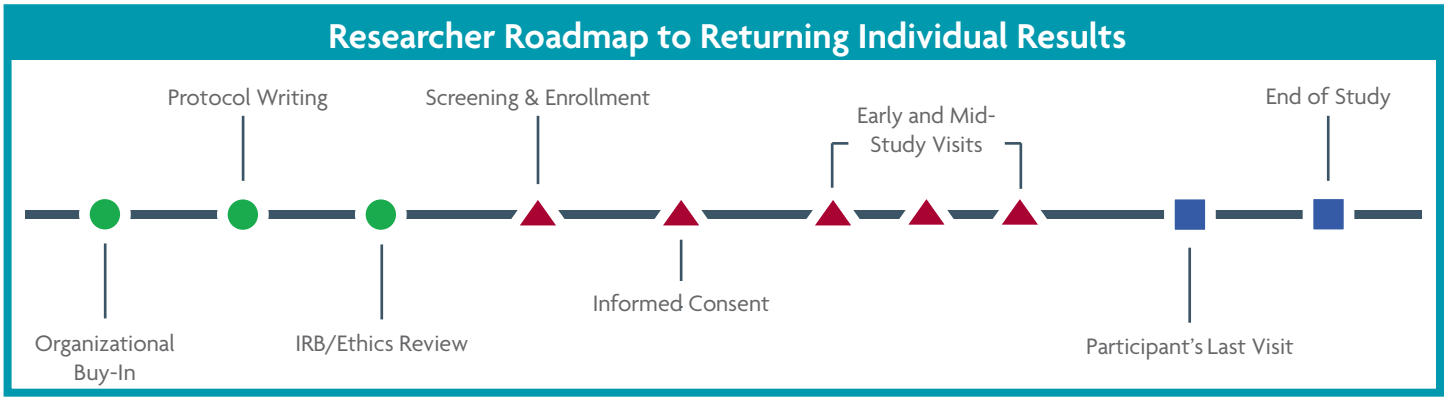
MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Responsibly Returning Secondary Findings

This case details the experience of a research team returning secondary findings to participants in a genetic testing study.



The roadmap above shows steps for researchers to consider when planning to return individual results to participants. This case study focuses on the pre- and on-study parts of the timeline illustrated by the green circles and red triangles.

Background

This case details the experience of a research team studying a group of serious disorders, termed Inherited Bone Marrow Failure Syndrome (IBMFS), characterized by the failure of bone marrow to produce blood. IBMFS has a significant risk of progressing to cancer (such as leukemia and lymphoma) and typically has an underlying inherited genetic cause. A study was designed to identify underlying inherited genetic causes of IBMFS in families with multiple affected members.

During the design of the study, the research team planned to return individual genetic testing results of IBMFS-related genes to participants. As a consequence of genetic sequencing, the team anticipated that they might discover unrelated but important genetic findings that may need to (or should) be returned to participants. During the research study, genetic sequencing revealed that an adult female patient had a previously undiscovered pathogenic variant in *BRCA1*, a gene that can (but may not) cause disease. Pathogenic variants in *BRCA1* can lead to Hereditary Breast and Ovarian Cancer syndrome, an adult-onset disorder with increased risk of breast and ovarian cancer in females, male breast cancer, and several other cancer risks.

Secondary findings are genetic test results that provide information about variants in genes unrelated to the primary purpose of the testing.

Approach

Anticipating unrelated but potentially important genetic findings, the research team was able to implement the following structured approach to return secondary findings to participants. The plan outlined a clear path for the research team to implement when secondary findings arose, reducing the need for ethical and legal consultations while the study was ongoing. Not only did the planning save time and resources, but most importantly, it protected the rights, health, and wellbeing of the research participants. Based on experience, the research team advised that any plan for the return of secondary genetic findings include detailed guidance on:

Topic	Questions to Consider	Practical Implementation
Data Analysis	• How will the genetic data be analyzed? • How long after data collection will samples be analyzed? • Will data be interrogated for secondary findings once or repeatedly and at what interval?	Detailed description of data sequencing, annotation, and analysis plan.
Clinical Laboratory Improvement Amendments (CLIA) Confirmation (US):	• If the original sequencing was not performed in a CLIA-approved laboratory, will the secondary findings be confirmed in a CLIA-approved laboratory? • Who will pay for the additional testing?	Procedure, study staff, and infrastructure to contact participants to obtain a second sample for CLIA-confirmation. Obtaining and paying for testing detailed in the informed consent: either confirmatory testing paid by research funds or clarity that participants will be responsible for arranging and/or paying for CLIA-approved laboratory confirmation.
Which Results to Return	• What type of results will be returned? Medically/clinically actionable? Those with reproductive risk implications? Only pathogenic/likely pathogenic variants? Variants of uncertain clinical significance? • What are the benefits and risks of sharing this information with participants? • Does the study provide for participants to opt out of receiving secondary findings?	Clear communication in both research protocol and informed consent as to which results will be returned and which will not. Consider a tiered consent: does the participant want all results returned whether or not they are actionable? Only actionable results? Only results directly related to the primary research question? Make clear to participants both in the consent process and thereafter that many results cannot or are not returned (e.g., research-grade testing, incomplete sequencing, time frame of analysis) so no assumptions should be made as to the presence or absence of any particular variant. If there is a clinical concern, referral for appropriate clinical genetic risk assessment and testing should be recommended.
Timeframe for Sharing Results	• Should results be returned after the study is completed, after interim analyses, or immediately? • Does the type of finding influence when participants should be notified?	Clear plan in the protocol and consents based on study infrastructure and capabilities.
Communicating with Participants and Follow-up Care	• What is the plan and infrastructure for providing results and any necessary follow-up care? • Do participants' healthcare providers or other medical professionals also receive results? Did the participant grant permission for such return? • Who is the most appropriate person to communicate the results to the patients? • What kind of counseling or educational framework is in place to support and educate patients about their results?	Some studies may have study personnel such as a nurse or genetic counselor who can facilitate return of results, answer questions, and coordinate appropriate follow up. Some studies may plan to return results directly to the participant's healthcare provider who would then coordinate appropriate follow up and management. Participants should understand who will or may have access to their genomic results as well as the potential medical and psychosocial risks, benefits, and limitations of receiving genomic results. Implications for family members, risk to children, undisclosed paternity, risks for life insurance coverage and other issues should all be considered *prior to electing to return or receive results.*

Topic	Questions to Consider	Practical Implementation
Data Storage and Access	• Where is genomic data stored? • Who has access to it? • How long are data stored?	Clear plan for data storage and access, with attention to confidentiality and security, should be outlined in the research protocol and consent.

The team relied on the American College of Medical Genetics and Genomics (ACMG) list for reporting of secondary findings and the joint consensus recommendations from the ACMG and Association of Molecular Pathology (AMP) to guide them on which specific genetic variants to return. Click here and here to view.

When the pathogenic *BRCA1* variant was found, the study team began the process of confirming and returning the result as described in the study protocol and informed consent document.

The participant was contacted and informed that a result was found in the research sequencing that had potential health implications. She elected to proceed with confirmatory testing and to obtain the result. For confirmation in a CLIA-approved laboratory, a second blood sample was requested and obtained. Single-site analysis of the *BRCA1* variant on the new sample confirmed its presence, and the participant was contacted with the results by the study's genetic counselor. After obtaining consent to share the result, the research team provided a copy of the test report to the participant's healthcare physician who facilitated referral of the participant to a high-risk genetics clinic at a local cancer center for appropriate management.

The participant underwent a screening mammogram which was normal. She ultimately chose to undergo prophylactic mastectomy and removal of her ovaries and fallopian tubes from which an occult ovarian cancer was diagnosed and treated.

Outcomes

Thanks to the foresight of and preparation by this team, a framework existed for the return of secondary genomic findings unrelated to the primary research objective. The framework and approach detailed each step while respecting the autonomy of the participant. In this case study, the information positively impacted the health and wellbeing of the participant.

Genomic researchers should develop a proactive strategy when planning their studies to be prepared for secondary findings if identified. Research participants should be informed of the possibility of secondary findings and understand the notification process, should secondary findings arise.

Institutions should support their researchers in developing policies and provide appropriate infrastructure and funding for returning individual results. Similarly, researchers (and sponsors) should anticipate the possibility, develop a plan before the situation arises and revise the plan as needed.

Key Takeaways

Integrate planning for the return of secondary findings into the overall study design.

Leverage existing guidance documents and recommendations to develop (1) an institutional policy and (2) a study-specific plan.

Consider and secure resources necessary for execution of the plan.

Ensure participants are given adequate information and support to understand and act on secondary findings.