The American Journal of Human Genetics, Volume *98*

Supplemental Data

Clinical Sequencing Exploratory Research Consortium:

Accelerating Evidence-Based Practice of Genomic Medicine

Robert C. Green, Katrina A.B. Goddard, Gail P. Jarvik, Laura M. Amendola, Paul S. Appelbaum, Jonathan S. Berg, Barbara A. Bernhardt, Leslie G. Biesecker, Sawona Biswas, Carrie L. Blout, Kevin M. Bowling, Kyle B. Brothers, Wylie Burke, Charlisse F. Caga-anan, Arul M. Chinnaiyan, Wendy K. Chung, Ellen W. Clayton, Gregory M. Cooper, Kelly East, James P. Evans, Stephanie M. Fullerton, Levi A. Garraway, Jeremy R. Garrett, Stacy W. Gray, Gail E. Henderson, Lucia A. Hindorff, Ingrid A. Holm, Michelle Huckaby Lewis, Carolyn M. Hutter, Pasi A. Janne, Steven Joffe, David Kaufman, Bartha M. Knoppers, Barbara A. Koenig, Ian D. Krantz, Teri A. Manolio, Laurence McCullough, Jean McEwen, Amy McGuire, Donna Muzny, Richard M. Myers, Deborah A. Nickerson, Jeffrey Ou, Donald W. Parsons, Gloria M. Petersen, Sharon E. Plon, Heidi L. Rehm, J. Scott Roberts, Dan Robinson, Joseph S. Salama, Sarah Scollon, Richard R. Sharp, Brian Shirts, Nancy B. Spinner, Holly K. Tabor, Peter Tarczy-Hornoch, David L. Veenstra, Nikhil Wagle, Karen Weck, Benjamin S. Wilfond, Kirk Wilhelmsen, Susan M. Wolf, Julia Wynn, Joon-Ho Yu, and and the CSER Consortium

Supplemental Note: Focus and Progress of Individual U-Award Projects

Children's Hospital of Philadelphia (CHOP; PediSeq)

The CHOP/UPENN Pediatric Genetic Sequencing Project (PediSeq) is working to optimize methods for bringing genomic sequencing into a pediatric clinical setting. We are focused on 6 genetically heterogeneous cohorts: bilateral sensorineural hearing loss, sudden cardiac arrest/death, intellectual disability, autism, platelet function disorders and nuclear encoded mitochondrial respiratory chain disorders. The primary goals of this project are: 1) to establish the study infrastructure and pipeline to validate a practical genomic sequencing approach in pediatrics; 2) to generate genome-scale sequence data for cohorts of uniformly phenotyped subjects for assessment and decision support for presenting actionable genomic findings to clinicians, patient participants, and families and 3) to evaluate the informed consent process for genomic sequencing from the perspective of parents and the provider obtaining consent to explore and understand the impact of genomic sequencing results from the perspective of patient participants, parents and providers.

To date, the PediSeq Project has designed and implemented a pipeline to identify, interpret and report medically relevant exome sequencing (ES) results to families and physicians, and created a comprehensive summary report, and allied online educational support modules, for primary variant findings (related to the indication for testing in our 6 cohorts) as well as secondary findings (that are immediately medically actionable, medically actionable in childhood and adulthood and carrier status). Through the PediSeq project has developed several new tools for phenotype capture and analysis have been developed including the Proband pedigree drawing program (now available in the Apple app store and widely used in a number of academic medical genetic programs) as well as a prototype algorithm that uses phenotypic information in gene

prioritization.[1] We have enrolled 200 families, evaluated sequence issues related to coverage and use of gene lists and have identified a positive result in 6-50% of probands (6% in the disorders, 20% in sudden cardiac death, 23% in sensorineural hearing loss and 50% in intellectual disability) with a VUS rate in these cohorts ranging from 38 (intellectual disability) to 67% (sudden cardiac death).[2] Secondary findings analysis includes a gene list of 2956 genes and our positive findings range from 10-15% for immediately medically actionable conditions and 83-88% for carrier status. We are focused on completing our analyses of informed consent data to understand patient participant and provider experiences with informed consent for genomic sequencing in pediatrics in addition to collecting post-results survey and interview data, and the dissemination of research across the CSER Consortium. To date, we have analyzed over 50 audio-recorded informed consent (IC) sessions to understand patient participant and provider experiences with informed consent for genomic sequencing in pediatrics. We are collecting audio recordings from return of results sessions, which are being transcribed and analyzed, post-return of results survey and interview data from parents, adolescents and primary care providers have been initiated.[3, 4] In analysis of the thematic and contextual elements in IC sessions where an adolescent proband has the cognitive capacity to participate in decision-making, we found that 1) there is considerable variability in the degree of adolescent involvement in the IC sessions, with older children more engaged in the session and more likely to be consulted by parents and providers for their opinions, and 2) several adolescents and young adults felt unprepared to make decisions about adult-onset secondary findings and looked to parents for guidance, and parents tended to take on protective roles, advising and cautioning their children.

PediSeq investigators have been involved in or led several cross-consortium working group activities.[3-7] The work on the PediSeq project and interactions across the

CSER consortium and the medical genetics community have formed a Clinical Genetic Think Tank of over 50 participants that met twice and have produced a white paper with practical recommendations for the implementation of genomic diagnostics into the clinical work flow. PediSeq has also informed practices for the creation of the Division of Genomic Diagnostics, with input from PediSeq to the exome sequencing test launched last year at CHOP.

PediSeq continues to optimize pediatric sequencing workflow and variant calling algorithms as well as to develop a decision support system for delivering genomic variants and interpretation into the EHR.

University of North Carolina at Chapel Hill (NCGENES)

NCGENES focuses on critical questions that must be addressed before genome-scale sequencing is routinely incorporated in medicine, including the diagnostic yield of whole exome sequencing (WES) in diverse clinical settings, the incidence and impact of secondary findings, participant attitudes towards secondary findings and the development of practical schemes for the holistic classification of genomic variants. Another major goal is optimizing minority enrollment to ensure social justice and improve genomic variant interpretation.

NCGENES has completed analysis of over 620 participants. An overarching question for any medical test is determining the clinical situations in which it should be applied. Accordingly, NCGENES is assessing diagnostic yield of WES in a variety of clinical settings spanning 7 diagnostic categories. Yields of possible or definitive diagnoses vary significantly. For example, the yield for cardiomyopathy is 53% and retinopathy 58%,[8] establishing WES as a viable diagnostic approach in such conditions. The yields for neurological disorders and dysmorphology are 36% and 39%, respectively, while WES in participants with apparent familial cancer yields a reportable

result in only 21% of those sequenced, demonstrating that WES adds little to standard approaches in this setting.

Assessing medical actionability of genes is critical when applying WES to participants, given the certainty of generating secondary results that may or may not be necessary to return. To deal with this central problem, NCGENES created a semi-quantitative "binning" metric[9] (now broadly adapted by other efforts such as ClinGen,[10] and EGAPP[11]). The NCGENES experience reveals that thus far, the rate of discovering a medically actionable secondary finding is 3.4%. To address the problem of whether and how to offer non-medically actionable secondary findings, NCGENES employs a study design that ascertains subjects' real-world choices to request such findings. Our results suggest that prior hypothetical studies overestimated the value such results hold for individuals: when a small (but realistic) barrier such as the need to make a phone call is implemented, interest in non-actionable results is considerably lower than participants' initially stated preferences and hypothetical estimates previously reported in the literature.

Our knowledge about the genomes of minority populations has lagged behind that of populations with European ancestry, with important implications for broad and just implementation of genomic medicine and the clinical interpretation of variants. Thus, a major aim of NCGENES has been to emphasize minority participation, currently 25.8% (14.1% AA, 8.9% Hispanic, 1.6% Native American, 1.2% Asian), although participation drops disproportionately, from initial enrollment through return of results and completion of final surveys. Strategies that have facilitated minority participation in NCGENES include geographically convenient clinics, reimbursement for even small expenditures by participants, working with well-established community groups, and offering accessible language resources.

Brigham and Women's Hospital/Harvard Medical School/Baylor/Duke (MedSeq Project)

The MedSeq Project is exploring the application of whole genomes sequencing and its rapid interpretation to provide maximal benefit in terms of both the indication for testing of a genetic condition (in this project, cardiomyopathy) and population screening of healthy individuals. It is also examining the impact of communicating secondary findings to clinicians within the currently existing medical model, and carefully tracking medical, behavioral and economic outcomes using a randomized, controlled trial design.[12]

Thus far, the MedSeq Project has designed and implemented a pipeline to identify, interpret and report medically relevant whole genome sequencing (WGS) results to physicians,[13, 14] and created a one-page summary report on monogenic disease variants, carrier status, pharmacogenomic findings and genetic liability for common complex diseases that even primary care physicians can understand and utilize in the care of their patient participantss.[15] We have found that 21% or our participants had an unanticipated finding of a pathogenic variant for a monogenic disease and 92% had at least 1 pathogenic variant for a recessive disease. Of the participants who had a known cardiomyopathy variant before or at study start, 95% (19/20) were confirmed by WGS and reported on the MedSeq Genome Report. Of those who did not have a known cardiomyopathy variant, 1 new pathogenic variant and 4 new variants of unknown significance in cardiac genes were identified as potential causes of the cardiomyopathy. We have also demonstrated how, for a minor increase in cost, red blood cell and platelet antigen prediction can become a routine part of WGS result reporting, informing clinical care decisions and providing important information for blood donation.[16] We have determined the feasibility of preparing non-geneticist physicians to use WGS in clinical care through a combination of upfront education and ongoing support.[17-21]

Early interactions between MedSeq Project investigators and collaborators in the CSER Consortium informed the development of the ACMG gene list for secondary findings and subsequent commentaries.[22-26] Importantly several investigators substantively contributed to foundational articles that are helping to set clinical standards for clinical sequencing.[27-31] MedSeq investigators, along with other CSER site investigators, have contributed significantly to the working groups that developed new ACMG standards for next generation sequencing,[32] variant classification,[33] and laboratory analysis of hearing loss;[34] along with consensus statements on the return of secondary findings in research biobanks,[35] and the return of incidental information to family members of research participants.[36] One group has built on the MedSeq data to analyze the successes and failures of the Genetic Information Nondiscrimination Act for clinical sequencing,[37] and to explore methods for modeling cost-effectiveness of genome sequencing.[38]

Data and experiences accrued in the MedSeq Project and across the CSER Consortium helped support awards in economics and decision science around genomics, pharmacogenomics and a successful application for the BabySeq Project sequencing newborns. In addition we are a site for one of the Mendelian Sequencing Centers, a site for the Undiagnosed Disease Network, an eMERGE III Genomics Center, and one of two Sequencing Centers for eMERGE III.

The MedSeq Project plans to collect additional information about clinical genomic penetrance through targeted phenotyping of those MedSeq Project participants who have received a pathogenic (P), likely pathogenic (LP), or variant of uncertain significance suspected to be pathogenic (VUS-favor path) for a dominantly inherited condition (or biallelic P, LP, VUS-favor path variants for a recessive condition), and to explore the clinical utility of WGS in minority populations by recruiting additional participants to be randomized in the extension phase of the project.

Baylor College of Medicine (BASIC3)

The goal of the Baylor College of Medicine (BCM) CSER project is to incorporate both tumor and germline whole exome sequencing into the care of newly diagnosed pediatric cancer patient participants (focusing on high risk solid tumors including brain cancers) at Texas Children's Hospital in order to determine: (1) the diagnostic yield, (2) potential clinical utility of both tumor and germline findings, and (3) the impact of clinical genomics on physicians and families. In order to complete this study, the Project 2 investigators led the development of the first entirely CLIA-certified clinical whole exome sequencing pipeline for diagnosis,[39, 40] with all components of the sequencing pipeline made publically available followed by development of a cancer whole exome sequencing clinical pipeline. As of September 2015, we have enrolled 20 pediatric oncologists and 230 participants with childhood cancer (as well as parents when available) into the BASIC3 (Baylor Advancing Sequencing in Childhood Cancer Care) trial and 20 pediatric oncologists. We have reported on our consent methodology,[41] which demonstrated high interest of parents and equitable enrollment of families of different population groups from our diverse patient participant population. We have reported key findings at national meetings recently published on the findings from the trial including demonstrating that nearly 40% of pediatric solid tumor participants have potentially actionable mutations when combining results of tumor and germline exome sequencing.[42] The analysis of the baseline interviews of physicians and parents demonstrates that both groups (for different reasons) do not expect integration of WES to be disruptive in the setting of childhood cancer care.[43] The analyses of the physician communication of exome results and their interpretation of their participants' exome results for treatment decisions are in progress. Based on these results we have recently revised our exome disclosure

practice to focus on clinically meaningful results (whether from tumor or germline) and decrease time spent on other findings such as variants of uncertain significance.

BCM investigators have given major presentations and education sessions at national cancer and genetics meetings including the American Society of Clinical Oncology and ACMG, in addition to publishing on the timeliness of implementing clinical genomics[44] and the appropriateness of the ACMG incidental finding recommendations in the setting of cancer testing.[45] The clinical sequencing experience of the Project 2 team has led to BCM becoming a clinical sequencing center for the Undiagnosed Disease Network (UDN) and the eMERGE III consortia as well as being a clinical study site for UDN and a ClinGen site.[10] The National Cancer Institute and Children's Oncology Group have committed to a nationwide prospective precision medicine trial using genetic analyses of tumors at relapse with BASIC3 investigators co-chairing of the germline reporting committee.

Kaiser-Permanente/Seattle Children's Hospital (NEXTGEN)

The NextGen study is investigating the clinical implementation of carrier screening using genome sequencing (GS) to aid reproductive decision-making in healthy adults. The study population includes individuals whose regular provider has already facilitated pre-conception carrier screening for any condition. This is a randomized trial to evaluate outcomes of adding GS versus usual care. Carrier screening is potentially relevant whenever genomic sequencing is used in reproductive aged adults, regardless of the indication for sequencing. This study's focus on individuals with an interest in learning their carrier results will allow us to rapidly assess the potential impact and outcomes of using GS for carrier screening.

We have established an analytic pipeline that includes initial sequencing, tools for sequence alignment and variant calls, variant interpretation, confirmation using

Sanger sequencing, and laboratory report generation. This work contributed to the development of guidelines by the ACMG for variant classification.[33] We have implemented clinical components including genetic counseling, integrating the clinical report into the electronic medical record, and are developing patient-focused materials including key messages to report positive findings and notification of negative findings. Overall, 71% of participants have at least one carrier result, with a range of 1 to 5 results per person, and a median of 1 result.

Our study team has explored patient participant and clinician perspectives on which carrier results to report. Through focus groups, we identified two types of potential participants, “hesitant” and “certain”, who have different perspectives.[46] This has guided our approach to disclose results by providing choices at every point, including the choice to change their mind and not receive results. We also classified conditions into broad categories, which are then used as a tool to understand participant preferences for receiving results. Initial work, guided by expert and focus group participant input, led to the development of a taxonomy with five categories: lifespan limiting, serious, mild, adult onset, and unpredictable. We then conducted a survey to assess whether participants perceive distinctions among these categories and found empirical support for treating these as separate categories, with the possible exception that serious and mild are the most difficult to distinguish.[47] An expert panel has now classified 790 conditions according to this taxonomy. There were a few gene/condition pairs that we decided we will not disclose, due to lack of information in the literature to support the association between the gene and condition. In practice, 91% of participants choose to receive results in all categories, with the adult onset and unpredictable categories most commonly not selected.

A major challenge has been conveying to participants uncertainty associated with variant classifications and their association with clinical disease. Primary questions that

our study was designed to address that remain unanswered include: 1) reactions (e.g., anxiety) to GS, 2) the impact of GS on downstream utilization of care, 3) satisfaction with how the results are delivered, 4) patient participant understanding and comprehension of the results and genetic concepts, and 5) reasons why potential participants might refuse participation in the study.

Dana-Farber Cancer Institute (CanSeq)

The CanSeq Project is a study of prospective germline and somatic WES in participants with advanced lung and colon cancer with return of clinically actionable and potentially actionable results to the patient participant and physician. CanSeq also studies the impact of information derived through WES on cancer patient participants as well as experiences of oncology providers as they implement WES into cancer care delivery.

The CanSeq Project has developed a production-scale platform for WES from archival formalin fixed paraffin-embedded (FFPE) material and implemented these analytic practices in the CLIA sequencing lab at the Broad Institute. It has designed and implemented a post-analytical pipeline for an effective and reproducible approach for the assessment and curation of genome variants and for interpretation and report of genome results. As part of the pipeline, the CanSeq Project developed an evidence-based list of clinically “actionable” alterations and has identified a broad range of biologically and clinically consequential somatic and germline alterations in our participants. As of September 2015, CanSeq has enrolled 211 patient participants and 27 treating oncologists. All patient participants and oncologists are asked to complete a baseline survey and subset of patient participants and oncologists are invited to participate in in-depth qualitative interview shortly after consent. The CanSeq Project has provided detailed sequencing genome reports to the treating oncologists of 155 patient

participants, and has asked all patient participants, and their treating oncologist to complete post-disclosure surveys after sequencing results have been discussed. One of the aims of the ELSI Project (Project 3) was to evaluate the process by which key decision-makers, working collaboratively, evaluate sequencing data and guide the integration of those data into clinical cancer care. In service to this aim, we are also conducting an ethnographic analysis of CanSeq's Cancer Genomics Evaluation Committee.

National Human Genome Research Institute (ClinSeq)

The ClinSeq® Project began in 2006 and joined the CSER Consortium in 2013 (but is reviewed and funded through a distinct mechanism). As a CSER precursor, ClinSeq® piloted several approaches and questions that are being more thoroughly explored across the consortium. Our main focus includes hypothesis-generating clinical research (including secondary findings and predictive medicine), novel modes of returning exome sequencing results, and empirical studies of participant views of sequencing.

The early results on secondary findings from ClinSeq[48] were the primary data that supported the policy development for the American College of Medical Genetics and Genomics (ACMG) report on returning secondary findings.[22] While some elements were controversial, that has now settled, and we believe that ClinSeq and CSER, through these recommendations, have changed the practice of genomic medicine.

Our novel approach has led to new insights on secondary findings including heart disease,[49] malignant hyperthermia,[50] diabetes,[51] a novel form of arrhythmia[52] and discovery of a late onset neurometabolic disorder.[53] Finally, we have generalized this approach to a genome-wide approach, identifying loss of function variants in haploinsufficiency genes, followed by phenotyping[54] Roughly half were positive, which

shows that 3% of the population have an autosomal dominant disorder resulting from these variants, and are unaware of it. We have shown that high penetrance alleles that can be used to predict diseases that are more common than previously known, and the yield for this type of screen is high. Also, it provides a pathway toward larger scale discovery, which we are proposing to pursue through a CSER collaboration to pool our data to allow for further hypothesis-generating research. This will provide CSER with the capability to not only pilot predictive medicine, but to perform discovery as well. CSER is the ideal setting for this effort as it combines the datasets and clinicians who are expert at deep phenotyping of rare diseases, which our efforts have shown are collectively, not rare after all.

The ClinSeq social and behavioral team has described altruistic and personal motivations for undergoing sequencing,[55] high interest in learning results,[56] promising communication and clinical use of returned variants and high perceptions of uncertainty about future results.[56] We have also explored novel constructs to evaluate preferences for the return of results. Our efforts have revealed participants with avoidance of information or forecasting high negative affects avoided learning variant results for both preventable and non-preventable disease risk.[57] Participants perceiving high ambiguity in results are less interested in variants for non-preventable disease and carrier status[58] and those seeking high injunctive and descriptive norms are more interested in receiving all types of results (unpublished data). We are currently completing a randomized controlled trial of return results comparing two delivery modes. Future studies are planned in an African American cohort that is under recruitment.

The ClinSeq investigators initiated a CSER project to develop a taxonomy of uncertainty for genomics information that will be made available as an interactive website for investigators. The taxonomy categorizes the dimensions of uncertainty throughout the sequencing process to promote consistent descriptors of uncertainty to

guide research and clinical care.

HudsonAlpha Institute for Biotechnology

The HudsonAlpha CSER project, conducted with investigators at the University of Alabama at Birmingham and the University of Louisville, and is providing genomic diagnoses to children with intellectual disability, developmental delay, and related phenotypes. We aim to not only diagnosis children with overtly pathogenic variants in well-studied genes, but also to discover novel genetic contributions and the mutational mechanisms, including pathogenic non-coding variants that lead to these phenotypes. We are also examining several more general issues related to the implementation of clinical genomic testing, including: partnering with community-based clinics outside of large academic medical centers to evaluate the psychological effects of genetic results, especially those that are uncertain; and determining how timing of soliciting preferences with respect to secondary genetic results influences the effects of those results.

In pursuit of the above goals, we enroll children with unexplained physical and cognitive disabilities via a pediatric neurology clinic. When available, one or both biological parents are also enrolled. To date, we have enrolled 293 affected probands from 265 families (776 participants) and with overall goal of 450 probands (1,350 participants). While originally based on exome sequencing, we now applying whole-genome sequencing (30x). Results to date indicate the considerable clinical utility of genomic testing in this population, including examples of improvements not only to management of symptoms in probands but also to the psychological well-being of parents. Our results, infrastructure, and experiences with CSER are facilitating dramatic expansions of clinical sequencing at HudsonAlpha along with clinical partners across Alabama and beyond.

University of Michigan (MI-ONCOSEQ)

Initiated in April of 2011, the Michigan Oncology Sequencing Center (MI-ONCOSEQ) project set out to translate and exploit advances in high throughput sequencing towards the development of a "personalized" strategy for cancer. A pilot "proof-of-principle" study was conducted which prospectively enrolled participants with advanced cancers for comprehensive mutational analysis.[59] Subsequently, a number of important discoveries resulted from this analysis including the discovery of a novel gene fusion, NAB2-STAT6 in a rare cancer, solitary fibrous tumor (SFT).[60] We also identified gene fusions involving the *FGFR* gene in diverse cancers, including breast and prostate cancer,[61] several of which are potentially targetable by available therapies.

Under the CSER mechanism, we carried out integrated sequencing (whole exome sequencing of tumor/normal and transcriptome sequencing) to obtain a view of the landscape across of the genetic alterations in individual tumor specimens that can identify informative and/or actionable mutations. Thus far, we have enrolled a total of 333 adult and 99 pediatric participants in the study. Of the 432 enrolled participants, 370 participants have undergone full sequence analysis, for whom a molecular report was returned to the treating physician. Overall, the average turnaround time from sample collection/receipt to return of results to physicians was 62 days. Clinically relevant results were identified in approximately 60% of participants and clinically significant germline aberrations were identified in 26 adults and 10 pediatric participants.

The MI-ONCOSEQ study has resulted in a number of significant research findings. Early on, we reported the activating mutations in *ESR1* that are an important mechanism of acquired endocrine resistance in breast cancer therapy.[62] Our UM team in

collaboration with investigators across the Prostate Cancer Foundation-Stand Up 2 Cancer (PCF-SU2C) Dream Team sites, led a study to develop a precision medicine framework for metastatic, castration-resistant prostate cancer (mCRPC) by obtaining a comprehensive picture of cancer-related mutations and to incorporate this information into therapeutic strategies and/or enrolling subjects into appropriate clinical trials.[63] Recently, we reported the results from 102 pediatric participants enrolled in the PEDS-ONCOSEQ study,[64] the first real-time, integrated genomic sequencing study in children with relapsed cancers. Surprisingly, we found that 10 percent of the participants had an inherited cancer risk potentially impacting multiple family members and these families were referred for genetic counseling. Finally, in order to improve the extractable data from low-quality samples such as FFPE, we developed an exome-capture transcriptome protocol showing greatly improved performance on degraded RNA[65] that enables measurement of absolute and differential gene expression, and of calling genetic variants and detecting gene fusions.

Our long-term goal is to achieve a more clinically feasible turnaround time for sequencing. To close the gap in this area, we have developed a targeted panel that significantly reduces the sequencing timeframe and we are exploring other approaches to narrow the analysis pipelines.

MI-ONCOSEQ included a multifaceted project to consider ethical and psychosocial aspects of patient participants with advanced and refractory cancers undergoing clinical sequencing. A mixed-methods approach - including observations of tumor board proceedings, qualitative interviews with key stakeholders, deliberative sessions, and quantitative surveys of patient participants and referring oncologists - has examined issues involved in the interpretation and disclosure of sequencing results to clinicians and patient participants. Findings to date suggest notable challenges for

informed consent and communication of genomic results, given high expectations of the clinical utility of next-generation sequencing and patient participant preferences for the disclosure of a wide range of secondary findings.[66] Future plans include the development and evaluation of different techniques for educating participants and clinicians about NGS in a cancer context, with a focus on a) effectively managing the high volume of information generated by sequencing and b) conveying both the clinical implications and limitations of test results.

University of Washington\ (NEXT Medicine)

The New Exome Technology in (NEXT) Medicine study is exploring the incorporation of exome sequencing into the clinical care of participants being evaluated for hereditary colorectal cancer and/or polyps.[67] The project's primary goal is to use a randomized controlled trial to evaluate the challenges and potential benefits of using this technology compared to usual care in the clinical genetics setting,[67] with an emphasis on diverse measured outcomes.[68, 69] NEXT Medicine personnel are developing a framework for the return of secondary findings and incorporating these results into the electronic health records (EHRs) of participants, piloting active clinical decisions support, as well as assessing downstream health and economic outcomes.

NEXT Medicine study personnel have established a CLIA laboratory pipeline that provides sequencing and annotation for study participant exomes. A secondary finding gene list has been developed[70] and continues to be revised by the NEXT Medicine Return of Results committee. Variants in these secondary finding genes are interpreted based on a framework established as part of the project, which requires a high threshold of pathogenicity evidence to return a secondary finding variant.[71] Two separate reports are given to participants and placed in their EHR;[72] one for diagnostic findings and one

for secondary findings. To date, 8.4% (7/83) of participants have had an additional diagnostic finding returned by exome sequencing that was not identified by their clinical test. In addition, 2.4% (2/83) of participants have had an actionable secondary finding variant. We have designed and implemented a tool to measure participant preferences.[73, 74] and have shown value in returning actionable secondary findings[68] and using panel testing for colorectal cancer.[68] We have studied and optimized active decision support rules using user centered design principles and working prototypes. We have also developed a process to enter results in a discrete choice format which has enabled piloting and evaluation of active decision support alerts in the EHR for this ongoing study.[75]

The work of the NEXT Medicine study has informed the medical genetics community regarding the likelihood of identifying a pathogenic, medically actionable secondary finding in a genomic test.[71] The NEXT Medicine incidental finding gene list has been shared with the ACMG committee tasked with developing an actionable gene list[22] and other researchers and laboratories providing a reference point for those addressing similar issues incorporating genomic sequencing into clinical practice. These investigators also lead a multi-site consensus paper on return of genomic results to research participants.[5] Their work with EHR vendors and other companies has aided in the prioritization of incorporating genomic information into the medical record in a scalable, usable way.[31, 76] A robust program in legal and regulatory issues[77, 78] related to next generation sequencing has supported the legality of returning certain non-CLIA research results[79] and suggested specific post-market FDA regulations to improve patient safety.[80]

Ongoing work of the NEXT Medicine study includes the discovery of new colorectal cancer and polyp risk genes and variants. Study personnel also explore

participant experiences with receiving exome sequencing results and non-genetics providers' views on integrating genomic sequencing into their clinical practice. The investigators will continue to respond to the dynamic legal and regulatory climate.

Supplemental Note: Focus and Progress of the Individual R-Awards

Boston Children's Hospital

Our R01 grant *"Returning Research Results in Children: Parental Preferences and Expert Oversight"* empirically explores the extent to which participant preferences can reliably guide the return of individual genomic research results in a pediatric setting.

Through an iterative series of interviews with parents, we developed a preference-setting tool that allows participants to choose which results to receive based on the severity and preventability of conditions.[81] The model also allows participant to opt out of receiving results for categories of conditions perceived by parents in our interviews to be highly sensitive – mental illness, developmental disorders, and childhood-onset degenerative conditions – as well as adult-onset conditions not treatable during childhood.

The goals of our study were to test participants' response to biobanks with different return of results policies and a preference setting model, and to use hypothetical research results to determine whether participants fully understand the implications of their stated preferences. We conducted an online survey of parents of children at BCH. Participants were randomized into one of four hypothetical biobanks with different result return policies: "All" results returned; "None" - no results returned; "Binary" - choice to receive all or none; or "Granular" – use preference setting tool to designate types of results to receive. Groups were shown a "Hypothetical Result Report" with results that they may/may not receive based on the group they were randomized to, and on their choices (Binary and Granular only). The Binary and Granular groups were then given the option to reset their preferences. Our initial data suggest that the ability to

designate preferences leads to greater satisfaction and may increase biobank participation,[82] and other manuscripts have been submitted or are in progress.

Finally, we conducted a series of interviews of parents who had received genomic research results on their child to assess the impact of return of research results on families and several key findings are under preparation for publication.

Cleveland Clinic

This 3-year R01 grant aims to develop best practices for "Presenting Diagnostic Results from Large-scale Clinical Mutation Testing". Its goals are to examine patients participants' and genetic professionals' perspectives on the presentation of diagnostic findings from clinical genomic testing. Using a combination of empirical methods, the project seeks to characterize patient participant and provider expectations of clinical genomic testing. In addition, the project will develop a short, 20-item instrument for measuring patient participants knowledge of clinical genetic testing.

The empirical studies proposed for this project were completed in 2013. These included participants' interviews and surveys, focus groups with genetic professionals, and development of an instrument for measuring participants' knowledge. Multiple peer-reviewed publications were produced by members of our study team.[83-87] These publications highlight the complexity of managing diagnostic results produced through highly multiplexed forms of genetic analysis, such as whole-exome sequencing. These studies also highlight a high level of interest in genomic risk profiling among participants seeking preventive health and wellness services. Additional publications are in preparation for publication. In addition to these empirical studies, members of the project team conducted conceptual studies of relevant issues in the adoption of clinical genomics. These studies resulted in multiple keynote presentations at national

conferences and peer-reviewed papers in prominent medical journals.[88, 89] Lastly, in partnership with other CSER Consortium sites, project leaders contributed to jointly authored papers that sought to define best practices for implementing new forms of genomic testing.[5, 90]

Johns Hopkins School of Medicine

The overarching goal of this project is to facilitate the development of the normative and legal framework necessary to return results of genomics research conducted using residual newborn screening dried blood samples (DBS) to the parents of individual research participants. Specifically, the project goals are to identify key gaps in the regulatory framework in which legal considerations related to the return of results of genomics research using DBS have not been fully considered and to develop specific recommendations regarding key elements that need to be addressed by state policy makers in order to implement a system in which results from genomics research with DBS are returned to parents. Careful consideration of these issues is important because newborn screening is a coordinated system of education, screening, follow up, diagnosis, and treatment that requires collaboration between state newborn screening programs and clinical care providers.

A manuscript that explores the circumstances under which returning a subset of results of genomics research conducted using DBS to parents may be beneficial to research participants, state newborn screening programs, and the research enterprise has been published.[91] Significant changes to the newborn screening program infrastructure would be needed to return results of research conducted using DBS to participants' parents. This manuscript explores whether research results should be returned in this context, what types of results should be returned, and by what

mechanism results should be returned. Manuscripts that discuss the lessons learned regarding the development of state policies in the context of historical experience with the expansion of newborn screening and the development of biorepositories using DBS and the ethical obligations of researchers to return unanticipated research results to infants' parents currently are in preparation.

Columbia University

The Columbia R01 Award has been examining research participants' preferences for learning secondary findings from genomic research studies. Two hundred and nineteen genetic research participants (38% response rate) completed a questionnaire on their preferences to learn about 11 categories of secondary findings including ancestry, pharmacogenetics, carrier status, and secondary findings associated with a personal disease risk of variable severity and penetrance. The majority (73%) of respondents indicated that they wanted to learn all results. There were only four types of secondary findings (depression, Alzheimer's disease, Huntington's disease and pancreatic cancer) for which more than 10% of respondents indicated they would not want to receive results. Respondents who reported higher levels of concern about genetic secrecy or had no college education were less inclined to request all results. There was a modest correlation between respondents who had children affected with a medical condition and not wanting to learn all results. In our interim analysis we have found no difference in the psychosocial and behavior measures administered pre-test and one month post disclosure including no difference in depression or anxiety. The genetic counselor for the study, reflected on her experience of obtaining consent and disclosing genomic results as part of this study, including the importance of an

interactive, patient participant -centered counseling model to facilitate informed patient participants choices.[92]

We have also assessed genomic researchers' perspectives on the return of secondary findings to research subjects. We found that researchers in general support the return of secondary findings but had concerns about the potential burdens it may have on research.[93] Support for returning certain types of results was correlated with the clinical experience of the researcher.[94]

Mayo Clinic/University of California- San Francisco/University of Minnesota

This 5-year R01 on "Disclosing Genomic Incidental Findings in a Cancer Biobank: An ELSI Experiment",[95] funded by NCI and NHGRI, combines empirical and normative bioethics methods to address the question of what genomic research results and secondary findings should be offered to a participant's family members, including after the participant's death. This is a pressing question for genomics projects involving participants with life-limiting diseases and projects archiving data for long-term research use. Balancing participant privacy and preferences regarding release of genomic data with family health and reproductive concerns is challenging. Data and policy guidance have been lacking on return to family in genomics research. Leveraging unique resources at the Mayo Clinic, University of Minnesota, and UCSF, this project is filling that gap.

Aim 1 has assessed individual and family member attitudes and preferences using in-depth qualitative interviews and a structured survey.[96] Aim 2 convened a multidisciplinary national working group to conduct an in-depth ELSI analysis of return of genomic results to family members, generating consensus recommendations published in *J Law Med Ethics* as part of a special issue produced by the project.[36, 97] We have

convened a national conference whose proceedings are archived online for free public access,[98] co-directed an international comparative workshop at the Brocher Foundation, and generated web-based resources, including an extensive bibliography. Aim 3 is prototyping and evaluating a procedure for offering probands' genomic results to family members. Aim 4 is developing tools for education on these issues, consent, and "best practice" governance by genomic biobanks.

Seattle Children's Hospital

The main goal of our project was to evaluate the use of a web-based tool, My46[99] for the management and return of secondary results from exome sequencing. We recruited 144 research participants or parents of minor research participants whose exomes were already sequenced as part of existing research studies on a range of Mendelian and complex phenotypes. Participants selected secondary result preferences using My46 by category: no primary results were offered for return. We offered a wide range of results for return, including results from the "ACMG list" and a range of secondary risk and carrier status results. Participants were randomized to receive results either by phone from a genetic counselor or through My46, with the option to talk to a genetic counselor after receiving results.

We assessed outcomes through online surveys (anxiety, depression, satisfaction, impact of results scales) and through interviews at three time points with a subset of participants. We evaluated use of My46, including result preference changing, reasons for preference changing, and site usage (e.g., review of educational material, time to set preferences and review results). We collected data about sharing of result information with family and health care providers. Analyses are ongoing, but suggest that there are no adverse impacts from use of My46 for return of results, when compared to return through a genetic counselor. We have published several papers on: 1) self-

guided management of CGES results,[100], 2) genetics professionals' attitudes towards return of CGES results[101] and 3) the practices and policies of existing ES clinical service providers.[102] Several manuscripts are in preparation about secondary results preferences, expectations and responses, parental decisions about secondary results for their children, and detailed comparison of endpoints between those receiving results from My46 and those receiving results from a genetic counselor.

Children's Mercy Hospital

This individual R21 project critically examines the conceptual and normative foundations of the claim that it is permissible, and perhaps even obligatory, to return certain individual research results in genomic research. It is, thus, philosophical in nature with an emphasis on clarifying important terms, concepts, and principles, drawing important distinctions, and analyzing and evaluating normative arguments related to ethical duties in genomic research. As such, the "results" of the research differ significantly in nature from standard empirical methodologies. That noted, in terms of measurable results, the project has thus far produced 5 publications in peer-reviewed medical and bioethics journals and 8 presentations at national meetings. The publications are as follows.[103-107]

Though funding for this project ended in August 2014, several journal articles remain under work with submission expected in the fall of 2015. These include a paper offering a historical and conceptual analysis of "actionability" as a fundamental criterion associated with the ethical duty to disclose individual research findings, as well as a paper examining how the purported right of children to an "open future" bears on ethical issues in pediatric genomics and pediatric genomic research (which will be presented and discussed within the CSER Pediatrics Working Group this fall).

Columbia University Medical Center

The aims of this study focused on the development of potential approaches for dealing with the key challenges regarding informed consent—especially for secondary findings—related to return of genomic data. Based on a systematic literature review, the investigators developed options for inclusion of information in the consent process, which were embodied in semi-structured interviews for genomic investigators (n=28) and research participants (n=20), and a survey for genomic researchers (n=254). (Interviews and survey were conducted jointly with the other Columbia R award described in this section.)

Ninety five percent of researchers surveyed believed that research participants should be offered secondary findings for highly penetrant disorders with immediate medical implications. However, there was no consensus on returning incidental results for other conditions. Regarding informed consent, most researchers and participants endorsed disclosure of extensive information about return of secondary findings. However, most researchers were willing to devote 30 minutes or less to this process.[108-110] Because of the disjunction between views about the information that should be disclosed and the time available, the findings strongly suggested a need for innovative approaches to informed consent. Based on the survey results and interviews, 4 models of consent were identified: traditional consent, staged consent, mandatory return, and outsourced consent.[111]

To ascertain how genomic investigators would respond to these models, we went back to our original subject pool. Responses from 198 genomic investigators indicated that, without resource constraints, approximately 1/3 would endorse either staged consent or traditional consent; outsourced consent and mandatory return were favored by only a small minority. However, taking resource constraints into account, roughly 50% would favor traditional consent, with support for staged consent only 13%. Thus,

traditional approaches are seen as most viable under current circumstances. However, there is considerable interest in staged consent, assuming the infrastructure to support it can be provided.[108]

Vanderbilt University

In our project, entitled "Returning Research Results of Pediatric Genomic Research to Participants," we proposed to focus primarily on the legal landscape in which these decisions are made. Put simply, our project could not have been more timely, given the enormous attention to pediatric genetic testing in recent years. Our group was quite productive, publishing four different papers that address legal and ethical issues in detail.[112-115] We have also contributed in important ways to the work of CSER regarding these issues.[7, 116, 117] Finally, several of us have been heavily engaged in discussions about pediatric genetic testing beyond the scope of this grant and the CSER Consortium in scholarly and in practical domains.

Supplemental Note: Focus and Progress of the CSER Working Groups

Electronic Health Records Working Group

This working group has a mission to "understand and facilitate cross site collaboration nationally around informatics work as related to a) integration into electronic health record (EHR), b) integration into decision support, and c) linkage to variant databases/knowledge bases (VDBKB). The group first focused on characterizing the current state of the art across the initial six CSER sites in terms of incorporating whole exome and genome sequencing data into the EHR for results review and for clinical decision support.[118] Key findings included heterogeneity in workflow and informatics tools with predominant mode of delivery of results being non-computable PDF documents with only two sites working on computerized decision support systems. Then in collaboration with the now eight CSER sites (the 9th not having an EHR) and eMERGE sites, the working group focused on identifying current approaches to the display of genetic information in the EHR (where in the record and how displayed) as well as making cross CSER/eMERGE recommendations for best practices.[31] Key findings included validating heterogeneity of information flow and importantly heterogeneity of results display even within a single institution depending on for example source of test results. Recommendations included improving consistency and interoperability among EHR systems that receive and display genetic information.[31] The working group is currently developing cross-institutional projects focused on genomic clinical decision implementation.[76]

Sequencing Standards Working Group

The mission of the Sequencing Standards working group is to develop a set of

technical standards for clinical sequencing, develop best practices for variant confirmation, and establish mechanisms for communicating uncertainty in clinical sequencing data. Key areas of focus include minimum coverage and quality metrics, turnaround time, data formats, and new approaches to sequence challenging genomic regions. The working group also helps establish tools to share sequence data between projects, and collaborates with other working groups and sites to share uniform quality standards. One of the main studies from the working group seeks to identify clinically relevant genomic regions that are poorly covered in whole genome and whole exome sequencing across all ten CSER sites. Briefly, the analysis of the working group identified poorly covered regions that are common to all sites, those that are dependent on specific methodology, and those that are unique to a single site. The study discusses factors that contribute to poorly covered regions, and examines the potential clinical impact of these poorly covered regions. In addition to highlighting clinically relevant poorly covered regions, the study provides a roadmap and tools for other sequencing centers to conduct similar analyses with their own data.

Genetic Counseling Working Group

This working group is investigating current genetic counseling topics related to clinical genome and exome sequencing (CGES), including but not limited to recruitment and enrollment, obtaining informed consent, returning sequencing results and interactions with patient participants and families in both research and clinical settings. The group has published the results of a qualitative interview study on experiences in informed consent for CGES.[3] These findings will contribute to the development of a guidance paper on informed consent in collaboration with the Informed Consent and Governance Working Group. In addition, the group has published case studies on challenging cases in informed consent and lessons learned in return of results.[4, 119]

Members of the working group have participated in the education of genetic counselors on the topic of informed consent at several national conferences including a plenary session at the National Society of Genetic Counselors (NSGC) Annual Education Conference in 2014. In addition, a two-part series was published in *Perspectives in Genetic Counseling*, a quarterly magazine published by the NSGC, on genetic counselors' roles within the CSER Consortium and balancing research and clinical roles.[120, 121] The group is in the planning stages for a second study analyzing experiences in return of results.

Actionability and Return of Results Working Group

This working group is defining the principles and processes guiding the definition of an "actionable" gene across the Consortium, highlighting common outcomes and seeking to understand the rationale underlying differences, to develop a consensus regarding the classification processes, and to develop resources to support decisions with respect to pathogenicity and actionability. The working group has published an in-depth report on the approach to secondary findings within each CSER project, the respective definitions of actionable genes, and examples of challenging cases,[70] as well as a collaborative paper with the eMERGE Consortium in which obligations and opportunities around the return of secondary results were further defined.[5] The working group is currently preparing a manuscript on best practices across the Consortium for variant sign out, as well as a manuscript summarizing the various CSER approaches to characterizing and returning recessive carrier traits, and undertaking initiatives around data sharing as well as the interface between clinical care and research.

Informed Consent Working Group

The Informed Consent & Governance (ICG) working group addresses the

pragmatics of the informed consent process and governance of genome sequencing by supporting the development of new and creative approaches to consent including standardized language and protocols; compiling CSER experiences with institutional governance of genomic data in research and clinical settings; and where appropriate, integrating governance recommendations with best practice and/or model language for consent. The working group has published a review of CSER project consent forms[90] and contributed to additional products led by the Pediatrics working group. The working group is currently preparing three manuscripts: one that provides guidance on consent for clinical sequencing, another commentary on the governance of returning results from genome sequencing, and a review of state disclosure laws and their impact on informed consent for CGES.

Outcomes and Measures Working Group

The goals of the Outcomes and Measures (OM) working group are to: (1) identify priority areas in psychosocial, behavioral, and outcomes research related to genome sequencing and return of results,[6] (2) facilitate the exchange of knowledge about psychosocial and behavioral outcome measurement across consortium projects, (3) develop research strategies to generate evidence that inform healthcare policies, and (4) develop new measures as needed. Early OM working group efforts centered on the coordination of measures across consortium sites for key outcomes such as anxiety, depression, multidimensional impact, and decision satisfaction. The OM working group is currently conducting preliminary cross-site analyses of psychosocial and healthcare resource utilization data in an effort to understand the heterogeneity of these outcomes across different populations and identify effective and pragmatic data collection approaches for future prospective studies. Additional ongoing projects include a cross-site investigation of participants' motivations for having sequencing and an evaluation of

the diverse range of qualitative methods used within the consortium research studies. The ultimate goal of the OM working group is to advance our understanding of the potential efficacy and harms of sequencing, as well as our understanding of the costs and impacts of genome sequencing on the healthcare system

Pediatrics Working Group

This working group seeks to (1) identify the unique ethical, legal, and practical challenges relating to clinical and translational genomics involving pediatric populations and (2) develop workable, appropriate solutions for addressing these challenges. The first product of the working group was a paper examining points of agreement and disagreement between two recommendation documents published in 2013,[7] the first issued jointly by the American Academy of Pediatrics (AAP) and American College of Medical Genetics and Genomics (ACMG) targeting genetic testing,[122] and the second issued by the ACMG focused on secondary genomic results.[22] A second product explores the responsibilities of parents and pediatric providers in making decisions related to genomic sequencing of children.[123]. A third paper, in press, proposes a framework for addressing consent for pediatric participants in genomic research as they reach the age of majority.[116] In the coming year, the working group is planning two projects: the first exploring how the concept of the child's right to an "open future" should be applied to pediatric genomic testing, and the second examining emerging methods used by investigators to keep pediatric research participants engaged with genomic research studies.

Tumor Working Group

The mission of the Tumor working group is to explore the unique technical, interpretive and ethical challenges and considerations involved in clinical tumor

sequencing and to contribute to the development of best practices for these tests. These collaborative efforts involve investigators from the three CSER sites performing clinical tumor sequencing as well as others focusing on germline studies of cancer phenotypes, given the critical shared challenges of tumor and germline sequencing. Working group efforts initially focused on education of the oncology community regarding the spectrum of potential results that can be revealed by clinical tumor and germline sequencing and their implications for laboratories, clinicians, and cancer patient participants. A manuscript on this topic related to the ACMG guidelines for reporting of germline secondary findings was published in the *Journal of Clinical Oncology* and a second manuscript focusing on the potential for discovery of clinically significant germline variants from tumor-only sequencing has recently been published in the Journal of the National Cancer Institute.[45, 124] Ongoing working group efforts have centered on annotation of tumor variants and the critical issue of determining "actionability". The working group and NIH staff organized a symposium on this topic at the 2015 AACR meeting and are currently partnering with the ClinGen Somatic working group to develop standards for tumor variant classification.

Practitioner Education

A core goal of the CSER Consortium is clinical implementation of genomics and there are a large number of practitioners participating in the ongoing trial. Given the accumulating experience with practitioner education within our consortium the CSER Steering Committee formed the Practitioner Education working group in Summer 2015 to explore the unique educational needs of healthcare providers. The term "practitioner" is broad and is meant to include physicians, nurses and other non-genetics specialist providers. We are currently compiling and assessing available resources and looking for gaps and avenues for using our expertise and shared experiences within CSER to help

practitioners better understand genomics and how to apply it in a clinical setting. Topics such as determining the most appropriate genetic test to order, how to interpret a genome sequence, dealing with uncertainty and discussing genomics with a patient/ patient participant will be important aspects to educational materials that are created and disseminated. Available educational resources for healthcare practitioners have been compiled and shared in a repository on the CSER Coordinating Center website.

Supplemental References

1. Masino, A.J., Dechene, E.T., Dulik, M.C., Wilkens, A., Spinner, N.B., Krantz, I.D., Pennington, J.W., Robinson, P.N., and White, P.S. (2014). Clinical phenotype-based gene prioritization: an initial study using semantic similarity and the human phenotype ontology. BMC Bioinformatics 15:248.
2. Li, M.H., Abrudan, J.L., Dulik, M.C., Sasson, A., Brunton, J., Jayaraman, V., Dugan, N., Haley, D., Rajagopalan, R., Biswas, S., et al. (2015). Utility and limitations of exome sequencing as a genetic diagnostic tool for conditions associated with pediatric sudden cardiac arrest/sudden cardiac death. Hum Genomics 9:15.
3. Bernhardt, B.A., Roche, M.I., Perry, D.L., Scollon, S.R., Tomlinson, A.N., and Skinner, D. (2015). Experiences with obtaining informed consent for genomic sequencing. Am J Med Genet A 167, 2635-2646.
4. Tomlinson, A.N., Skinner, D., Perry, D.L., Scollon, S.R., Roche, M.I., and Bernhardt, B.A. (2015). "Not tied up neatly with a bow": professionals' challenging cases in informed consent for genomic sequencing. J Genet Couns, 10.1007/s10897-015-9842-8.
5. Jarvik, G.P., Amendola, L.M., Berg, J.S., Brothers, K., Clayton, E.W., Chung, W., Evans, B.J., Evans, J.P., Fullerton, S.M., Gallego, C.J., et al. (2014). Return of genomic results to research participants: the floor, the ceiling, and the choices in between. Am J Hum Genet 94, 818-826.
6. Gray, S.W., Martins, Y., Feuerman, L.Z., Bernhardt, B.A., Biesecker, B.B., Christensen, K.D., Joffe, S., Rini, C., Veenstra, D., McGuire, A.L., et al. (2014). Social and behavioral research in genomic sequencing: approaches from the Clinical Sequencing Exploratory Research Consortium Outcomes and Measures Working Group. Genet Med 16, 727-735.
7. Clayton, E.W., McCullough, L.B., Biesecker, L.G., Joffe, S., Ross, L.F., Wolf, S.M., and Clinical Sequencing Exploratory Research Consortium Pediatrics Working, G. (2014). Addressing the ethical challenges in genetic testing and sequencing of children. Am J Bioeth 14, 3-9.
8. Lee, K., Berg, J.S., Milko, L., Crooks, K., Lu, M., Bizon, C., Owen, P., Wilhelmsen, K.C., Weck, K.E., Evans, J.P., et al. (2015). High diagnostic yield of whole exome

sequencing in participants with retinal dystrophies in a clinical ophthalmology setting. Am J Ophthalmol 160, 354-363.

9. Berg, J., Adams, M., Nassar, N., Bizon, C., Lee, K., Schmitt, C., Wilhelmsen, K., and Evans, J. (2013). An informatics approach to analyzing the incidentalome. Genet Med 15, 36-44.
10. Rehm, H.L., Berg, J.S., Brooks, L.D., Bustamante, C.D., Evans, J.P., Landrum, M.J., Ledbetter, D.H., Maglott, D.R., Martin, C.L., Nussbaum, R.L., et al. (2015). ClinGen--the Clinical Genome Resource. N Engl J Med 372, 2235-2242.
11. Goddard, K.A., Whitlock, E.P., Berg, J.S., Williams, M.S., Webber, E.M., Webster, J.A., Lin, J.S., Schrader, K.A., Campos-Outcalt, D., Offit, K., et al. (2013). Description and pilot results from a novel method for evaluating return of incidental findings from next-generation sequencing technologies. Genet Med 15, 721-728.
12. Vassy, J.L., Lautenbach, D.M., McLaughlin, H.M., Kong, S.-W., Christensen, K.D., Krier, J., Kohane, I.S., Feuerman, L.Z., Blumenthal-Barby, J., Roberts, J.S., et al. (2014). The MedSeq Project: a randomized trial of integrating whole genome sequencing into clinical medicine. Trials 15, 85-97.
13. McLaughlin, H.M., Ceyhan-Birsoy, O., Christensen, K.D., Kohane, I.S., Krier, J., Lane, W.J., Lautenbach, D., Lebo, M.S., Machini, K., MacRae, C.A., et al. (2014). A systematic approach to the reporting of medically relevant findings from whole genome sequencing. BMC Med Genet 15:134.
14. Kong, S.W., Lee, I.H., Leshchiner, I., Krier, J., Kraft, P., Rehm, H.L., Green, R.C., Kohane, I.S., MacRae, C.A., and MedSeq Project. (2015). Summarizing polygenic risks for complex diseases in a clinical whole-genome report. Genet Med 17, 536-544.
15. Vassy, J.L., McLaughlin, H.L., MacRae, C.A., Seidman, C.E., Lautenbach, D., Krier, J.B., Lane, W.J., Kohane, I.S., Murray, M.F., McGuire, A.L., et al. (2015). A one-page summary report of genome sequencing for the health adult. Public Health Genomics 18, 123-129.
16. Lane, W.J., Westhoff, C.M., Boehler, S., Uy, J.M., Aguad, M., Smeland-Wagman, R., Kaufman, R.M., Rehm, H.L., Green, R.C., Silberstein, L.E., et al. (In press). Comprehensive red blood cell and platelet antigen prediction from whole genome sequencing: proof of principle Transfusion, 10.1111/trf.13416.

17. Blumenthal-Barby, J.S., McGuire, A.L., and Ubel, P.A. (2014). Why information alone is not enough: behavioral economics and the future of genomic medicine. Ann Intern Med 161, 605-606.
18. Christensen, K.D., Vassy, J.L., Jamal, L., Lehmann, L.S., Slashinski, M.J., Perry, D.L., Robinson, J.O., Blumenthal-Barby, J., Feuerman, L.Z., Murray, M.F., et al. (2015). Are physicians prepared for whole genome sequencing? A qualitative analysis. Clin Genet, 10.1111/cge.12626.
19. Vassy, J.L., Christensen, K.D., Slashinski, M.J., Lautenbach, D., Raghavan, S., Robinson, J.O., Blumenthal-Barby, J., Feuerman, L.Z., Lehmann, L.S., Murray, M.F., et al. (2015). 'Someday it will be the norm': physician perspectives on the utility of genome sequencing for patient care in the MedSeq Project. Per Med 12, 23-32.
20. Blumenthal-Barby, J.S., McGuire, A.L., Green, R.C., and Ubel, P.A. (2015). How behavioral economics can help to avoid 'the last mile problem' in whole genome sequencing. Genome Med 7:3.
21. Vassy, J.L., Korf, B.R., and Green, R.C. (2015). How to know when physicians are ready for genomic medicine. Sci Transl Med, 10.1126/scitranslmed.aaa2401.
22. Green, R.C., Berg, J.S., Grody, W.W., Kalia, S.S., Korf, B.R., Martin, C.L., McGuire, A.L., Nussbaum, R.L., O'Daniel, J.M., Ormond, K.E., et al. (2013). ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med 15, 565-574.
23. Krier, J.B., and Green, R.C. (2013). Management of incidental findings in clinical genomic sequencing. Curr Protoc Hum Genet Chapter 9, Unit 9.23.
24. McGuire, A.L., Joffe, S., Koenig, B.A., Biesecker, B.B., McCullough, L.B., Blumenthal-Barby, J.S., Caulfield, T., Terry, S.F., and Green, R.C. (2013). Point-counterpoint. Ethics and genomic incidental findings. Science 340, 1047-1048.
25. Green, R.C., Lupski, J., and Biesecker, L.G. (2013). Reporting genomic sequencing results to ordering clinicians: incidental, but not exceptional. JAMA 310, 365-366.
26. Christensen, K.D., and Green, R.C. (2013). How could disclosing incidental information from whole-genome sequencing affect patient behavior? Per Med 10, 377-386.
27. Rehm, H.L. (2013). Disease-targeted sequencing: a cornerstone in the clinic. Nat Rev Genet 14, 295-300.

28. Green, R.C., Rehm, H.L., and Kohane, I.S. (2013). Clinical genome sequencing. In Genomic and Personalized Medicine, G.S. Ginsburg and H.F. Willard, eds. (San Diego, Academic Press), pp 102-122.
29. Biesecker, L.G., and Green, R.C. (2014). Diagnostic clinical genome and exome sequencing. N Engl J Med 370, 2418-2425.
30. MacArthur, D.G., Manolio, T.A., Dimmock, D.P., Rehm, H.L., Shendure, J., Abecasis, G.R., Adams, D.R., Altman, R.B., Antonarakis, S.E., Ashley, E.A., et al. (2014). Guidelines for investigating causality of sequence variants in human disease. Nature 508, 469-476.
31. Shirts, B.H., Salama, J.S., Aronson, S.J., Chung, W.K., Gray, S.W., Hindorff, L.A., Jarvik, G.P., Plon, S.E., Stoffel, E.M., Tarczy-Hornoch, P.Z., et al. (2015). CSER and eMERGE: current and potential state of the display of genetic information in the electronic health record. J Am Med Inform Assoc 22, 1231-1242.
32. Rehm, H.L., Bale, S.J., Bayrak-Toydemir, P., Berg, J.S., Brown, K.K., Deignan, J.L., Friez, M.J., Funke, B.H., Hegde, M.R., Lyon, E., et al. (2013). ACMG clinical laboratory standards for next-generation sequencing. Genet Med 15, 733-747.
33. Richards, S., Aziz, N., Bale, S.J., Dick, D., Das, S., Gastier-Foster, J., Grody, W.W., Hedge, M., Lyon, E., Spector, E., et al. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17, 405-423.
34. Alford, R.L., Arnos, K.S., Fox, M., Lin, J.W., Palmer, C.G., Pandya, A., Rehm, H.L., Robin, N.H., Scott, D.A., Yoshinaga-Itano, C., et al. (2014). American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. Genet Med 16, 347-355.
35. Wolf, S.M., Crock, B.N., Van Ness, B., Lawrenz, F., Kahn, J.P., Beskow, L.M., Cho, M.K., Christman, M.F., Clayton, E.W., Green, R.C., et al. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived datasets. Genet Med 14, 361-384.
36. Wolf, S.M., Branum, R., Koenig, B.A., Petersen, G.M., Berry, S.A., Beskow, L.M., Daly, M.B., Fernandez, C.V., Green, R.C., LeRoy, B.S., et al. (2015). Returning a research participant's genomic results to relatives: analysis and recommendations. J Law Med Ethics 43, 440-463.

37. Green, R.C., Lautenbach, D., and McGuire, A.L. (2015). GINA, genetic discrimination, and genomic medicine. N Engl J Med 372, 397-399.
38. Christensen, K.D., Dukhovny, D., Siebert, U., and Green, R.C. (2015). Assessing the costs and cost-effectiveness of genomic sequencing. J Pers Med 5, 470-486.
39. Yang, Y., Muzny, D.M., Xia, F., Niu, Z., Person, R., Ding, Y., Ward, P., Braxton, A., Wang, M., Buhay, C., et al. (2014). Molecular findings among patients referred for clinical whole-exome sequencing. JAMA 312, 1870-1879.
40. Yang, Y., Muzny, D.M., Reid, J.G., Bainbridge, M.N., Willis, A., Ward, P.A., Braxton, A., Beuten, J., Xia, F., Niu, Z., et al. (2013). Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med 369, 1502-1511.
41. Scollon, S., Bergstrom, K., Kerstein, R.A., Wang, T., Hilsenbeck, S.G., Ramamurthy, U., Gibbs, R.A., Eng, C.M., Chintagumpala, M.M., Berg, S.L., et al. (2014). Obtaining informed consent for clinical tumor and germline exome sequencing of newly diagnosed childhood cancer patients. Genome Med 6:69.
42. Parsons, D.W., Roy, A., Monzon, F.A., Yang, Y., López-Terrada, D.H., Chintagumpala, M.M., Berg, S.L., Hilsenbeck, S.G., Wang, T., and Kerstein, R.A. (2014). Diagnostic yield of clinical tumor and germline exome sequencing for newly diagnosed children with solid tumors. JAMA Oncology 74, 5169.
43. McCullough, L.B., Slashinski, M.J., AL, M., Street, R., Eng, C., Gibbs, R., Parsons, D., and Plon, S. (2015). Is whole-exome sequencing an ethically disruptive technology? Perspectives of pediatric oncologists and parents of pediatric patients with solid tumors. Pediatr Blood Cancer, 10.1002/pbc.25815.
44. Biesecker, L.G., Burke, W., Kohane, I., Plon, S.E., and Zimmern, R. (2012). Next-generation sequencing in the clinic: are we ready? Nat Rev Genet 13, 818-824.
45. Parsons, D.W., Roy, A., Plon, S.E., Roychowdhury, S., and Chinnaiyan, A.M. (2014). Clinical tumor sequencing: an incidental casualty of the American College of Medical Genetics and Genomics recommendations for reporting of incidental findings. J Clin Oncol 32, 2203-2205.
46. Schneider, J.L., Goddard, K.A., Davis, J., Wilfond, B., Kauffman, T.L., Reiss, J.A., Gilmore, M., Himes, P., Lynch, F.L., Leo, M.C., et al. (2015). "Is it worth knowing?" Focus group participants' perceived utility of genomic preconception carrier screening. J Genet Couns, 10.1007/s10897-015-9851-7.
47. Leo, M.C., McMullen, C., Wilfond, B.S., Lynch, F., Reiss, J.A., Gilmore, M.J., Himes, P., Kauffman, T.L., Davis, J.V., Jarvik, G.P., et al. (Under review). Patient

perceptions of genetic disease: empirical validation of a taxonomy for autosomal recessive or X-linked conditions. Am J Med Genet.

48. Johnston, J.J., Rubinstein, W.S., Facio, F.M., Ng, D., Singh, L.N., Teer, J.K., Mullikin, J.C., and Biesecker, L.G. (2012). Secondary variants in individuals undergoing exome sequencing: screening of 572 individuals identifies high-penetrance mutations in cancer-susceptibility genes. Am J Hum Genet 91, 97-108.
49. Ng, D., Johnston, J.J., Teer, J.K., Singh, L.N., Peller, L.C., Wynter, J.S., Lewis, K.L., Cooper, D.N., Stenson, P.D., Mullikin, J.C., et al. (2013). Interpreting secondary cardiac disease variants in an exome cohort. Circ Cardiovasc Genet 6, 337-346.
50. Gonsalves, S.G., Ng, D., Johnston, J.J., Teer, J.K., Stenson, P.D., Cooper, D.N., Mullikin, J.C., and Biesecker, L.G. (2013). Using exome data to identify malignant hyperthermia susceptibility mutations. Anesthesiology 119, 1043-1053.
51. Rees, M.G., Ng, D., Ruppert, S., Turner, C., Beer, N.L., Swift, A.J., Morken, M.A., Below, J.E., Blech, I., Mullikin, J.C., et al. (2012). Correlation of rare coding variants in the gene encoding human glucokinase regulatory protein with phenotypic, cellular, and kinetic outcomes. J Clin Invest 122, 205-217.
52. Posokhova, E., Ng, D., Opel, A., Masuho, I., Tinker, A., Biesecker, L.G., Wickman, K., and Martemyanov, K.A. (2013). Essential role of the m2R-RGS6-IKACh pathway in controlling intrinsic heart rate variability. PLoS One 8, e76973.
53. Sloan, J.L., Johnston, J.J., Manoli, I., Chandler, R.J., Krause, C., Carrillo-Carrasco, N., Chandrasekaran, S.D., Sysol, J.R., O'Brien, K., Hauser, N.S., et al. (2011). Exome sequencing identifies ACSF3 as a cause of combined malonic and methylmalonic aciduria. Nat Genet 43, 883-886.
54. Johnston, J.J., Lewis, K.L., Ng, D., Singh, L.N., Wynter, J., Brewer, C., Brooks, B.P., Brownell, I., Candotti, F., Gonsalves, S.G., et al. (2015). Individualized iterative phenotyping for genome-wide analysis of loss-of-function mutations. Am J Hum Genet 96, 913-925.
55. Facio, F.M., Brooks, S., Loewenstein, J., Green, S., Biesecker, L.G., and Biesecker, B.B. (2011). Motivators for participation in a whole-genome sequencing study: implications for translational genomics research. Eur J Hum Genet 19, 1213-1217.
56. Facio, F.M., Eidem, H., Fisher, T., Brooks, S., Linn, A., Kaphingst, K.A., Biesecker, L.G., and Biesecker, B.B. (2013). Intentions to receive individual results from

whole-genome sequencing among participants in the ClinSeq study. Eur J Hum Genet 21, 261-265.

57. Taber, J.M., Klein, W.M., Ferrer, R.A., Lewis, K.L., Harris, P.R., Shepperd, J.A., and Biesecker, L.G. (2015). Information avoidance tendencies, threat management resources, and interest in genetic sequencing feedback. Ann Behav Med 49, 616-621.
58. Taber, J.M., Klein, W.M., Ferrer, R.A., Han, P.K., Lewis, K.L., Biesecker, L.G., and Biesecker, B.B. (2015). Perceived ambiguity as a barrier to intentions to learn genome sequencing results. J Behav Med 38, 715-726.
59. Roychowdhury, S., Iyer, M.K., Robinson, D.R., Lonigro, R.J., Wu, Y.M., Cao, X., Kalyana-Sundaram, S., Sam, L., Balbin, O.A., Quist, M.J., et al. (2011). Personalized oncology through integrative high-throughput sequencing: a pilot study. Sci Transl Med,10.1126/scitranslmed.3003161.
60. Robinson, D.R., Wu, Y.M., Kalyana-Sundaram, S., Cao, X., Lonigro, R.J., Sung, Y.S., Chen, C.L., Zhang, L., Wang, R., Su, F., et al. (2013). Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet 45, 180-185.
61. Wu, Y.M., Su, F., Kalyana-Sundaram, S., Khazanov, N., Ateeq, B., Cao, X., Lonigro, R.J., Vats, P., Wang, R., Lin, S.F., et al. (2013). Identification of targetable FGFR gene fusions in diverse cancers. Cancer Discov 3, 636-647.
62. Robinson, D.R., Wu, Y.M., Vats, P., Su, F., Lonigro, R.J., Cao, X., Kalyana-Sundaram, S., Wang, R., Ning, Y., Hodges, L., et al. (2013). Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet 45, 1446-1451.
63. Robinson, D., Van Allen, E.M., Wu, Y.M., Schultz, N., Lonigro, R.J., Mosquera, J.M., Montgomery, B., Taplin, M.E., Pritchard, C.C., Attard, G., et al. (2015). Integrative clinical genomics of advanced prostate cancer. Cell 161, 1215-1228.
64. Mody, R.J., Wu, Y.M., Lonigro, R.J., Cao, X., Roychowdhury, S., Vats, P., Frank, K.M., Prensner, J.R., Asangani, I., Palanisamy, N., et al. (2015). Integrative clinical sequencing in the management of refractory or relapsed cancer in youth. JAMA 314, 913-925.
65. Cieslik, M., Chugh, R., Wu, Y.M., Wu, M., Brennan, C., Lonigro, R., Su, F., Wang, R., Siddiqui, J., Mehra, R., et al. (2015). The use of exome capture RNA-seq for

highly degraded RNA with application to clinical cancer sequencing. Genome Res 25, 1372-1381.

66. Roberts, S. (2015). Patient understanding and expectations about use of next generation sequencing in oncology. Annals of Behavioral Medicine 49, S70.
67. Gallego, C.J., Bennette, C.S., Heagerty, P., Comstock, B., Horike-Pyne, M., Hisama, F., Amendola, L.M., Bennett, R.L., Dorschner, M.O., Tarczy-Hornoch, P., et al. (2014). Comparative effectiveness of next generation genomic sequencing for disease diagnosis: design of a randomized controlled trial in patients with colorectal cancer/polyposis syndromes. Contemp Clin Trials 39, 1-8.
68. Bennette, C.S., Gallego, C.J., Burke, W., Jarvik, G.P., and Veenstra, D.L. (2015). The cost-effectiveness of returning incidental findings from next-generation genomic sequencing. Genet Med 17, 587-595.
69. Gallego, C.J., Shirts, B.H., Bennette, C.S., Guzauskas, G., Amendola, L.M., Horike-Pyne, M., Hisama, F.M., Pritchard, C.C., Grady, W.M., Burke, W., et al. (2015). Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: a cost-effectiveness analysis. J Clin Oncol 33, 2084-2091.
70. Berg, J.S., Amendola, L.M., Eng, C., Van Allen, E., Gray, S.W., Wagle, N., Rehm, H.L., DeChene, E.T., Dulik, M.C., Hisama, F.M., et al. (2013). Processes and preliminary outputs for identification of actionable genes as incidental findings in genomic sequence data in the Clinical Sequencing Exploratory Research Consortium. Genet Med 15, 860-867.
71. Dorschner, M.O., Amendola, L.M., Turner, E.H., Robertson, P.D., Shirts, B.H., Gallego, C.J., Bennett, R.L., Jones, K.L., Tokita, M.J., Bennett, J.T., et al. (2013). Actionable, pathogenic incidental findings in 1,000 participants' exomes. Am J Hum Genet 93, 631-640.
72. Dorschner, M.O., Amendola, L.M., Shirts, B.H., Kiedrowski, L., Salama, J., Gordon, A.S., Fullerton, S.M., Tarczy-Hornoch, P., Byers, P.H., and Jarvik, G.P. (2014). Refining the structure and content of clinical genomic reports. Am J Med Genet C Semin Med Genet 166C, 85-92.
73. Bennette, C.S., Trinidad, S.B., Fullerton, S.M., Patrick, D., Amendola, L., Burke, W., Hisama, F.M., Jarvik, G.P., Regier, D.A., and Veenstra, D.L. (2013). Return of incidental findings in genomic medicine: measuring what patients value--development of an instrument to measure preferences for information from next-generation testing (IMPRINT). Genet Med 15, 873-881.

74. Regier, D.A., Peacock, S.J., Pataky, R., van der Hoek, K., Jarvik, G.P., Hoch, J., and Veenstra, D. (2015). Societal preferences for the return of incidental findings from clinical genomic sequencing: a discrete-choice experiment. CMAJ 187, E190-197.
75. Nishimura, A.A., Shirts, B.H., Dorschner, M.O., Amendola, L.M., Smith, J.W., Jarvik, G.P., and Tarczy-Hornoch, P. (2015). Development of clinical decision support alerts for pharmacogenomic incidental findings from exome sequencing. Genet Med 17, 939-942.
76. Nishimura, A.A., Tarczy-Hornoch, P., and Shirts, B.H. (2014). Pragmatic and ethical challenges of incorporating the genome into the electronic medical record. Curr Genet Med Rep 2, 201-211.
77. Evans, B.J., Dorschner, M.O., Burke, W., and Jarvik, G.P. (2014). Regulatory changes raise troubling questions for genomic testing. Genet Med 16, 799-803.
78. Burke, W., Evans, B.J., and Jarvik, G.P. (2014). Return of results: ethical and legal distinctions between research and clinical care. Am J Med Genet C Semin Med Genet 166, 105-111.
79. Evans, B.J. (2014). The First Amendment right to speak about the human genome. Univ Pa J Const Law 16, 549-636.
80. Evans, B.J., Burke, W., and Jarvik, G.P. (2015). The FDA and genomic tests--getting regulation right. N Engl J Med 372, 2258-2264.
81. Bacon, P.L., Harris, E.D., Ziniel, S.I., Savage, S.K., Weitzman, E.R., Green, R.C., Huntington, N.L., and Holm, I.A. (2015). The development of a preference setting model for the return of individual genomic research results. J Empir Res Hum Res Ethics 10, 107-120.
82. Holm, I.A., Iles, B.R., Ziniel, S.I., Bacon, P.L., Savage, S.K., Christensen, K.D., Weitzman, E.R., Green, R.C., and Huntington, N.L. (2015). Participant satisfaction with a preference-setting tool for the return of individual research results in pediatric genomic research. J Empir Res Hum Res Ethics 10, 414-426.
83. Uhlmann, W.R., and Sharp, R.R. (2012). Genetic testing integration panels (GTIPs): a novel approach for considering integration of direct-to-consumer and other new genetic tests into patient care. J Genet Couns 21, 374-381.
84. McGowan, M.L., Cho, D., and Sharp, R.R. (2013). The changing landscape of carrier screening: expanding technology and options? Health Matrix Clevel 23, 15-33.

85. Cho, D., McGowan, M.L., Metcalfe, J., and Sharp, R.R. (2013). Expanded carrier screening in reproductive healthcare: perspectives from genetics professionals. Hum Reprod 28, 1725-1730.
86. Koay, P.P., and Sharp, R.R. (2014). Managing expectational language: translational genetic professionals consider the clinical potential of next-generation sequencing technologies. New Genet Soc 33, 126-148.
87. McGowan, M.L., Glinka, A., Highland, J., Asaad, G., and Sharp, R.R. (2013). Genetics patients' perspectives on clinical genomic testing. Per Med 10, 339-347.
88. Sharp, R. (2011). Downsizing genomic medicine: Approaching the ethical complexity of whole-genome sequencing. Genet Med 13, 191-194.
89. Goldenberg, A.J., and Sharp, R.R. (2012). The ethical hazards and programmatic challenges of genomic newborn screening. JAMA 307, 461-462.
90. Henderson, G.E., Wolf, S.M., Kuczynski, K.J., Joffe, S., Sharp, R.R., Parsons, D.W., Knoppers, B.M., Yu, J.H., and Appelbaum, P.S. (2014). The challenge of informed consent and return of results in translational genomics: empirical analysis and recommendations. J Law Med Ethics 42, 344-355.
91. Lewis, M.H., and Goldenberg, A.J. (2015). Return of results from research using newborn screening dried blood samples. J Law Med Ethics 43, 559-568.
92. Wynn, J. (2015). Genomic testing: a genetic counselor's personal reflection on three years of consenting and testing. J Genet Couns, 10.1007/s10897-015-9868-y.
93. Klitzman, R., Appelbaum, P.S., and Chung, W. (2013). Return of secondary genomic findings vs patient autonomy: implications for medical care. JAMA 310, 369-370.
94. Wynn, J., Martinez, J., Duong, J., Zhang, Y., Phelan, J., Fyer, A., Klitzman, A., Appelbaum, P.S., and Chung, W.K. (2015). Association of researcher characteristics with views on return of incidental findings from genomic research. J Genet Couns 24, 833-841.
95. National Institutes of Health. (2011). Disclosing genomic incidental findings in a cancer biobank: an ELSI experiment (project information). In Research Portfolio Online Reporting Tools (RePORT). (Bethesda, MD, National Institutes of Health).
96. Radecki Breitkopf, C., Petersen, G., Wolf, S.M., Robinson, M., Chaffee, K., Lindor, N.M., Gordon, D., and Koenig, B.A. (2015). Preferences regarding return of genomic results to relatives of research participants, including after participant death: empirical results from a cancer biobank. J Law Med Ethics 43, 464-475.

97. Wolf, S.A., Koenig, B.A., and Petersen, G. (2015). Should we offer genomic research results to a participant's family, including after the participant's death? J Law Med Ethics 43, 437-593.
98. University of Minnesota consortium. (2014). Should we offer genomic research results to a participant's family, including after the participant's death? In Consortium on Law and Values in Health, Environment, and the Life Sciences. (University of Minnesota).
99. University of Washington. (2015). My46. www.my46.org
100. Yu, J.H., Jamal, S.M., Tabor, H.K., and Bamshad, M.J. (2013). Self-guided management of exome and whole-genome sequencing results: changing the results return model. Genet Med 15, 684-690.
101. Yu, J.H., Harrell, T.M., Jamal, S.M., Tabor, H.K., and Bamshad, M.J. (2014). Attitudes of genetics professionals toward the return of incidental results from exome and whole-genome sequencing. Am J Hum Genet 95, 77-84.
102. Jamal, S.M., Yu, J.H., Chong, J.X., Dent, K.M., Conta, J.H., Tabor, H.K., and Bamshad, M.J. (2013). Practices and policies of clinical exome sequencing providers: analysis and implications. Am J Med Genet A 161A, 935-950.
103. Eckstein, L., Garrett, J.R., and Berkman, B.E. (2014). A framework for analyzing the ethics of disclosing genetic research findings. J Law Med Ethics 42, 190-207.
104. Garrett, J.R. (2015). Collectivizing rescue obligations in bioethics. Am J Bioeth 15, 3-11.
105. Garrett, J.R. (2015). Beyond harms and benefits: rethinking duties to disclose misattributed parentage. Hastings Cent Rep 45, 37-38.
106. Garrett, J.R. (2013). Reframing the ethical debate regarding incidental findings in genetic research. Am J Bioeth 13, 44-46.
107. Garrett, J.R. (2012). Ethical considerations for biobanking: should individual research results be shared with relatives? Pers Med 9, 159-162.
108. Klitzman, R., Appelbaum, P.S., Fyer, A., Martinez, J., Buquez, B., Wynn, J., Waldman, C.R., Phelan, J., Parens, E., and Chung, W.K. (2013). Researchers' views on return of incidental genomic research results: qualitative and quantitative findings. Genet Med 15, 888-895.
109. Klitzman, R., Buquez, B., Appelbaum, P.S., Fyer, A., and Chung, W.K. (2014). Processes and factors involved in decisions regarding return of incidental genomic findings in research. Genet Med 16, 311-317.

110. Appelbaum, P.S., Waldman, C.R., Fyer, A., Klitzman, R., Parens, E., Martinez, J., Price, W.N., 2nd, and Chung, W.K. (2014). Informed consent for return of incidental findings in genomic research. Genet Med 16, 367-373.
111. Appelbaum, P.S., Parens, E., Waldman, C.R., Klitzman, R., Fyer, A., Martinez, J., Price, W.N., 2nd, and Chung, W.K. (2014). Models of consent to return of incidental findings in genomic research. Hastings Cent Rep 44, 22-32.
112. Clayton, E.W. (2015). How much control do children and adolescents have over genomic testing, parental access to their results, and parental communication of those results to others? J Law Med Ethics 43, 538-544.
113. Zawati, M.H., Parry, D., and Knoppers, B.M. (2014). The best interests of the child and the return of results in genetic research: international comparative perspectives. BMC medical ethics 15:72.
114. McGuire, A.L., Knoppers, B.M., Zawati, M.H., and Clayton, E.W. (2014). Can I be sued for that? Liability risk and the disclosure of clinically significant genetic research findings. Genome Res 24, 719-723.
115. Ross, L.F. (2013). Predictive genetic testing of children and the role of the best interest standard. J Law Med Ethics 41, 899-906.
116. Brothers, K.B., Lynch, J.A., Aufox, S.A., Connolly, J.J., Gelb, B.D., Holm, I.A., Sanderson, S.C., McCormick, J.B., Williams, J.L., Wolf, W.A., et al. (2014). Practical guidance on informed consent for pediatric participants in a biorepository. Mayo Clin Proc 89, 1471-1480.
117. Khan, C.M., Rini, C., Bernhardt, B.A., Roberts, J.S., Christensen, K.D., Evans, J.P., Brothers, K.B., Roche, M.I., Berg, J.S., and Henderson, G.E. (2015). How can psychological science inform research about genetic counseling for clinical genomic sequencing? J Genet Couns 24, 193-204.
118. Tarczy-Hornoch, P., Amendola, L., Aronson, S.J., Garraway, L., Gray, S., Grundmeier, R.W., Hindorff, L.A., Jarvik, G., Karavite, D., Lebo, M., et al. (2013). A survey of informatics approaches to whole-exome and whole-genome clinical reporting in the electronic health record. Genet Med 15, 824-832.
119. Amendola, L.M., Lautenbach, D., Scollon, S., Bernhardt, B., Biswas, S., East, K., Everett, J., Gilmore, M.J., Himes, P., Raymond, V.M., et al. (2015). Illustrative case studies in the return of exome and genome sequencing results. Pers Med 12, 283-295.

120. Wynn, J., Scollon, S., and Lautenbach, D. (2014). Genetic counselors breaking ground in genomic sequencing research. In Perspectives in genetic counseling. pp 7-9.
121. Raymond, V.M. (2014). What did I do this time? Balancing the expanding and evolving roles of genetic counselors. In Perspectives in genetic counseling. pp 6-7.
122. AAP Committee on Bioethics, AAP Committee on Genetics, and American College of Medical Genetics Social Ethical and Legal Issues Committee. (2013). Ethical and policy issues in genetic testing and screening of children. Pediatrics 131, 620-622.
123. McCullough, L.B., Brothers, K.B., Chung, W.K., Joffe, S., Koenig, B.A., Wilfond, B., Yu, J.H., and Clinical Sequencing Exploratory Research Consortium Pediatrics Working, G. (2015). Professionally responsible disclosure of genomic sequencing results in pediatric practice. Pediatrics 136, e974-982.
124. Raymond, V.M., Gray, S.W., Roychowdhury, S., Joffe, S., Chinnaiyan, A.M., Parsons, D.W., and Plon, S.E. (2015). Germline findings in tumor-only sequencing: points to consider for clinicials and laboratories. JNCI J Natl Cancer Inst 108.