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Return of Results from Genomic Sequencing: A Policy Discussion of Secondary Findings for Cancer Predisposition

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Abstract

Advances in DNA sequencing technology now allow for the rapid genome-wide identification of inherited and acquired genetic variants including those that have been identified as pathogenic alleles for a number of diseases including cancer. Whole genome and exome sequencing are increasingly becoming a part of both clinical practice and research studies. In 2013 the American College of Medical Genetics and Genomics (ACMG) recommended that results of pathogenic genetic variants in 56 genes, nearly half of which comprise cancer genes (including *BRCA1*, *BRCA2*, *TP53*, *MLH1*, *MLH2*, *MSH6*, *PMS2*, and *APC*),be returned to patients who have their genome sequenced independent of the purpose for the test. This recommendation has been highly controversial for several reasons, particularly the recommendation that individuals be returned secondary findings of disease causing variants for adult onset conditions regardless of age and without consideration of patient preferences. In addition, the policy regarding returning results of secondary findings from genomic sequencing studies in research settings is currently unclear. In response to these emerging ethical issues, the Washington University Brown School in St. Louis, MO, United Stateshosted a policy forum entitled *"First do no harm: Genetic privacy in the age of genomic sequencing"* on February 25th, 2014. The forum included a panel of experts to discuss their views on ethical issues related to return of results in both the clinical and research settings. In this report, we highlight key issues related to return of results from genome sequencing tests that emerged during the forum.

Keywords

Secondary findings; incidental findings; ACMG; cancer; results; return; genome; genetic; testing; *BRCA1*; *BRCA2*

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INTRODUCTION

The completion of the human genome sequence in 2003[1] has been followed by rapid advances in genomic technology and subsequent exponential increases in knowledge of human genetic variation, including that associated with both Mendelian and non-Mendelian diseases. Plummeting costs of genome sequencing technology[2] make it increasingly feasible to rapidly scan the whole genome (both genic and non-genic DNA sequence) and exome (genic DNA sequence) for inherited variants including those that have been previously identified or suspected as pathogenic alleles for cancer. Genome-wide genetic testing offers the potential to identify high risk populations for cancer prevention and control, which could ultimately lead to reductions in cancer morbidity and mortality. As a consequence, there has been intense interest in developing guidelines for returning results of pathogenic variants that are detected in genome sequencing tests for diseases, including cancer, for which prevention and/or early intervention is possible.

In March 2013, the American College of Medical Genetics and Genomics (ACMG), an organization that supports the medical genetics profession, published recommendations for reporting what was termed “incidental findings” of pathogenic variants detected in genomic sequencing tests in 2013[3]. The ACMG recommended that pathogenic or presumed pathogenic variants in 56 genes be reported to individuals who have their genome sequenced. The report defined incidental findings as “the results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered” [3]. However, on the basis of a definition published by the U.S. Presidential Commission *for the* Study of Bioethical Issues, we use the term “secondary findings” throughout the manuscript in lieu of “incidental findings” to describe the active search for variants in genes recommended by the ACMG [4]. The genes were selected by the committee on the basis of their medical action ability. Nearly half of the recommended genes are well-known cancer susceptibility genes including: *BRCA1*, *BRCA2*, *TP53*, *STK11*, *MLH1*, *MLH2*, *MSH6*, *PMS2*, *APC*, *MUTYH*, *VHL*, *MEN1*, *RET*, *PTEN*, *RB1*, *TSC1*, *TSC2*, *WT1*, and *NF2*. The ACMG recommendation has been highly controversial, in particular the recommendation that results be returned to parents/legal guardians of children for pathogenic variants in genes associated with adult onset conditions. In addition, the lack of patient autonomy over whether to receive secondary findings in their clinical sequencing data has also been a subject of intense debate [5, 6].

In response to these emerging policy issues, on February 25th, 2014, Washington University in St. Louis, MO, United Stateshosted a 90 minute policy forum entitled *“First do no harm: Genetic privacy in the age of genomic sequencing”* that featured a panel of experts concerned about ethical issues associated with genomic sequencing (panelist biographies are provided in Appendix A). We note that the debate generated by the ACMG report is not specific to the U.S. [7, 8] nor is it the only position articulated in the U.S., but the forum mainly focused on this report as a starting point for the policy conversation. The 90 minute policy forum format allowed for considerable audience discussion following each 4–7 minute panelist presentation on return of results in both clinical and research settings (video

is available upon request). In this report, we discuss key issues regarding return of results that emerged during the policy forum.

Return of results in clinical settings

The central controversy surrounding return of results from whole genome or exome sequencing tests in clinical settings is whether patients should have the choice of receiving secondary findings that are detected during testing that was performed for other purposes. The panelists expressed opposing viewpoints on this controversy. Lainie Ross, MD, PhD, Professor of Clinical Medical Ethics at the University of Chicago, pointed out that patients have the right *not* to be informed of results from genetic tests for reasons including: the information may not be relevant for decades, the information may inaccurately predict risk, the information may only be wanted if effective treatments or preventions are available, and the tests may reveal unanticipated information that might produce harm (e.g. misattributed paternity). Other experts believe that the rationale for returning results of secondary/ incidental findings from genomic sequencing differently than return of results from other types of medical tests is unclear[5].Laura Bierut, MD, Professor of Psychiatry at the Washington University School of Medicine raised this issue during her opening remarks in a thought experiment. If a patient gets a chest X-ray and the radiologist notes a lesion incidental to the purpose of the imaging, shouldn't the radiologist tell the doctor and the doctor tell the patient? She emphasized that if the healthcare provider believes that the finding may be life changing, that it should be provided to the patient. For further discussion of this analogy see Solomon 2014 [9].Ellen Wright Clayton, JD, MD, Professor of Pediatrics at Vanderbilt University School of Medicine and Professor of Law at Vanderbilt University School of Law, emphasized the point about definitions of types of findings in her opening remarks; the ACMG recommendation for reporting variants in 56 genes does not actually constitute reporting of 'incidental' findings as was defined by the ACMG report. One must actively search for, sequence and analyze these genes for variants, which as Dr. Ross noted, mandates the addition of opportunistic screening any time whole genome sequencing is performed. It requires the clinical laboratory to actively sequence, analyze, and interpret variants in 56 highly penetrant genes, and if found, report them back to the physician. She believes that this poses serious ethical issues including: 1) it does not require the consent of the ordering physician or patient, and 2) there is predictive uncertainty—i.e., pathogenic variants in genes identified by the ACMG may be highly penetrant in high-risk populations where the most research has been conducted but it is unclear whether the same is true for populations where research has not been conducted.

Return of results in research settings

The issues surrounding return of results from genomic sequencing studies in research settings differs from clinical settings. Jonathan Green, MD, Executive Chair of the Washington University Institutional Review Board (IRB) reminded the audience that the IRB is charged with determining that research involving human subjects meets specific regulatory criteria (45 CFR 46.111) that are derived from the Belmont Principles[10].Human subjects' regulations require that informed consent include a statement that the study involves *research*. Returning genetic information, particularly if unrelated to the aims of the study, crosses into the realm of clinical medicine. Individuals who enroll in research studies

where there is a promise made to return results and secondary findings, are likely to equate this with going to their primary care doctor and having a test done for clinical purposes. Dr. Green noted that the informed consent document must include a description of any reasonable foreseeable risks or discomforts as well as benefits to the subject. Because anticipated and secondary findings that are generated in genomic research meet the standard of being reasonably foreseeable, the informed consent process must clearly disclose the possibility of returnable results and secondary findings and their implications for the participant. It is less clear, according to Dr. Green, whether returning results on secondary findings should be considered a risk or a benefit. In ideal circumstances, the benefit is obvious. That is to say, the participant is made aware of a medical condition for which an action can be taken, and a poor outcome is averted. However, Dr. Green stressed that potential harms may also occur when participants receive results including unnecessary additional tests and procedures each with their own associated costs, risks, and morbidities. For example, the penetrance of *BRCA1* pathogenic variants may be lower in the general community than in those women who have a family history of breast cancer[11]. Returning results to women for rare *BRCA1* variants with uncertain penetrance could lead to potential harms including leading some women to undergo prophylactic measures to reduce their risk[12, 13].

Dr. Green discussed the current state of affairs for guidelines on return of results in research settings. Current United States regulations require that participants be fully informed about the nature of the research, and therefore they must be informed about the possibility of research results or secondary findings being generated in a study. Furthermore, they must be informed about what the researcher plans to do with the information (return themor not). If results are to be returned, participants should be asked at the outset whether they want the results, ideally at the time of informed consent, and then perhaps again at the time they are available. When returned, risks must be minimized by assuring the results are valid and that the participant is provided with appropriate resources and follow-up to act on the information. Dr. Green stated that he does not believe that current regulations require researchers to routinely look for secondary findings, nor to always promise to return research results or secondary findings. Nor does he believe that it should be made mandatory for researchers to do so. Mandating return of results promotes confusion between the roles of researcher and clinician, as well as the roles of participants and patients. Research is not clinical care and the researcher-participant relationship is not the same as the physician-patient relationship. Researchers should be wary of accepting new obligations that cross over into the clinical realm. Imposing a mandatory duty on all researchers to look and warn, places undue burdens on the research enterprise. Such a requirement may force researchers to make promises they cannot keep. Dr. Green noted that furthermore, it will be impossible to ensure that the results are returned in a way that minimizes risk, by providing valid results, with appropriate counseling and follow up. Doing this poorly is worse than not doing it at all, he noted.

ISSUES RELATED TO RETURN OF RESULTS ACROSS SETTINGS

The concept of “To do no harm”

The panel was asked by the moderator (S. Gehlert) for their views on the consistency between the ACMG recommendations and the “to do no harm” concept in medicine and healthcare ethics. Dr. Green noted that explicitly following the ACMG recommendations runs counter to this concept in medicine because there is no process for informed consent of the patient. He also noted that the impact of all mutations on disease risk is not understood. “To do no harm” comes with “respect for persons”[10], the ability of individuals to make their own choices as to what information they receive. Vence L. Bonham, JD, Associate Investigator, Division of Intramural Research, Social and Behavioral Research Branch and Senior Advisor to the U.S. National Human Genome Research Institute (NHGRI) Director on Genomics and Health Disparities, NHGRI concurred that the question of harm is complex. This sentiment was also echoed by Dr. Clayton, who gave the example that parents of children with life-threatening diseases (children who may be more likely to have their genomes sequenced), may not want anymore “bad news”. In contrast, the reality as Dr. Bierut pointed out, is that genetics is entering clinical practice, and the more salient issue is how best to consent and deliver secondary findings. The informed consent process for clinical sequencing should inform individuals of the potential of uncovering of defined incidental findings, such as genetic cancer predispositions, and patients do not want to receive these results should consider not undergoing genetic testing. In contrast, as Dr. Ross suggested, it seems likely that patients may not wish to know all that can be known about their health. Respect for persons [10] requires that patients have a choice over whether to receive secondary findings from genetic testing. Dr. Ross also suggested that providing individuals in the clinical setting with a choice not to get sequenced isn’t a solution because it may be the only way to obtain a diagnosis.

An important consideration raised by an audience member related to the concept of “to do no harm” regards the evidence on harms, such as anxiety and distress, after receiving genetic results. Dr. Bierut gave the example of return of results for Apolipoprotein E (*APOE*), a gene where certain common alleles have been associated with a strongly increased risk for Alzheimer’s disease (AD), from The Risk Evaluation and Education for Alzheimer’s disease (REVEAL) study. The objective of the REVEAL study was to determine the effect on depression and anxiety up to 1 year of returning *APOE* risk allele (ε4) results to individuals who did not have AD symptoms. Participants were randomized to either disclosure of results for the risk allele or non-disclosure. The authors reported no significant differences between the two groups in anxiety or depression up to one year[14]. However, Dr. Clayton noted that the REVEAL study was comprised of individuals who were already aware of their AD risk because of family history, were extensively counseled about AD risk as part of their participation, and had consented to the study. Dr. Green also commented that the generalizability of findings from this study is limited by the highly controlled research setting in which the study took place and it isn’t clear how these results will extrapolate to the general population. However, additional evidence shows that anxiety and distress is transient after receiving genetic results, even potentially life altering incidental findings such as cancer predisposition risk. A study of the effects of direct to consumer testing identified

individuals who carried BRCA variants, the variants which carry a high predisposition to breast and ovarian cancer. In follow up, there was no significant evidence of serious emotional distress or inappropriate actions by the individuals[15]. Research funded by the U.S. NHGRI should help to further clarify the issue of harms and benefits of returning genetic information pertaining to secondary findings.

Inequities in genomic studies

The issue of equality in knowledge about genetic variation between different ancestral groups was also identified during the policy forum as a major issue related to return of genomic sequencing results. The vast majority of genomic knowledge on human genetic variation is derived from individuals of European descent. Mr. Bonham emphasized this issue and the issue of who has access to genome sequencing that could benefit patient outcomes. He discussed the principle of justice and fairness in health inequities recommendation 5 from a report by the U.S. Presidential Commission for the Study of Bioethics [4]: *"The principle of justice and fairness requires that all individuals have access to adequate information, guidance, and support in making informed choices about what medical tests to undergo, what kind of information to seek, and what to do with the information once received. The principle of justice and fairness also requires affordable access to quality information about incidental and secondary findings, before and after testing, which when coupled with access to care can be potentially lifesaving or life enhancing."* Mr. Bonham noted that this is an audacious recommendation but contended that we need to understand the barriers to affordable access to clinical use of genomic data for all patient populations.

In addition, the issue of who will benefit from return of results needs to be addressed. Even if diverse communities have access to clinical sequencing genotype based testing, it isn't clear that they will benefit. Knowledge of genetic variation in non-Northern European populations is markedly less in comparison to that of Northern European populations that have been most well studied—which could impact interpretation of genome testing results. Dr. Bonham referenced a study by Dorschner et al, 2013[16] that examined 'pathogenic incidental findings' in 1000 exomes from 500 European and 500 African-descent individuals. The authors examined 114 genes associated with medically actionable conditions for disease causing variants that were listed in the Human Gene Mutation Database (HGMD)[17]. The authors reported that 23 participants with variants that were listed in HGMD were "disproportionately" of European descent (n=17) vs. African descent (n=6). These data highlight that any benefit derived from returning results of secondary findings will disproportionately apply to individuals of European descent. Mr. Bonham concluded that if ancestrally diverse groups are not included in research, they may not benefit to the same extent as those populations that are included and that there is much to do to ensure that the health benefit of clinical sequencing and genotype guided treatment is equally accessible to all communities. An audience member echoed this point with the comment that the focus of the policy discussion really shouldn't be about whether to give people information but instead about who has access to information.

Health literacy

Another issue raised during the forum is the issue of health literacy, defined by the Institute of Medicine as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions”[18].Even if informed consent of the patient/research participant for return of results is obtained, it is unclear that individuals who opt to receive information on secondary genomic findings will understand the potential implications. These may include: the possibility of genetic discrimination, strengths and limitations of genomic data, and implications of testing children. The need for increased genomic health literacy among the general U.S. population was recently emphasized in a study that surveyed 2500 adults following the actress Angelina Jolie’s New York Times editorial [19] announcing that she was a carrier of the *BRCA1* mutation and had chosen to have a double mastectomy. The survey results indicated that although 75% of adults had heard her story, less than 10% knew the relationship between *BRCA1* mutations and breast cancer risk [20].

Obtaining informed consent in the clinical setting maybe challenging as alluded to by Dr. Bierut. Although healthcare providers may wish to ensure that their patients have an understanding of the implications of agreeing to the return of results from genomic testing, the limited time spent in patient care may be a barrier. For example, a U.S. study published in 2012 that examined 2470 cancer patient office visits reported that the average duration was 22.9 minutes[21]. Since cancer patients are likely to be one of the largest patient groups to undergo clinical sequencing, the ability of healthcare providers to obtain informed consent has important implications for considering return of secondary findings. Dr. Bierut noted that spending more time on educating patients about genomic testing and the implications of the results will come at the expense of other conversations related to clinical care, and she emphasized that alternate delivery systems such as delivery of genetic information through the internet (as has been done in direct-to-consumer testing) may provide a solution to this challenge. Research on the harms and benefits of new health communication tools is needed.

Return of results to children

The ACMG recommended that age not be a factor in the return of results (The Working Group recommended that “incidental variants should be reported regardless of the age of the patient”) [3]. According to the ACMG report, this recommendation was based on a number of considerations including:(1) concerns that reporting of secondary findings relevant to adult disease may be the only way that parents themselves become aware of the pathogenic variant that affects them; (2) laboratory capacity to mask variants identified in clinical sequencing tests for children specifically; and (3) a favorable risk benefit ratio of providing children with results of genomic testing for adult onset diseases in cases where intervention is possible[3].Some evidence suggests that parents want these results. For example, a 2013 study by Sapp et al.[22] examined parental preference for receiving secondary findings in their children with undiagnosed diseases and suggested that although parents express preference for receiving results on variants associated with actionable disorders that occur during childhood, they are less likely to agree to receive results about adult-onset diseases for which there is no treatment. An audience member reported that in her experience as a

clinical genetics fellow, parents rarely opt out of receiving results. Moreover, no long term data currently exists on any harms that emerge during adulthood in individuals who were returned results as children. There is clearly a need for longitudinal research to understand harms to individuals who are returned results as minors. Interestingly, a statement prepared by the ACMG and the American Academy of Pediatrics published a month before the ACMG report, recommended that genetic testing in children for adult-onset conditions be deferred [23]. Dr. Ross pointed out that even when a *BRCA* mutation is found, mammograms are not recommended for individuals until they are adults. However, as noted above, one of the rationales for this ACMG recommendation was that "an incidental finding relevant to adult disease that is discovered and reported to the clinician through clinical sequencing of a child may be the only way which the variant will come to light for the parent"[3]. In other words, a *BRCA1* pathogenic variant that is incidentally identified in the child through genomic testing may have implications for cancer risk in the parent, even though, as Dr. Ross emphasizes, the gene may not be pathogenic in this family and its identification may cause more harm (e.g., stress and unnecessary surveillance) than benefit.

Predictive uncertainties in genetic testing results

The predictive uncertainty of genetic variants from genomic testing, including ACMG recommended genes (particularly *BRCA1* and *2*) emerged as another important issue. Dr. Ross described the ACCE model process for evaluating genetic tests that provides criteria for returning results to patients[24]. The ACCE model considers **A**nalytic Validity, **C**linical Validity, **C**linical Utility, and **E**thical, Social and Legal Implications. Evaluation using the ACCE criteria suggests that returning secondary genomic testing results may not necessarily meet the criteria, particularly with respect to clinical validity. For example, the significance of some variants, including those in the breast cancer susceptibility genes *BRCA1* and *2*, may not always be known, especially in individuals where there is no family history of breast cancer. *BRCA1* or *2* pathogenic variants that have previously been identified in high risk families may be highly penetrant in these communities but penetrance in the general population is not as well understood. For example, a recent well-designed study conducted in the Netherlands indicated a lower penetrance of breast cancer in *BRCA1* mutation carriers in families with fewer breast cancer cases versus those with more cases (although the life time risk is still higher than in non-carriers), emphasizing that genotype phenotype correlations may be less strong than previously thought, as well as the need to consider gene environment interactions[25].

The concept of predictive uncertainty of genomic sequence findings is also important to consider when offering research participants results from genomic sequencing as Dr. Green commented on in his opening remarks. Minimization of risk requires that any sequence results reported back to participants be analytically valid and that participants are provided with adequate counseling and resources to be able to interpret the result and to determine appropriate next steps. This is challenging for IRBs to evaluate and research teams to implement. There are questions about what constitutes analytic validity in the research setting where tests are not required to be conducted in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory that meets standards for U.S. laboratory testing [17, 26]. Requiring that sequencing be conducted in a CLIA-certified environment in

research settings may be prohibitively expensive. In addition, it may also be prohibitively expensive to include a genetic counselor on any research projects that generate genomic sequencing data.

Update on ACMG recommendations

The authors would like to note that a little over a month (April 1, 2014) after the policy forum on this topic, the ACMG published a revision to their 2013 recommendation stating "…that patients should have an opportunity to opt out of the analysis of medically actionable genes when undergoing whole exome or genome sequencing"[27]. Of note is that the issue of the impracticality of pre-test counseling of patients about secondary findings in the 56 genes that served as one of the reasons for not giving patients an opportunity to opt out still needs to be addressed.

Summary and Future directions

From the policy forum, it became clear that much work is still needed to inform and develop policies on the return of results from genomic testing. Clinical sequencing is being implemented rapidly in medicine making this topic an urgent area for policy research, discussion, and formulation. Experts and community audience members did not necessarily agree about whether secondary results from genomic testing should be returned and under which circumstances. Several issues emerged that indicated a clear need for additional research and community input that is needed for policy formulation. These issues include: return of results to children, health literacy, inequities in genomic testing, and alternative modes of delivering genetic information outside of traditional clinic settings. It is clear that advances in our ability to detect and identify human genetic variation associated with cancer susceptibility and other diseases have enormous potential for prevention and early treatment. However, we must continue to be thoughtful about issues related to inequities in genomic data and how best to deliver genomic testing results that hold immense promise for reducing disease morbidity and mortality.

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Appendix

Speaker Biographies:

Laura Jean Bierut, MD is the Alumni Endowed Professor of Psychiatry at Washington University School of Medicine in St. Louis. She earned her Bachelor of Arts degree at Harvard/Radcliffe Colleges and her medical degree from Washington University School of Medicine. She has built a successful research program devoted to understanding the genetics of substance dependence and has authored over 200 scientific articles. She is an active member in the NIDA Genetics Consortium, a national group of scientists who are leading NIDA's efforts to understand genetic causes of substance dependence. Dr. Bierut was

invited by the Secretary of Health and Human Services to serve on the National Advisory Council on Drug Abuse. Dr. Bierut was elected to the Alpha Omega Alpha Honor Medical Society, and she has been honored by the American Psychiatric Association and Washington University for her efforts to teach and mentor medical students, residents, post-doctoral trainees, and junior faculty. In recognition of her clinical work, she has been named as a "Best Doctor" in America.

Vence L. Bonham, Jr., JD is an Associate Investigator in the National Human Genome Research Institute Division of Intramural Research Social and Behavioral Research Branch. He is also the Senior Advisor to the NHGRI Director on Genomics and Health Disparities and Chief of the Education and Community Involvement Branch. He earned a Bachelor of Arts degree at Michigan State University in 1978 and his juris doctorate degree from The Ohio State University Moritz College of Law in 1982 and completed a Health Services Research Fellowship with the Association of American Medical Colleges in 1998. Mr. Bonham's research and scholarship is at the intersection of law, public policy, health care and genomics. His research focuses primarily on the social and clinical influence of new genomic knowledge, particularly in communities of color. Prior to joining the National Institutes of Health, Mr. Bonham was an Associate Professor at Michigan State University in the Colleges of Medicine and Law.

Ellen Wright Clayton, JD, MD earned a Bachelor of Science degree in Zoology at Duke University in 1974, a Master of Science degree in Biology from Stanford University in 1976, a law degree from Yale University in 1979, and her medical degree from Harvard University in 1985. She completed her residency in pediatrics at the University of Wisconsin in 1988. Ellen Wright Clayton came to Vanderbilt in 1988 as an Assistant Professor of Law and Assistant Professor of Pediatrics. She was promoted to Associate Professor in both schools in 1996 and to Professor in 1999, when she became the Rosalind E. Franklin Professor of Genetics and Health Policy and founded the Center for Genetics and Health Policy. She co-founded and directed the Center for Biomedical Ethics and Society in 2005 and was appointed to the Craig-Weaver Chair in Pediatrics in 2012. Author of more than 150 articles, chapters, and official reports, her research has focused on the ethical, legal, and social issues (ELSI) raised by genetics and genomics research and the translation of new findings into clinical care. She has served on the National Advisory Council for Human Genome Research of the NIH, as Co-Chair of the ELSI Working Group of the International HapMap Project, and on the HUGO Committee on Ethics, Law, and Society. In other activities, she was President of the American Society of Law, Medicine, and Ethics and Editor-in-Chief of the Journal of Law, Medicine, and Ethics. In the last decade, she has been very active in the work of the Institute of Medicine, serving on tencommittees and chairing five, two boards, one of which she chairs, and on the IOM Council and its Executive Committee. She was elected a member of the Institute of Medicine, the American Pediatric Society, and Alpha Omega Alpha, and as well as a fellow of the American Association for Advancement of Science.

Jonathan Green, MD is Professor of Medicine, Pathology and Immunology, as well as Associate Dean for Human Studies and Executive Chair of the IRB at Washington University School of Medicine in St Louis, MO. He received his medical degree from

Wayne State University followed by residency training in Internal Medicine at Boston City Hospital. He then completed a fellowship in Pulmonary and Critical Care Medicine at the University of Michigan and additional post-doctoral training at the University of Chicago. He is board certified in Internal Medicine, Pulmonary Diseases and Critical Care Medicine. Currently, Dr. Green is an attending physician in the Medical Intensive Care Unit at Barnes-Jewish Hospital, and conducts both basic science and clinical research on the regulation of the immune response.

Lainie Friedman Ross, MD, PhD is the Carolyn and Matthew Bucksbaum Professor of Clinical Medical Ethics at the University of Chicago where she is also a professor in the Departments of Pediatrics, Medicine, Surgery, and the College. She is an associate director of the MacLean Center for Clinical Medical Ethics, and co-Director of the University of Chicago Institute of Translational Medicine (ITM). Dr. Ross graduated Princeton University (AB 1982); the University of Pennsylvania School of Medicine (MD 1986); and Yale University (PhD, philosophy, 1996). She trained in Pediatrics at the Children's Hospital of Philadelphia and at Columbia University (New York). Dr. Ross' research focuses on ethical and policy issues in organ transplantation, genetics, and pediatrics. She published 2 books with Oxford University Press: Children, Families and Health Care Decision Making [1996] and Children in Research: Access versus Protection [2006], and is currently co-writing Transplantation Ethics, second edition with Robert Veatch, PhD (Georgetown University Press, 2014). She recently was awarded a fellowship from the John Simon Guggenheim Memorial Foundation. During her Guggenheim term, Dr. Ross will focus on writing a book that she has tentatively titled: "From peapods to whole genomes: Incidental Findings and Unintended Consequences in a Post-Mendelian World."

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