Review

Biobanking of Residual Specimens from Diagnostic Genetic Laboratories: Standard Operating Procedures, Ethical and Legal Considerations, and Research Applications

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Clinical applications of high-throughput technologies such as microarray analysis, next generation sequencing and tandem mass spectrometry have significantly improved the diagnostic performance and research capacity for many genetic diagnostic laboratories. Biobanking of patients' residual specimens and test records could be a useful resource for further research applications but related technical, ethical and legal issues need to be resolved. In this review, standard operating procedures and laboratory information management system for short-term and/or long term storage of residual original patient specimens and processed patient specimens have been outlined. To comply with current ethical and legal requirements, procedures for case-oriented consent, general informed consent and waiver of consent as well as methods for returning incidental findings and individual research results have been summarized. Diagnostic residual specimens have been used in many research projects to improve clinical quality and to characterize genetic defects for underlying disease-causing mechanisms. The advantages and disadvantages of diagnostic biobanking for research applications have been discussed. A model of 'Diagnostics-Biobanking-Research-Returning' is proposed to promote rapid transition and effective collaboration from diagnostic to research and eventually provide better preventive and therapeutic approaches for patients with genetic disorders.

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INTRODUCTION

In the United States, genetic testing has been performed for patients with suspected constitutional and somatic genetic defects by CLIA (Clinical Laboratory Improvement Amendments) certified laboratories specialized in cytogenetics, biochemical genetics and molecular genetics. Clinical cytogenetics laboratories analyze chromosomal abnormalities and genomic copy number variants from various types of patient specimens including peripheral blood (PB), amniotic fluid (AF), chorionic villus sample (CVS), bone marrow (BM) and skin biopsy. Biochemical genetics laboratories detect inborn errors of metabolism through the analysis of metabolites and/or enzymatic functions from plasma, serum, urine, cerebrospinal fluid (CSF) and cultured skin fibroblasts. Molecular genetics laboratories use various methods to detect disease-causing mutations from extracted DNA or RNA samples. After reporting test results and archiving patient's test records (PTRs), most diagnostic laboratories will store residual original patient specimens (ROPSs) and processed patient specimens (PPSs) for a defined period of time. Many ROPSs and PPSs with unique clinical indications and specific abnormal findings or those collected at critical disease stages are of great value for validating new genetic testing and characterizing disease mechanisms.[1,2] Rapid advance in genomic technologies and their immediate applications onto diagnostic services have significantly improved the abnormality detection rate and have demanded more efforts to elucidate disease mechanisms and to develop preventive and therapeutic approaches.[3-5] A smooth and rapid transition from diagnostic practice to research applications could be beneficial and cost-effective towards the best interests of the patients and society. However, several technical hurdles and legal and ethical issues need to be resolved. Firstly, diagnostic laboratories need to build a physical biobanking facility and a management system within the current service infrastructure.

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Secondly, general informed consent or a waiver of consent from an institutional review board and methods of returning clinically significant research results should be considered. Thirdly, mechanisms for independent and collaborative multi-center or international research projects on clinical quality improvement, disease-causing mechanisms and preventive and therapeutic approaches should be developed. We reviewed the current guidelines and literature to outline the technical procedures and general consensus on legal and ethical requirements for biobanking diagnostic residual specimens. We also presented typical examples of translational and basic research applications using residual diagnostic specimens and associated clinical data.

STANDARD PROCEDURES FOR BIOBANKING RESIDUAL SPECIMENS

American College of Medical Genetics and Genomics (ACMG) guideline states that various components of a PTR should be maintained for time periods as shown in the specialty standards or as required by specific state laws. In general, PTRs and duplicated copies are kept for one generation (20 years). Specialty-specific standards recommend that any ROPSs and PPSs are retained until requested analysis is completed and the final report has been signed. Long-term retention of those with abnormal results is at the discretion of the laboratory director.[6] Biobanking of diagnostic residual samples for research applications is a systematic upgrade of current diagnostic practice with a built-in physical long-term storage facility and an extended laboratory information management system (LIMS).

Standard Operating Procedures for ROPS and PPS

The fresh ROPSs (PB, BM, CVS, AF, skin and tissues) and PPSs of various types of cultured cells are of most potential for research applications because they could be used to extract DNA, RNA and proteins and possibly transformed into cell lines for functional analysis. Cryopreservation in liquid nitrogen has been the standard operating procedure for cell suspensions from ROPSs and cultured cells. Due to the high cost in sample processing and storage maintenance, this procedure should be considered only for cases with unique clinical phenotypes and/or significant diagnostic findings. Prior to storage, mononuclear cells are isolated from PBs by density gradient centrifugation using Ficoll-Plague, in situ cultured cells can be trypsinized and fresh tissue can be treated with collagenase to release single cells. Collected cell suspensions are mixed with complete medium (including fetal bovine serum) with 10% final concentration of dimethyl sulfoxide (DMSO). The cell concentration should not be less than $2x10^6$/ml. Aliquots (~ 1ml) of cell suspension are immediately transferred to pre-cooled (-20^{o}C) cryovials, placed into a freezing isopropanol container for gradual freezing with a cooling rate of 1^{o}C/min to below -20^{o}C and then moved to a liquid nitrogen tank for long term storage. Cell viability analysis by trypan blue exclusion and cell identity by karyotyping and genotyping could be introduced as quality control procedures. A recent analysis on the effects of long-term cryopreservation of blood progenitor cells noted that cells frozen up to 10 years showed no loss of clonogenic capacity but longer storage may affect cell viability and activity.[7]

Different storage methods have been used for different types of PPSs. Liquid PPSs such as plasma, serum, CSF and urine can be directly frozen in -20^{o}C for short term storage (1~3 years) or -80^{o}C for long term storage (> 3 years). These PPSs are usually stored for validating new tests and evaluating laboratory proficiency. Selected biomarkers with known reference values could be used in quality control procedures for these PPSs. Cell pellets kept in Carnoy's fixative from a cytogenetics laboratory can be stored at room temperature for 1~3 months. The gradual evaporation of methanol will leave the cell pellet mostly in acetic acid and likely affect the metaphase quality for chromosome analysis. Long-term storage of cell pellets in -20^{o}C freezer can be used for chromosome analysis, fluorescence in situ hybridization (FISH) and DNA extraction. High molecular weight DNA extracted from fixed cell pellets stored up to nine years can be used in Southern blot, PCR analysis and chromosome microarray analysis, but the integrity of DNA on the nucleotide level from long-term storage has not been examined.[8,9] Cell slides can be stored at room temperature for 3~5 years but their research usage is limited to in situ FISH mapping. Residual DNA samples could easily be stored in -20^{o}C and -80^{o}C freezer and then directly used for genetic study. Residual DNA samples from fresh and archived dried blood spots of biochemical newborn screening programs have been considered a rich resource for large scale genetic epidemiology studies. The quality and functionality of these DNA samples have been accessed and quality control guidelines have been introduced.[10] DNA quantitation, gel electrophoresis and genotyping can be used as quality control procedures to ensure the quality and identity of stored DNA samples. Extracted RNA is sensitive to RNase degradation and should be processed in a RNase-free environment and stored in special collection tubes with RNA stabilization medium.[11] Several methods, such as microfluidics-based systems to calculate an RNA integrity number (RIN) or an RNA quality indicator (RQI) and a reference gene/target gene 3':5' integrity assay, can be introduced as quality control procedures.[12] **Table 1** lists the types of ROPSs and PPSs from cytogenetics, biochemical genetics and molecular genetics laboratories, their storage conditions and quality control procedures.

LIMS and QC/QA Procedures

Almost all diagnostic laboratories have a validated LIMS with properly designed functional modules for every aspect of the laboratory workflow including data entry, result entry, administrative and system maintenance.[13] The LIMS must have a security system to safeguard patient confidentiality and sufficient back-up to prevent interruption and data loss. A module for biobanking of residual samples can be built into the LIMS. The module can be used to de-identify or code PTRs, ROPSs and PPSs and to track the date, type, quantity, quality and usage. Additionally, this system can map the input and outputs to re-identify the source materials and data of research results for potential return to patients.[14]

Table 1. Diagnostic residual specimens, their storage conditions and quality control procedures.*

Laboratories	Residual Specimens		Storage Conditions	Storage Time	Quality Control Procedures	Refs.
Cytogenetics	**ROPS:**	PB, BM, CVS, AF, Skin	Cryopreservation	~10 yrs	Viability, Karyotype, genotype	7
	PPS:	Cultured Cells	Cryopreservation	~10 yrs	Viability, Karyotype, genotype	7
		DNA	Frozen (-20°C; -80°C)	>20 yrs	AS, GE, Genotype	10
		Cell pellet	Frozen (-20°C; -80°C)	~3-10 yrs	Karyotype, FISH	8, 9
		Slide	Room Temperature	~3 yrs	Karyotype, FISH	
Biochemical Genetics	**ROPS:**	PB, Urine, Skin, CSF	Frozen (-20°C; -80°C)	3~10 yrs	Selected biomarker	7, 10
	PPS:	Cultured Cells	Cryopreservation	~10 yrs	Viability, Karyotype, genotype	7
		Plasma, Serum	Frozen (-20°C; -80°C)	~3 yrs	Selected biomarker	
		CSF	Frozen (-20°C; -80°C)	~3 yrs	Selected biomarker	
		Urine	Frozen (-20°C; -80°C)	~3 yrs	Selected biomarker	
Molecular Genetics	**ROPS:**	PB, BM, CVS, AF, Skin	Cryopreservation	~10 yrs	Viability, Karyotype, genotype	7
	PPS:	DNA	Frozen (-20°C; -80°C)	>20 yrs	AS, GE, Genotyping	10
		RNA	Frozen (-80°C)	> 3 yrs	AS, RIN, RQI, 3':5' integrity assay	11, 12

*ROPS, residual original patient specimen; PPS, processed patient specimen; PB, peripheral blood; BM, bone marrow; CVS, chorionic villus sample; AF, amniotic fluid; CSF, cerebrospinal fluid; AS, absorption spectrophotometry; GE, Gel electrophoresis: RIN, RNA integrity number; RQI, RNA quality index.

Table 2. Ethical and legal requirements on biobanking diagnostic residual specimens for research use.

Requirements	Interactions	Essential Elements
Informed Consent		
Case-oriented consent	Patient >> Physician	Patient and legal guardian to physician, use of clinical data for educational and research, returning results
General informed consent	Patient >> Physician	Patient and legal guardian, open consent for research use, benefits and risks, privacy and confidentiality, returning of IFs and IRRs
Waiver of consent	IRB <<>> Lab directors	Institutional review board (IRB), exempt studies design, de-identified or coded, re-identify and returning of IFs and IRRs
Research Applications		
	Lab directors <<>> Researchers	Material transfer agreement, clinical quality improvement, case series, case-control, collaborative methods of returning results
Returning of IFs & IRRs		
	Researcher >> Lab director	Valid and confirmed results
	Lab directors >> Physician	Significant clinical implications and actionable treatment
	Physician >> Patient	Supplemental diagnostic report to physician, clinic visit

ETHICAL AND LEGAL CONSIDERATIONS

Guidelines for Human Biobanks in a Research Setting

Hundreds of biobanks for population-based and disease-specific genetic research have been developed and many guidelines and position papers pertaining to the storage and use of biological tissue samples have been proposed by governance and professional organizations.[15,16] The Organization for Economic Cooperation and Development (OECD) with 30 member countries published "Guidelines for Human Biobanks and Genetic Research Databases".[17] These guidelines describe in details the rights and benefits for participants (donors) and the legal frameworks, ethical principles and technical requirements for operators and researchers. The participants should be fully respected for their human rights and freedoms, be securely protected for their privacy and confidentiality, and be clearly informed with the foreseeable risks and benefits from research findings including related intellectual property and potential commercial products. Careful consideration should be given to any special issues related to the participation of vulnerable populations or groups such as children, pregnant women, prisoners and psychiatric patients. Informed consent should be obtained from all participants or from the legal guardians of children although waiver of consent can be judged by an institutional review board or ethics committee. The biobank operators should develop and maintain policies complying with ethical and legal requirements and clearly documented operating procedures for the procurement, collection, labeling, registration, processing, storage, tracking, retrieval, transfer, use and destruction of human biological materials and related data. The researchers should present aims and scope of their research projects to get access and use of de-identified or anonymized materials and data. They are also required to publish research findings and return significant results to operators and/or re-identified participants. The goals for developing and implementing these guidelines are to ensure that the collection and use of biobanking materials and data are scientifically, ethically and legally appropriate.

Ethical and Legal Considerations for Diagnostic Biobanking

The biobanking of diagnostic residual specimens for research applications should follow the OECD guidelines. However, the interactions among participants (patients), operators (clinical and laboratory geneticists) and researchers could be quite different in a clinical setting, which in turn affects the informed consent procedure, the method of returning results and the scope of research applications. Unlike the prior informed consent and volunteering recruiting procedure for a research biobank, the patient's specimen is delivered to a diagnostic genetics laboratory based on the clinical indications determined by a referring physician. No explicit written consent is required for the processing and storage of patient specimen. Many physicians will obtain consent for using patient's materials and associated clinical data for educational and research purposes. This case-oriented informed consent has been the routine for many clinical case reports of unique or novel genetic abnormalities. The idea of a general or open consent has been recommended as a more practical model, in which patients would give a general consent regarding the use of their residual samples in medical research without receiving previous notification about the details of the research.[16] Clinically-oriented recommendations on essential content and the process of informed consent for diagnostic whole-genome sequencing have been proposed.[18] The elements to be included in the informed consent are pre-testing counseling, procedure description in comparison with alternative methods, benefits and risks, privacy and confidentiality for patients and their relatives, storage of residual specimens and future use of test results, and management of incident findings (IFs). Given the fact that residual diagnostic specimens are a rich source for translational research and that re-contacting patients for consent may be unfeasible or unpractical, waiver of consent can be assessed by an institutional review board for exempt studies deemed to have minimal or no risk and performed on anonymous or de-identified patient materials and data.[19] The exempt studies usually involve in the analysis of existing data, documents, records, pathological or diagnostic specimens provided that these sources are publicly available or the information has been de-identified or anonymized. Exemption status does not obviate other obligations and researchers should be prepared to respond to any issues that arise in the course of exempt research to ensure minimal or no risk and possible benefit of returning significant findings. For multi-center or international collaborative research projects, material transfer agreements are generally used and accepted as binding contract when samples are exchanged from the biobank operator to researcher.[20]

Recently, ACMG released recommendations on returning IFs from high through-put genomic analysis with a list of mandatorily reported pathogenic variants on 57 genes for 24 disorders.[21] There have been debates on the pros and cons of laboratories' obligation to report clinically beneficial IFs and the patients' autonomy to deny IF disclosure, which opens more in-depth discussion on the ethical issues and will likely lead to further modifications on the recommendations.[22,23] Another challenging situation for a diagnostic laboratory is the identification of variants of unknown clinical significance. Follow up analysis on both parents to determine if these variants are de novo or familial is recommended routinely. Further functional analysis on de novo variants and likely pathogenic familial variants is warranted. The rationale on the returning of these individual research results (IRRs) are: 1) the results are scientifically valid and confirmed, 2) the results have significant implications for the patients such as causing early-onset treatable or preventable diseases, and 3) a course of action to ameliorate or treat these diseases is readily available.[24-26] **Table 2** lists the elements for informed consent and returning IFs and IRRs.

The concerns of legal or ethical violations by clinical geneticists and diagnostic laboratory staff have been the major barrier towards the use of diagnostic collection of DNA samples for research.[27] The trend of international guidelines have moved towards presumed consent of possible research uses of diagnostic samples or waiver of consent on de-identified or anonymized clinical materials and data.[20,27] Research applications using resourceful diagnostic residual

specimens should be more practical by fulfilling the ethical and legal requirements and complying with international guidelines.

RESEARCH APPLICATIONS

In the post Human Genome Project era, rapid advances in high-throughput genomic technologies and their immediate diagnostic applications have changed the scope and depth of genetic and genomic medicine. On the technical front, diagnostic laboratories need continuous efforts to improve the quality and efficacy through evaluation and validation of novel technologies. As a routine quality control practice, residual diagnostic specimens with known abnormalities are commonly employed for intra-laboratory validation of new reagents and methods and for cross-laboratory proficient testing. On the clinical part, multiple lines of evidence for 'genotype-phenotype' correlations from individual case studies, disease-specific case series or large case-control studies are needed to warrant accurate interpretation and reporting of tested results. Guidelines and recommendations have to be developed based on peer-reviewed reports and experts' consensus from many diagnostic laboratories. This technology-driven and evidence-based clinical genetics practice relies heavily on the translational research to improve diagnostic quality and further basic research to dissect disease mechanisms and to develop better treatment strategies.[5]

Research on Clinical Quality Improvement

The Centers for Disease Control and Prevention (CDC) sponsored the development of a standardized and rigorous *ACCE* model to evaluate genetic screening and diagnostic tests.[28] The *ACCE* acronym derives from the four main domains evaluated: *A*nalytic validity (the ability of a test to measure the genotype of interest both accurately and reliably); *C*linical validity (the ability of a test to detect or predict the disorder/phenotype of interest); *C*linical utility (the risks and benefits associated with the introduction of a test into practice); and *E*thical, legal, and social implications (including both general issues as well as those specific to genetic tests). The principles of *ACCE* model have been applied onto the evaluation and validation of many in-use and newly-developed genetic tests. For instance, using residual DNA samples with normal karyotypes as controls and a known abnormality of 45,X as tests, a pyrosequencing-based high throughput assay has been validated as an accurate and rapid screening method for Turner syndrome.[1] The analytical validity of array comparative genomic hybridization (aCGH) was determined using receiver operating curve statistics on residual DNA samples from stored cell lines.[29] The clinical utility was also evaluated for pediatric, prenatal and cancer cases using selected residual DNA samples.[29-31] Further collaborative studies to access the diagnostic yield by a multi-center comparison and the International Standard Cytogenomic Array Consortium (ISCA) provided clinical evidence to support experts' consensus on making chromosome microarray as the first-tier genetic test for developmental disabilities and congenital anomalies.[3,32] Built upon the superior diagnostic results from many clinical laboratories using microarray technologies, ACMG published recommendations for diagnostic use of copy number microarrays.[33] The College of American Pathologists (CAP) developed proficiency testing for diagnostic microarray analysis.[34] The implementation of practice guidelines and proficiency testing indicates that the chromosome microarray analysis has been the 'gold standard' in clinical diagnosis of chromosomal and genomic imbalances.

Recently, many academic and commercial molecular laboratories have validated the whole-exome or whole-genome sequencing based disease-specific multi-gene panels for clinical diagnosis, which has revolutionized and transformed current medical genetic practice.[4] For example, residual samples with mutations in disease-causing genes characterized by Sanger-sequencing were used to assess the clinical validity of next generation SOLiD sequencing; the results showed 100% concordance on known mutations with false-positive rates of 5.88% for single nucleotide polymorphisms and 42.8% for deletions.[35] Guidelines for reporting IFs from whole exome sequencing and clinical laboratory standards for next-generation sequencing have been proposed by ACMG.[21,36] The practice standards and guidelines for interpretation and reporting of diagnostic whole-exome or whole-genome sequencing will soon be developed based on the accumulated clinical reports and experts opinions.

Case-Oriented and Disease-Specific Studies

Follow up studies on cases diagnosed with unique and novel genetic defects have led to the identification of many disease-causing genes. Diagnostic microarray analysis delineated the genomic coordinates and gene content for chromosomal imbalances, which allows fine mapping of critical regions harboring dosage-sensitive genes and results in more informative genetic counseling.[37,38] Further molecular analysis of a patient with a balanced 9q/13q translocation mapped the genes flanking the breakpoints and revealed the over-expression of the α-Klotho gene as the cause of the hypophosphatemic rickets and hyperparathyroidism.[39] The identification of potentially pathogenic variants with no obvious clinical relevance or variable phenotypes could provide useful information tackling clinical and genetic heterogeneity likely caused by variable expressivity and modifying effects.[40,41] Follow-up familial studies and possibly further functional analysis on many variants of unknown clinical significance have been the standard in many diagnostic laboratories. A study of incidental copy number variants detected from 9,005 patients revealed the genes potentially conferring susceptibility to adult-onset disease, some of which may be medically actionable.[42] For diagnostic laboratories, returning of IRRs and significant IFs can be done through a supplemental report to the referring physicians.

Due to the low frequency nature of gene mutations and/or genomic abnormalities in rare and complex diseases, an individual diagnostic laboratory will encounter a shortage of sufficient number of cases for a disease-specific cohort or a case-control study. Being aware of this problem, more and more multi-center and/or international research projects have

been developed through the collaboration of diagnostic laboratories. A successful example was the developmental genome anatomy project (DGAP), in which abnormal cases with a apparently balanced translocation were recruited from clinical cytogenetics laboratories to analyze encompassing and disrupting genes and their associated phenotypes of developmental disabilities and congenital anomalies.[2] Sequencing analysis of the DGAP case series revealed many candidate genes functioning in human neurodevelopment.[43] Diagnostic laboratories can also contribute their cases to disease-specific case-control studies as shown in a study on cardiovascular malformations with extracardiac abnormalities.[44] Furthermore, members from the ISCA and the Cancer Cytogenomic Microarray Consortium (CCMC) participated in the ACMG working group to develop recommendations, standards and guidelines for diagnostic interpretation of constitutional and somatic genomic copy number variants.[33,45] As the high throughput genomic technologies are getting more in-depth and large-scale applications, the diagnostic genetic laboratories will definitely play a more important role in both clinical service and translational research.

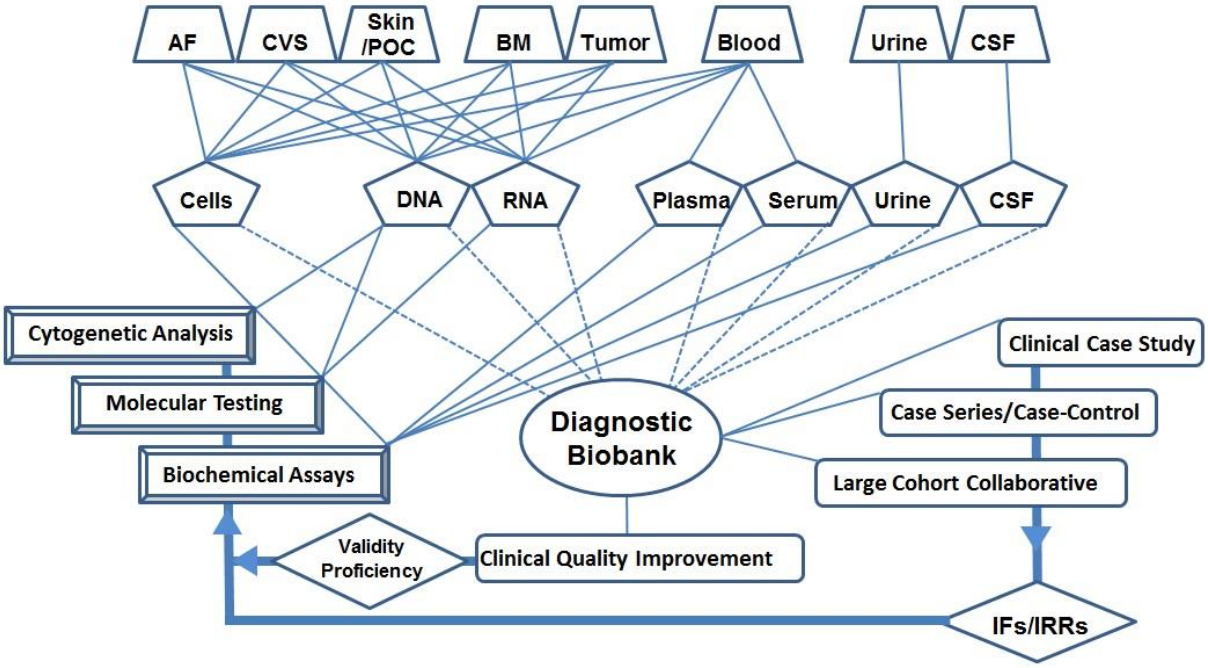

Figure 1. A Diagnostics-Biobanking-Research-Returning model for diagnostic genetic laboratories. Original patient specimens of amniotic fluid (AF), chorionic villus (CVS), skin biopsy, products of conception (POC), bone marrow (BM) and tumor tissues, peripheral blood, urine and cerebrospinal fluid (CSF) are processed to culture cells, extract DNA and RNA, purify plasma, serum, urine and CSF for cytogenetic analysis, molecular testing and biochemical assays. Residual original patient specimens and processed patient specimens are stored in a diagnostic biobank for clinical quality improvement and other translational research projects. Incidental findings (IFs) and significant individual research results (IRRs) are returning to diagnostic laboratories for reporting to referring physicians.

FUTURE DIAGNOSTIC BIOBANKING FOR GENETIC RESEARCH

Genetic diagnostics is shifting from a service-focused practice toward a service and research dual-function operation. This 'Diagnostics-Biobanking-Research-Returning' model is outlined in Figure 1. As described in the previous section, major academic diagnostic laboratories have used PTRs, ROPSs and PPSs to improve the quality of genetic diagnosis and to dissect disease causing genes and mechanisms. The advantages of diagnostic biobanking research are: 1) direct analysis on detected genetic defects most likely causing or predisposing to clinically defined phenotypes, 2) proper collection and storage of PTRs, ROPSs and PPSs for research is time-saving, cost-effective, and potentially beneficial for patients and general populations, 3) returning of IRRs and significant IFs could be built into a diagnostic laboratory's reporting routine to referring physicians and the patient could be followed up and treated in a clinical setting. However, there are also obvious disadvantages including: 1) extra efforts and funding are needed to process and maintain a biobanking facility, 2) the PTRs in a diagnostic laboratory could be incomplete and limited to a few clinical indications, 3) the insufficient amount or suboptimal condition of some ROPSs and PPSs can limit its value in research use, and 4) the banking materials may not meet the requirements for some large disease-specific case series and case-control genetic studies. For most genetics diagnostic laboratories, accurate and

timely diagnosis is always the first priority and biobanking of diagnostic residual specimens falls into secondary or even lower priority. Biobanking of diagnostic residual specimens may be more feasible for large genetic diagnostic centers with collaborative research activities and supportive funding. However, for small or medium diagnostic genetics laboratories, collection and storage of residual specimens with known normal or abnormal findings could be an important and useful resource for validating diagnostic methods and evaluating laboratory proficiency.

The importance of biobanking of large series of cancer cases including high quality samples and their associated data for translational cancer research has been recognized; comprehensive cancer centers developed networks to enable large-scale multi-center research projects.[46] Biobanking of oncological residual materials from pathological waste and biopsies of neoplasias in formalin has been a common practice in many Pathology Departments.[47] The development of a biobanking functionality into the current genetic diagnosis will promote rapid transition and effective collaboration from diagnostic to research and eventually provide better evidence for interpreting genetic findings and more effective preventive and therapeutically approaches for patients with genetic disorders.

CONFLICT OF INTEREST

None.

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REFERENCES

1. Rivkees SA, Hager K, Hosono S, et al. A highly sensitive, high-throughput assay for the detection of Turner syndrome. J Clin Endocrinol Metab. 2011;96(3):699-705.
2. Higgins AW, Alkuraya FS, Bosco AF, et al. Characterization of apparently balanced chromosomal rearrangements from the developmental genome anatomy project. Am J Hum Genet. 2008;82(3):712-22.
3. Xiang B, Zhu H, Shen Y, et al. Genome-wide oligonucleotide array CGH for etiological diagnosis of mental retardation: A multi-center experience of 1,499 clinical cases. J Mol Diagn. 2010;12(2):204-212.
4. Yu Y, Wu BL, Wu J, Shen Y. Exome and whole-genome sequencing as clinical tests: a transformative practice in molecular diagnostics. Clin Chem. 2012;58(11):1507-1509.
5. Wei Y, Xu F, Li P. Technology-driven and evidence-based genomic analysis for integrated pediatric and prenatal genetic evaluation. J Genet Genomics. 2013;40(1):1-14.
6. American College of Medical Genetics and Genomics: Standards and guidelines for clinical genetics laboratories. 2008 Edition, Revised 02/2007 (http://www.acmg.net)
7. Vosganian GS, Waalen J, Kim K, et al. Effects of long-term cryopreservation on peripheral blood progenitor cells. Cytotherapy. 2012;14(10):1228-1234.
8. Li S, Tuck-Muller CM, Yan Q, Wertelecki W, Chen H. A rapid method for PCR amplification of DNA directly from cells fixed in Carnoy's fixative. Am J Med Genet. 1995;55(1):116-119.
9. MacKinnon RN, Selan C, Zordan A, Wall M, Nandurkar H, Campbell LJ. CGH and SNP array using DNA extracted from fixed cytogenetic preparations and long-term refrigerated bone marrow specimens. Mol Cytogenet. 2012;5:10.
10. Sj?holm MI, Dillner J, Carlson J. Assessing quality and functionality of DNA from fresh and archival dried blood spots and recommendations for quality control guidelines. Clin Chem. 2007;53(8):1401-1407.
11. Duale N, Brunborg G, R?nningen KS, et al. Human blood RNA stabilization in samples collected and transported for a large biobank. BMC Res Notes. 2012;18(5):510.
12. Bustin SA, Benes V, Garson JA, et al. The MIQE guidelines: minimum information for publication of quantitative real-time PCR experiments. Clin Chem. 2009;55(4):611-622.
13. Xiang B, Hemingway S, Qumsiyeh M, Li P. CytoAccess: A relational laboratory information management system for a clinical cytogenetics laboratory. J Assoc Genet Technol. 2006;32(4):168-170.
14. Bemmels HR, Wolf SM, Van Ness B. Mapping the inputs, analyses, and outputs of biobank research systems to identify sources of incidental findings and individual research results for potential return to participants. Genet Med. 2012;14(4):385-392.
15. Hens K, Nys H, Cassiman JJ, Dierickx K. Biological sample collections from minors for genetic research: a systematic review of guidelines and position papers. Eur J Hum Genet. 2009;17(8):979-990.
16. Sandor J, Bard P, Tamburrini C, Tannsjo T. The case of biobank with the law: between a legal and scientific fiction. J Med Ethics. 2012;38(6):347-350.
17. OECD Organization for Economic Cooperation and Development. OECD guidelines on human biobanks and genetic research databases. Eur J Health Law. 2010;17(2):191-204.
18. Ayuso C, Millán JM, Manche?o M, Dal-Ré R. Informed consent for whole-genome sequencing studies in the clinical setting. Proposed recommendations on essential content and process. Eur J Hum Genet. 2013;21(10):1054-1059.
19. Bathe OF, McGuire AL, The ethical use of existing samples for genome research. Genet Med. 2009;11(10):712-715.
20. Kiehntopf M, Krawczak M. Biobanking and international interoperability: samples. Hum Genet. 2011;130(3):369-376.
21. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013;15(7):565-574.
22. Wolf SM, Annas GJ, Elias S. Point-counterpoint. Patient autonomy and incidental findings in clinical genomics. Science. 2013;340(6136):1049-1050.
23. McGuire AL, Joffe S, Koenig BA, et al. Point-counterpoint. Ethics and genomic incidental findings. Science. 2013;340(6136):1047-1048.
24. National Bioethics Advisory Commission. Research involving human biological materials: Ethical issues and policy guidance. Vol 1. Rockville, MD, 1999.
25. Hens K, Nys H, Cassiman JJ, Dierickx K. The return of individual research findings in paediatric genetic research. J Med Ethics. 2011;37(3):179-183.
26. Wolf SM, Crock BN, Van Ness B. et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genet Med. 2012;14(4):361-384.
27. Hens K, Nys H, Cassiman JJ, Dierickx K. The use of diagnostic collections of DNA for research: interviews at the eight Belgian centers for human genetics. Eu J Med Genet. 2010;53(5):274-279.
28. Gudgeon JM, McClain MR, Palomaki GE, Williams MS. Rapid ACCE: experience with a rapid and structured approach for evaluating gene-based testing. Genet Med. 2007;9(7):473-478.
29. Xiang B, Li A, Valentin D, Novak N, Zhao HY, Li P. Analytical and clinical validity of whole genome oligonucleotide array comparative genomic hybridization for pediatric patients with mental retardation and developmental delay. Am J Med Genet. 2008;146A(15):1942-1954.
30. Li P, Pomianowski P, DiMaio SM, et al. Genomic characterization of prenatally detected chromosomal structural abnormalities using oligonucleotide array comparative genomic hybridization. Am J Med Genet. 2011;155A(7):1605-1615.
31. Bajaj R, Xu F, Xiang B, et al. Evidence-based genomic diagnosis characterized chromosomal and cryptic imbalances in 30 elderly patients with myelodysplastic syndrome and acute myeloid leukemia. Mol Cytogenet. 2011;4:3.
32. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010;86(5):749-764.
33. Kearney HM, South ST, Wolff DJ, et al; working Group of the American College of Medical Genetics. American College of Medical Genetics recommendations for the design and performance expectations for clinical genomic copy number microarrays intended for use in the postnatal setting for detection of constitutional abnormalities. Genet Med. 2011;13(7):676-679.

34. Brothman AR, Dolan MM, Goodman BK, et al. College of American Pathologists/American College of Medical Genetics proficiency testing for constitutional cytogenomic microarray analysis. Genet Med. 2011;13(9):765-769.
35. Chin EL, da Silva C, Hegde M. Assessment of clinical analytical sensitivity and specificity of next-generation sequencing for detection of simple and complex mutations. BMC Genet 2013;14:6.
36. Rehm HL, Bale SJ, Bayrak-Toydemir P, Berg JS, Brown KK, Deignan JL, Friez MJ, Funke BH, Hegde MR, Lyon E. ACMG clinical laboratory standards for next-generation sequencing. Genet Med 2013;15(9):733-747.
37. Rossi MR, DiMaio M, Xiang B, et al. Clinical and genomic characterization of distal duplications and deletions of chromosome 4q: Study of two cases and review of the literature. Am J Med Genet. 2009;149A(12):2788-2794.
38. Wei Y, Gao XF, Yan LY, Xu F, Li P, Zhao YY. Prenatal diagnosis and postnatal follow up of partial trisomy 13q and partial monosomy 10p: A case report and review of the literature. Case Rep Genet 2012;821347:1-5.
39. Brownstein CA, Adler F, Nelson-Williams C, et al., A translocation causing increased α -Klotho level results in hypophosphatemic rickets and hyperparathyroidism. Proc Natl Acad Sci USA. 2008;105(9):3455-3460.
40. Khattab M, Xu F, Li P, Bhandari V. A de novo 3.54 Mb deletion of 17q22-q23.1 associated with hydrocephalus: A case report and review of literature. Am J Med Genet. 2011;155A(12):3082-3086.
41. Hoang D, Sue GR, Xu F, Li P, Narayan D. Absence of aneuploid and gastrointestinal tumors in a man with a chromosomal 2q13 deletion and BUB1 monoallelic deficiency. BMJ Case Reports 2013;doi:10.1136/bcr-2013-008684.
42. Boone PM, Soens ZT, Campbell IM, et al. Incidental copy-number variants identified by routine genome testing in a clinical population. Genet Med 2013;15(1):45-54.
43. Talkowski ME, Rosenfeld JA, Blumenthal I, et al. Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries. Cell. 2012;149(3):525-537.
44. Lalani SR, Shaw C, Wang X, et al. Rare DNA copy number variants in cardiovascular malformations with extracardiac abnormalities. Eur J Hum Genet 2013;21(2):173-181.
45. Cooley LD, Lebo M, Li MM, Slovak ML, Wolff DJ. Working Group of the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee. American College of Medical Genetics and Genomics technical standards and guidelines: microarray analysis for chromosome abnormalities in neoplastic disorders. Genet Med. 2013;15(6):484-494.
46. Riegman PH, Morente MM, Betsou F, de Blasio P, Geary P, Marble Arch International Working Group on Biobanking for Biomedical Research. Biobanking for better healthcare. Mol Oncol. 2008;2(3):213-222.
47. Caenazzo L, Tozzo P, Pegoraro R. Biobanking research on oncological residual material: a framework between the rights of the individual and the interest of society. BMC Med Ethics. 2013;14:17.