nature genetics

Perspective

https://doi.org/10.1038/s41588-026-02724-6

Recommendations for return of secondary genomic findings in observational cohort studies

Received: 2 April 2026

Accepted: 22 July 2026

Published online: 11 September 2026

Check for updates

Iftikhar J. Kullo[1,25] ✉, Carol R. Horowitz[2,25], Lisa Bastarache[3], Benjamin Berkman[4], Leslie Biesecker[4], Kyle Brothers[5], April P. Carson[6], Keith Diaz[7], Richard A. Gibbs[8], Robert C. Green[9,10,11,12], Heather Hampel[13], Candace Henley[14], Jodell E. Linder[3], Gail P. Jarvik[15], Sadiya S. Khan[16], Barry Make[17], Samuli Ripatti[18], Mimsie Robinson[19], Juliann M. Savatt[20], Gabriel Q. Shaibi[21], Stephen Olufemi Sodeke[22], Colin Wise[23], Yuling Hong[24], Ye Yan[24,25] & Ronit I. Yarden[24,25]

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 National Heart, Lung and Blood Institute-sponsored workshop and the broader literature to provide updated guidance for ROSF. Building on the 2010 National Heart, Lung and Blood Institute Working Group recommendations and the 2014 Clinical Sequencing Exploratory Research/Electronic Medical Records and Genomics '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.

Few questions in genomic research have generated as much debate as whether, when and how to return secondary findings to research participants[1–4]. 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 (ref. 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[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]. Some of these concerns persist. However, data from cohort studies, such as Geisinger's MyCode Community Health Initiative[6], the All of Us Research Program[7], the Electronic Medical Records and Genomics (eMERGE) Network[8,9], Clinical Sequencing Exploratory Research (CSER)[10] and FinnGen[11], indicate

A full list of affiliations appears at the end of the paper. ✉e-mail: ikullo@mcw.edu

that carefully implemented return programs are feasible at scale, that the psychological harms initially feared are largely transient and minimal[5] and that participants overwhelmingly want their results[12–15]. It should be noted that these studies either comprised predominantly participants of European descent 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 virtual 2-day workshop in June 2024 entitled 'Return of Individual Research Results to Participants in Observational Cohort Studies,' organized in collaboration with the National Human Genome Research Institute (NHGRI), 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]. 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 the National Institutes of Health, 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[16], which established initial guidance on criteria for return, time limits on investigator obligations and community engagement, and the CSER and eMERGE consensus[17], which articulated the 'floor and ceiling' framework stipulating 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 (PRSs), 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 importance. The ACMG has established a standardized gene list (currently ACMG SF v3.3, encompassing 84 genes) for reporting pathogenic or likely pathogenic variants in clinical settings[18,19]. 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 Institutional Review Board (IRB), should decide on the appropriateness of ROSF for their study'[18]. This guidance does not extend to studies conducted on pre-existing samples collected without consent for the return of results.

Table 1 | Best practices for ROSF in observational cohort studies

Phase	Recommendations
Planning phase	Establish clear policies for secondary findings analysis and return before enrollment begins. Define the scope of findings to be analyzed and potentially returned. Budget adequately for all components (confirmation, counseling and 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 the research setting. Use validated bioinformatics pipelines with regular updates. Confirm findings in a CLIA-certified laboratory before disclosure. Apply standardized variant classification (ACMG/AMP criteria). Maintain sample chain of custody documentation.
Disclosure process	Develop a tiered disclosure model based on severity. Ensure genetic counseling availability for positive findings. Provide educational materials appropriate for the 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 and technology).
Long-term considerations	Address recontact when clinically important new information emerges. Maintain contact infrastructure for the duration of the study. Evaluate outcomes of return of results programs. Contribute to the evidence base through publications and data sharing.

ACMG, American College of Medical Genetics and Genomics; AMP, Association for Molecular Pathology; CLIA, Clinical Laboratory Improvement Amendments; IRB, institutional review board; ROSF, return of secondary genomic findings.

Ethical foundations for ROSF in observational cohort studies

The ethical case for ROSF rests on principles derived from the Belmont Report (the 1979 foundational US 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[20,21]. In particular, three principles apply here—beneficence and justice from the Belmont framework, together with nonmaleficence. Beneficence supports returning clinically actionable results that can provide direct health benefits through early detection, prevention or treatment modification[17]. Nonmaleficence 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[22,23].

These principles must be weighed against countervailing concerns. Critics of routine ROSF have argued that (1) the time and resources required may divert personnel and funds from primary research objectives, (2) offering results may exacerbate therapeutic misconception despite mitigation efforts, (3) returning uncertain or probabilistic findings may cause psychological harm without commensurate benefit, and (4) the evidence base for long-term outcomes

https://doi.org/10.1038/s41588-026-02724-6

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

Result type	Potential utility	Implementation challenges
PRSs[75]	Could inform screening and treatment decisions and health behaviors; can be integrated into validated risk prediction equations (for example, for breast cancer and coronary heart disease). Top PRS percentiles are 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 individuals not of European descent.
CHIP[82]	Prevalence increases with age (>10% in those older than 70 years); associated with blood cancers and 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 and chemotherapy.	Requires EHR integration and clinical decision support; many genetics clinics do not accept pharmacogenomic referrals; variable insurance coverage; participants may have to pay out of pocket for clinical validation.
Cell-free DNA[128]	Noninvasive option for fetal aneuploidies and cancer detection; circulating tumor DNA can be used 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[129]	Can reveal autozygosity, increasing recessive disease risk; can identify consanguinity; can detect uniparental disomy causing imprinting disorders.	Population-specific thresholds needed; sensitive disclosure issues around consanguinity; limited clinical guidelines for return.
Mitochondrial variants[130]	Pathogenic variants can be highly penetrant with multisystem 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.

CHIP, clonal hematopoiesis of indeterminate potential; CLIA, Clinical Laboratory Improvement Amendments; EHR, electronic health record; PRS, polygenic risk score.

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 take clinically appropriate actions when indicated[5]. However, these reassuring data derive largely from cohorts with stable health care 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 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'[1,24,25]. 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[20,26,27].

Transparency requires researchers to be truthful and to avoid withholding information that participants would reasonably want to receive[2,28]. This obligation is especially salient in longitudinal cohort studies where relationships are 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'[29–31]. 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[17,32]. This distinction, also endorsed by the Presidential Commission for the Study of Bioethical Issues[33], 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)[34], 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'[35], both of which must be accommodated through informed consent[36,37]. 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[35]. 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[16]. Some participants may harbor 'earned skepticism' of health care and research systems[38], and concerns about 'inflicted insight', being told about a problem without resources to address it, are especially relevant in low-resource settings[39].

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[40]. Staged or tiered consent[41] 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[42,43]. Dynamic consent allows participants to modify preferences over time, often through technology-enabled platforms that accommodate evolving knowledge and preferences[44].

During pre-test counseling, participants should be informed whether ROSF will occur and given options to opt in or out by broad

result types[45–47]. The CSER and eMERGE consensus 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[17]. Based on the 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; Clinical Laboratory Improvement Amendments (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[48–50]. Importantly, consent should clarify that the absence of a reported finding does not exclude the presence of a pathogenic variant; research sequencing may not be as sensitive as clinical single-gene or gene panel testing[28].

Special situations

Cascade testing and deceased participants

The obligation to return results to relatives, particularly when the proband is deceased, remains debated[51]. Return is generally limited to cases where findings have direct, substantial health implications for family members[52,53].

Pediatric populations

Returning findings to minors requires balancing parental rights with the child's future autonomy[54–56]. 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 may evolve as new evidence emerges[48,49]. A 2019 American Society of Human Genetics position statement 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[50]. The 2010 NHLBI Working Group established that a researcher's obligation to return results should not ordinarily extend beyond the study funding period[16]. 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 and eMERGE consensus established that secondary data users should relay findings to primary investigators but are not obligated to contact participants directly[17].

Stakeholder perspectives

The empirical literature on stakeholder preferences has grown substantially since the 2010 Working Group recommendations and consistently demonstrates high participant interest in receiving results. A systematic review of 221 articles covering 118,874 stakeholders found consistently high interest in receiving results, with 79–81% of participants electing to receive them where uptake was measured[13–15]. Data from the eMERGE Network (4,664 participants offered choices) showed that 94.5% chose to receive all genetic results, whereas 5.5% selected subsets, with adult-onset conditions without prevention options most commonly declined[12]. Participants cite personal health management, understanding disease risk for themselves and family and respect for their right to their own data as primary motivations[57]. Concerns include privacy and genetic discrimination fears, psychological impact, insurance and employment implications and limited understanding of result implications[58].

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[59–61]. Health care providers generally support returning actionable findings but express concerns about preparedness to interpret results, the need for genetics education and workload implications[62,63]. 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[16]. 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[17]. 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[64,65].

Pathogenic variants in actionable genes

The ACMG SF v3.3 list (2025) includes 84 genes associated with cancer, cardiovascular conditions and inborn errors of metabolism[19]. This list continues to be updated. Large-scale programs have demonstrated that 2–4% of screened individuals harbor pathogenic variants in actionable genes on this list[6]. 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 after disclosure[6,66]. New evidence may support return of additional population-specific actionable variants, such as glucose-6-phosphate dehydrogenase deficiency in individuals of African or Asian descent and *APOL1* variants that mediate kidney disease in individuals of African genetic ancestry; such variants should be sought across the genome in all participants, with ancestry informing interpretation rather than restricting analysis to particular groups[34,67,68].

Variants of uncertain significance

Variants of uncertain significance (VUS) represent results for which data are inadequate to classify a variant as pathogenic or benign[69,70]. VUS are identified more frequently with broader testing panels, especially among populations not of European descent due to underrepresentation in genomic databases[71]. 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. VUS may be reclassified over time, raising questions about recontact protocols, costs and communication strategies[72,73]. 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[28]. Practical approaches include periodic database queries, automated alerts for ongoing registries and clear consent language about recontact policies[74]. 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 consequential 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 2). These novel result types each raise distinct considerations.

https://doi.org/10.1038/s41588-026-02724-6

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

Study	Design and return mechanism	Key lessons
eMERGE III (2015–2020)[122]	A total of ~25,000 participants across ten sites; targeted sequencing of 109 genes, of which 68 were designated actionable for return. P/LP returned by genetic counselor and the remaining by mail.	Frequency of secondary findings <3%; challenges in returning results included loss to follow-up, deceased individuals, nonresponders and variant reclassification.
eMERGE IV[9] (ongoing)	~25,000 enrolled, ages 3–75; validated PRSs and monogenic testing; GIRA with tiered return: high-risk participants met a clinician, and lower-risk participants 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[115,116]	Transitioned from no notification to active ROSF with genetic counseling and clinical confirmation; expanded actionable gene list (for example, *TTR* for hereditary transthyretin 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[123,124]	WGS of all participants; a subset consented for ACMG secondary findings return; GC-led disclosure for P/LP findings with three-generation family history.	Participants interested in results and family implications; demonstrated feasibility of ROSF in multigenerational cohorts.
MyCode (Geisinger)[6,125]	A total of more than 350,000 enrolled, more than 230,000 with exome sequencing; ACMG SF v3.3 genes; results confirmed in a CLIA laboratory; GCs contact positive participants; EHR integration.	Actionable yield of 3.4%; >5,000 received results; 70% pursued risk management; 13% received new diagnosis; industry partnership (Regeneron) enabled sustainable sequencing.
All of Us[7]	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; costly confirmatory clinical testing; community partners essential; participant surveys refined processes.
Finnish GeneRisk[81]	PRS return for cardiovascular disease, T2D and cancers; pilot studies on feasibility and health behavior impact.	Clear, actionable information and follow-up support are crucial; need for multiple risk presentation formats as well as ongoing integration with health care systems.

ACMG, American College of Medical Genetics and Genomics; CLIA, Clinical Laboratory Improvement Amendments; EHR, electronic health record; FDA, Food and Drug Administration; GC, genetic counselor; GIRA, genome-informed risk assessment; IRB, institutional review board; P/LP, pathogenic/likely pathogenic; PRS, polygenic risk score; ROSF, return of secondary genomic findings; T2D, type 2 diabetes; WGS, whole-genome sequencing.

PRSs aggregate the effects of many common variants to estimate disease risk[75]. PRSs present unique challenges: population-specific calibration requirements, variable predictive performance across ancestries, uncertain clinical utility for many conditions and the complexity of communicating probabilistic risk. The eMERGE Phase IV study returned validated PRSs for multiple conditions to 23,840 participants, demonstrating feasibility but also highlighting variable clinician uptake[76,77]. The Finnish GeneRisk study[11,78–81] 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[82]. The dynamic nature of clones, with 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 pharmacogenomic 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[83–85]. Consensus on returning pharmacogenomic results has therefore not emerged.

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 2) 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[7,66,86–88]. Studies demonstrate equivalent outcomes, participant 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. 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[66]. 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[94]. 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[95]. Digital tools, including artificial intelligence-driven chatbots tailored to health literacy, language and cultural background, are being increasingly used for scalable disclosure[96–102]. 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

Level 1 findings

These are medically actionable results associated with a high likelihood of severe illness and potential need for burdensome interventions (for example, hereditary cancer syndromes, *BRCA1*/*BRCA2*), which would ideally be disclosed by genetic counselors followed by specialist consultation[103]. Across programs, 2–4% of participants carry an actionable

pathogenic variant in genes from the ACMG list[6], disclosure sessions average 30–60 min, and the shortage of genetic counselors presents scalability challenges[104].

Level 2 findings

These are pharmacogenomic results and findings manageable by non-specialists (for example, *APOL1*-mediated kidney disease, hereditary amyloidosis and 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 specific conditions is strongly population stratified. *HFE* p.C282Y homozygosity occurs in ~0.6% of individuals of European descent in the UK Biobank and is rarer in other ancestries[105]. The *APOL1* high-risk genotype is present in ~13% of individuals of African descent but is nearly absent in individuals of European or Asian descent[106]. The *TTR* p.V142I variant (also reported as p.V122I), the most common cause of hereditary transthyretin amyloidosis, is carried by ~3.4% of African Americans and is rare in other ancestries[107]. The Incidental Genomics Study used 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[85]. In *APOL1* disclosure studies, over 95% of participants 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[108].

EHR integration and core services

Genetic results from CLIA-validated research testing are often stored in the EHR as nonsearchable PDFs, limiting clinical utility[109]. Results should ideally be integrated using Health Level Seven International (HL7) standards, including Fast Healthcare Interoperability Resources (FHIR), by adding them to discrete fields that can trigger clinical decision support and automated reclassification[109,110]. The NIH has implemented a centralized secondary genomic findings service model that provides four functions: identifying potential clinically relevant secondary findings, resampling participants, confirming findings via CLIA testing and providing medical and genetic counseling[28]. Cost estimates range from $26 to $83 per exome when amortized across all submitted sequences. Such centralized ROSF services could help ensure equitable and consistent reporting[28].

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[16]. 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[31,111].

Culturally appropriate strategies are essential for ensuring that historically marginalized populations are represented in and benefit from genomic research[112]. This requires attention at multiple levels: individual factors (language and literacy), family considerations (cascade-testing provisions), setting factors (access to specialists), community factors (the importance of representation) and public health context (nongenetic 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 drivers substantially affect access to postdisclosure resources, including genetic counseling, follow-up testing and recommended interventions[112]. For participants from resource-poor settings, returning results that a participant cannot act on may cause distress[28]. Mitigation strategies include telehealth options, partnerships with community health centers, coverage for confirmatory testing within research protocols and connection to patient assistance programs. In lower-resource settings, use of scarce funds for clinical confirmation and counseling pipelines can divert funds from investments in the social and environmental factors that exert a larger day-to-day effect on health, a trade-off that warrants recognition.

The barriers to equitable ROSF are well documented, including historical research missteps and resulting mistrust, limited representation in genomic databases (typically >80% European descent, but improving in All of Us), reduced clinical validity in diverse populations and language and literacy barriers[22,113]. More genomic research is needed in low-resource settings, such as federally qualified health centers, where the intersection of precision medicine and social drivers of health can be directly studied[112]. 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[114–116].

Persistent challenges

Resource constraints

With an expected yield of 2–4% for actionable secondary findings (depending on the number of genes examined)[6], costs for ROSF can be substantial in large studies, including for developing informed consent documents, IRB review, patient and provider education, EHR storage, clinical validation, access to specialists and genetic counselors and quality assurance[41]. Disclosure of all clinically important secondary findings is further constrained by workforce shortages; wait times of up to 4 years for genetics services have been reported in North America[85,104]. 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, whereas others emphasized that CLIA-specified processes offer substantial protections, including analytic validity and reduced risk of returning results to the wrong person[16]. The All of Us Research Program received FDA Investigational Device Exemption 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 substantial resources[7,95,117]. The All of Us trajectory (research-only return under an Investigational Device Exemption and then a shift to clinical-grade testing for actionable variants) is instructive for future large cohort studies that plan 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.

BOX 1

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-in and opt-out methods, ensuring participants who want results can access them without overly complex consent processes; develop educational resources to facilitate 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 and 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 that can trigger 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 the research to incorporate diverse perspectives, using community or multistakeholder 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 PRSs, CHIP, cell-free DNA and pharmacogenomic variants, with emphasis on improving performance across diverse populations and establishing evidence-based actionability frameworks.

Lessons from large-scale programs

Implementation experience across large-scale return-of-results programs (summarized in Table 3)[6–9,11,78–81,114–116,95,117,121–125] converges on three lessons: population-scale genomic screening is feasible within integrated health systems, clinical-grade confirmation and EHR integration are the principal rate-limiting steps, and sustained community engagement determines whether return is equitable[6–9,11,78–81,114–116,95,117,121–125].

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 (for example, European Union General Data Protection Regulation), health care 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 ROSF[16], the field has been transformed by the advent of whole-genome sequencing, expanded understanding of novel result types including PRSs and 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[6,126]. As genomic sequencing becomes increasingly integrated into both health care 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.

Data availability

Supplementary material detailing the workshop agenda, participants and methodology is available at https://www.nhlbi.nih.gov/events/2024/return-individual-research-results-participants-observational-cohort-studies.

References

1. Wolf, S. M. Return of individual research results and incidental findings: facing the challenges of translational science. *Annu. Rev. Genomics Hum. Genet.* **14**, 557–577 (2013).
2. Green, R. C. et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet. Med.* **15**, 565–574 (2013).
3. Wolf, S. M. et al. Managing incidental findings in human subjects research: analysis and recommendations. *J. Law Med. Ethics* **36**, 219–248 (2008).
4. Wolf, S. M. et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genet. Med.* **14**, 361–384 (2012).

5. McCormick, C. Z. et al. Investigating psychological impact after receiving genetic risk results—a survey of participants in a population genomic screening program. *J. Pers. Med.* **12**, 1943 (2022).
6. Savatt, J. M. et al. Genomic screening at a single health system. *JAMA Netw. Open* **8**, e250917 (2025).
7. All of Us Research Program Genomics Investigators. Genomic data in the All of Us Research Program. *Nature* **627**, 340–346 (2024).
8. Lennon, N. J. et al. Selection, optimization and validation of ten chronic disease polygenic risk scores for clinical implementation in diverse US populations. *Nat. Med.* **30**, 480–487 (2024).
9. Linder, J. E. et al. Returning integrated genomic risk and clinical recommendations: the eMERGE study. *Genet. Med.* **25**, 100006 (2023).
10. Hart, M. R. et al. Secondary findings from clinical genomic sequencing: prevalence, patient perspectives, family history assessment, and health-care costs from a multisite study. *Genet. Med.* **21**, 1100–1110 (2019).
11. Kurki, M. I. et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature* **613**, 508–518 (2023).
12. Hoell, C. et al. Participant choices for return of genomic results in the eMERGE Network. *Genet. Med.* **22**, 1821–1829 (2020).
13. Vears, D. F. et al. Return of individual research results from genomic research: a systematic review of stakeholder perspectives. *PLoS ONE* **16**, e0258646 (2021).
14. Facio, F. M. et al. Intentions to receive individual results from whole-genome sequencing among participants in the ClinSeq study. *Eur. J. Hum. Genet.* **21**, 261–265 (2013).
15. Shahmirzadi, L. et al. Patient decisions for disclosure of secondary findings among the first 200 individuals undergoing clinical diagnostic exome sequencing. *Genet. Med.* **16**, 395–399 (2014).
16. Fabsitz, R. R. et al. Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from a National Heart, Lung, and Blood Institute working group. *Circ. Cardiovasc. Genet.* **3**, 574–580 (2010).
17. Jarvik, G. P. et al. Return of genomic results to research participants: the floor, the ceiling, and the choices in between. *Am. J. Hum. Genet.* **94**, 818–826 (2014).
18. Miller, D. T. et al. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* **25**, 100866 (2023).
19. Lee, K. et al. ACMG SF v3.3 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* **27**, 101454 (2025).
20. National Academies of Sciences, Engineering and Medicine; Health and Medicine Division; Board on Health Sciences Policy & Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories. *Returning Individual Research Results to Participants: Guidance for a New Research Paradigm* (eds Downey, A. S., Busta, E. R., Mancher, M. & Botkin, J. R.) (National Academies Press, 2018).
21. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US Department of Health, Education, and Welfare, 1979).
22. Popejoy, A. B. & Fullerton, S. M. Genomics is failing on diversity. *Nature* **538**, 161–164 (2016).
23. Jooma, S., Hahn, M. J., Hindorff, L. A. & Bonham, V. L. Defining and achieving health equity in genomic medicine. *Ethn. Dis.* **29**, 173–178 (2019).
24. Kohane, I. S. et al. Reestablishing the researcher–patient compact. *Science* **316**, 836–837 (2007).
25. Richardson, H. S. & Belsky, L. The ancillary-care responsibilities of medical researchers. An ethical framework for thinking about the clinical care that researchers owe their subjects. *Hastings Cent. Rep.* **34**, 25–33 (2004).
26. Kaufman, D. J., Baker, R., Milner, L. C., Devaney, S. & Hudson, K. L. A survey of US adults' opinions about conduct of a nationwide precision medicine initiative cohort study of genes and environment. *PLoS ONE* **11**, e0160461 (2016).
27. Facio, F. M. et al. Motivators for participation in a whole-genome sequencing study: implications for translational genomics research. *Eur. J. Hum. Genet.* **19**, 1213–1217 (2011).
28. Darnell, A. J. et al. A clinical service to support the return of secondary genomic findings in human research. *Am. J. Hum. Genet.* **98**, 435–441 (2016).
29. Pike, E. R., Rothenberg, K. H. & Berkman, B. E. Finding fault? Exploring legal duties to return incidental findings in genomic research. *Georgetown Law J.* **102**, 795–843 (2014).
30. Ulrich, M. The duty to rescue in genomic research. *Am. J. Bioeth.* **13**, 50–51 (2013).
31. Beskow, L. M. & Burke, W. Offering individual genetic research results: context matters. *Sci. Transl. Med.* **2**, 38cm20 (2010).
32. Gliwa, C. & Berkman, B. E. Do researchers have an obligation to actively look for genetic incidental findings? *Am. J. Bioeth.* **13**, 32–42 (2013).
33. Wagner, J. W. The Presidential Commission for the Study of Bioethical Issues. *Presentation to the President's Council of Advisors on Science and Technology* https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/pcast-wagner-1-7-2011.pdf (2010).
34. Dorschner, M. O. et al. Actionable, pathogenic incidental findings in 1,000 participants' exomes. *Am. J. Hum. Genet.* **93**, 631–640 (2013).
35. Gold, N. B. & Green, R. C. Reevaluating the 'right not to know' in genomics research. *Genet. Med.* **24**, 289–292 (2022).
36. Andorno, R. The right not to know: an autonomy based approach. *J. Med. Ethics* **30**, 435–439 (2004).
37. Delanne, J. et al. Secondary findings from whole-exome/genome sequencing evaluating stakeholder perspectives. A review of the literature. *Eur. J. Med. Genet.* **62**, 103529 (2019).
38. Kaplan, B. et al. A culture of understanding: reflections and suggestions from a genomics research community board. *Prog. Community Health Partnersh.* **11**, 161–165 (2017).
39. Anderson, J. A. et al. Parents' perspectives on whole genome sequencing for their children: qualified enthusiasm? *J. Med. Ethics* **43**, 535–539 (2017).
40. Appelbaum, P. S. et al. Models of consent to return of incidental findings in genomic research. *Hastings Cent. Rep.* **44**, 22–32 (2014).
41. Blout Zawatsky, C. L. et al. Returning actionable genomic results in a research biobank: analytic validity, clinical implementation, and resource utilization. *Am. J. Hum. Genet.* **108**, 2224–2237 (2021).
42. Bunnik, E. M., Schermer, M. H. & Janssens, A. C. Personal genome testing: test characteristics to clarify the discourse on ethical, legal and societal issues. *BMC Med. Ethics* **12**, 11 (2011).
43. Berg, J. S., Khoury, M. J. & Evans, J. P. Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. *Genet. Med.* **13**, 499–504 (2011).
44. Kaye, J. et al. Dynamic consent: a patient interface for 21st century research networks. *Eur. J. Hum. Genet.* **23**, 141–146 (2015).
45. Sanderson, S. C. et al. Psychological and behavioural impact of returning personal results from whole-genome sequencing: the HealthSeq project. *Eur. J. Hum. Genet.* **25**, 280–292 (2017).

46. Robinson, J. O. et al. Psychological outcomes related to exome and genome sequencing result disclosure: a meta-analysis of seven Clinical Sequencing Exploratory Research (CSER) Consortium studies. *Genet. Med.* **21**, 2781–2790 (2019).
47. Burke, W. et al. Recommendations for returning genomic incidental findings? We need to talk! *Genet. Med.* **15**, 854–859 (2013).
48. Rehm, H. L. et al. ClinGen—the Clinical Genome Resource. *N. Engl. J. Med.* **372**, 2235–2242 (2015).
49. Mersch, J. et al. Prevalence of variant reclassification following hereditary cancer genetic testing. *JAMA* **320**, 1266–1274 (2018).
50. Bombard, Y. et al. The responsibility to recontact research participants after reinterpretation of genetic and genomic research results. *Am. J. Hum. Genet.* **104**, 578–595 (2019).
51. Chan, B. et al. Genomic inheritances: disclosing individual research results from whole-exome sequencing to deceased participants' relatives. *Am. J. Bioeth.* **12**, 1–8 (2012).
52. Wolf, S. M. et al. Pragmatic tools for sharing genomic research results with the relatives of living and deceased research participants. *J. Law Med. Ethics* **46**, 87–109 (2018).
53. Wolf, S. M. et al. Returning a research participant's genomic results to relatives: analysis and recommendations. *J. Law Med. Ethics* **43**, 440–463 (2015).
54. Bonini, K. E., Smith, H. S., Bonkowski, E. S., Berkman, B. E. & Jamal, L. Modern family: an ethical justification for system-led contact of relatives eligible for cascade screening in the United States. *Public Health Genomics* **28**, 19–33 (2025).
55. Wilfond, B. S., Fernandez, C. V. & Green, R. C. Disclosing secondary findings from pediatric sequencing to families: considering the 'benefit to families'. *J. Law Med. Ethics* **43**, 552–558 (2015).
56. Pereira, S. et al. Parents' decision-making regarding whether to receive adult-onset only genetic findings for their children: findings from the BabySeq Project. *Genet. Med.* **25**, 100002 (2023).
57. Murphy Bollinger, J., Bridges, J. F., Mohamed, A. & Kaufman, D. Public preferences for the return of research results in genetic research: a conjoint analysis. *Genet. Med.* **16**, 932–939 (2014).
58. Daack-Hirsch, S. et al. 'Information is information': a public perspective on incidental findings in clinical and research genome-based testing. *Clin. Genet.* **84**, 11–18 (2013).
59. Appelbaum, P. S. et al. Researchers' views on informed consent for return of secondary results in genomic research. *Genet. Med.* **17**, 644–650 (2015).
60. Kleiderman, E. et al. Returning incidental findings from genetic research to children: views of parents of children affected by rare diseases. *J. Med. Ethics* **40**, 691–696 (2014).
61. Madden, J. A. et al. Impact of returning unsolicited genomic results to nongenetic health care providers in the eMERGE III Network. *Genet. Med.* **24**, 1297–1305 (2022).
62. Wynn, J. et al. Clinical providers' experiences with returning results from genomic sequencing: an interview study. *BMC Med. Genomics* **11**, 45 (2018).
63. Ormondroyd, E. et al. 'Not pathogenic until proven otherwise': perspectives of UK clinical genomics professionals toward secondary findings in context of a Genomic Medicine Multidisciplinary Team and the 100,000 Genomes Project. *Genet. Med.* **20**, 320–328 (2018).
64. Hunter, J. E. et al. A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation. *Genet. Med.* **18**, 1258–1268 (2016).
65. Berg, J. S. et al. A semiquantitative metric for evaluating clinical actionability of incidental or secondary findings from genome-scale sequencing. *Genet. Med.* **18**, 467–475 (2016).
66. Schwartz, M. L. B. et al. A model for genome-first care: returning secondary genomic findings to participants and their healthcare providers in a large research cohort. *Am. J. Hum. Genet.* **103**, 328–337 (2018).
67. eMERGE Clinical Annotation Working Group. Frequency of genomic secondary findings among 21,915 eMERGE network participants. *Genet. Med.* **22**, 1470–1477 (2020).
68. Gallego, C. J. et al. Penetrance of hemochromatosis in *HFE* genotypes resulting in p.Cys282Tyr and p.[Cys282Tyr];[His63Asp] in the eMERGE Network. *Am. J. Hum. Genet.* **97**, 512–520 (2015).
69. Richards, S. et al. Standards and guidelines for the interpretation of sequence variants. *Genet. Med.* **17**, 405–424 (2015).
70. van Lint, F. H. M. et al. Large next-generation sequencing gene panels in genetic heart disease: yield of pathogenic variants and variants of unknown significance. *Neth. Heart J.* **27**, 304–309 (2019).
71. Pottinger, T. D. et al. Pathogenic and uncertain genetic variants have clinical cardiac correlates in diverse biobank participants. *J. Am. Heart Assoc.* **9**, e013808 (2020).
72. Costa, S. et al. Impact of genetic variant reassessment on the diagnosis of arrhythmogenic right ventricular cardiomyopathy based on the 2010 Task Force criteria. *Circ. Genom. Precis. Med.* **14**, e003047 (2021).
73. Quiat, D., Witkowski, L., Zouk, H., Daly, K. P. & Roberts, A. E. Retrospective analysis of clinical genetic testing in pediatric primary dilated cardiomyopathy: testing outcomes and the effects of variant reclassification. *J. Am. Heart Assoc.* **9**, e016195 (2020).
74. Carrieri, D. et al. Recontacting patients in clinical genetics services: recommendations of the European Society of Human Genetics. *Eur. J. Hum. Genet.* **27**, 169–182 (2019).
75. Kullo, I. J. Clinical use of polygenic risk scores: current status, barriers and future directions. *Nat. Rev. Genet.* **27**, 246–263 (2026).
76. Lawson, L. P. et al. Return of genome-informed risk-assessment results for common conditions to 23,840 adults and children: an eMERGE network study. *Am. J. Hum. Genet.* **113**, 678–691 (2026).
77. Limdi, N. et al. The Electronic Medical Records and Genomics study: design and analytic framework for assessing the impact of genome-informed risk assessments. *Am. J. Hum. Genet.* **113**, 664–677 (2026).
78. Mars, N. et al. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. *Nat. Med.* **26**, 549–557 (2020).
79. Mars, N. et al. Systematic comparison of family history and polygenic risk across 24 common diseases. *Am. J. Hum. Genet.* **109**, 2152–2162 (2022).
80. Ripatti, S. et al. A multilocus genetic risk score for coronary heart disease: case–control and prospective cohort analyses. *Lancet* **376**, 1393–1400 (2010).
81. Widén, E. et al. How communicating polygenic and clinical risk for atherosclerotic cardiovascular disease impacts health behavior: an observational follow-up study. *Circ. Genom. Precis. Med.* **15**, e003459 (2022).
82. Ahmad, H., Jahn, N. & Jaiswal, S. Clonal hematopoiesis and its impact on human health. *Annu. Rev. Med.* **74**, 249–260 (2023).
83. Cohn, I., Cohn, R. D. & Ito, S. Professional opportunity for pharmacists to integrate pharmacogenomics in medication therapy. *Can. Pharm. J.* **151**, 167–169 (2018).
84. Haga, S. B., Burke, W., Ginsburg, G. S., Mills, R. & Agans, R. Primary care physicians' knowledge of and experience with pharmacogenetic testing. *Clin. Genet.* **82**, 388–394 (2012).
85. Kodida, R. et al. A model for the return and referral of all clinically significant secondary findings of genomic sequencing. *J. Med. Genet.* **60**, 733–739 (2023).

86. Grzymski, J. J. et al. Population genetic screening efficiently identifies carriers of autosomal dominant diseases. *Nat. Med.* **26**, 1235–1239 (2020).
87. Ohneda, K. et al. A pilot study for return of individual pharmacogenomic results to population-based cohort study participants. *JMA J.* **5**, 177–189 (2022).
88. Wiesner, G. L. et al. Returning results in the genomic era: initial experiences of the eMERGE Network. *J. Pers. Med.* **10**, 30 (2020).
89. Abul-Husn, N. S. et al. Implementing genomic screening in diverse populations. *Genome Med.* **13**, 17 (2021).
90. Beri, N. et al. Preferences for in-person disclosure: patients declining telephone disclosure characteristics and outcomes in the multicenter Communication Of GENetic Test Results by Telephone study. *Clin. Genet.* **95**, 293–301 (2019).
91. Bradbury, A. R. et al. Randomized noninferiority trial of telephone vs in-person disclosure of germline cancer genetic test results. *J. Natl Cancer Inst.* **110**, 985–993 (2018).
92. Brown, E. G. et al. Videoconferencing to deliver genetics services: a systematic review of telegenetics in light of the COVID-19 pandemic. *Genet. Med.* **23**, 1438–1449 (2021).
93. Savatt, J. M. et al. Testing and management of iron overload after genetic screening-identified hemochromatosis. *JAMA Netw. Open* **6**, e2338995 (2023).
94. All of Us Research Program Investigators. The 'All of Us' Research Program. *N. Engl. J. Med.* **381**, 668–676 (2019).
95. Ramirez, A. H. et al. The All of Us Research Program: data quality, utility, and diversity. *Patterns* **3**, 100570 (2022).
96. Bombard, Y. et al. The Genomics ADvISER: development and usability testing of a decision aid for the selection of incidental sequencing results. *Eur. J. Hum. Genet.* **26**, 984–995 (2018).
97. Bracke, X., Roberts, J. & McVeigh, T. P. A systematic review and meta-analysis of telephone vs in-person genetic counseling in *BRCA1*/*BRCA2* genetic testing. *J. Genet. Couns.* **30**, 563–573 (2021).
98. Rana, H. et al. Patient and clinician perspectives on a digital health platform for the longitudinal management of genetic cancer predisposition. *Genet. Med. Open* **2** (Suppl. S1), 101416 (2024).
99. Schmidlen, T. et al. Use of a chatbot to increase uptake of cascade genetic testing. *J. Genet. Couns.* **31**, 1219–1230 (2022).
100. Sebastian, A. et al. Effect of genetics clinical decision support tools on health-care providers' decision making: a mixed-methods systematic review. *Genet. Med.* **23**, 593–602 (2021).
101. Shickh, S. et al. The role of digital tools in the delivery of genomic medicine: enhancing patient-centered care. *Genet. Med.* **23**, 1086–1094 (2021).
102. Lee, W. et al. Patient-facing digital tools for delivering genetic services: a systematic review. *J. Med. Genet.* **60**, 1–10 (2023).
103. Hallquist, M. L. G. et al. Application of a framework to guide genetic testing communication across clinical indications. *Genome Med.* **13**, 71 (2021).
104. Hoskovec, J. M. et al. Projecting the supply and demand for certified genetic counselors: a workforce study. *J. Genet. Couns.* **27**, 16–20 (2018).
105. Pilling, L. C. et al. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. *BMJ* **364**, k5222 (2019).
106. Clapp, S. W. et al. *APOL1* monoallelic and biallelic genotypes and CKD, proteinuria and FSGS in African Americans from the Vanderbilt Biobank (BioVU). Preprint at *medRxiv* https://doi.org/10.1101/2025.11.05.25339478 (2025).
107. Jacobson, D. R., Alexander, A. A., Tagoe, C. & Buxbaum, J. N. Prevalence of the amyloidogenic transthyretin (*TTR*) V122I allele in 14,333 African-Americans. *Amyloid* **22**, 171–174 (2015).
108. Nadkarni, G. N. et al. Effects of testing and disclosing ancestry-specific genetic risk for kidney failure on patients and health care professionals: a randomized clinical trial. *JAMA Netw. Open* **5**, e221048 (2022).
109. Shirts, B. H. et al. 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 (2015).
110. Rasmussen, L. V. et al. Practical considerations for implementing genomic information resources. Experiences from eMERGE and CSER. *Appl. Clin. Inform.* **7**, 870–882 (2016).
111. Horowitz, C. R. et al. The genomic medicine integrative research framework: a conceptual framework for conducting genomic medicine research. *Am. J. Hum. Genet.* **104**, 1088–1096 (2019).
112. Shaibi, G. Q. et al. Returning genomic results in a federally qualified health center: the intersection of precision medicine and social determinants of health. *Genet. Med.* **22**, 1552–1559 (2020).
113. Landry, L. G., Ali, N., Williams, D. R., Rehm, H. L. & Bonham, V. L. Lack of diversity in genomic databases is a barrier to translating precision medicine research into practice. *Health Aff.* **37**, 780–785 (2018).
114. Joffe, S. et al. Preferences for return of genetic results among participants in the Jackson Heart Study and Framingham Heart Study. *Circ. Genom. Precis. Med.* **12**, e002632 (2019).
115. Taylor, H. A. Jr. et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn. Dis.* **15**, S6-4-17 (2005).
116. Lewis, K. L. et al. Engagement and return of results preferences among a primarily African American genomic sequencing research cohort. *Am. J. Hum. Genet.* **108**, 894–902 (2021).
117. Venner, E. et al. Whole-genome sequencing as an investigational device for return of hereditary disease risk and pharmacogenomic results as part of the All of Us Research Program. *Genome Med.* **14**, 34 (2022).
118. Naderian, M., Norland, K., Schaid, D. J. & Kullo, I. J. Development and evaluation of a comprehensive prediction model for incident coronary heart disease using genetic, social, and lifestyle-psychological factors: a prospective analysis of the UK Biobank. *Ann. Intern. Med.* **178**, 1–10 (2025).
119. Norland, K., Schaid, D. J., Naderian, M., Na, J. & Kullo, I. J. Associations of self-reported race, social determinants of health, and polygenic risk with coronary heart disease. *J. Am. Coll. Cardiol.* **84**, 2157–2166 (2024).
120. Saban, K. L., Mathews, H. L., DeVon, H. A. & Janusek, L. W. Epigenetics and social context: implications for disparity in cardiovascular disease. *Aging Dis.* **5**, 346–355 (2014).
121. Harrison, S. M. et al. Harmonizing variant classification for return of results in the All of Us Research Program. *Hum. Mutat.* **43**, 1114–1121 (2022).
122. Leppig, K. A. et al. The reckoning: the return of genomic results to 1444 participants across the eMERGE3 Network. *Genet. Med.* **24**, 1130–1138 (2022).
123. Tsao, C. W. & Vasan, R. S. Cohort profile: the Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology. *Int. J. Epidemiol.* **44**, 1800–1813 (2015).
124. Andersson, C., Johnson, A. D., Benjamin, E. J., Levy, D. & Vasan, R. S. 70-year legacy of the Framingham Heart Study. *Nat. Rev. Cardiol.* **16**, 687–698 (2019).
125. Carey, D. J. et al. The Geisinger MyCode community health initiative: an electronic health record-linked biobank for precision medicine research. *Genet. Med.* **18**, 906–913 (2016).
126. Smith, E. J., Hill, M., Chitty, L. S. & Morris, S. Costs and cost-effectiveness of returning secondary findings from genomic sequencing based on the return of additional findings in the 100,000 Genomes Project. *Genet. Med.* **27**, 101479 (2025).

127. Relling, M. V. et al. The Clinical Pharmacogenetics Implementation Consortium: 10 years later. *Clin. Pharmacol. Ther.* **107**, 171–175 (2020).
128. Corcoran, R. B. & Chabner, B. A. Application of cell-free DNA analysis to cancer treatment. *N. Engl. J. Med.* **379**, 1754–1765 (2018).
129. Kirin, M. et al. Genomic runs of homozygosity record population history and consanguinity. *PLoS ONE* **5**, e13996 (2010).
130. Gorman, G. S. et al. Mitochondrial diseases. *Nat. Rev. Dis. Primers* **2**, 16080 (2016).
131. Armanios, M. & Blackburn, E. H. The telomere syndromes. *Nat. Rev. Genet.* **13**, 693–704 (2012).

Acknowledgements

This article is based on the proceedings of an NHLBI-sponsored 2-day virtual workshop titled 'Return of Individual Research Results to Participants in Observational Cohort Studies' in June 2024. This workshop was organized in collaboration with the National Human Genome Research Institute, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Diabetes and Digestive and Kidney Diseases and the All of Us Research Program. The views expressed by the National Institutes of Health (NIH)-employed authors are those of these authors and do not necessarily represent those of the NIH.

Author contributions

I.J.K. and C.R.H. conceived and drafted the manuscript. I.J.K., C.R.H., L. Bastarache, B.B., L. Biesecker, K.B., A.P.C., K.D., R.A.G., R.C.G., H.H., C.H., J.E.L., G.P.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. and R.I.Y. contributed to workshop discussions and the draft, critically revised the manuscript and approved the final version.

Competing interests

I.J.K. is on the advisory boards for Illumina and InformedDNA and is founder of ARC-OMIX. R.C.G. receives compensation for advising Allelica, Fabric and Genomic Life and is cofounder of Genome Medical and Nurture Genomics. R.A.G. has equity in Codified Genomics. L. Biesecker receives honoraria from Wolters Kluwer, receives research support from Merck and is a member of the Ambry medical advisory committee. L. Bastarache receives royalties from Nashville Biosciences. H.H. is on the scientific advisory board of Ambry Genetics and LynSight. The other authors declare no competing interests.

Additional information

Correspondence should be addressed to Iftikhar J. Kullo.

Peer review information *Nature Genetics* thanks Ellen Clayton and Bartha Knoppers for their contribution to the peer review of this work.

[1]Medical College of Wisconsin, Milwaukee, WI, USA. [2]Institute for Health Equity Research, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [3]Vanderbilt University Medical Center, Nashville, TN, USA. [4]National Institutes of Health, Bethesda, MD, USA. [5]Norton Children's Research Institute Affiliated with the University of Louisville School of Medicine, Louisville, KY, USA. [6]University of Mississippi Medical Center, Jackson, MS, USA. [7]Columbia University Medical Center, New York, NY, USA. [8]Baylor College of Medicine, Houston, TX, USA. [9]Ariadne Labs, Boston, MA, USA. [10]Harvard Medical School, Boston, MA, USA. [11]Mass General Brigham, Boston, MA, USA. [12]Broad Institute, Cambridge, MA, USA. [13]City of Hope National Medical Center, Duarte, CA, USA. [14]The Blue Hat Foundation, Chicago, IL, USA. [15]University of Washington, Seattle, WA, USA. [16]Northwestern University, Chicago, IL, USA. [17]National Jewish Health, Denver, CO, USA. [18]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland. [19]Bethel Gospel Assembly, New York, NY, USA. [20]Geisinger, Danville, PA, USA. [21]Center for Health Promotion and Disease Prevention, Edson College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ, USA. [22]Center for Biomedical Research at Tuskegee University, Tuskegee, AL, USA. [23]Story Wise Science, Baltimore, MD, USA. [24]National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA. [25]These authors contributed equally: Iftikhar J. Kullo, Carol R. Horowitz, Ye Yan, Ronit I. Yarden. ✉e-mail: ikullo@mcw.edu