SUMMARY STATEMENT

(Privileged Communication)

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PROGRAM CONTACT:
Jean McEwen
301-402-4997
mcewenj@mail.nih.gov

Application Number: 1 R21 HG006612-01

Principal Investigator

CLAYTON, ELLEN W MD, JD

Applicant Organization: VANDERBILT UNIVERSITY

Review Group: ZHG1 ELSI-P (O1)
National Human Genome Research Institute Special Emphasis Panel
ELSI - SEP

Meeting Date: 06/21/2011
Council: OCT 2011
Requested Start: 09/30/2011

RFA/PA: HG11-004
PCC: X5JM

Dual IC(s): DC

Project Title: Returning Research Results of Pediatric Genomic Research to Participants

SRG Action: Priority Score

Human Subjects: 10-No human subjects involved

Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Project Year	Direct Costs Requested
1	125,000
2	125,000
TOTAL	250,000

DC Recommended

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R21HG006612-01 CLAYTON, ELLEN

RESUME AND SUMMARY OF DISCUSSION: This application was received in response to RFA-HG-11-004, "ELSI Implications of Returning Research Results to Genomic Research Participants." The objective of this RFA is to stimulate research on the normative and legal issues involved in the decision of whether, when and how to return results to research subjects, particularly those who participated in studies that collect whole-genome datasets, or individuals who have provided samples or data to biobanks or databases.

The principal investigator (PI) proposes to study US and International law, policies and guidelines that address decision-making by and for minors, in an effort to determine what criteria should be applied to the process of returning individual results when children are enrolled in pediatric genomic research studies.

This application was received with substantial enthusiasm by the members of the Special Emphasis Panel (SEP). The reviewers acknowledged that the applicants have chosen to investigate an under-studied topic, and the plan to look at foreign laws and policies might reveal comparative information that could be useful to policy makers. The research team was judged to be outstanding. The investigators were recognized world experts in their fields. The application presents a good division of labors among the research team members that sensibly matches their expertise to the research topics, and an adequate plan is presented that describes how they will interact and coordinate the products of their individual research activities to bring about a final integrated research product.

The SEP did note a few minor weaknesses with the application. The proposal does not adequately explain why the investigators chose to focus the international study on Canada and a few countries in Western Europe. While differences will almost certainly be found in the laws and policies of these nations, there is little expectation that very divergent findings will come from these countries. Was this a convenience sampling, or is there a scientific rationale behind the choice of nations to be studied? The SEP noted that gaps and differences in laws and policies will emerge from this study, but it wasn't clear to the SEP what the applicants would then do to address these gaps.

A minority of the SEP expressed disappointment that the application did not do a better job explaining how this project would change the research landscape. But the majority of panel members remained very positive about this application, noting the track records of the research team and the under-studied topic of returning results in pediatric genomic research projects.

The comments in the CRITIQUE section were prepared by the reviewers assigned to this application and are provided without significant editing by staff. The critiques may or may not have been revised by reviewers following discussion at the review. The RESUME AND SUMMARY OF DISCUSSION documents the overall conclusions of the committee and the basis for the assigned priority score.

DESCRIPTION (provided by applicant): The specific aim of this project is to determine what criteria should govern return of individual results of pediatric genomic research, using analysis of US law and international guidelines regarding decision making for and by minors as the foundation. This issue, which has received remarkably little attention, must be resolved if this research, which is vital to understanding the contributions of genetic variation to the health of children, is to proceed. In order to develop these criteria, it will be necessary to draw upon a host of ethical, legal, and sociocultural factors, using standard legal analytic tools.

There is a long tradition within genetics, embodied in policy statements, such as those by the American Society of Human Genetics, the American College of Medical Genetics, and the American Academy of Pediatrics, of performing genetic tests on minors only when the results would alter the minor's immediate medical care. These limits are justified in part by the claim that, in the absence of

need for immediate intervention, the minor should be allowed to decide about genetic testing upon reaching adulthood.

More generally, decisions regarding the health care of children are treated differently from those of adults because children, as a matter of law, typically cannot make their own health care decisions. Procedurally, ethical and legal decision making authority, instead, is allocated among: 1) Parents who have broad authority to make choices among available options that affect their children. The scope of parental permission for their children's care, however, is not as broad as their discretion with regard to their own health care; 2) Clinicians who have an independent obligation to the welfare of the minor, which is bounded by the standards of clinical practice as well as legal requirements; 3) Minors who many hold have an increasingly important ethical and legal voice as they mature; and 4) In cases of abuse, neglect, or need to protect public health, the state. Substantively, defining the minor's best interest is often contested. One issue that is particularly challenging is deciding what weight should be given to various potential benefits from returning results, ranging from immediate benefit to the minor's health or reproductive information for the minor's later use to benefits that redound primarily to the family unit as a whole or exclusively to the parents or even to other minors of the same age or with the same condition.

Research involving minors is subject to more legal and ethical requirements and limitations than apply to adults.

This project brings together three internationally known lawyers, each of whom has written extensively about legal and policy issues in genomics research and in pediatrics, as well as an internationally known pediatrician-philosopher as a consultant, to define the applicable legal rules and to develop guidelines for returning results of genomic research involving minors.

PUBLIC HEALTH RELEVANCE: Determining what criteria should govern the return of individual results of pediatric genomics research has to date received remarkably little attention. This issue must be resolved if this research, which is vital to understanding the contributions of genetic variation to the health of children, is to proceed. This project brings together three internationally known lawyers, each of whom has written extensively about legal and policy issues in genomics research and in pediatrics, as well as an internationally known pediatrician-philosopher as a consultant, to define the applicable legal rules and to develop guidelines for returning results of genomic research involving minors.

CRITIQUE 1:

Significance: 2
Investigator(s): 1
Innovation: 3
Approach: 3
Environment: 1

Overall Impact:
This proposal aims to examine the distinctive and complex issues presented by the return of individual results from pediatric genomic research. It is well focused and considers how issues of minor consent, capacity, and best interests present additional complexity to the already difficult issues presented by the return of research results to subjects.

1. Significance:
Strengths

- The focus on pediatric research results is well considered and significant. It is deserving of the sustained analysis the project proposes.

Weaknesses

- The proposal makes much of the "imminent deployment of whole exome and whole genome sequencing in the clinical setting," as making these issues more urgent but it would be good to

elaborate on whether this presents qualitatively different sorts of issues or whether the prospect simply makes existing issues arise more frequently.

2. Investigator(s):
Strengths
- The investigators are highly experienced and have relevant expertise in areas bearing directly on the issues covered by this proposal.

Weaknesses
- None noted

3. Innovation:
Strengths
- The focus on pediatric research results it's well conceived and distinctive. The international approach is significant and often lacking from such studies.

Weaknesses
- The claim that "most of the legal discussion about return of research results to date has focused on the applicability of [CLIA}" construes the concept of legal discussion rather narrowly.

4. Approach:
Strengths
- The approach is straightforward and generally well-conceived. The strategy of having each Co-Investigator develop a paper in her area of expertise and then work together to develop a synthetic piece with recommendations promised to be productive.

Weaknesses
- It would be helpful to have a clearer definition of what the investigators mean by the term "genetic research results" as this could apply to many types of information not directly involving genomic testing per se. With respect to the aim of determining criteria to govern the return of results, the project might more explicitly consider not only the abstract criteria but also the stakeholders involved – e.g. how should the criteria be applied and by whom? IRBs? Clinicians? Parents? How might individual actors be held accountable for failure to apply the criteria? Etc. The international aspect of the project appears to focus primarily on Canada and Western Europe even though it asserts it will also review some 4,230 international laws and policies. If the focus truly is on Canada and Western Europe this should be made more explicit and acknowledged as a focus and limitation of the project. If the project truly aims to provide a comprehensive analysis of 4,230 international laws and policies then the scope seems too broad to be accomplished under this limited proposal.

5. Environment:
Strengths
- The environment seems well-suited to the project.

Weaknesses
- None noted

Protections for Human Subjects:
Not Applicable (No Human Subjects)

Budget and Period of Support:
Recommend as Requested

CRITIQUE 2:

Significance: 1
Investigator(s): 1
Innovation: 2
Approach: 2
Environment: 1

Overall Impact:
There is potential for very high impact of the proposed legal analysis both in informing current practice regarding return of individual results of genomic research with minors, and in grounding future legal, regulatory, and policy research and deliberations. The comprehensiveness of the analysis to be undertaken, its national and international scope, and the expertise and reputation of the collaborators are the ingredients of this high impact.

1. Significance:
Strengths

- The great significance of this project lies first in its plan to address comprehensively the neglected issue of which individual results of genomic research with minors should be returned, how, and to whom and second in the exceptional expertise of the three investigators and consultant.
- Its attention to law and normative arguments made beyond the borders of the US or North America increase its potential to ground future legal analysis as necessary and also to supply relevant normative arguments often absent from discussion of return of results.

Weaknesses

- None noted

2. Investigator(s):
Strengths

- Clayton, Knoppers, McGuire, and Ross are leading experts on the issue and on the topics that form the issue: health law concerning minors, parental autonomy and authority, the best interest's standard for parental decision-making, and clinical duties of care.
- The investigators' plan to work independently and together is appropriate and adequately explained and supported. Given the employment of high-level research assistance, the allocation of 10% effort on the part of the investigators is adequate, though it is not clear why Clayton, who is PI, overseeing the project, and hosting the meetings, commits slightly less (8%).
- The substantial consultant fee for Ross and the degree to which this project is integral to her overall research indicates that she will commit substantial effort to the project.
- The well-deserved reputation of the collaborators (including Ross) should help to ensure the impact of the project's products. Their connections within the genomic research community—as evidenced by their quite relevant preliminary studies—may also help to ensure the dissemination and impact of their analyses.

Weaknesses

- None.

3. Innovation:
Strengths

- Although standard methods of legal analysis will be used, their application to the issue of returning individual results from genomic research with minors is innovative. The comprehensiveness of the analysis proposed may be unique.
- To date, international treatment of issues surrounding return of individual results has had relatively little impact on the development of consensus positions regarding such return; this

project proposes to give substantial weight to how the issue of return of minors' information is treated outside of the US. This fact is important not only because much research is multinational in scope, but also because of the potential normative relevance of arguments made and experience had elsewhere in cases where US law is silent.

Weaknesses

- None.

4. Approach:

Strengths

- Standard methods of legal research and analysis are appropriate to the project's aims. Employing the human and database resources of the Centers in which the investigators work should streamline the data collection, freeing the investigators to focus on analysis of what precedents and legal guidance/requirements exist, though the personnel to be hired are also to be of an appropriate level to exercise some independent judgment during the data collection phase under the investigators' supervision.
- The products of the project seem to be very useful. The standard format for all three papers seems to provide a useful and comprehensive framework. The whitepaper is an appropriate means of synthesizing the analysis and moving toward recommendations.

Weaknesses

- Given that the law will often "run out" with respect to this topic, there will be a need to extend the legal analysis and argumentation into the domain of ethics. Although Ross's expertise in this area—and indeed the ability of the three investigators to engage in ethical, as well as legal reasoning—is clear, the proposal itself might have more explicitly acknowledged the degree to which arguments and recommendations not grounded in law will be made and indicated the resources or ethical framework(s) to be employed when the law does "run out."
- In this regard, it is not obvious that "ethical and legal norms regarding the allocation of decision making authority among children, parents …" are the sole norms to be consulted. Unless norms regarding allocation of decisional authority are construed to include ethical arguments concerning the substance of child welfare, a child's so-called open future, appeals to human rights and basic human capacities, and so on.
- Despite plans to use the legal analysis, "informed by ethical and policy analysis," it was not entirely clear to what degree recommendations can actually be made to investigators regarding returning results to minors, given the substantial gaps in law anticipated. It is not clear to what degree the investigators plan to make recommendations in such cases, as opposed to merely identifying the gaps. Perhaps it is impossible to determine prior to identifying the *specific* gaps.

5. Environment:

Strengths

- The environments in which this research will be conducted have excellent resources to support the work proposed.

Weaknesses

- None noted

Budget and Period of Support:

Recommend as Requested

Additional Comments to Applicant (Optional):

- I would like to have seen greater detail about when the investigators and consultant would turn from existing law/precedent to create, analogize, or otherwise go beyond the existing law (indeed moving from the legal to the ethical).
- I would also like to see a somewhat larger role for Ross because her clinical experience seems to be somewhat underutilized. She is to be called upon to assist with ethical analysis, but as one

of two MDs – and the one with a larger current clinical role – she might have valuable insight regarding the feasibility of some requirements or recommendations, additional gaps that are not identified by the investigators, and so on. I anticipate that she will serve this role in any event; however, the proposal might benefit from articulating it.

CRITIQUE 3:

Significance: 4
Investigator(s): 1
Innovation: 3
Approach: 3
Environment: 1

Overall Impact:
Investigators, biobank initiatives, and IRBs are trying to determine whether some research results from pediatric genetic/genomic studies should be offered to parents and what criteria should be used to make such a determination. The investigators of this project will develop criteria for the return of results informed by legal, ethical and socio-cultural factors related to parental decision-making in the clinical context, clinician obligations to minors, and regulatory protections for pediatric research participants. The project's recommendations will fill a gap in the biobank ethics literature. However, it is unclear whether the recommendations will have an impact on how investigators, biobank initiatives and IRBs establish policies and criteria governing the return of pediatric genomic research results.

1. Significance:
Strengths
- Little guidance exists about whether individual results from pediatric genomic research should be returned and if so, what criteria should govern the decision to return results.
- The legal, regulatory, and policy analysis will fill an existing gap in the literature regarding the return of genomic research results.
- Emphasis on legal applicable rules is strength but also a weakness (see below).

Weaknesses
- Although the project will develop criteria based upon an analysis of legal, ethical, and socio-cultural factors, the emphasis is weighted toward defining the legal applicable rules for returning pediatric genomic research results.
- Given the emerging empirical evidence that many parents want the results of genomic research conducted with their child's DNA sample and that several research initiatives are providing some results to parents, it is unclear what impact the project's elucidation of applicable legal rules and development of ethical/policy guidance will have on the criteria for and practice of returning pediatric genomic research results, or on the development of policy and regulatory guidance.

2. Investigator(s):
Strengths
- The investigators have substantial subject matter expertise.
- The investigators have conducted high quality relevant research.

Weaknesses
- None identified.

3. Innovation:
Strengths
- Attention given to parental decision-making, children's choices and future interests, and health care providers' legal and ethical obligations to minors.

- Attention to the international legal context regarding decision-making authority for minors and minors' participation in research.

Weaknesses

- Defining the legal environment or underpinnings for determining the criteria for returning pediatric genomic results is not in itself novel.

4. Approach:

Strengths

- Including both the research and clinical contexts in the analysis of rules governing the allocation of decision-making authority.
- Extending the analysis to the international context.

Weaknesses

- The emphasis on legal analysis as a key basis for recommendations seems narrow in that parental and researcher preferences that differ from "expert recommendations" may be relevant to whether results are returned. In addition, the legal analysis doesn't appear to take into account the meaning of evidentiary criteria such as personal utility that for parents, researchers and clinicians may play a role in whether results are returned, especially in the absence of legal/regulatory requirements and guidance.

5. Environment:

Strengths

- Excellent environments in which to conduct the project.

Weaknesses

- None identified.

Resource Sharing Plans:
Acceptable

Budget and Period of Support:
Recommend as Requested

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

DATA AND RESOURCE SHAING PLANS: The SEP expressed no concerns about these plans.

ROP

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-10-080 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-080.html.
The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the

overall impact score. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.