7. SPECIAL CONSIDERATIONS: RETURNING GENOMIC RESULTS

The development of this *Recommendations Document* for Returning Individual Results illuminated certain conditions that demanded special consideration. Specifically, the complexity of – and the dynamic and growing understanding of – genetic (the study of specific genes) and genomic (the study of an organism's entire genetic makeup) information requires further discussion.

Genetic results may have implications for family and related individuals, a consideration that does not apply generally to other types of results that may be returned, and that have been considered above. We hold to the idea that **the overall principles and considerations for returning individual results to clinical trial participants (Section 5 and Section 6) can and will apply to genetic and genomic results**. The complexity, novelty, national and state/local regulations of clinical laboratories, and evolving nature of the genetic information, however, will require decisions to be made on a case-by-case basis. This chapter is a conceptual discussion rather than a set of additional principles.

Genetic information produced in a clinical trial context is often generated as a result of exploratory research, meaning that a direct association between the genomic variation(s) identified and clinical response is still being hypothesized, tested and validated. It follows that these exploratory results can be generated during the study, years after the end of the study or, in some cases, both. Therefore, it is necessary to discuss the responsibility of the trial sponsors investigators, research institutions and trial investigators to return exploratory data and the timeframe during which they may be provided.

In this section, we begin by discussing, briefly, the nature and significance of genetic information, provide an overview of genomics techniques, discuss why the return of genetic information requires special consideration, and offer specific informed consent content and questions. We then describe what and how results should be returned, as well as some recommendations about who should return genetic results. Finally, we consider national laws and regulations that apply specifically to this evolving area of research.

7.1 Complexity of Genetic Information

DNA provides information for the growth, development, and biochemistry of humans and all other living organisms. Human genetic mutation is an essentially random process of change in DNA sequence that occurs during the replication of DNA within cells. Such mutation can occur in the germline (the source of DNA for all other cells in the body, originating from the egg and sperm cells that join to form an embryo), in which case it is expected to be found in all nucleated cells of the offspring that inherits it. Germline

mutations may occur *de novo,* in the process of egg or sperm cell formation, or they may be inherited and can result in, or predispose to, various genetic syndromes or diseases.

DNA mutation could also be somatic, meaning that it occurs after conception and therefore cannot be passed on to children. Somatic mutations can happen during normal cell division or as a result of environmental insult (e.g., UV-radiation, carcinogen exposure). While the cellular DNA-repair machinery generally repairs somatic mutations, when this repair does not occur as it should, the end result can be as significant as the development of cancer in one or more areas of the body. However, most genetic variation does not lead to disease and is largely insignificant in the life of the individual.

Genetic information has been characterized in the scientific literature, the popular press, and popular ethical discourse as fundamentally different from other kinds of biological data. The decoding of the human genome resulted in rapid advances in science and medicine and has propelled insights into human disease and variation in drug response. There is already evidence in dozens of drug labels of the contributions genomic research can make to drug development, efficacy, metabolism, and delivery (U.S. Food and Drug Administration, 2017). This research is making a contribution to a personalized approach to the practice of medicine.

Compared to other medical information generated during a clinical trial, however, genetic information has broader implications than standard medical test results. A blood test or x-ray provides static knowledge at the point of time it is collected. To understand changes in health, subsequent blood tests and imaging would need to be done. Inherited or germline genetic information, however, is stable: it is our understanding of the significance of genetic variants, association to disease, and risk that is constantly being refined. Similarly, understanding somatic mutations in the context of disease (e.g., cancer) is also critically important—and also an evolving science. It is therefore important to weigh the present, and potential future, utility of genetic data along with the uncertainty of their current interpretation when determining a patient's current and future health risks. Genetic information may also have implications for immediate family members and a patient's future reproductive decisions, and these added complexities must be considered.

The debate continues as to whether these considerations are sufficient reason to grant special status to genetic information, a position often referred to as "genetic exceptionalism." Special laws and policies have already been established to require specific consent for genetic testing and for the disclosure of genetic information, and to disallow the use of genetic information to refuse employment and/or other social benefits. The United States Congress passed the Genetic Information Non-Discrimination Act of 2008 (GINA) to prohibit the use of genetic information in health insurance and employment decisions, and many other countries have similar regulations.

While, in theory, it would seem straightforward to provide individual genetic results upon request, it is a much harder task in practice. Individual genetic results that are both reliable and significant to an individual's health should, in general, be returned to individuals consistent with their wishes, according to the principles explored in Section 5, assuming that doing so is consistent with applicable law.

In some cases, however, we must also respect a patient's right to refuse such results, even if highly relevant. Those who refuse will cite many of the same reasons as people who wish to receive these results, such as the aforementioned implications for family members, the lack of clarity around medical implications, and in some instances, the lack of medical actionability. This difference of opinion amongst trial participants should remind the research team that their own personal values should not be assumed to be the same as the personal values of the trial participant and that genetic information should, or should not, be returned based on the participant's values and express wishes.

The comprehensive content, potential predictive power for future disease phenotypes, and familial nature of the human genome are important points to consider in decisions about the return of research results. However, as stated under Principle 6, clinical investigators do not have an ongoing responsibility to seek out participants after the trial is over to inform them of secondary findings or results that subsequently become known to be significant. The complex relationship between the sponsor, investigator, research participant and primary care provider make delivery of genetic research results particularly difficult especially since these results are often generated years after a clinical trial has been completed, participants may be difficult to contact, and access to genetic counseling and other services has a limited global reach.

7.2 Influence of Technologies on Genetic Information

7.2.1 Genotyping Technologies are Numerous and Diverse

Understanding available genetic technologies, the breadth of data that they generate, the bioinformatics and computational tools used to interrogate and analyze this data to answer research questions provides further appreciation for why returning genetic data is complex.

a. **Sanger sequencing** was the first widely used form of DNA sequencing, is a valuable research tool due to its accuracy, and due to high cost and low throughput, is used primarily for the interrogation of smaller DNA fragments.

b. **Microarray technology** allows simultaneous genotyping of many thousands of single nucleotide polymorphisms (SNPs). In addition, the application of statistical imputation techniques predict the presence of millions of variants not directly genotyped, thus providing a discovery tool to understand the relationship between genetic variation, disease, and drug response.

c. Microarray technology has allowed **genome-wide association studies** (GWAS) to successfully identify thousands of common genetic risk factors for hundreds of different diseases (http://www.ebi.ac.uk/gwas/). Common variants can describe one's relative risk of developing conditions such as type 2 diabetes, Crohn's disease, macular degeneration, and Alzheimer disease. However, genetic risk factors tend to be numerous and of weak or modest penetrance; thus, they rarely have a clear or compelling clinical utility for individual patients at this time.

d. **Next Generation sequencing** (NGS) technology has enabled scalable, simultaneous DNA sequencing reactions in parallel (Mardis, 2017), and is revolutionizing our understanding of the human genome. NGS enables sequencing of whole genomes or exomes and is currently the diagnostic method of choice when many genes or entire genomes must be interrogated for disease-causing mutations (Katsanis & Katsanis, 2013). NGS enables researchers to study common and rare genetic variation. However, buried within the large breadth of genomic data generated by NGS may lie predictors or determinants of a wide array of genetic conditions that can present throughout the lifespan. Thus, the increasingly routine approach of NGS in research, where the analysis aims to identify variants associated with a particular disease or drug response, heightens the probability of "incidental findings" related to undiagnosed, prodromal, or future disease, and the discovery of variants of unknown significance.

Due to the type of genetic information generated from some of these technologies, there is the possibility of encountering genetic mutations that are unrelated to the primary research question but are associated with a known inherited genetic condition. The term "incidental findings" is used to describe findings that are not being sought as a goal of research, but are discovered in the course of genetic data analysis; "secondary findings" are sought specifically in addition to the primary reason for genotyping (e.g., clinical diagnosis, exploratory research, etc.) (Anastasova, Blasimme, Julia, & Cambon-Thomsen, 2013). Whether a researcher is ethically obligated to interrogate a list of known genomic mutations that are associated with risks for developing serious and treatable genetic conditions is debated. If as part of a primary or secondary objective, the decision is made to perform an analysis for known genetic mutations, the list should be defined in advance of the research, if possible,[45] and detailed in the consent form. The participant should consent to the analysis and agree, or not, to learn of findings that are of interest to them. Similarly, if researchers do not intend to perform a search for known genetic mutations

[45] There are times, of course, when creating a list in advance of the research will not be possible. For example, having performed next generation genome sequencing, emerging science may prompt, or a regulatory agency may request, the research to return to the data to test retrospectively for the presence or absence of a mutation.

that are medically actionable, the consent form and process should clearly explain the limited study to which the participant consents.

Whether or not (and how best) to report incidental or secondary findings has been a topic of recent intense debate and discussion, particularly in the American College of Medical Genetics (ACMG), revolving around five main considerations: (1) analytical validity (Rehm et al., 2013); (2) clinical validity (Richards et al., 2015); (3) medical actionability (Kalia et al., 2017); (4) patient and physician preferences (Brothers et al., 2017); and (5) practical considerations including communication of information, health policy implications, and implementation in various settings (e.g., clinical care vs. various research contexts). Of these, the first three considerations are primarily "technical" in nature and are covered below, being functions of diagnostic technology, data analytics, and the clinical genotype-phenotype evidence base, noting that our understanding of the significance of secondary (and incidental) genetic findings is constantly evolving. Regarding the patient and physician preferences, the ACMG has revised its earlier position of mandatory analysis and return of results, in favor of offering to patients an opt-out of the analysis and return of incidental findings. There has been further discussion of the implementation of return of results in research settings. Notably, members of the Clinical Sequencing Exploratory Research (CSER) Consortium and eMERGE (Electronic Medical Records and Genomics) committees 46 discussed and identified areas of consensus regarding the return of results to research participants. They have written that research investigators should return results and incidental findings that are discovered in the course of their research, that are actionable (see Section 7.2.4 below) and for which participants have consented to receipt, with referral for appropriate clinical follow up. Researchers have no obligation to search actively for results and research participants have the option to decline receipt of genomic results, even when doing so might threaten their health. Remaining major area of controversy are the return of pathogenic variants for adult-onset conditions to children, the role of CLIA compliance (see Section 7.7.1) and the optimal methods of return (Jarvik et al., 2014).

7.2.2. Analytical Validity

Do genotyping results effectively detect the presence or absence of genetic mutation?

The term "analytical validity" in genetics refers to the degree to which a laboratory assay accurately determines a genotype of interest. The performance of genotyping assays is assessed in terms of analytical sensitivity and analytical specificity. The analytical sensitivity is the "proportion of biological samples that have a positive test result or known mutation and that are correctly classified as positive" (Rehm et al., 2013). The analytical specificity is the "proportion of biological samples that have a negative test result or no

[46] eMERGE (Electronic Medical Records and Genomics) is a US National Human Genome Research Institute (NHGRI)-organized network that couples DNA biorepositories with electronic medical record (EMR) systems for large scale, high-throughput genetic research in support of implementing genomic medicine (https://emerge.mc.vanderbilt.edu). See also (Jarvik et al., 2014) for additional considerations.

identified mutation (being tested for) and that are correctly classified as negative" (Rehm et al., 2013).

If performed according to benchmark quality standards (Rehm et al., 2013), genotyping assays can be of sufficient analytical validity to support high-confidence molecular diagnosis for nearly all disorders caused by single nucleotide mutations throughout most of the human genome. Importantly, procedures should be in place to ensure that the analyzed sample is actually from the person it is believed to be from (Viberg et al., 2014) and the results should be independently confirmed for accuracy (Nuffield Council on Bioethics, 2003). Quality metrics should also be reported in language understandable to the recipient of genetic data. For certain regions of the genome (e.g., within highly repetitive DNA sequence), and for certain types of mutations (e.g., trinucleotide repeats, copy number alteration, insertion-deletions, or somatic mosaic mutations present in only a small percentage of DNA molecules in a sample), the sensitivity of genotyping assays such as NGS and microarray may be reduced compared to methods specifically designed to test the variant in question. Specificity can likewise be suboptimal even for a single nucleotide variant call,[47] for example when there exists another gene with high sequence similarity that creates ambiguity about the true location of the mutation.

7.2.3 Clinical Validity

Is a given mutation pathogenic in a particular patient, and if so, what is the probability that it explains an existing disease phenotype or will increase risk of disease in the future?

When DNA sequencing is applied for the diagnosis of rare diseases, molecular geneticists, genetic counselors, clinical geneticists, bio-informaticians, and physicians with sub-specialty expertise generally work together as a clinical interpretation team. Incidental and secondary genetic findings in clinical research are equally likely to require a multi-disciplinary team approach to determine relevance to individual research subjects. The key categories into which pathogenicity criteria fit are complex.[48] Although bioinformatics

[47] Variant calling is the process of assigning specific genotypes at each analyzed nucleotide. For example, in NGS, a key parameter for maximization of sensitivity and specificity is "depth of coverage," meaning the number of times that a given nucleotide is included when the innumerable "short reads" are matched up to the human genome reference sequence. The more times a mutation is observed, the more likely it is to be a true mutation rather than an error. A mean read depth of 30X for whole genomes or about 100X for exome analysis generally produces a "quality threshold" > 95% of nucleotides being re-sequenced at least 10X. The greater read depth for exomes is to compensate for uneven capture and enrichment of different sections of the exome, and a small percentage of the exome is not captured at all by exome sequencing. Thus, a subset of patients with genetic disorders may potentially have an exonic mutation detected by whole genome sequencing if prior exome sequencing failed to detect a pathological mutation to explain the patient's phenotype.

[48] Pathogenicity criteria include data on the relative frequencies of a particular mutation in diseased versus non-disease populations, functional impact of the mutation in relation to known disease mechanisms, co-segregation of mutation with disease in families, appearance as a *de novo* mutation in an affected child but neither parent, and finally, the details of the specific allele (i.e.,

tools[49] can automate certain standardized functions designed to characterize and annotate the likely effects of mutations, a holistic human judgment considering the totality of evidence for and against pathogenicity of particular mutations remains the gold standard in support of medical decision-making.

Critically, experts often disagree about the classification of mutations. In a recent study involving nine molecular diagnostic laboratories in the Clinical Sequencing Exploratory Research (CSER) consortium (Amendola et al., 2016), labs were challenged with 99 selected mutations spanning all clinical significance categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign). Discordant categorization of mutations persisted even after extensive discussion for 29 (29%) of the 99 variants assessed in the CSER study, and 5 of the 29 involved a difference substantial enough to affect medical management. At some point in the future, a critical mass of empirical genotype-phenotype correlation data will permit precise probabilistic disease risk estimation. Without such real-world quantitative data, however, legitimate differences of opinion among experts will persist. As we have stated in Principle 6, there is no ongoing responsibility to re-interpret genetic or genomic analyses performed for research. That said, scientific understanding is advancing, and while the appreciation of clinical significance[50] may change over time, the limitations of the research must be communicated effectively to participants and their primary physicians.

7.2.4 Medical Actionability

Can a genetic diagnosis potentially alter clinical management of the patient and lead directly to improved medical outcomes?

Even in the clinical genetic setting, there is no professional consensus on how secondary findings should be handled, although the American College of Medical Genetics and Genomics and others have made important preliminary contributions to the ongoing debate. Pathologically mutated genes are considered "medically actionable" if important diagnostic, prognostic, or therapeutic decisions pivot on the genetic finding (Kalia et al., 2017). In many cases, a presumed deleterious mutation may be the only known sign that the patient has the condition in question, and timely implementation of available therapy may improve patient outcomes. Whether researchers who analyze genes considered medically actionable should have the same obligation to return results as their clinical counterparts is a matter of debate, given that classifying individual mutations as

transmission in "*trans*" from each parent on separate chromosomes rather than in "*cis*" from a single parent in the case of a recessive allele, and also a search for other mutations in *cis* that would mitigate or eliminate pathogenicity).

[49] Examples of bioinformatics tools included InterVar (Li & Wang, 2017); ClinGen Pathogenicity Calculator (Patel et al., 2017); Genetic Variant Interpretation Tool (Kleinberger, Maloney, Pollin, & Jeng, 2016)

[50] Even in the context of Mendelian disease diagnosis, re-interpretation led to new or additional diagnostic findings in 10% (4 of 40) of cases after a 1-3 year interval, according to a recent report (Wenger, Guturu, Bernstein, & Bejerano, 2017).

pathogenic is often challenging. A mutation may be novel, may have been observed in only a small number of patients or families, or may be predicted—but never previously observed—on the basis of a computer algorithm. The penetrance (i.e., conditional probability of disease, given mutation) and expressivity (i.e., range of pathological and/or benign phenotypes associated with a given mutation) are rarely fully known.

Further, the research context itself adds further complexity. For example, whole genome sequencing (WGS) technology may be selected for hypothesis generation purposes since it enables the full genome to be interrogated for any possible correlation with disease or drug response. While all genes would be included in WGS, any given gene may not be singled out if it is not the object of the research; it would not be identified as a correlative "hit." Additional screening for mutations that may cause pathogenic disease would add cost and time, and would be of uncertain utility in many cases. These considerations should be addressed in advance of the clinical research, explained in the protocol, reviewed by the IRB/REC, and described in the informed consent document and process.

7.3 Considerations in Returning Genomic Results

Genetic data, collected during clinical studies, may be applied to and correlated with disease heterogeneity and drug response.[51] While the incorporation of genetic data in clinical studies may be exploratory in nature (e.g., see Figure 1, Data Type D)—and therefore not always appropriate for returning individual results—there are special considerations that deserve exploration and for which planning should occur.

The ethical foundations and operational principles that we discussed in Section 4, Section 5 and Section 6 apply in the return of genetic information, and here we describe an abbreviated list of the key points to consider when applying these principles in the context of genetic results along with a brief description of each.

7.3.1 Balancing Autonomy with Other Values

Respect for persons and participant autonomy are critically important in the context of clinical studies. There are times when respect for persons is in tension with other ethical principles. This seems to be particularly acute in the context of returning genomic information where we may see individuals' autonomy interests in conflict with duties of non-maleficence and beneficence. For example, since genomic research conducted as part of a clinical trial is often hypothesis-generating and exploratory in nature, results are often poorly understood by researchers and clinicians alike. In these cases, providing data

[51] Of course, correlation or association does not imply that one is a risk factor nor causative of the other.

back to research participants could be more harmful than helpful. However, such judgments must be made with caution and should avoid undue paternalism.

7.3.2 The Complexity of Genetic Information

Some monogenic diseases are easier to describe and contextualize for research participants since their inheritance pattern and disease course are well understood. However, genetic disease is often quite complex. Scientists are still trying to understand why certain conditions manifest very differently in different families and in different members of a given family. Dissecting the roles that our environment, compounding genetic factors, epigenetic differences, and other factors may play in explaining this variability is both difficult scientifically and challenging to explain to patients. Further, our understanding of multifactorial genetic diseases, including the nature of disease, and the roles of inherited and acquired mutations, are constantly evolving.

7.3.3 Ambiguity in Interpretation of Results

Interpretation of genetic information varies. Results generated in an exploratory environment might not meet the standard for analytical validity because of the laboratory testing methodology, quality assurance standards, or informatics tools. Further, our understanding of the significance of genetic data—and its association with disease—is dynamic; current interpretation is subject to refinement or reversal over time, in response to new data.[52] It is important to recognize the potential for misinterpretation of genetic information or differences across labs in interpretation, even when the information is generated in an accredited clinical laboratory environment such as a CLIA-certified lab.

7.3.4 Medical Actionability And Responsibility Changes Over Time

Medical actionability is contextual and subjective. It is important to situate genetic data around the participant and the current state of knowledge. This will include a detailed conversation between the patient and the treating physician, and a determination of whether updated interpretation of the genetic data generated in a research setting will be communicated in the future, who is responsible for follow-up, and how long this obligation extends.

[52] As genetic technologies improve and associated costs decrease, interpretation of the genetic information will become the primary rate limiting step to empowering people with their genetic data. Each person's unique genome, history and family history requires careful interpretation. As scientific technologies and the application of big data methodologies advance, artificial intelligence is likely to take a prominent role in the interpretation.

7.3.5 Laboratory Testing and Consent Conditions In Which Return Of Results Are Merited

One subset of results that seems intuitive to return are those that represent a significant health risk to the research participant where *not* informing them could cause an increased risk of injury. While this type of result is not unique to genetics (e.g., incidental findings on x-ray), the definition of "risk"—and therefore the threshold for return—is difficult in genetic data, as our knowledge base is changing and there are laboratory differences in interpretation. Expert consultation is therefore advisable, and addressing who will advise, and the role of the IRB/REC in the decision, while planning the research is an important preparatory step. When testing is research-grade rather than clinical-grade (e.g., conducted to CLIA-approved standards in the U.S.), it may be illegal to return the finding. In such cases, other mechanisms than return of the specific genetic result might be adopted instead so that the participants and their physicians can seek clinically appropriate testing through licensed laboratories.

7.3.6 To Whom One Can Release Genetic Information

In many cases, it is unclear whether genetic information should be released directly to clinical trial participants or instead to the treating physician. Benefits, drawbacks, and feasibility of returning genetic information to the patient or the health care provider need to be considered. Questions also arise about ethical obligations to communicate relevant genetic information to members of the trial participant's family, who themselves may have personal reasons to want this information, but whose access to this information may be limited due to family relationships, potential legal barriers, or regulatory constraints that exist on the return of genetic information.

7.3.7 International Regulations And Policies Regarding Return Of Genetic Information

There is a lack of international alignment with respect to guidance or policy on the return of genetic information. Clinical investigators and researchers need to be aware of variation in national and local legislation, regulation, guidance and institutional policy. This includes the requirement, in the U.S., that laboratories be licensed and certified in order for test results to be returned to participants/patients for treatment purposes and the conflict between this policy and certain provisions of the Health Insurance Portability and Accountability Act (HIPAA) (see below, Section 7.7.1).

7.4 Points to Consider for Genetic/Genomic Research Informed Consent

Informed consent for genetic/genomic research is driven by Good Clinical Practices (GCP) consent regulations, and country, state or local requirements, as well as by the research

study protocol. If genetic or genomic research is the primary objective of the research study, the entire informed consent form (ICF) is dedicated to describing the applicable regulatory and ethical requirements (e.g., ICH, CFR [FDA, HHS/Common Rule], CIOMS, EU GDPR) for informed consent. However, if the genetic/genomic research is one component of the overall clinical study, the genetic or genomic consent is often included in a separate section of the ICF, in an addendum, or in a separate stand-alone form (Note: some countries require a separate ICF for genetic/genomic consent). When the genetic/genomic research is an optional component of a clinical study, it is recommended that a separate signature be obtained to document consent.

The following considerations for genetic/genomic research informed consent were adapted from "Issues to be Addressed in Obtaining Informed Consent Involving DNA Banking and Genetic Research" (Selwitz, 2014).

Note that there may be overlap/repetition with components of the main ICF in the considerations listed below that can be omitted if appropriate.

Purpose of study: Participants should be informed of the purpose for the genetic/genomic portion of the study and that samples will be used for genomic/genetic research.

- Define genomic/genetic research in general and how it fits in with the overall study purpose/objective (what is being studied, why and how)
- Explain primary as opposed to secondary or exploratory objectives, if applicable

Confidentiality and privacy: Address procedures for maintaining confidentiality

- Explain the level of certainty with which the data has been de-identified or anonymized, or whether there will be identifiers linked to genetic/genomic data or material
- Describe plans for security of genetic/genomic data/material
- If applicable, indicate if a US HHS Certificate of Confidentiality has been obtained
- Address limits to confidentiality (e.g., who will have access and under what circumstances)
- Indicate which third parties (e.g., family, third party payers, participant's physician, outside researchers) will have access to samples/data

Access to Genetic Information/Results and Incidental Findings

- Define incidental/secondary findings
- Inform participants what information/results they can expect to receive
- Inform participants if results or incidental findings will or will not be provided and explain why
    - If findings are to be disclosed, describe specific disclosure procedures (e.g., genetic counseling)

- If findings are to be disclosed, explain implications of making primary results or incidental findings available to participants
- Provide the participant with the opportunity to choose whether he/she wants to receive primary or incidental results

Secondary Use/Re-use of Samples or Data

- Inform participants if other researchers may be given access to samples or genetic/genomic data (with or without direct or indirect identifiers)
- Give participants option of consenting or refusal to future/secondary use
- Inform participants if/how they may be re-contacted (and by whom)
  or
- Give participants option to indicate if willing to be re-contacted
- Participants may want to limit use of sample and associated data

Potential Risks to consider

- Social Risks: Breach of confidentiality could impact insurability, employability, reproduction plans, family relationships, immigration status, paternity suits, stigmatization
- Psychological Risks: If information is disclosed, impact of learning results; impact if no effective therapy exists; psychological stress for family members
- Physical Risks: Physical risks associated with collecting samples for research purposes
- Unknown Risks: Participants should be informed that there may be risks of which we are currently unaware

Examples of Variables Potentially Impacting Risks

- What is currently known with respect to the gene and disease being studied?
- Will identifiers be linked directly or indirectly to the samples? (define how)
- Are safeguards for maintaining confidentiality adequate?
- Will participants be informed of test results?
- Does an effective intervention/therapy exist?
- Will the investigator collect more tissue than needed for clinical purposes?
- Are family members included in the study?

Benefits

- Inform participant of no direct benefit, if applicable
- Inform participants of uncertainties regarding benefits

- Include other potential benefits as appropriate: advancement of knowledge; clinical relevance to individual, family, or society as a whole; long term benefit if investigator plans to re-contact participants to disclose clinically relevant information

Alternatives

- Explain if the genomic/genetic component of the study is optional or required
- If required, the alternative is not to participate in the study

Costs to Participant (if not already part of the main consent): Inform participant of any costs not covered in study such as the costs of genetic counseling

Duration: Participants should be informed of sample storage and destruction timelines/logistics

Control of the Specimens/Materials (if not already part of the main consent)

- Explain who controls the specimen/materials (e.g., custodian)
- Participants should be informed if research could lead to commercially valuable product and whether participants will receive a portion of any profits

Significant new findings: Discuss policy regarding willingness to inform participants if later tests have clinical relevance and whether participants wishes to know

Withdrawal from research study (if not already part of the main consent)

- Inform participants of rights to withdraw without penalty and include procedures for doing so
- Inform participants of procedures for subsequently requesting that samples/materials be destroyed, or
- Inform participants of procedures for subsequently requesting that identifiers be removed from materials
- Describe any limitations on ability of participants to withdraw data or genetic samples

Inform participants of country-specific genetic discrimination law. The U.S. Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans and most employers to discriminate against participants

based on their genetic information. The Canadian Genetic Non-Discrimination Act (GNDA) provides similar protections. f genetic testing is anticipated and the data is to be submitted to the National Institutes of Health (NIH) database of Genotypes and Phenotypes (dbGaP) Genome-Wide Association Studies (GWAS) database or other open or controlled-access health research databases (e.g., European Genome Archive) for broad sharing with other researchers, inform participants that de-identified genotype or phenotype data will be submitted to such a database.

7.5 How to Return?

When returning genetic research results, it is important to put results in context for research participants. In most cases, the influence of genomics (including genetics, epigenetics, proteomics, transcriptomics and other evolving "-omic" paradigms) on disease is **probabilistic rather than deterministic**. Genomics is often one of several factors -- including but not limited to family history and environmental exposures -- that have an impact on the development, onset, progression, and outcome of human disease. In addition, our knowledge base is rapidly expanding and being refined, such that variants of unknown significance today may become known pathogenic variants tomorrow. It is important to convey that test results may be incorrect (false negatives or false positives), and therefore appropriate measures (e.g., re-testing) should be considered before taking action.

During the consent process, and at the point of return, it is important to convey that the absence of a finding does not necessarily mean there is no disease risk (nor, often, does the presence of a gene predict disease with certainty). There may be other genomic factors (e.g., variants within the same gene, variants within different genes, epigenetic changes, etc.) that, independent of or together with environmental and lifestyle factors, contribute to whether the participant will develop a disease. In the absence of a particular genetic variant linked to disease, healthy lifestyle recommendations and regular clinical care, including monitoring and screening for conditions that are represented in the participant's family history, should be advised. In addition, it is important to emphasize that knowledge and understanding of genetic risk, and linkage to disease, are constantly evolving.

If research results are given to a study participant, a result indicating that an individual **possesses a genetic variant** should be presented in such a way as to communicate both what is known about the variant and the uncertainties involved. In some cases, particularly for research assays or laboratory developed tests involving variants that are not well characterized, a research finding may not be analytically validated. In other instances, confirmation of a finding will be necessary in order to provide the result to the participant. If the original test was not conducted in an accredited laboratory (see Section 7.7), however, confirmatory testing may not be paid for by the participant's insurance provider, government insurance program, or trial sponsor, meaning that the individual research

participant would need to pay out-of-pocket for this testing. For this reason, the benefit and limits of confirmatory testing should be explained alongside the risk associated with out-of-pocket costs, so that participants can make informed choices about whether to receive research findings that have not been validated. As mentioned, the plan for return of genetic research results and the risks and benefits of return should be detailed for the research participant during the informed consent process.

While many individuals may handle the return of genetic test results well and adapt even to serious results, other individuals may experience anxiety, feelings of helplessness, or fear, any of which could lead an individual to take subsequently regrettable actions. All individuals should be provided with information about additional support that may be available (e.g., names of counselors, support groups). Additional research will help us optimize strategies for informing prospective research participants about the potential return of genetic research results, so that they can make informed decisions about whether and when to receive such information.

7.6 Who Will Return?

While the return of some genetic test results can be simple and straightforward, results with more complex and serious health implications may require a team approach to ensure that results are communicated in a meaningful and relevant manner to a study participant. A major challenge in some settings will be the lack of resources or expertise necessary to enable this collaborative approach. Of note, additional resources are often needed to return genomic results to minors and their parents or to adults who lack capacity and their caregivers.

At a minimum, it is clear that someone with genetic expertise is needed to interpret complex genomic findings in light of the current understanding of their significance and future health relevance. In some settings, this could be a medical geneticist or a genetic counselor. The treating physician or nurse often lacks the genetic expertise needed to place the result in an appropriate context to enable recommendations regarding the proper prevention, modification or treatment of disease. At sites without a genetics professional, another member of the team might be designated and trained for this role through targeted continuing education materials. Genetic expertise might also be centralized for the study and be made available via phone or videoconference. Educational materials developed for physicians could be helpful in managing the patient, especially in cases where a genetics expert is not available. High quality written materials designed for the participant could also facilitate communication about the meaning and importance of the genomic findings; however, it is important for this to be contextualized in light of the patients' full medical and family history.

In addition to genetic and medical expertise, the return of some complex, serious results may require psychological and social support. Psychological support may be provided by a psychiatrist, psychologist, social worker, or a support group, and may help the participant or family to receive and contextualize serious or uncertain results in a way that enables them to avoid undue fear and anxiety.

It is important to consider the educational and socio-economic constraints in which genomic results may be returned. In some settings, study team members and participants may not understand the nature of genomic testing, and education must begin from a very basic level. Because follow up or confirmatory testing may be constrained by resources or health insurance coverage, the team may also include a medical insurance advisor who could investigate coverage for confirmatory testing or other follow up interventions.

Finally, some communities and cultures may not endorse individual, autonomous decision-making and, instead, may involve family members, community leaders or elders in important decisions. Professionals who can appreciate local constraints, different levels of understanding of genomic data, and cultural differences are needed to facilitate the design of appropriate frameworks for decision-making and communication of results in a manner that is sensitive to needs of the participant.

7.7 National Laws, Regulations, and Ethics Guidance

Laws, regulations, and guidance (including Ethics Committee and regulatory guidance or position papers) vary considerably across countries on the issue of return of individual research results to study participants. The complexities and challenges faced due to a lack of agreement in international regulations and guidance are amplified in the context of the evolving landscape of genetic research.

In particular, two types of regulations need to be considered: (1) regulations for the return of genetic results by researchers, and (2) rules governing the individual's right of access to personal information. Countries may have special regulations for genetic data and results; for example, regarding under what conditions certain tests such as WGS or NGS may be performed, handling genetic results from deceased research participants, and communication of genetic results to family members. In some countries, laws grant study participants broad access to their individual research results upon request; in other countries, laws may place restrictions on access, where exploratory genetic research results may not meet the quality standards for use in clinical decision making. It follows that these laws can conflict; for example, certain regulations may require researchers to return genetic results, while other regulations may require researchers *not* to return results from non-approved laboratories.

Below are examples illustrating the complexity and variability of the global environment and return of individual genetic research results. This is not intended to be a

comprehensive analysis of relevant law or guidance, but rather offers a broad overview of the intricacies for consideration of return of individual genetic research results. Further resources for global regulations can be found in the Toolkit (Tool 3).

7.7.1 United States – CLIA and HIPAA Regulatory Issues Regarding Return of Test Results; FDA Regulatory Considerations

In the United States, the Clinical Laboratory Improvement Amendments of 1988 (CLIA) do not allow the return of results for the prevention, diagnosis or treatment of any disease or the assessment of health of individual patients, unless the test is analytically validated and generated in a CLIA certified laboratory (U.S. Government, 42 C.F.R. § 493). This requirement is intended to help ensure that results used for clinical decision making are valid, reliable and accurate. Genomic research analysis in clinical trials using methodologies, such as WGS, is often performed in non-CLIA research labs, or in a CLIA-certified lab but under research use standards, and may not consist of validated assays.

The CLIA regulations contain an exception to the CLIA certification requirement for research laboratories that do *not* report individual results for the diagnosis, prevention or treatment of any disease or the assessment of health of individual patients (U.S. Government, 42 C.F.R. § 493.3(b)(2)). The Centers for Medicare and Medicaid Services (CMS), the office within HHS that oversees CLIA, has taken the position that this provision also prohibits a research lab from returning results to study participants, even if accompanied by a disclaimer that these results are not for treatment purposes and a recommendation that the participants consider pursuing additional confirmatory testing (through their treating physician) at a CLIA-certified lab (Meyers, 2015).

In 2014, CMS and the HHS Office for Civil Rights (OCR), which administers the HIPAA Privacy Rule, jointly published a final rule, amending the HIPAA Privacy Rule to provide individuals the right to access test reports directly in their "designated record set" (DRS) from HIPAA covered entity laboratories, including those test results performed in a non-CLIA-certified research laboratory ("CLIA Program and HIPAA Privacy Rule; Patients' Access to Test Reports 79 F.R. § 7289," 2014, 79 F.R. § 7289). The DRS includes medical and billing records, as well as any other records that may be used in whole or in part to make a decision about an individual (Security and Privacy, 45 C.F.R. § 164.501). The DRS would therefore include research test results if these results are available for the covered entity to make decisions about individuals. For this reason, it is important that all covered entities with research laboratories review how they have defined their DRS in order to understand a patient's right of access to research records. HIPAA covered entities that conduct research testing should also consider referencing the application of the DRS to research testing in their Notice of Privacy Practices so that patients are aware of the extent of their ability to access research test results. Notably, HHS has broadly interpreted the DRS to include the laboratory test report and all underlying data generated as part of the test.

> *For example, a clinical laboratory that is a HIPAA covered entity and that conducts next generation sequencing (NGS) of DNA on an individual must provide the individual, upon the individual's request for PHI [Protected*

> *Health Information] concerning the NGS [next generation sequencing], with a copy of the completed test report, the full gene variant information generated by the test, as well as any other information in the designated record set concerning the test*. (U.S. Department of Health & Human Services)

This poses an apparent conflict between the CLIA regulations and the HIPAA Privacy Rule with respect to patient right-of-access when the genomic testing is performed in a non-CLIA-certified lab that is part of a HIPAA covered entity.

However, there is no requirement that a HIPAA covered laboratory interpret lab results for an individual.

> *There is no requirement in the HIPAA Privacy Rule that clinical laboratories interpret test results to patients . . . . Laboratories may continue to refer patients with questions about test results back to their ordering or treating providers. However, while not required, a laboratory providing a test report to an individual . . . may also provide education or explanatory materials regarding the test results to individuals if it chooses to do so. Similarly, a laboratory that wishes to include a disclaimer, caveat, or other statement explaining the limitations of the laboratory data for diagnosis or treatment or other purposes may do so*. (Barnes et al., 2015)

At the time of the issuance of this document, this discord between the CLIA and HIPAA regulations regarding return of results to study participants has not been resolved. Resolution of this conflict would greatly aid researchers in understanding requirements for returning genomic test results in the US. In June 2017, the National Academies of Sciences, Engineering, and Medicine announced the launch of a Consensus Study, supported by NIH, FDA, and CMS, to review and evaluate issues regarding the return of individual research results from research laboratories to individuals. One of the aims is to review the regulatory environment for conducting tests and returning individual research results and regulatory considerations. The consensus study may lead to possible professional standards and regulatory reform in this area, in order to reconcile these apparent contradictions in U.S. regulatory regimes. (http://nationalacademies.org/hmd/Activities/Research/ResearchResultsGeneratedinResearchLaboratories/)

7.7.2 FDA Regulatory Considerations

The Food and Drug Administration (FDA) regulates the use of diagnostic tests in clinical research under the Federal Food, Drug, and Cosmetic Act (FDCA) and its implementing regulations. FDA requires that clinical research involving diagnostic tests from which results are intended to be submitted to FDA to support a research or marketing application comply with regulations on investigational device exemptions (IDE) (21 C.F.R. Part 812), informed consent (21 C.F.R. Part 50), and institutional review board oversight (21 C.F.R. Part 56).

Study protocols may include non-exploratory genetic testing on biospecimens using investigational assays not clinically validated. Lab tests that are classified as *in vitro* diagnostic (IVD)[53] devices are generally subject to FDA regulations on medical devices (in addition to the CLIA regulations) unless the lab test is considered a "laboratory developed test" (LDT). LDTs are designed, manufactured and used within a single laboratory,[54] and FDA has historically not enforced applicable regulations except under certain conditions. If the LDT is not clinically validated and is the object of the clinical investigation, FDA likely would apply its clinical research regulations to the conduct of that study.

In general, an IVD may be intended for research use only (RUO) or investigational use only (IUO).[55] An IVD intended for RUO is in the laboratory phase of development and should not be used for diagnostic purposes. IVDs labeled RUO are generally exempt from FDA's clinical research regulations (*see* 21 C.F.R. § 809.10(c)(2)(i)). In contrast, an IVD intended for IUO is not yet validated for commercial marketing in that its performance characteristics have not been established but it can be used in the research context for diagnostic purposes (*see* 21 C.F.R. § 809.10(c)(2)(i)).

If a clinical investigation involving an IVD is subject to FDA's IDE regulations, the return of results to subjects for diagnosis, treatment or prevention of human disease could cause the study to become subject to heightened regulatory requirements. FDA's IDE regulations apply to clinical investigations involving one or more subjects to determine the safety or effectiveness of a device (*see* 21 C.F.R. § 812.3(h)). A clinical study of an investigational device may be exempt from IDE requirements if certain criteria are met, one of which is that the investigational IVD will not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure, e.g., an FDA-cleared or approved IVD or culture (21 C.F.R. § 812.2(c)(3)). Requirements for a non-exempt IDE vary depending on whether the IVD presents a significant risk or non-significant risk to subjects (*see* 21 C.F.R. § 812.2(b)). A significant risk study of an IVD is one in which misdiagnosis and/or error in treatment caused by inaccurate test results could lead to life-threatening harm or permanent injury to the participant.

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[53] IVD products are those reagents, instruments and systems intended for use in diagnosis of disease or other conditions including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae through the collection, preparation and examination of specimens taken from the human body (U.S. Food and Drug Administration, 21 C.F.R. § 809.3).

[54] FDA defines a "single laboratory" to be "5 Single laboratory refers to a facility with a single CLIA certificate as described in 42 C.F.R. § 493.43(a)-(b). See FDA draft guidance on "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm416685.pdf). Accessed October 19, 2017. For further information on FDA's oversight of LDTs, *see* FDA's Discussion Paper on LDTs (issued January 13, 2017) (https://www.fda.gov/downloads/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/laboratorydevelopedtests/ucm536965.pdf). Accessed October 19, 2017.

[55] https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm376118.pdf. Accessed October 16, 2017.

When a research study involves an IVD, the first step should be to determine whether FDA regulations apply. If so, the IVD study could meet all of the criteria for an IDE exemption if, among other things, any results disseminated to the subject or subject's physician for diagnostic purposes will first be confirmed by a medically established procedure. Notably, established diagnostic products or procedures may not exist for tests that use new technologies or represent a significant technological advance. If the results will not be confirmed before return, the study will not be IDE-exempt, and a determination must be made by the sponsor, and confirmed by the cognizant IRB, as to whether the IVD is a significant risk or a non-significant risk (*see* 21 C.F.R. § 812.66). Importantly, however, FDA's requirements for informed consent and IRB review and approval continue to apply even if the study is IDE exempt (*see* 21 C.F.R. §§ 50.1 and 56.101).

7.7.3 Outside the United States: Variations in Legal Treatment of Genetic/Genomic Results

Several countries outside of the United States have laws and/or regulations that explicitly address an individual's right to access results of genetic testing. Many of these laws and/or regulations also include the requirement to provide access to genetic counseling when applicable. For example, in Brazil, a study participant has the right to access his/her genetic data and may choose whether or not he or she wants to be informed of genetic research results and to receive guidance on their implications, including genetic counseling when applicable (Brazil Ministry of Health CNS Resolution 320/2004, 2004). Similarly, Spain's Biomedical Research Law 14/2007 establishes the right of a participant to be informed of genetic data in accordance with the terms of the consent to testing that he/she provided (Spanish Parliament Law 14/2007 of 3 July on Biomedical Research, 2007). Italy's General Authorisation No. 8/2014, issued by the Data Protection Authority, establishes requirements for the processing of genetic data (Italian Data Protection Authority, 2014). This includes the ability of an individual to be informed of genetic findings if he/she chooses, including unexpected findings that may be helpful to the treatment or prevention of illness or may contribute to the awareness of reproductive choices. In Germany, the Genetic Diagnostic Act of 2010 requires that research participants must be re-tested at an approved genetic laboratory if they wish to receive their individual result (Soini, 2012)

In countries such as Norway, Argentina and France with data privacy laws allowing subjects to access their data (see Section 5.9), the definition of personal data may include DNA. Thus, researchers may find themselves legally required to provide access to genetic results in certain countries but with little guidance on exactly how or what is expected to be returned in those jurisdictions. The EU GDPR, which will become effective on May 25, 2018 in EU member states, considers genetic data, along with health data, to be "Special Categories" of personal data, as discussed in Section 5.9.

In other jurisdictions, there are laws/regulations that are somewhat contradictory and provide vague guidance on the return of genetic information and on the return of research information. For example, in Taiwan, the Human Biobank Management Act explicitly prohibits participants from accessing information concerning biological specimens and prohibits use of specimens for anything other than biomedical research (Taiwan Human

Biobank Management Act, 2010). The restriction on access rights does not apply to personal information that can identify the participant. The same law also establishes that a participant must be informed of "any possible impacts of the genetic information derived from the biological specimens on the participant, and his/her relatives or an ethnic group." Thus, similar to the CLIA-HIPAA conflict in the US, the contradiction in regulation makes it difficult for the researcher to navigate requirements.

7.7.4 Research Ethics Committee Requirements and Positions

In addition to complexity created by laws and regulations, research ethics committees also differ in their interpretation of local requirements, resulting in variability in conditions imposed on a single research study within the same country (Warner et al., 2011). Furthermore, certain research ethics committees may issue guidance documents or position statements on genetic testing that impact return of results in their jurisdiction. In Denmark, for example, the National Committee on Health Research Ethics (DNVK) has issued a guideline on research projects involving "comprehensive mapping of personal genomes" which are defined as research studies utilizing next generation sequencing technologies (DNVK Guideline on Mapping of Personal Genomes, 2013). Such research projects must allow for the return of information regarding serious genetic diseases under certain conditions unless the participant explicitly indicates he/she does not wish to receive this information. These conditions include if there is a reasonable degree of likelihood that the genetic predisposition is present, there is a proven link between genetic predisposition and disease progression, and the disease can be substantially prevented or treated. Similarly, the Marsilius College at the University of Heidelberg in Germany has issued a position paper on ethical and legal aspects of WGS (Project EURAT – Marsilius College at the University of Heidelberg, 2013). This paper suggests that critical individual results that indicate risk of additional harm or increased suffering must be returned.

In Australia, the National Health and Medical Research Council (NHMRC) issued a *Statement on Ethical Conduct in Human Research (2007)* (updated May 2015) ("National Statement"),[56] which includes a chapter on human genetics. Citing the National Statement, Human Research Ethics Committees in Australia require that, for research that may discover or generate information of potential importance to the future health of participants, or their blood relatives, that researchers prepare and follow an ethically defensible plan to disclose or withhold that information. The elements of an "ethically defensible plan" is outlined in Chapter 3.5 that can be accessed at https://www.nhmrc.gov.au/book/chapter-3-5-human-genetics.

As noted, many laws concerning the return of individual genetic results are broadly and vaguely written with no supporting guidance, leaving them open to varying interpretations. It is also important to recognize the distinction between binding laws and

[56]Australian Government National Health and Medical Research Council. National Statement on Ethical Conduct in Human Research (2007) (Updated May 2015). https://www.nhmrc.gov.au/book/national-statement-ethical-conduct-human-research. Accessed 30 September 2017.

regulations, and position papers and guidance issued by research ethics committees or non-regulatory authorities. To complicate matters further, there may be regional differences in interpretive guidance within the same country, as well as an evolving regulatory landscape. As such, it is incumbent upon the researcher to be aware of all legal requirements as well as ethical positions pertaining to the return of genetic research results in the jurisdictions in which the study is being conducted. Ideally, harmonized guidance within and across jurisdictions will be developed.

7.8 Additional Information

This chapter was finalized in late 2017. Technologies, the state of knowledge, laws and regulations will change over time and most current information needs to be sought for interpretation of genetic data.

One of the currently -developed projects for returning genomic information is Geisinger's MyCode (https://www.geisinger.edu/research/departments-and-centers/genomic-medicine-institute/mycode-health-initiative), which began returning results in 2015, and includes a web-based portal (GenomeConnect) that enables participants to connect with other individuals in the project. Another tool is My46, an interactive web-based information management system developed by University of Washington researchers as part of a project funded by NIH National Human Genome Research Institute. The tool is designed to return genetic test results and educate patients about genetic traits, and includes in-line access to a genetics counselor. Holly K. Tabor et al, My46: a Web-based tool for self-guided management of genomic test results in research and clinical settings, Genetics in Medicine (Sept. 2016). This is an area that is actively evolving.

8. CONCLUSIONS

Ethical values (Section 4) and Return of Individual Results Principles (Section 5) should be carefully weighed on a case-by-case basis when considering the responsibility to return individual research results. Additional considerations apply to the return of genetic and genomic results (Section 7). The obligation to return results is mitigated by a variety of factors including lack of feasibility, insufficient validity, and the absence of clinical utility.

We encourage sponsors and stakeholders in the clinical trial enterprise to voluntarily promote, adopt and implement the principles that have been developed by the MRCT Center Multi-Stakeholder Workgroup for the purpose of sharing individual research results with study participants. We appreciate any feedback.

APPENDIX 1: GENETIC AND GENOMIC RESEARCH DATA TYPES AND RESULTS

There is a distinction between research "data" and research "results" in the context of genomic sequencing. For example, research using whole genome sequencing methodology generates raw or uninterpreted data. There are no research "results" until the data is analyzed through a research query.

Methods and Technology. Genomic data and research results may be generated using various methodologies, such as:

- Whole genome sequencing (WGS)
- Next generation sequencing (NGS), including DNA sequencing and RNA sequencing
- Whole exome sequencing (WES)

Analysis. Genetic/genomic and protein information identified by a method performed on DNA/RNA extracted from a biosample (e.g., tumor tissue, blood)

- Analysis of somatic mutation(s) (may be pre-specified)
- Analysis of germ-line mutation(s) (may be pre-specified)
- Comprehensive targeted NGS genomic panels (e.g., FoundationOne®)
- Biomarker expression (e.g., PD-L1, HER2)
- Circulating tumor DNA (ctDNA)
- Identification of germline versus somatic mutations involving collection of tissue and blood samples to allow for comparison of DNA from tissue samples with DNA from blood samples
- Future exploratory research on biorepository biosamples

Timeline. Analyses may occur along a timeline of the clinical study

- Pre-screening or screening assessment to determine eligibility
- Pre-treatment assessments for patient stratification (may be blinded study)
- During the ongoing study
- At the end of the study
- Months or years after of the close of the study

Classification. In vitro diagnostic (IVD) assay used may be (1) investigational (including lab developed tests (LDTs)); (2) research use only; or (3) approved/cleared by regulatory authority (e.g., FDA)

- Assay may have been performed in either an accredited (e.g., CLIA) lab or in a research lab

Biosamples. Collection of biosample(s) may be required under the main protocol ("mandatory"), or optional under an additional signed consent.

- May be single-coded or double-coded

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