent Protocol

From an ethical perspective, there are compelling reasons for MGIC to adopt, and for NIH/NHGRI to approve, the open informed consent protocol. First, the proposed protocol represents a sincere commitment to *veracity*. It is our belief that veracity is fundamental to the solicitation of informed consent from prospective research subjects, and we treat veracity as an ethical obligation closely connected to the basic human research principles of respect for autonomy and beneficence.[16] Moreover, veracity is a crucial element in establishing and preserving the public trustworthiness of the scientific research community.[17]

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[13] PERSONAL GENOME PROJECT, *PGP Website Description*, http://arep.med.harvard.edu/PGP/ (accessed 28 April 2007).
[14] [citation]
[15] PERSONAL GENOME PROJECT, Draft Consent Form. (vs. 10, July 2006).
[16] Tom L. Beauchamp & James F. Childress, PRINCIPLES OF BIOMEDICAL ETHICS. FIFTH EDITION. Oxford University Press, Oxford, New York, 2001, p. 284
[17] Editorial, *In Science We Trust*. (2001) NATURE MEDICINE 7:871.

Second, the open protocol directly addresses the validity of the subject's informed consent. The MGIC proposal devotes explicit attention to two crucial elements of a valid informed consent:

1) Voluntariness: Full freedom in decision making demands the absence of constraints. In order to minimize the risk of coercion, including the threat of social and economic harm, the first participants under the open consent protocol will be recruited from among healthy senior geneticists who are not at risk for either insurance or employment discrimination. The protocol also provides that participants "will be selected as well-informed and not subordinate to the PI in terms of employment".[18]

2) Information: It is important that prospective research subjects possess an accurate and sufficient understanding of the possible impacts of participation, including worst-case scenarios.[19] In order to facilitate this, the MGIC protocol demands that all research participants possess "a master's degree in genetics or equivalent,"[20] which will ensure that the volunteers are capable of fully understanding the impact and possible outcomes of their participation.

Similarly, from a legal perspective, research investigators and sponsors are obligated to ensure the fully informed consent of research participants to the extent possible and, for this reason, MGIC's open informed consent protocol offers distinct advantages when viewed through a legal lens as well.

NIH/NHGRI sponsored research, including that conducted by MGIC, is subject at a minimum to the protective human research guidelines issued by the Department of Health and Human Services at 45 C.F.R. § 46.101 et. seq. According to these regulations, one of the "basic elements of informed consent" is the "description of *any* reasonably foreseeable risks…to the subject."[21] It is unclear whether a traditional informed consent protocol – one which deemphasizes the risk of re-identification and implicitly or explicitly guarantees the confidentiality of identifying genetic information – could be found to violate this statutory requirement, or any of the other myriad informed consent requirements imposed upon Federally-funded nontherapeutic research,[22] in the event of an accidental disclosure of identifying genetic information. However, we find ourselves unable to ignore the growing body of evidence which suggests that the confidentiality of such information cannot be guaranteed.

Rather than sailing as close to the wind as possible, it is our belief that the applicable legal guidelines, in addition to ethical considerations, demand that MGIC fully disclose

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[18] PERSONAL GENOME PROJECT, Human Study Protocol Application (last approved July 27, 2006).
[19] George M. Church, *Editorial: The Personal Genome Project.* (2005) MOLECULAR SYSTEMS BIOLOGY 1:30.
[20] PERSONAL GENOME PROJECT, Human Study Protocol Application (last approved July 27, 2006).
[21] 45 C.F.R. § 46.116(a)(2)(emphasis added).
[22] See, e.g., NATIONAL HUMAN GENOME RESEARCH INSTITUTE, http://www.genome.gov/10002332 (accesed 28 April, 2007).

the risks attendant to its ongoing nontherapeutic investigations, and to assure the confidentiality of potentially identifying genetic information only where we are certain that this level of privacy can and will be maintained into the future.

Finally, the social impact of employing an open consent protocol must be considered with respect to potential research participants, as well as to their relatives and their communities. Whether accidental or intentional, the publication of an individual's identifying genetic information would have consequences not only for the subject, but potentially for her family and for her community as well. Awareness of these consequences – which include stigmatization and the disruption of self-image at both the individual, family, and community levels - might induce certain individuals not to participate in genetic research projects, a reality that must not be overlooked.[23]

Rather than shying away from this difficult issue, the open consent protocol straightforwardly addresses it, and encourages potential subjects to carefully consider the possibility of disclosure and to consult with families and with communal groups where it is appropriate. We consider this form of advance planning, and the more broadly inclusive consent it engenders, to be one of the major advantages of the open protocol.

With respect to subject selection, preliminary responses to the PGP protocol indicate that, even if the open protocol might result in certain individuals declining to participate, it is quite likely that the subject pool will be of a sufficient size, and that it will represent a more suitable subject subset as well. Some potential subjects have indicated that they particularly like the open aspects of the protocol. Others have indicated that they would be willing to participate in either an "open" or a "closed" protocol, but that their reaction to the accidental release of identifying genetic information might depend heavily on the phrasing of the consent protocol.

The success of large-scale genetic research projects is dependent upon the continuing participation, and upon the trust, of individual subjects, as well as the families and the communities that support them. It is our conclusion that, especially in light of the very real risk of unconsented disclosure of identifying genetic information, this trust is most thoroughly safeguarded by promoting a research protocol founded upon openness.

IV. Conclusion and Recommendation

The critical advantage of the proposed open consent protocol is its ability to achieve voluntary and fully informed consent without relying on or encouraging the subject to expect that her genetic information will remain private or anonymous. Consenting research participants under such an open and expansive protocol protects those subjects, as well as their families and communities, from the unanticipated publication of their identifying genetic information, and preserves the broadest possible range of possibilities for the future collaborative usage and sharing of that data.

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[23] AMERICAN ACADEMY OF PEDIATRICS, *Policy Statement: Ethical Considerations in Research with Socially Identifiable Populations*. (2004) PEDIATRICS 113:148-151 .

For all of the reasons discussed above, we believe that the open consent protocol offers the most suitable means for collecting comprehensive identifying genetic information, while simultaneously respecting basic moral, legal, and ethical principles, and avoiding harm to the individuals and to the communities whose continuing participation is vital to the long-term success of human genetic research.

We urge NIH/NHGRI to approve the open protocol outlined in this single coherent document for immediate use in all ongoing and future CEGS-supported research at MGIC.

ELSI Contributors and Reviewers:

This document was compiled and written principally by Jeantine Lunshof,[24] and Daniel Vorhaus,[25] under the supervision of George Church.[26] The authors are grateful for the helpful comments and suggestions provided by six reviewers on the original paper as submitted to NHGRI August 2006. This document does not represent their views, and their decision to review this document does not constitute an endorsement of its conclusions.

[24] Department of Clinical Genetics, Section Community Genetics, & EMGO Institute, VU university medical center, Amsterdam, The Netherlands.
[25] Harvard Law School.
[26] Dept. of Genetics, Harvard Medical School.