Recommendations for return of secondary genomic findings in observational cohort studies

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Abstract

The return of secondary genomic findings (ROSF) to participants in observational cohort studies has evolved from a topic of debate to an accepted standard. This Perspective synthesizes the proceedings of a 2024 NHLBI-sponsored workshop and the broader literature to provide updated guidance for ROSF. Building on the 2010 NHLBI Working Group recommendations and the 2014 CSER/eMERGE “floor and ceiling” framework, we address four areas: an integrated ethical framework for observational cohort settings; the emerging challenge of returning novel result types beyond monogenic variants, including polygenic risk scores, somatic mosaicism, and pharmacogenomic findings; health equity and community engagement as structural prerequisites for ethical ROSF; and scalability challenges including technology-assisted disclosure. Drawing on implementation experience from large-scale sequencing programs, we offer recommendations that balance researcher obligations with participant autonomy and equitable access to the benefits of genomic research.

Keywords: secondary findings; return of results; observational cohort studies; genomic screening; informed consent; polygenic risk scores; community engagement; health equity

Main

Few questions in genomic research have generated as much debate as whether, when, and how to return secondary findings to research participants.[1-3] Since the American College of Medical Genetics and Genomics (ACMG) first recommended analysis and reporting of secondary findings in clinical exome and genome sequencing in 2013,[2] the landscape has shifted markedly. What began as a controversial proposition, that laboratories should actively seek and report pathogenic variants unrelated to the clinical indication, has evolved into a field with substantial empirical experience from large cohort studies, acceptance of core principles, and a growing recognition that the question is no longer whether to return actionable secondary findings, but how to do so responsibly, equitably, and at scale.[4,5]

This evolution has not been without debate. Early objections centered on the potential for psychological harm, the specter of therapeutic misconception, the diversion of research resources, and the limited evidence base for clinical utility.[3,6] Some of these concerns persist. However, data from cohort studies, such as Geisinger's MyCode Community Health Initiative,[7] the All of Us Research Program, the eMERGE Network,[8,9] CSER,[10] and FinnGen[11], indicates that carefully implemented return programs are feasible at scale, that the psychological harms initially feared are largely transient and minimal,[4,5] and that participants overwhelmingly want their results.[12-15] It should be noted that these studies either comprised predominantly European-ancestry participants or were conducted in relatively well-resourced settings and may not generalize to return of results in diverse, lower-resource settings.

Against this backdrop, the National Heart, Lung, and Blood Institute (NHLBI) convened a two-day workshop in June 2024, "Return of Individual Research Results in Observational Cohort Studies," organized in collaboration with the National Human Genome Research Institute, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute of Diabetes and Digestive and Kidney Diseases, and the All of Us Research Program.[7,16] The workshop brought together genomicists, bioethicists, implementation scientists, clinicians, and patients/patient advocates to assess what has been learned and what remains unresolved. There were 350 attendees (85 from NIH), including 32 speakers and organizers and 4 patient advocates.

This article synthesizes the proceedings of that workshop with the broader scholarly literature to offer updated best practices for the return of secondary genomic findings (ROSF) in observational cohort studies (**Table 1**). We build on two foundational documents: the 2010 NHLBI Working Group recommendations,[17] which established initial guidance on criteria for return, time limits on investigator obligations, and community engagement; and the 2014 CSER and eMERGE consensus statement,[18] which articulated the "floor and ceiling" framework—that researchers should at minimum offer well-established, important actionable findings (the "floor"), while having flexibility to return additional results up to the entire genome (the "ceiling"), depending on research goals.

Our contribution extends prior work in four specific ways. First, we present an integrated ethical framework that synthesizes reciprocity, transparency, duty to rescue, and participant autonomy as they apply specifically to observational cohort studies. Second, we address the emerging and largely unsettled issue of returning novel genomic result types beyond monogenic variants, including polygenic risk scores (PRS), somatic mosaicism, and pharmacogenomic results (**Table 2**), for which prior guidance is limited. Third, we place health equity and community engagement not as ancillary considerations but as structural prerequisites for ethical ROSF, drawing on lessons from genomic research in federally qualified health centers and historically underrepresented populations. Fourth, we address scalability challenges and the role of

technology-assisted disclosure models, including artificial intelligence, in enabling equitable ROSF as cohort sizes expand into the hundreds of thousands.

Definitions

Clarity of terminology is essential in a field where definitions have varied across guidelines and jurisdictions. We use secondary findings to refer to pathogenic or likely pathogenic variants, as well as additional types of genomic findings identified during genomic sequencing that are unrelated to the primary research objective but have potential clinical significance. The ACMG has established a standardized gene list (currently ACMG SF v3.2, encompassing 81 genes) for reporting pathogenic or likely pathogenic variants in clinical settings.[19] In clinical settings, ACMG recommendations apply explicitly to exome and genome sequencing, with established protocols for secondary-finding analysis and return. In research settings, the ACMG has stated that "researchers, in consultation with their local IRB, should decide on the appropriateness of ROSF for their study." This guidance does not extend to studies conducted on pre-existing samples collected without consent for the return of results.

Ethical foundations for ROSF in observational cohort studies

The ethical case for ROSF rests on principles derived from the Belmont Report (the 1979 foundational U.S. statement of research ethics, which articulates respect for persons, beneficence, and justice) but applied in a context that the Belmont authors could not have envisioned.[20] In particular, three foundational principles apply. Beneficence supports returning clinically actionable results that can provide direct health benefits through early detection, prevention, or treatment modification.[18] Non-maleficence demands that results be sufficiently validated to avoid harm from false positives, unnecessary anxiety, or inappropriate clinical interventions.[3] Justice requires equal opportunity to receive results and benefit from genomic research, with particular attention to historically underrepresented populations, who have contributed to research while receiving fewer of its benefits.[21,22]

These principles must be weighed against countervailing concerns. Critics of routine ROSF have argued that: (a) the time and resources required may divert personnel and funds from primary research objectives; (b) offering results may exacerbate therapeutic misconception despite mitigation efforts; (c) returning uncertain or probabilistic findings may cause psychological harm without commensurate benefit; and (d) the evidence base for long-term outcomes following ROSF remains limited.[1,3] The empirical record, however, increasingly favors disclosure of secondary findings. Multiple studies now demonstrate that negative psychological impacts of ROSF are largely minimal and transient, with most participants reporting no significant increases in anxiety or depression at follow-up, and the majority taking clinically appropriate actions when indicated.[4,5] However, these reassuring data derive largely from cohorts with stable healthcare access; psychological outcomes may differ for participants who receive an actionable result without an affordable pathway to confirmatory testing, surveillance, or treatment. Protections under the Genetic Information Nondiscrimination Act (GINA) have further reduced, though not eliminated, concerns about discrimination.

Specific ethical obligations

Beyond these general principles, three specific ethical obligations apply to researchers conducting genomic studies in cohort settings: reciprocity, transparency, and duty to rescue.

Reciprocity acknowledges that research participants contribute their private data, specimens, and time to advance scientific knowledge; therefore, they should be considered research

partners, not “passive, disenfranchised purveyors of biomaterials and data.”[1,23,24] The obligation of reciprocity flows from this partnership: researchers owe participants meaningful acknowledgment of their contribution, which could include sharing findings that could benefit their health.[20,25,26]

Transparency requires researchers to be truthful and to avoid withholding information that participants would reasonably want to receive.[2,27] This obligation is especially salient in longitudinal cohort studies where relationship is maintained over years or decades.

Duty to rescue creates an obligation to act when actionable findings are identified—specifically, “when, in the course of research, an investigator discovers genetic information that clearly indicates a high probability of a serious condition for which an effective intervention is readily available.”[28-30] Critically, the CSER and eMERGE consensus established that this duty does not extend to a “duty to hunt”; researchers have no ethical obligation to actively search for actionable variants beyond those identified in the course of their research.[18] This distinction, also endorsed by the Presidential Commission for the Study of Bioethical Issues,[31] is practical: confirming a purported disease-causing variant as pathogenic requires extensive expert review (an average of 20 min per variant, with some requiring hours),[32] and a broad mandate to hunt would overwhelm most research programs.

Participant rights and the right not to know

Participants have both a right to receive information about themselves and a “right not to know”[33], both of which must be accommodated through informed consent.[34,35] Some have challenged this notion on the basis that returning life-saving genomic information to research participants whose initial decisions are uninformed or may change over time, should be the default process in every research project.[33] The 2010 NHLBI Working Group debated whether exceptional circumstances might justify overriding an opt-out decision when evidence of potential harm is clear and the potential for reducing harm is compelling; consensus favored honoring participant decisions, recognizing that individuals may opt out for deeply held reasons.[17] Some participants may harbor “earned skepticism” of healthcare and research systems,[36] and concerns about “inflicted insight”, being told about a problem without resources to address it, are especially relevant in low-resource settings.[37]

Informed consent

The consent process for ROSF has evolved considerably since 2010, with multiple models now in use. Traditional comprehensive consent provides full details about secondary findings analysis and return at enrollment.[38] Staged or tiered consent[39] provides a brief overview at enrollment with detailed consent when results become available, allowing time-separated decisions and reducing enrollment burden; results are organized into categories by actionability level, and participants choose categories rather than individual genes.[40,41] Dynamic consent allows participants to modify preferences over time, often through technology-enabled platforms that accommodate evolving knowledge and preferences.[42]

During pre-test counseling, participants should be informed whether ROSF will occur and given options to opt in or out by broad result types.[43-45] The CSER/eMERGE consortium emphasized that consent conversations should be framed as “if we find…would you want” rather than “we have…do you want,” avoiding potentially coercive framing.[18] Based on NHGRI and professional guidance, consent should address the following: types of findings that may be discovered and returned; participant choices including opt-in/opt-out rights; CLIA status and confirmation requirements; downstream implications, including insurance, family, and psychological considerations; and limitations, including point-in-time knowledge and the possibility of future

reinterpretation.[46] Importantly, consent should clarify that a lack of confirmed positive results does not mean no pathogenic variants are present—research sequencing may not be as sensitive as clinical single-gene or gene-panel testing.[27]

Special situations

Cascade testing and deceased participants

The obligation to return results to relatives, particularly when the proband is deceased, remains debated.[46] Return is generally limited to cases where findings have direct, substantial health implications for family members.[47,48]

Pediatric populations

Returning findings to minors requires balancing parental rights with the child's future autonomy.[49-51] Key considerations include whether to return adult-onset conditions to parents, the practicality of banking results for future disclosure when the child reaches majority, re-consent procedures at age of majority, and how to handle discordance between parental and adolescent preferences.

Recontact

Variant interpretation evolves as new evidence emerges.[52,53] The ASHG Position Statement (2019) indicates that the responsibility to recontact is stronger when research is active and funded, contact information is current, certainty about reinterpretation is high, and reinterpretation would affect medical management.[54] The 2010 NHLBI Working Group established that a researcher's obligation to return results should not ordinarily extend beyond study funding period.[17] Researchers do not have an obligation to hunt for changes in interpretation or recontact after research funding ends; however, an exception exists when an investigator also serves as the clinical care provider, in which case clinical obligations may persist. For studies involving data sharing, the CSER/eMERGE consensus established that secondary data users should relay findings to primary investigators but are not obligated to contact participants directly.[18]

Stakeholder perspectives

The empirical literature on stakeholder preferences has grown substantially since the 2010 Working Group and consistently demonstrates high participant interest in receiving results. A systematic review of 221 studies involving 118,874 participants found that 79–94% elected to receive results when offered.[13-15] Data from the eMERGE Network (4,664 participants offered choices) showed that 94.5% chose to receive all genetic results, while 5.5% selected subsets, with adult-onset conditions without prevention options most commonly declined.[13] Participants cite personal health management, understanding disease risk for themselves and family, and respect for their right to their own data as primary motivations.[55] Concerns include privacy and genetic discrimination fears, psychological impact, insurance and employment implications, and limited understanding of result implications.[56]

Researchers, meanwhile, must balance recognition of ethical obligations with resource constraints, lack of established infrastructure, concerns about therapeutic misconception, and uncertainty about which results to return.[57-59] Healthcare providers generally support returning actionable findings but express concerns about preparedness to interpret results, the need for genetics education, and workload implications.[60,61] The tension between participant enthusiasm

and provider caution underscores the importance of tiered disclosure models that match the complexity of results to the expertise of the disclosing professional.

Results to be considered for return

Actionability has been the organizing principle for ROSF since the 2010 NHLBI Working Group defined actionable results as those where disclosure has the potential to lead to an improved health outcome through established therapeutic or preventive interventions, surveillance, delayed disease onset, earlier diagnosis, or expanded treatment options.[17] An important unresolved issue is whether to return what clinicians can use (clinical actionability) versus what participants themselves find useful; the latter encompasses a broader set of findings, including those with reproductive and personal utility.[18] The ClinGen Actionability Working Group has established a semiquantitative framework assessing severity of disease outcome, likelihood of disease, effectiveness and burden of intervention, and strength of the knowledge base.[62,63]

Pathogenic variants in actionable genes

The ACMG SF v3.2 list (2023) includes 81 genes associated with cancer, cardiovascular conditions, and inborn errors of metabolism, with annual updates planned.[19] This list continues to be updated. Large-scale programs have demonstrated that 3-4% of screened individuals harbor pathogenic variants in actionable genes on this list.[7] Geisinger's MyCode program, with over 230,000 participants undergoing exome sequencing, has returned results to more than 5,000 individuals; 70% of those eligible pursued recommended risk management, and 13% received a relevant new clinical diagnosis post-disclosure.[7,64] New evidence may support return of additional population-specific actionable variants, such as glucose-6-phosphate dehydrogenase deficiency in individuals of African or Asian ancestry and *APOL1* variants that mediate kidney disease in individuals of African genetic ancestry; such variants would be sought genome-wide in all participants, with ancestry informing interpretation rather than restricting analysis to particular groups.[32,65,66]

Variants of uncertain significance

Variants of uncertain significance (VUS) represent results for which data are inadequate to classify a variant as pathogenic or benign.[67,68] VUS are identified more frequently with broader testing panels, especially among non-European ancestry populations due to under-representation in genomic databases.[69] The current consensus is not to return VUS detected as secondary findings, although some programs return VUS with appropriate counseling when participants have specifically opted to receive such information.[70,71] VUS may be reclassified over time, raising questions about recontact protocols, costs, and communication strategies. For practical reasons of cost and logistics, secondary findings analysis is typically performed once after original research sequencing data are generated, with the intention of the investigator to perform a single analysis clearly conveyed in the consent process.[27] Practical approaches include periodic database queries, automated alerts for ongoing registries, and clear consent language about recontact policies.[72] In some cases, a participant can establish an account with the CLIA Laboratory that performed the genomic testing, to be able to receive an alert in case a VUS is reclassified.

Beyond monogenic variants

Perhaps the most significant new challenge for ROSF, and one largely unaddressed by prior guidance documents, involves result types that extend beyond pathogenic variants in Mendelian disease genes (**Table 3**). These novel result types each raise distinct considerations.

Polygenic risk scores (PRS) aggregate the effects of many common variants to estimate disease risk.[73] PRS present unique challenges: population-specific calibration requirements, variable predictive performance across ancestries, uncertain clinical utility for many conditions, and the psychological complexity of communicating probabilistic risk. The eMERGE Phase IV study returned validated PRS for multiple conditions to approximately 23,840 participants, demonstrating feasibility but also highlighting variable clinician uptake.[74,75] FinnGen's GeneRisk study[11,76-79] has provided initial evidence that PRS disclosure can influence health behaviors, though effects are modest. Consensus on PRS return criteria has not been reached, and this remains an area of investigation.

Somatic mosaicism such as clonal hematopoiesis of indeterminate potential (CHIP) is associated with both hematologic malignancy and cardiovascular disease, has highly variable penetrance, and lacks established clinical interventions for most carriers.[80] The dynamic nature of clones, undergoing growth, stability, or shrinkage over time, means that legacy samples may not reflect current genomic status. Whether and how to return CHIP findings requires further study.

Pharmacogenomic variants can guide selection and dosing of medication or treatment but face implementation challenges: many genetics clinics do not accept referrals solely for pharmacogenetic counseling, clinical validation may require out-of-pocket payment, and electronic health record (EHR) integration with clinical decision support is needed for real-time utility.[81-83] Thus, there is not a consensus regarding these variants.

Additional emerging result types, including cell-free DNA findings, runs of homozygosity, mitochondrial variants, and telomere length, each carry distinct considerations for clinical utility, validation requirements, and disclosure challenges (see **Table 3)** that require further study.

Models, infrastructure, and resources for ROSF

Once the decision about which results to return has been made, a critical operational question is how best to communicate findings in a manner that builds trust, ensures comprehension, and promotes appropriate follow-up.[84-88] Studies demonstrate equivalent outcomes, patient satisfaction, and appropriate downstream care regardless of whether results are disclosed by genetic counselors, trained non-specialist providers, or via video conferencing—though participant preferences vary.[89-93]

Disclosure models

Four models have emerged from implementation experience. In the genetics-led model, genetic counselors and/or medical geneticists disclose results, an approach that is resource-intensive but provides interpretive and counseling expertise.[94] In the primary care–integrated model, results are disclosed through existing care relationships, as exemplified by Geisinger's MyCode program, where primary care providers receive notification with the option for genetics referral.[88] The hybrid model combines clinical laboratory reporting with tiered genetic counseling based on result complexity, as implemented in *All of Us*, where positive results require a genetic counseling appointment.[95] The technology-assisted model uses online platforms for viewing and understanding results, supplementing but not replacing human interaction; the All of Us participant portal exemplifies this approach.[96] Digital tools, including AI-driven chatbots tailored to health literacy, language, and cultural background, are being increasingly used for scalable disclosure.[97-103] Because such digital-first approaches assume reliable broadband and digital

literacy, they risk excluding participants who lack them and should supplement rather than replace direct human contact.

Tiered disclosure matching complexity to resources

Tier 1 findings

These are medically actionable results associated with high likelihood of severe illness and potential need for burdensome interventions (e.g., hereditary cancer syndromes, BRCA1/2), which would ideally be disclosed by genetic counselors followed by specialist consultation.[104] Across programs, ~ 3–4% of participants carry an actionable pathogenic variant,[7] disclosure sessions average 30–60 min, and the shortage of genetic counselors presents scalability challenges.[105]

Tier 2 findings

These are pharmacogenomic results and findings manageable by non-specialists (e.g., *APOL1*-mediated kidney disease, hereditary amyloidosis, hereditary hemochromatosis type 1); they can be transmitted by primary care providers or study personnel, aided by digital tools.[93] Actionable pharmacogenomic findings are present in nearly everyone, whereas the prevalence of these three monogenic conditions is strongly population stratified. *HFE* C282Y homozygosity occurs in ~0.6% of European-ancestry individuals in UK Biobank and is rarer in other ancestries.[106] The *APOL1* high-risk genotype is present in ~13% of individuals of African ancestry but is near-absent in European or Asian ancestry.[107] The p.V142I variant, the most common cause of hereditary transthyretin amyloidosis, is carried by ~3.4% of African Americans and is rare in other ancestries.[108] The Incidental Genomics Study demonstrated a practical referral model where common and non-urgent secondary findings were directed to family physicians rather than genetics specialists, recognizing that specialist referral for all findings would be infeasible.[83] In *APOL1* disclosure studies, over 95% of patients were satisfied with receiving results via a study assistant, and fewer than 0.5% chose to speak with a genetic counselor despite being offered free access.[109]

EHR integration and core services

Genetic results from CLIA-validated research are often stored in EHRs as non-searchable PDFs, limiting clinical utility.[110,111] Therefore, results should ideally be integrated using Health Level Seven International (HL7) or Fast Health Interoperability Resources (FHIR) standards by adding them into discrete fields that enable clinical decision support and automated reclassification.[112,113] The NIH has implemented a centralized secondary-genomic-findings service model providing four functions: identifying potential clinically relevant secondary findings, re-sampling participants, confirming findings via CLIA testing, and providing medical and genetic counseling.[27] Cost estimates range from $26–$83 per exome when amortized across all submitted sequences. Such centralized ROSF services could help ensure equitable and consistent reporting.[27]

Community engagement and health equity

An important question is to whom to return secondary findings, and we argue that the answer must be to “everyone, equitably.” An emerging consensus holds that research should be conducted “with” participants, patients, caregivers, clinicians, and advocates, not “on” them.[17] Community advisory boards provide essential input into how ROSF is addressed in consent

processes, ensuring appropriate reading levels, incorporating community perspectives, identifying supporting resources, and building trust.[30,114,115]

Culturally appropriate strategies are essential for ensuring that historically marginalized populations are represented in and benefit from genomic research.[116] This requires attention at multiple levels: individual factors (language, literacy), family considerations (cascade-testing provisions), setting factors (access to specialists), community factors (the importance of representation), and public health context (non-genetic causes of illness).[20] The decision to return a secondary finding should not depend on socioeconomic status; if actionable, it should be returned regardless of circumstances. However, it is clear that social determinants significantly affect access to post-disclosure resources, including genetic counseling, follow-up testing, and recommended interventions.[116] In lower-resource settings, use of scarce funds for clinical confirmation and counseling pipelines can draw away from investments in the social and environmental determinants that exert a larger day-to-day effect on health, a trade-off that warrants recognition. For participants from resource-poor settings, returning results that a participant cannot act upon may cause distress.[27] Mitigation strategies include telehealth options, partnerships with community health centers, coverage for confirmatory testing within research protocols, and connection to patient assistance programs.

The barriers to equitable ROSF are well documented: historical research missteps and resulting mistrust; limited representation in genomic databases (historically >80% European ancestry, but improving in All of Us); reduced clinical validity in diverse populations; and language and literacy barriers.[21,117] More genomic research is needed in low-resource settings, such as federally qualified health centers, where the intersection of precision medicine and social determinants of health can be directly studied.[116] The Jackson Heart Study, which enrolled approximately 5,300 African American adults in the Jackson, Mississippi metropolitan area, offers a particularly instructive example: the study transitioned from a no-notification policy to actively providing individual genetic results with genetic counseling and clinical confirmation, working closely with community stakeholders to shape communication and prepare audience-appropriate materials.[118-121]

Persistent challenges

Resource constraints

With an expected yield of 2–4% for actionable secondary findings (depends on number of genes examined),[7] costs for ROSF can be substantial in large studies, including for developing informed consent, IRB review, patient and provider education, EHR storage, clinical validation, access to specialists and genetic counselors, and quality assurance.[39] Disclosure of all clinically significant secondary findings is further constrained by workforce shortages; wait times of up to four years for genetics services have been reported in the United States.[83,105] Key unresolved questions include how should clinical validation and ROSF be budgeted in grant applications? Will variant interpretation be updated during longitudinal studies, and if so by whom and from which funds? How can equity be ensured in settings without genetic counselors or access to specialized tests and treatments?

Regulatory and compliance considerations

The 2010 NHLBI Working Group debated whether research laboratories that are not CLIA-certified may return individual results; some argued that ethical obligations to disclose beneficial information and free-speech considerations supersede regulatory requirements, while others

emphasized that CLIA-specified processes offer significant protections, including analytic validity and reduced risk of returning results to the wrong person.[17] The *All of Us* Research Program received FDA Investigational Device Exemption (IDE) for ROSF without an ordering physician on the condition that results were labeled "research-only" and participants were offered counseling; the program ultimately chose to use research sequencing to prompt clinical testing, and later shifted to clinical testing for actionable variant return for all participants, requiring significant resources.[84,122,123] The *All of Us* trajectory (research-only return under an IDE, then a shift to clinical-grade testing for actionable variants) is instructive for future large cohort studies that include ROSF.

Environmental data

Social factors, such as chronic stress and environmental exposures, interact with genetic factors to influence disease risk.[118-120] In some cohorts, data from environmental measures and wearable devices may be available and could contextualize genetic results. These data types raise novel quality control, analysis, and return-of-results challenges that will require dedicated frameworks as cohort studies expand the scope of what is measured and what is potentially returnable.

Lessons from large-scale programs

Implementation experience across these programs (summarized in **Table 3**)[7,8,11,121-125] converges on three lessons: population-scale genomic screening is feasible within integrated health systems; clinical-grade confirmation and electronic health record integration are the principal rate-limiting steps; and sustained community engagement determines whether return is equitable.[7,8,11,76-79,121-125]

Limitations

This report has several limitations. Recommendations for ROSF and future research in this area (**Table 1** and **Box 1**) arose from deliberation at a single workshop followed by iterative revision, rather than formal Delphi methodology; areas of disagreement may not be fully captured. Furthermore, the discussion is US-centric; international contexts involving different regulatory frameworks (e.g., European Union General Data Protection Regulation), healthcare systems, and cultural norms require separate consideration. Participant and patient representatives were involved in the workshop, but their perspectives may not be fully reflected in all recommendations.

Conclusions and future directions

Participants in observational cohort studies overwhelmingly want to receive their individual results, and the ethical principles of transparency and reciprocity direct researchers to honor those preferences. Since the 2010 NHLBI Working Group established foundational recommendations for ROSFs,[17] the field has been transformed by the advent of whole-genome sequencing, by expanded understanding of novel result types including polygenic risk scores, and by implementation experience from programs that have returned findings to hundreds of thousands of individuals. Return of clinically validated secondary findings is now routinely considered and should be addressed in informed consent.

Responsible ROSF requires balancing research goals and resources with respect for participant autonomy and well-being. Success depends on community engagement, attention to ethical, legal, and social implications, and sustained commitment to diverse populations. Equitable

return is not the same as uniform return: offering an identical process to every participant can entrench existing gaps, whereas the structural, financial, and educational support required by communities with limited access is what makes return equitable in practice. While the ACMG secondary-findings gene list provides a foundation, additional genes and emerging genomic result types should be considered as evidence of clinical utility accumulates. Given the substantial resources required, centralized institutional services can help ensure consistent, equitable ROSF. Guidelines that establish shared expectations and standards across the research community may also help mitigate liability concerns such as participants who are not offered findings and then subsequently suffer preventable harm and argue breach of duty.[1]

Looking ahead, continued research is needed on optimal approaches for ROSF and on the long-term impacts on participants' psychological well-being, health behaviors, clinical care, and health outcomes (**Box 1**). Equally critical is the need to understand and implement ROSF across diverse populations using mixed-methods research to address concerns about benefits and harms. Emerging data from programs including the 100,000 Genomes Project and Geisinger MyCode are providing important insights into yield, costs, and clinical impact.[7,126] As genomic sequencing becomes increasingly integrated into both healthcare delivery and research, the principles and practices outlined here provide a roadmap for ensuring that research participants realize the full benefit of actionable genomic findings, delivered in a manner that is ethical, equitable, and sustainable.

Author contributions

I.J.K. and C.R.H. conceived and drafted the manuscript; I.J.K., C.R.H., L.B., B.B., L.G.B., K.B., A.P.C., K.D., R.A.G., R.C.G., H.H., C.H., J.E.L., G.J., S.S.K., B.M., S.R., M.R., J.M.S., G.Q.S., S.O.S., C.W., Y.H., Y.Y., R.I.Y. contributed to workshop discussions and the draft, critically revised the manuscript, and approved the final version.

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Competing interests

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Tables

Table 1. Best practices for ROSF in observational cohort studies

Phase	Recommendations
Planning phase	Establish clear policies for SF analysis and return before enrollment begins. Define scope of findings to be analyzed and potentially returned. Budget adequately for all components (confirmation, counseling, infrastructure). Obtain IRB approval for return protocols including consent language. Engage community stakeholders in protocol development.
Consent process	Provide information about what findings may be returned. Categorize results to facilitate informed decision-making. Allow dynamic preferences that can be updated over time. Address CLIA status and confirmation requirements explicitly.
Laboratory and quality	Establish quality management systems appropriate to research setting. Use validated bioinformatics pipelines with regular updates. Confirm findings in CLIA-certified laboratory before disclosure. Apply standardized variant classification (ACMG/AMP criteria). Maintain sample chain of custody documentation.
Disclosure process	Develop tiered disclosure model based on severity. Ensure genetic counseling availability for positive findings. Provide educational materials appropriate to population. Facilitate clinical follow-up and cascade testing. Document results appropriately in medical records.
Equity and access	Prioritize diverse enrollment to ensure equitable benefit. Address barriers to follow-up care for underserved populations. Provide culturally appropriate communication. Ensure accessibility (language, literacy, technology).
Long-term considerations	Address recontact when clinically significant new information emerges. Maintain contact infrastructure for duration of study. Evaluate outcomes of return of results programs. Contribute to evidence base through publications and data sharing.

ACMG/AMP = American College of Medical Genetics and Genomics/Association for Molecular Pathology; CLIA = Clinical Laboratory Improvement Amendments; SF = secondary findings

Table 2. Utility and implementation challenges of returning genomic result types beyond pathogenic monogenic variants

Result Type	Potential utility	Implementation challenges
Polygenic risk scores (PRS)	Could inform screening and treatment decisions, and health behaviors; can be integrated into validated risk prediction equations (e.g., breast cancer, coronary heart disease). Top PRS percentiles typically used as cutoffs for reporting.	Need for CLIA confirmation; underdeveloped result return procedures; EHR integration with clinical decision support; ensuring participants understand probabilistic risk; potential for false reassurance or overdiagnosis; reduced performance in non-European ancestry populations.
Clonal hematopoiesis (CHIP)[80]	Prevalence increases with age (>10% in those older than 70-y); associated with blood cancers, cardiovascular, and inflammatory diseases.	Dynamic clones change over time; legacy samples may not reflect current status; evolving therapeutic landscape with ongoing clinical trials; unclear clinical actionability for most carriers.
Pharmacogenomic variants[127]	Can guide medication selection and dosing; pre-emptive testing enables immediate application at prescribing. Relevant for opioids, anticoagulants, antidepressants, chemotherapy.	Requires EHR integration and clinical decision support; many genetics clinics do not accept PGx referrals; variable insurance coverage; participants may pay out-of-pocket for clinical validation.
Cell-free DNA (cfDNA)[128]	Non-invasive option for fetal aneuploidies and cancer detection; circulating tumor DNA for prognosis, therapy selection, and minimal residual disease monitoring.	False negatives could delay treatment; false positives could lead to unnecessary procedures; overdiagnosis risk for indolent cancers; increased patient anxiety.
Runs of homozygosity (ROH)[129]	Can reveal autozygosity, increasing recessive disease risk; identify consanguinity; detect uniparental disomy causing imprinting disorders.	Population-specific thresholds required; sensitive disclosure issues around consanguinity; limited clinical guidelines for return.
Mitochondrial variants[130]	Pathogenic variants can be highly penetrant with multi-system manifestations; carrier status relevant for maternal inheritance counseling.	Heteroplasmy complicates interpretation; phenotypic variability makes penetrance estimation difficult; limited population data; CLIA validation not readily available.
Telomere length[131]	Short telomeres associated with pulmonary fibrosis, bone marrow failure, and liver disease; potential utility in inherited telomeropathies.	Measurement variability across methods; age- and population-specific reference ranges needed; limited evidence for general population actionability.

CLIA = Clinical Laboratory Improvement Amendments; DNA = Deoxyribonucleic Acid; EHR = electronic health record; PRS = polygenic risk score

Table 3. Select examples of return of genomic results in observational cohort studies

Study	Design and return mechanism	Key lessons
eMERGE III (2015–2020)[132]	24,520 participants across 10 sites; targeted sequencing of 68 actionable genes. P/LP by genetic counselor; remaining by mail.	Low SF frequency (<3%); challenges included loss to follow-up, deceased individuals, non-responders, variant reclassification.
eMERGE IV[9] **(ongoing)**	25,000 participants age 3–75; validated PRS and monogenic testing; genome-informed risk assessment (GIRA) with tiered return: high-risk participants met a clinician, lower-risk participant received results via portal/mail.	Sites funded preventive care tests not typically reimbursed; IRB denied requests to cover additional tests for underserved populations; creation of comprehensive reports required cross-disciplinary expertise.
Jackson Heart Study[133,134]	Transitioned from no notification to active ROSF with genetic counseling and clinical confirmation; expanded actionable gene list (e.g., transthyretin variant for amyloidosis).	Additional resources are needed for ROSF and confirmation; community advisory board essential for culturally appropriate communication; demonstrated need for equitable access and tailored approaches.
Framingham Heart Study[135,136]	WGS of all participants; subset consented for ACMG SF return; GC-led disclosure for P/LP findings with 3-generation family history.	Participants interested in results and family implications; demonstrated feasibility of ROSF in multi-generational cohorts.
MyCode (Geisinger)[7,137]	350,000+ enrolled, 230,000+ with exome sequencing; ACMG SF v3.2 genes; results confirmed in CLIA lab; GCs contact positive participants; EHR integration.	3.4% actionable yield; >5,000 received results; 70% pursued risk management; 13% received new diagnosis; industry partnership (Regeneron) enabled sustainable sequencing.
All of Us[84,138]	National cohort; opt-in for DNA result types; genetic counseling required for P/LP; educational learning center; English and Spanish resources.	Challenges in obtaining FDA/IRB approvals; confirmatory clinical testing costly; community partners essential; participant surveys refined processes.
FinnGen/GeneRisk[79]	PRS return for cardiovascular disease, T2D, cancers; pilot studies on feasibility and health behavior impact.	Clear, actionable information and follow-up support are crucial; multiple risk presentation formats needed; ongoing integration with healthcare systems.

ACMG SF = American College of Medical Genetics and Genomics secondary findings; CLIA = Clinical Laboratory Improvement Amendments; FDA/IRB = Food and Drug Administration/Institutional Review Board; GC = genetic counselor; GIRA = genome-informed risk assessment; P/LP = pathogenic/likely pathogenic; PRS = polygenic risk score; SF = secondary findings; T2D= type 2 diabetes; WGS = whole genome sequencing

Recommendations for future research and ROSF implementation

1. Develop institutional-level policies for tiered paths for returning secondary findings, emphasizing transparency, reciprocity, equity, and beneficence.

2. Research and improve opt-out methods, ensuring participants who want results can access them without overly complex consent processes; develop educational resources for informed decisions.

3. Adopt team-based approaches involving genetic counselors, primary care clinicians, and support staff to tailor disclosures based on participant preferences and result complexity. Advance genomics literacy for clinicians and participants.

4. Use multiple modalities (visual aids, detailed reports, digital tools) to enhance understanding and continuously refine communication strategies based on participant feedback.

5. Integrate genetic test results into EHRs in structured, machine-readable formats enabling clinical decision support.

6. Develop processes for monitoring reinterpretation of secondary findings including VUS; help participants understand their results and follow-up care options.

7. Engage community stakeholders early and throughout research to incorporate diverse perspectives, using community or multi-stakeholder advisory boards and iterative feedback processes.

8. Expand genomic research in underserved and low-income populations, including at federally qualified health centers, to improve interpretation of secondary findings and ensure equitable benefit.

9. Continue evaluation of clinical utility of emerging result types including PRS, CHIP, cell-free DNA, and pharmacogenomic variants, with emphasis on improving performance across diverse populations and establishing evidence-based actionability frameworks.

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