Chapter 7
Laboratory Medicine and Biorepositories

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Abstract Biorepositories provide access to specimens for biomarker investigation of subjects with or without a given condition or clinical outcome. They must record collection, transport, processing, and storage information to ensure that specimens are fit-for-use once a particular analyte has been identified as a candidate biomarker. Ongoing (post-collection) clinical and outcome documentation provides more value to researchers than a static, clinical snapshot at the time of collection. Frequently,

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biorepository specimens are residua from those obtained for clinical management of a patient; whether routine clinical processing is acceptable, given the stability profile for a given analyte, will dictate whether non-standard processing will be required. Introducing nonstandard steps into clinical lab processing in order to preserve an analyte such as RNA or protein requires careful workflow planning. Accreditation for biorepositories is now available; standards have been developed to ensure that biorepository personnel, equipment, laboratory space, information systems, and policies/procedures, including those for quality management, meet the same high standards by which clinical laboratories are judged and accredited. An additional accreditation standard relates to the development of, and adherence to, policies surrounding informed consent. The current regulatory landscape for pediatric specimen research requires consideration of many issues around informed consent, assent, and reconsent at the age of majority for the collection and use of identifiable specimens for research. Consideration of these requirements based on the current (and evolving) regulatory landscape can be difficult, in light of pending legislative and regulatory changes. Issues surrounding return of incidental findings is another challenge for institutional review boards.

Keywords Biobanking of biospecimens • Consent and assent • Genomics • Incidental findings • Sample tracking

7.1 Introduction

The challenge in bioinformatics for the support of biorepositories is anticipating, and fulfilling, the data requirements of future biomedical researchers who wish to solicit samples that have been in storage, from days to decades.

What future questions will be posed to the biorepository manager? We can anticipate these questions:

- What is the specimen type, and how was it obtained?
- What were the demographics of the subject who was the source of the specimen?
- What were the clinical condition and the medical/family/social history of the subject?
- Since collection, how has the subject's clinical condition evolved?
- What were the environmental conditions, timing, and processing steps that characterized the pre-storage handling of the collected specimen, and how do these handling conditions relate to the stability of the analyte(s) of interest to the researcher?
- How has the specimen been stored, and how has the storage condition and time of storage affected the ability to recover the analyte(s) at levels equal to that at the time of collection?

- What is the nature of the consent obtained at the time of specimen collection with regard to research use, access to demographics, use of subject medical/family/social history before and after specimen collection, subject identification, and return of results (including incidental findings and genetic discoveries); what changes in this consent, if any, have occurred since the original consent?
- Can the above parameters be specified in an automated data search that could identify acceptable stored specimens for a given research investigation?
- Is the biorepository accredited, if so by what agency, and what operational implications does that accreditation carry?

7.2 Data Collection

Specimen type is of course a basic parameter for biobanks, but information on the method of collection, as well as the conditions under which collection occurred, must also be captured. For example, a clean-catch urine, catheterized urine, and a urine obtained by suprapubic aspiration are all different with respect to probable microbial contamination. Liver tissue obtained during a surgical operation versus an autopsy may be vastly different in regards to the particular analytes present. For autopsies, the interval between the time of death and the collection of an autopsy specimen must be recorded, as must the temperature conditions of body storage, since analytes can degenerate or move variably from one body compartment to another after death. All of these factors must be recorded and available to maximize the specimen's value for research.

Alongside specimen data, basic demographic information must be effectively captured. While the biobank may have access to complete information on the subject, including birthdate and other protected health information (PHI), restrictions to the release of PHI in most situations and many jurisdictions would mean, for example, that instead of the birthdate, age at the time of collection would accompany the specimen. Since date of collection is also provided to researchers, the biobank must ensure that the specification of the age (e.g., in days, weeks, or months) does not run afoul of PHI definitions.

Basic demographic information includes the sex of the subject. While assignment of sex is typically straightforward for most subjects, it is more complex for transgender individuals, because the relation between the time of specimen collection and interventions (such as hormone treatment) may be relevant. Ancestry and ethnicity are of obvious interest; the accuracy with which ancestry and ethnicity have been determined may be uncertain. It is helpful to record capture method for said data.

These are the most fundamental demographics, but there are others that are relevant for particular research studies. For example, where the subject lives, and has lived, their current and past socioeconomic status, and other such data may be relevant (e.g., studies of environmental exposure, etc.). For other studies, body-mass index may also be an important variable to consider.

The clinical condition of the subject is of prime importance; the International Classification of Disease (ICD) codes are important data to capture and are often used to dramatically narrow a search of study relevant subjects, increasing the usefulness of biobanked materials. While helpful, the limited specificity of ICD codes demands further data interrogation. Knowing that a patient has been diagnosed with type I diabetes mellitus raises questions about the length of their illness, the status of comorbidities, type, length, and effectiveness of treatment, etc., even in the absence of the confidence that this diagnosis is the most appropriate for the patient in question. Their disease age-of-onset, past medical history, social history, family history, habits (e.g., smoking), are all likely to be important, as research studies involving biorepository samples will often be case-control studies for which the investigator will match study subjects and controls for many of parameters that can be found in the patient's history.

The value of a biorepository is enhanced by continuing to collect and store data on the clinical condition of subjects from whom samples have been collected. Not only could future clinical information include a disease that was present, but not yet diagnosed at the time of specimen collection, but also the record may also provide follow up information such as treatment response or clinical course that would be essential to a researcher who is studying a prospective biomarker for its value in treatment choice and/or assessment of prognosis.

Data documented at time of specimen collection may not include all of the demographic and clinical status data that might be desirable to a future researcher. The logical choices for accessing future data include medical record review, and if permitted, recontact of the subject. Both of these choices demand careful attention to the details of the relevant Institutional Regulatory Board-approved, protocol and consent. Both the protocol and the consent documents must specifically authorize researcher access to PHI (protected health information) and or subject recontact. Permission for direct contact with the subject may be prohibited, but in instances where the subject has approved of it, direct contact with the subject may permit an opportunity to gain information that does not reside in the medical record.

One effective strategy to deal with the need to protect the identity of research subjects, while permitting researchers to gain access to medical record information that was in the record at the time of specimen collection as well as information that was subsequently placed there, is the use of an "honest broker" (Choi et al. 2015). The broker stands between the medical record of the institution and the researcher; the broker can examine the nature of the consent and provide permitted data about the subject without revealing the identity of the subject to the researcher.

7.3 Specimen Handling, Processing, Labelling, and Storage

While many data elements can be retrieved from the medical record, details about the handling, processing, labelling, and storage of the specimen will not be in the medical record and so must be captured in the biorepository's software application.

There are a number of commercially-available software packages that may be used to capture this data (Boutin et al. 2016; McIntosh et al. 2015); in-house developed software may provide needed customized features, although the requirements demanded of the software by biobank accrediting standards make in-house-developed software a challenging, but not insurmountable choice (College of American Pathologists 2015).

The data elements relevant to handling, processing, labelling, and storage may be found in Table 7.1.

A common unique identifier is the patient medical record number; if the patient sample comes from a multi-institutional setting such as a hospital consortium, there may be a master index number that supercedes the medical record number. The medical record number is unique to the subject, but is typically used for all encounters, and so an encounter-specific, unique identifier is also needed; typically, this encounter-specific number is the financial information number (FIN) or a clinical

Table 7.1 Data records for specimen handling, processing, labelling, and storage

Date, time, name and description of each sample handoff transaction
Medical Record Number
Unique identifier for each subject, including encounter identification
Project identifier and project name
Time and date of collection
Specimen type, including anticoagulant (tube type), preservative, additives
Specimen volume
Specimen concentration
Sample processing instructions including Standard Operating Procedure (SOP) name and version
Temperature or any other exceptional conditions during handling and processing, if outside the SOP
Conditions of initial centrifugation and any subsequent centrifugation for derivative samples
Method used for preparing derivative samples
Quality and purity of parent and derivative samples
Time and date of entry into storage
Unique identifier for each aliquot of each parent specimen (and each of its derivatives)
Number of aliquots, with volume of each
Date and time of each freeze and thaw with the residual volume
Storage location: room, freezer, shelf, rack, box, position within box
Storage barcode identifier
Sample requester name and contact information
Sample requester designee information
Sample request IRB protocol ID
Total # of samples retrieved per retrieval
Date of sample retrieval request
Date of sample retrieval provision
Sample request description of each sample (concentration, Optical Density, container type)
Sample request release information: signature of releasee, date and time

laboratory intake identifier, often known as the accession number. If the subject was seen as part of a clinical trial, there is also typically a study encounter number.

The time and date of collection are routinely collected, but care must be taken to ensure that the time of collection is not defaulted as the time the specimen arrived in the laboratory; this default may be used when the data field for collection time is not a required field to be completed by the specimen collector.

"Plasma" is not a suitable description of a biological sample, as there are many varieties, including EDTA, lithium heparin, sodium heparin, and sodium citrate. Tube type is a preferred description, as it will contain additional information such as presence or absence of a separator gel, or presence of additives such as protease or RNAse inhibitors.

Specimen volume, as well as the volume of the final aliquot(s) is important when requests for distribution are processed.

Temperature conditions carry implications for stability that vary across multiple analytes (Ellervik and Vaught 2015; Riondino et al. 2015). A general consensus is that the more efficiently a sample can be processed and then stored at −80 degrees Centigrade (−150 degrees Centigrade, or liquid nitrogen for cells), the better. However, in much of biobanking, and especially in pediatric biobanking, the specimens collected are residua from specimens submitted for clinical testing. They are usually collected at room temperature, processed within minutes for specimens collected near a laboratory but not processed for hours for specimens collected in a remote location, held at room temperature during the testing process, then refrigerated for up to 1 week before being discarded (or directed to the biorepository). These conditions are suitable for genomic DNA extraction from anticoagulated blood or the subsequent evaluation of antibody titers in serum, but problematic for many other analytes. Cooperation between the clinical laboratory and the biorepository can help to overcome this challenge for unstable analytes, e.g., by parallel processing of a specimen that is split for clinical and research uses. Centrifugation conditions (rpm, *g*-force, temperature) during the initial separation of plasma or serum from cells, and during any subsequent centrifugation to produce derivative products, such as washed cells, must be recorded. The method for producing such derivatives, such as density gradient centrifugation, must be recorded.

The quality of the stored products should be recorded. The methods to rate quality are evolving but many have been proposed for DNA, RNA, and protein (Shabihkhani et al. 2014; Betsou et al. 2013). These quality measures can be obtained at the time of specimen entry into the biorepository, but they can also be applied to a sampling of specimens after various time intervals in freezer storage.

The time and date of entry into the storage system and all instances of removal from the storage system must be documented. Re-entry into storage following thawing, aliquoting a distribution sample, and re-freezing all need to be documented.

The labels used in storage must remain adherent to the tube; the use of bar-coded freezer tubes with no labels provides a suitable alternative. Each tube must be uniquely identified, down to the individual aliquots. The volume of sample within each tube must be recorded, and the recorded volume adjusted if the entire volume is not distributed.

Finally, the exact location of each tube (freezer room, freezer, shelf, rack, box and position within the box) is essential to facilitate quick retrieval; quick retrieval protects the contents of the freezer from excessive exposure to room temperature. Although robotic systems permit retrieval of a sample without exposing all the contents to room temperature when a sample is removed, they are expensive, especially when calculated for the amortized expense for each retrieved specimen.

7.4 Clinical Lab Processing Versus Biorepository Processing

Increasingly, clinical laboratories are pressured to turn around the processing, analysis, and result reporting of clinical laboratory specimens in order to speed the flow of patients through diagnostic and therapeutic episodes of care. Standardization with the intent to preserve uniformity and consistency in laboratory result values is the goal, with standard operating procedures written and strictly followed to ensure that specimens are handled the same way, every time.

The introduction of non-standard steps and non-standard documentation requirements into a high-volume, rapid throughout clinical lab processing area, for a small percentage of processed specimens that are destined for research use, lengthens turnaround times for all results and introduces risk that protocol-required steps for the research samples are omitted or performed with unacceptable delay. Further, the documentation of exceptional processing is often lax, adding to the difficulties thereby derived. Employees are stressed when put in a position to choose between processing a specimen from a sick child in the intensive care unit or risking a protocol violation with a research sample that must be processed within a tight time frame. Processing steps for research specimens, including those going into the biorepository, often involve producing multiple aliquots, each of which must be labelled and frozen quickly; this process is unlike that performed for clinical laboratory samples, and it is time-consuming.

Furthermore, documentation suitable for clinical lab processing is captured, often automatically, by clinical laboratory information systems, but the data capture points are insufficient for research or biorepository requirements. Table 7.2 lists the typical data elements captured by clinical laboratory information systems, and Table 7.3 lists the additional data elements that research protocols and/or

Table 7.2 Data elements captured by clinical laboratory information systems

Time and date of collection
Time and date of laboratory receipt
Time and date of analysis
Time and date of preliminary result acceptance
Time and date of final result verification

Table 7.3 Data elements often required for research but not captured by clinical laboratory information systems

Time of entry into the centrifuge
Time of centrifugation
Temperature of centrifugation
Centrifugation *g*-force
Model and serial number of centrifuge
Time of exit out of the centrifuge
Time of entry into freezer or refrigerator storage

biorepositories typically require that are not captured as a part of routine clinical lab processing; capturing the latter data may require a research coordinator accompanying the sample to the clinical lab, either personally performing the processing steps or at least recording the times and other data.

A more satisfactory approach is to separate clinical lab processing from research processing, creating a fast lane and slow lane, respectively. This approach is admittedly resource-intensive, as samples for the slow lane may come at any time on any day, and the volume of samples in the slow lane may seem insufficient to justify 24×7 staffing.

7.5 Accreditation

The College of American Pathologists (CAP), which accredits clinical laboratories around the world, has recently begun to accredit biobanks (College of American Pathologists 2015). The CAP requirements for biorepository informatic technology (IT) systems mirror their requirements for the mission-critical IT systems for clinical laboratories.

Of note, the information systems must be robust, i.e., automatically backed-up and able to be restored quickly when a hardware or software failure occurs. Logon-associated security levels, tied to responsibility and authority, must reflect roles that are certified by the institution. Logons must be secure and not shared. An audit capability must track additions, deletions, and corrections in the system, positively identifying which staff member made any such changes. Staff must include a senior administrator(s) who is responsible for approving all changes to the system. Standard operating procedures must direct staff activities when downtimes occur, and they must specify conditions (such as checks on data integrity) that are required before re-starting the system after a downtime. There must be documentation of the software functionality including any custom alterations to the standard programs. Training records for staff must record their ability to successfully interact with the software program, and staff must have a defined escalation strategy when problems cannot be resolved in a timely manner.

Each specimen must be labeled with a unique identifier, and this identifier must be used as the specimen and aliquots/derivatives associated with it, move through the testing process. Labeling specimens in intermediate stages of processing as 1, 2, 3 or A, B, C, etc., is not acceptable. Time points for collection, processing, and storage must be captured, either automatically, or if necessary, manually. The storage records must indicate the storage temperature; ideally, the storage temperature is tracked continuously with frequent, e.g., hourly, temperature data points captured and recorded. Software for maintaining storage records should also track all additions to, and distributions from, the biorepository, providing information about who received a sample, what samples were provided, and when requests were processed and distributed. If there are parent-child relationships between specimens, the derivative specimens must be labeled so that those relationships are encoded. There must be a method to generate new labels as needed. Coding for sample identification, e.g., a letter code for different types of specimens, must be defined. All patient-related data associated with the specimens must be secured, and unauthorized access through programs or interfaces to this secure data must be prevented.

7.6 Ethical and Regulatory Issues

Before a biobank begins collecting or otherwise receiving samples it is important to consider several important ethical issues. An important factor in these considerations is the institution's decision around the type of samples and method of acquisition that will be used to collect samples for the biobank. An institution may begin with a strategic commitment to systematically collect and store some or all residual clinical samples for future unspecified research. For some institutions residual clinical samples may be a valuable source of research samples; in other cases an institution may choose to target specific types of samples, specific diseases/conditions or specific types of patients. Each of these decisions has its own set of unique cost, resource, logistic and scientific drivers. One could reason that the collection of residual clinical samples minimizes the impact to the patient providing the sample, e.g., limiting blood loss and invasive specimen collection procedures, and may have lower associated sample acquisition costs. However, broad-based consenting, often employed for institution-wide residual clinical sample collection, may present specific ethical challenges. Without careful distribution planning prior to biobank conception, this approach is vulnerable to resulting in a substantive number of samples being stored in the biobank and underutilized for scientific research. With that said, in this section we will explore several of the regulatory and ethical challenges associated with approaches to informed consent and return of secondary and incidental findings associated with a biobank designed to collect residual clinical samples.

7.6.1 Consent and Assent for Use of Residual Clinical Samples

One of most significant and complex decisions to be made at the outset of a biobanking initiative, focused on the collection of residual clinical samples, is whether and how to obtain informed consent and how to address the issue of informed assent. This choice will have implications for a hospital's electronic health record (or similar patient tracking) system, human resources, infrastructure, and patient flow. Once an institution gets beyond the basic requirement of choosing a consenting process and developing a document that complies with baseline federal, state, and local laws and regulations, more complex and strategic considerations will be needed. Specifically, in developing the consenting documents, the institution should give significant consideration to intended future use of the samples. For example, the institution needs to address questions such as whether the primary use of the samples will be for procedures such as large scale genomic sequencing (e.g. whole genome/whole exome sequencing). Secondly, the distribution rules are equally critical to patients and the users of the stored samples. Patients and families may have strong feelings, both positive and negative related to the sharing of their sample with industry. Therefore, it is important that the institution address whether the samples will be for internal use only, made available to external academic collaborators, provided to external industry partners and/or potentially shared with international collaborators. Once questions around future sample use are addressed, the institution must also address whether and how available clinical and phenotypic information will be linked to and available for use with the stored samples. The availability of this information and specifically its breadth and depth is vital to the utility of the stored samples for future research purposes. From a strategic standpoint, institutions must decide whether to store consent documents (and in most cases a HIPAA (Health Insurance Portability and Accountability Act) authorization) in the medical record, thereby creating a link to all available clinical information. Alternatively, institutions may elect to obtain permission at the time of consent to recontact the patient in the future if there is a need to link their stored sample to their available clinical information.

Both of these decisions present unique challenges, including associated upfront investments in time and resources or increased burden at the time of sample use. Some of these challenges may be addressed at the time of sample distribution; however, most important is that the consenting documents used to allow the acquisition of samples into the biobank completely address each one of the institutional decisions related to the planned use, desired strategy for sharing, and plans for linking data to the stored samples. This will ensure that the patients and families provide an adequate consent to cover the desired future uses of the samples. Creating and maintaining a biobank requires a significant investment, and learning years down the road, after tens of thousands of people have been consented, that the consents obtained for the samples are not adequate for the desired uses of the samples is a disastrous error that could mark the failure of a biobank. However, this vulnerability can usually be easily mitigated with sufficient and robust advanced planning.

Within the context of a pediatric setting, biobank managers may find a significant value added from engaging both parents and children in the planning process, particularly regarding the development of consent documents and processes as the interests of the biobank, the research community and parents and children are not necessarily the same (Avard et al. 2011). From an IRB oversight perspective the literature generally supports the notion that the consent/permission of one parent is typically sufficient (Brothers et al. 2014). In the spirit of meeting the ethical underpinnings of the Belmont Report, institutions should also consider the need to provide developmentally-appropriate materials to explain the biobank. Importantly these documents should address the questions of how, why and by whom would the minor's stored samples be used in the future. Although there is some variability in the literature on this topic, a reasonable approach would be to consider directly engaging the great majority of children in a formal assenting process around the ages of 10 or 11 (Brothers et al. 2014). Lastly, with regard to pediatrics, and of specific importance to informaticians charged with developing and maintaining systems to support biobank operations, if the biobank will retain any ability to identify a specific sample, donor systems should support the tracking of patient age such that the biobank can be alerted when a patient reaches the age of majority (typically 18 years of age), triggering processes to secure the independent adult consent of the patient for the continued use of the stored samples and/or for use of future samples collected and corresponding linked clinical data.

Once decisions driving the content of the consenting documents have been made by institutions, typically in collaborations with their IRBs, there is a need to address the method that will be used, at least initially, to obtain informed consent. Several options regarding how the research informed consent will be obtained and documented should be considered: (1) request IRB approval for a waiver of the requirement to obtain an informed consent; however, proposals from US Department of Health and Human Services (HHS) and others, in the Notice of Proposed Rule Making for Changes to the Common Rule (80 FR 53931 September 8, 2015) suggest that this option may be prohibited in future revisions to the federal regulations; (2) incorporate the biobank-related consenting language into the institution's standard consent for medical treatment; (3) similar to #2, require an additional affirmative acknowledgement regarding participation in the biobank, either as a proactive opt in or as an opt out, as part of the standard consent for medical treatment; (4) develop a specific standalone consenting document for the biobank but incorporate the execution of that consent into the institutional clinic registration process; or (5) similar to #4, execute the consent as a separate research consenting process by dedicated personnel. Each of these options presents its own unique risk and benefit profile. Among the proposed changes, in September 2015, release of the Notice of Proposed Rulemaking for Changes to the Common Rule would be a requirement for written consent for research involving any biospecimens. Interestingly, the proposed rule change is specific to biospecimens only and does not introduce a comparable new consenting requirement to access personal information. Public comment has overwhelmingly opposed this proposal for numerous reasons, including its potential impact on the ongoing operations of *existing* biobanks (Cadigan et al.

2015). Regardless, institutions developing biobanks should anticipate the need for robust consent and assent processes, driven by potential federal regulatory changes as well as by a growing expectation for increased and proactive patient/stakeholder engagement.

In support of the growing national consensus of the importance of patient and other stakeholder engagement, and given the complexity and sensitivity of the issues, institutions may benefit from seeking input from patients, families and local community representatives regarding their perception of biobanking, types of specimen sharing, linkage to medical record data and the consenting process. Although the opinions of patients and families may be colored by the realities of the diseases and conditions that afflict them, and although local community representatives will likely approach these issues from their own internal biases, remarkably consistent commentary has been obtained from these groups of stakeholders in our own experience which ultimately was utilized in the structure and implementation of our local biobank.

Although we leveraged considerable input from patient, family and community stakeholders we also made several internal strategic decisions regarding the overall purpose of our local biobank. Our decisions have resulted in some successes, such as a custom-built informatics interface with our electronic health record. This solution allows for easy presentation and documentation of a patient or guardian biobank consent decision during the regulatory clinic visit registration workflow. In our instance of the consent process, a variety of consent responses are available for participants: (1) Agreement to participate with a desire for return of incidental findings; (2) Agreement to participate with a prohibition on the return of incidental findings; (3) Consent deferred or undecided; (4) Decline to participate. The decision of the patient or guardian is recorded in the electronic medical record system, which is then tracked with any potential biobank's sample in the acquisition and management system. Consistent with local IRB approval requirements, patients over age 10 are engaged in a verbal assenting process, with no specific requirement to document the assent decision.

With regard to the design of an informatics platform it is important to clearly distinguish "consent deferred" from "decline to participate". "Consent deferred" indicates that the patient/family is unable to make a decision or that the registration team decides based on clinic flow/volume that there is not time to sufficiently present the biobank consent at the time of registration. This option is anticipated to be temporary and will terminate when the patient or guardian either obtains additional information or presents at another clinic with sufficient time to consider participation in the biobank. In contrast, "decline participation" is a definitive choice of the patient or guardian regarding the use of their residual clinical samples as part of the biospecimen repository. This is intended to be a more permanent decision with the consenting system holding that refusal for 1 year following the decision, at which point the patient again becomes eligible to be approached regarding study participation. Finally, research participants must always be able to withdraw from a study. Therefore, an informatics platform supporting a biobank must be able to capture a withdrawal of consent, inclusive of its effective date, to ensure no confusion when samples are considered for collection or release (see Sample Retention).

More broadly, informatics input into storing and propagating consent data is essential. At the most basic level, researchers must track consent information corresponding to each study sample. Storage and tracking capacity of said data is not usually offered or managed by sample tracking systems. With regard to biobanks that will store samples collected from children, it may also be important to store information like the child's date of birth, as well as information about the person that provides the parental consent (e.g. name and relationship). This information may be needed for verification, especially if questions about the validity of the parental consent are raised at a later date. For an institutional biobanking effort, this is a daunting challenge and can only be accomplished using an informatics solution. Additionally, although there is some debate around how much effort institutions should expend in contacting and obtaining consent from a research participant once they reach the age of majority, generally biobanks should be prepared to engage in some level of effort to obtain a typical research consent from minors once they reach the age of majority, unless samples in the biobank are stored in a completely anonymized manner (Brothers et al. 2016). Biobanks are encouraged to proactively engage with their local IRBs in developing and understanding the limits of these efforts, including the ability to continue using samples once attempts to secure adult consent have been exhausted.

7.6.2 Return of Incidental Findings

Other than issues related to how consent is obtained, the other most significant ethical challenge facing biobanks is how they will manage the discovery of secondary and incidental findings. These terms are sometimes used interchangeably; however, for our purposes, we will differentiate these terms. "Secondary findings" are those findings that are discovered as a result of proposed future research involving banked samples. In general, biobanks should expect that researchers planning such secondary research projects should incorporate plans for handling/reporting secondary findings as part of the research plan. In the case of this future research and potentially important secondary findings, biobank personnel need to ensure that the consents used to obtain and store the biobank samples allow the proposed future research, and that any institutional assurance will be followed.

Any discussion of biobanking in the post-genomic era would be incomplete without a meaningful discussion of return of 'incidental findings'. This group of findings represents information that is learned about an individual that is unexpected or otherwise goes beyond the scope of the planned research or clinical evaluation. At the close of the twentieth century, bioethicists believed return of research results should occur rarely, if at all (National Bioethics Advisory Commission 1999). Yet, this position was never universally accepted, and bioethicists have moved toward an ethical obligation to return incidental findings to research participants, grounded in the Belmont Report's principles of respect for persons, beneficence, and justice (Presidential Commission for the Study of Bioethical Issues 2013; Kohane et al. 2007; Wolf et al. 2008) Current guidelines for adult and pediatric biobanks suggest

that if incidental findings are to be returned, then the possibility should be raised when informed consent is obtained (Brothers et al. 2014; Presidential Commission for the Study of Bioethical Issues 2013; Jarvik et al. 2014). Some have argued that if biobanks *have* genetically based incidental findings on hand, they are ethically obligated to return them, but they are not obligated to *search* for incidental findings (Jarvik et al. 2014). Others have argued that certain incidental findings are so important, they must always be sought and returned (Green et al. 2013). Given the ongoing debate about what results should be returned, including whether or not certain results are even actionable in a pediatric settings, some have suggested it is acceptable for a biobank to choose whether they wish to return results obtained from pediatric samples (Brothers et al. 2014).

Implementing a strategy to meet a perceived ethical obligation to return incidental findings can be challenging and requires understanding values and preferences of the local community. We designed a consenting process with two levels of participation. One level (participation with return of incidental findings) allows the patient or guardian to receive information regarding individual, clinically actionable incidental findings discovered during future research with the stored samples. A second option (participation without return of incidental findings) allows samples to be included in the biobank with the understanding that there is no mechanism for returning incidental research findings to the patient or guardian. Consultation with our local community has greatly informed our strategy. As described, during the consenting procedure, the patient or guardian is asked if they would like incidental findings returned or not. This selection is recorded as a component of the consent document; however, this recorded decision only allows our institution to initiate a multiple step process to evaluate whether a particular incidental finding is eligible for return. We will consider several of the major components of this process in more detail below; however, in general if researchers believe that they have learned important incidental information about a particular sample the recommended procedure follows the algorithm in Fig. 7.1

In executing this algorithm the IRB is attempting to establish a framework for what results should be returned; who should return them and who should receive

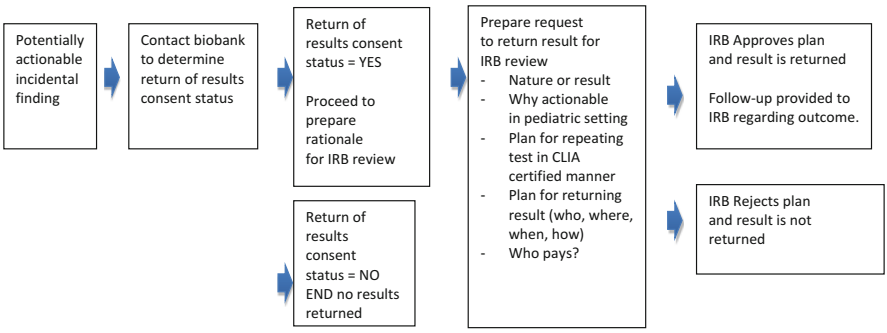

Fig. 7.1 Algorithm for incidental finding return

these results; how the results should be returned; and what additional obligations researchers and clinicians have to ensure participants have sufficient resources to act on the report of incidental findings (Wolf et al. 2008; Fernandez et al. 2003). All of these issues are further complicated in pediatric settings by the tripartite relationship among clinician, child, and parent and the evolving intellectual capacity of pediatric, especially adolescent, patients.

7.6.3 What Results Should Be Returned?

Bioethicists argue that results that can be actionable ought to be returned. "Actionability" covers three areas: (1) clinical utility, (2) reproductive planning and decision making, and (3) life-planning and decision-making (e.g., reporting *APOE4* which increases risk for Alzheimer's). While this standard seems intuitive, it is complicated by two factors. Research results are not always obtained with an FDA approved test and their significance is not always clear (Bookman et al. 2006; Miller et al. 2008; Shalowitz and Miller 2005). In order to be FDA approved in the United States, a test undergoes extensive testing and validation to ensure that the test is robust and results are both specific and sensitive. Tests that are not approved are of less certain validity. Also, many research laboratories are not CLIA certified to perform clinical testing (Wolf et al. 2008; Bookman et al. 2006; Clayton 2005). In the United States, clinicians and researchers are currently faced with an ethical conundrum brought on by narrowly interpreted CLIA regulations versus HIPAA privacy regulations. Specifically, while it makes sense to simply inform a patient and/or clinician of a non-validated research lab result that may need to be clinically validated in a CLIA-certified lab, doing so is interpreted by some as a CLIA violation that may invoke potential monetary penalties, since patients and clinicians may be tempted to use the results for clinical/diagnostic purposes. This concern is not supported by HIPAA regulations which suggest that the patient has a right to any information in possession of the healthcare entity that might be relevant to the individual's current or future health.

The landscape for evaluating incidental findings is further complicated in a pediatric setting when faced with an incidental finding about an adult-onset condition. IRB(s), ethicists and biobank professionals are faced with the decision of whether incidental findings for adult onset conditions (e.g., *BRCA1* and *BRCA2* mutations that increase risk for breast cancer) should be returned to a child or guardian based on the consent of the parent or guardian, or if the child should be given the right to consent to having their results returned once he/she reaches the age of 18. An American College of Medical Genetics (ACMG) policy statement suggested that large-scale biobanks and genomic studies should return results for 56 genes with clinical significance for life-long and adult-onset conditions (Green et al. 2013), but a joint ACMG-American Academy of Pediatrics policy statement advises that children should not be tested for adult onset conditions (American

Academy of Pediatrics 2013). While these statements do not directly address the issue of incidental findings in minors, they establish a framework for differentiating the burden for return of incidental findings in pediatric versus adult patients.

7.6.4 Who Should Return Results and Who Should Receive Them?

There is no consensus on who should return incidental findings from research. While researchers may be most familiar with the science supporting the results, they may not have the appropriate clinical experience or training and most likely lack the requisite genetic counseling experience to effectively explain results to participants (Avard et al. 2011; Wolf et al. 2008; Bookman et al. 2006; Sharp 2011) There is also concern about researchers contacting individuals with whom they have never had contact, e.g., as in research performed on stored samples (Wolf et al. 2008). On the other hand, primary healthcare providers will have a rapport with their patient and his or her parents or guardians, but the primary healthcare providers are not likely to have the expertise to interpret the results of genetic tests, especially those that are not frequently performed in a clinical setting. Typically in these circumstances the preferred approach is to have a qualified professional genetic counselor involved in the return of any unusual genetic result, including incidental findings. Finally, there is the challenge of providing results to providers and patients in an easily accessible format. The electronic health record has been identified as an ideal vehicle of returning information (Brothers et al. 2016); however, the EHR cannot be used when research results come from non-CLIA approved laboratories. In research-intensive institutions, a research patient data warehouse, research registries, and special software applications to connect researchers with patients may need to be developed (See Chap. 6, Data Governance and Strategies for Data Integration). As described previously, the role of the institutional IRB should not be overlooked in developing these processes to be certain they comply with applicable institutional policies, laws and regulations.

There is also some question about who should receive results. As discussed previously, it is fairly well established that participants in a biobank or similar research study should be given the opportunity either to request that available incidental findings be returned or to refuse return of such results (Wolf et al. 2008; Fernandez et al. 2003; Bookman et al. 2006; Clayton 2005). Yet, some argue that others, such as immediate family members, might benefit as well, in the event that serious health risks are identified (Avard et al. 2011; Black and McClellan 2011). Pediatric research raises additional complications since minors, including older adolescents, do not technically have the authority to make decisions related to return of results, and no clear guidance exists for managing the ethical issues raised when parents and older adolescents strongly disagree on whether a result should be returned (Avard et al. 2011; Wolf et al. 2008). While current regulations allow researchers to return

these results to parents or guardians, the ethical reservation remains that current and future autonomy is compromised when results are returned over the objection of an adolescent. Additionally, there is a concern that parents or guardians may make decisions regarding return of genetic results that do not represent any change in clinical risk during childhood. Patients are consented for enrollment in the biobank during registration at their initial visit to our hospital. As part of our institutional broad-based consent project, Better Outcomes for Children, parents or guardians of patients have been asked to provide consent for utilization of residual clinical samples; over 80% have agreed to participate and have asked to be informed of results that the institution believes are indicators of a major disease that may be prevented or treated or any findings that the researcher deems would affect the subject's medical care.

7.6.5 What Is Owed to the Research Subject?

A final question to be considered is what is owed to the subject. If subjects agree to enroll in a biobank, it is impossible to identify all future research that might occur with those samples. Neither research subjects, the researchers, or biobank staff can anticipate what information will be produced. Therefore, a plan must be developed to help participants understand and process information relevant to incidental findings. Yet, the extent of that help is hard to define. Grants that support research rarely (if ever) provide resources to counsel participants, and researchers do not have external financial resources to contribute. Specific guidelines about additional support are still being developed, although a consensus seems to be developing that the minimal requirements include referral to additional sources of relevant expertise or services such as genetic counseling (Wolf et al. 2008; Bookman et al. 2006; McCullough et al. 2015).

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