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Review

Preanalytical Variables Affecting the Integrity of Human Biospecimens in Biobanking

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BACKGROUND: Most errors in a clinical chemistry laboratory are due to preanalytical errors. Preanalytical variability of biospecimens can have significant effects on downstream analyses, and controlling such variables is therefore fundamental for the future use of biospecimens in personalized medicine for diagnostic or prognostic purposes.

CONTENT: The focus of this review is to examine the preanalytical variables that affect human biospecimen integrity in biobanking, with a special focus on blood, saliva, and urine. Cost efficiency is discussed in relation to these issues.

SUMMARY: The quality of a study will depend on the integrity of the biospecimens. Preanalytical preparations should be planned with consideration of the effect on downstream analyses. Currently such preanalytical variables are not routinely documented in the biospecimen research literature. Future studies using biobanked biospecimens should describe in detail the preanalytical handling of biospecimens and analyze and interpret the results with regard to the effects of these variables.

Biobanking involves the collection, processing, transport, storage (biopreservation), and retrieval of biospecimens for future purposes. Evidence-based practices are critical to the future of biobanking, but more research is needed. Many factors influence the analytical results in clinical biochemistry, i.e., preanalytical biological or environmental variability, preanalytical technical variability, analytical variability, and postanalytical variability (Fig. 1). The term preanalytical is defined as anything that comes before the analysis phase. Thus, in biobanking preanalytical handling is basically all processes that occur until the analysis of a biospecimen after it is removed from storage. Preanalytical variables are factors in handling that affect the integrity of the biospecimens, and later the results of analyses. Preanalytical variables can introduce in vitro modifications, either systematically or randomly, that adversely affect results. When the result of a test deviates from the expected, the analytical integrity of the results is often questioned rather than the preanalytical integrity of the result. The test analysis can be perfect but still get a wrong answer. Most errors in a clinical chemistry laboratory are due to preanalytical errors *(1–4)*. Preanalytical errors may result in inaccurate test results or systematic biases *(5)*. Assessing and controlling the preanalytical handling of biospecimens is fundamental for the optimal future use of biospecimens, because the quality of the study will depend on the integrity of the biospecimens.

The scope of this review is to cover the preanalytical variability affecting the integrity of human biospecimens in biobanking with a focus on blood, saliva, and urine as well as the DNA, RNA, and proteins derived from these biospecimens.

Preanalytical Factors in Biospecimen Collection

All biospecimens should be treated as biohazards and all processes involving biospecimens should adhere to principles of general laboratory safety. Collecting biospecimens in cohort studies is a balance between sample size, number and types of biospecimens, accrual rate, location, costs, transport logistics, and storage requirements. The resulting participation rate may depend on what is reasonable to request from a participant *(6)*. Handling protocols developed for one type of biospecimen research do not always apply for other types of research. Thus, the decision on what type and volume of biospecimens to include in a biobank for specific purposes affects all other downstream analyses and logistical processes.

The biospecimens collected may be invasive (e.g., blood), less-invasive [e.g., dried blood spot (DBS)[6]], or

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[6] Nonstandard abbreviations: DBS, dried blood spot; BMI, body mass index; ccfDNA, circulating cell-free DNA; miRNA, microRNA; 2-D, 2-dimensional; ACP, all-cell pellet; LIMS, laboratory information management system; SOP, standard operating procedure; BRISQ, Biospecimen Reporting for Improved Study Quality.

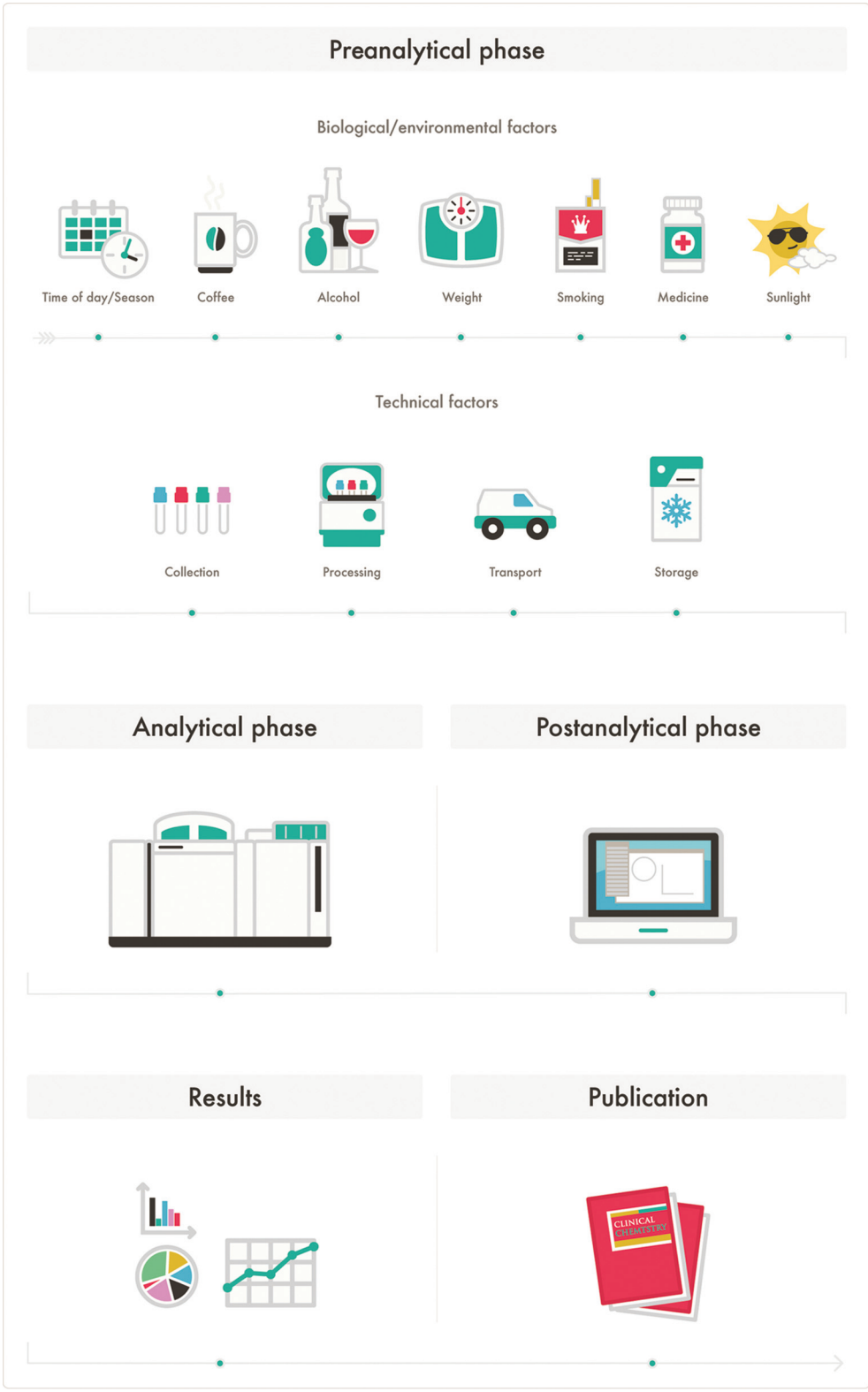

Fig. 1. Preanalytical, analytical, and postanalytical phases of the biobanking process.

Table 1. Advantages and disadvantages for major biospecimen categories.

Biospecimen	Advantages	Disadvantages
Blood	Most analyses possible	Patient-rest Requires trained staff Invasive: painful collection Number of tubes may affect participation rate Analytes are tube-additive dependent
Dried blood spot	Minimally invasive Easy collection No processing Easy room temperature transport Less painful Patient self-collection Small blood volume Equivalent to whole blood No processing Minimal risk Pediatric collection Long-term storage at room temperature Space-saving Cost-effective	No staff training: risk of disposal of samples due to bad collection technique Low or high hematocrit may interfere with analyses Too small blood volume: requires high sensitivity of analytical method
Urine	Noninvasive Easy collection Patient self-collection Pediatric collection	Transport and short-term storage on ice Contamination
Saliva	Noninvasive Easy collection Patient self-collection Pediatric collection DNA is only the donor's DNA Cost-effective Patients afraid of needles Minimal risk of contracting infections Suitable for large-scale collection Easy transport	Low concentration of analytes

noninvasive (e.g., urine or saliva). Blood, saliva, and urine are biospecimens commonly collected for clinical analyses *(7, 8)*. Less-invasive and noninvasive methods minimize use of valuable blood samples and may lead to an increased sample size of the study population owing to their reduced costs, ease of collection without specialized staff, and willingness of participants to donate *(9–11)* (Table 1). Issues concerning patients' willingness to donate are especially important in pediatric biobanking *(12)*.

Biological and environmental factors may also affect downstream analyses *(13–19)* (Table 2). The total variability of these factors may impact levels of analytes. Thus it is important that these factors are standardized, documented, and taken into consideration when interpreting results or comparing or pooling the results of studies. Repeated measurements from the same individual taken a few days apart may attenuate the effects of preanalytical and analytical variation. Serial measurements may also be taken with longer time intervals in between, to measure changes or effects of intervention over time.

In a clinical chemistry laboratory, preanalytical variables related to ordering or receiving biospecimens may also impact the quantity or quality of biospecimens (e.g., missed, incorrect, or duplicate collection; data entry error; incorrect patient or collector ID; insufficient sample; diluted sample; improper labeling; lost biospecimens) (Table 3). Furthermore, biospecimens may be obtained without consent, with a forgotten or lost consent, or a restricted consent, and their analytical value may thus be limited.

BLOOD

Collection of biospecimens should be carried out by trained staff, and blood collection from children requires staff with specialized experience in pediatric phlebotomy *(12)*. Professionalism of the collection personnel is important to ensure quality of the biospecimens and to avoid discomfort to the participants. Patients' willingness to participate may be negatively impacted if samples have to be retaken.

Table 2. Biological and environmental variability affecting downstream analyses measured in blood, urine, and saliva.

Biological variability	Environmental variability
Age	Seasonal changes
Sex	Temperature
Ethnicity	Humidity
BMI	Moisture
Menstrual cycle	Geographic location
Pregnancy	Altitude
Lactation	Sunlight
Diet	
Alcohol	
Medication	
Caffeine	
Smoking	
Fasting/nonfasting	
Exercise	
Posture	
Circadian variation	
Diurnal variation	
Hydration status	
Fever	
Disease	

Depending on the expected downstream analyses, multiple collection tube types involving different additives may be needed according to the anticipated immediate and future analyses *(20)* (Table 3–5). The composition of blood depends on the order in which blood is drawn; the first draw is the most representative *(21)*. Collection tubes are color coded according to the type of additive. The general clinical chemistry laboratory recommendation is to follow a special order of draw dependent on the additive in the tube to avoid cross-contamination among the tubes (departments of laboratory medicine have appropriate guidelines), but such a recommendation may have negligible effects on biospecimen integrity in closed-loop systems *(22, 23)*. The same tube brand, and preferably the same lot number (depending on the length of the study), should be used throughout the study and between studies (cases/controls, collaborations), because different brands may use different additives or anticoagulants, and lot-to-lot variation may introduce bias. Expiration dates on tubes should be checked, because the vacuum in evacuated systems decreases with tube age and can affect the blood draw and filling of the tube. Blood collection devices and components (tube stoppers, stopper lubricants, tube walls, surfactants, clot activators, and separator gels) may interfere with the endogenous analytes, add extraneous materials, or bind blood components *(24)* and thus result in a bias in downstream measurements of these elements. Differences in posture (standing, sitting, supine) cause changes in plasma volume resulting in hemoconcentration from supine to sitting to standing, and thereby increased analyte levels *(25)*. Using a too-thin needle may result in hemolysis, distorting results for hematological cell counts and potassium concentrations *(26)*. Prolonged use of a tourniquet results in hemoconcentration and changes in analyte concentrations *(14, 27)*. Although mixing is recommended by manufacturers of collection tubes, a recent study showed that lack of mixing did not lead to clinically significant differences in analytes compared to mixing *(28)*. Hemolysis, icteria, and lipemia may result in spurious and unreliable test results *(29)*. Inadequate filling will decrease blood/additive ratio, which may lead to inaccurate results *(30)*.

A rule of thumb for common analyses is that EDTA tubes are suitable for DNA (whole blood, buffy coat), hematology (whole blood), hemoglobin A_{1c} (glycated hemoglobin; whole blood), and a range of proteins (plasma) *(17)*. Sodium-fluoride tubes are suitable for plasma glucose *(17)*. Lithium-heparin plasma is suitable for a wide range of assays such as iron parameters, thyroid hormones, kidney function, liver enzymes, C-reactive protein, and other proteins *(17)*. Citrate-stabilized tubes are preferred for coagulation testing *(30)*. Coagulation testing requires special care. Excessive mixing of tubes may result in hemolysis or platelet clumping, leading to erroneous results *(30)*. Problematic phlebotomy collections may produce spurious activation of the hemostatis system and hemolytic specimens, and prolonged venous stasis may cause hemoconcentration and unreliable variations in many coagulation assays *(31)*.

DBS are an easy source of biospecimens that can be collected at remote sites in resource-poor areas *(19)*. DBS consist of small volumes (50–100 μL) of capillary blood collected from peripheral anatomic sites (Table 4) and deposited onto dedicated paper cards *(19)*. Samples should dry at room temperature in the horizontal position for 3–4 h. DBS should be rejected if they exhibit clotting, layering, supersaturation, insufficient volume, wetness, serum rings, visible traces of hemolysis, or exogenous contamination *(19, 32)*. The collection paper is inexpensive, relatively easy to manufacture, readily printed, and has good adsorption properties *(19)*. DBS may be used for various analyses *(19, 32, 33)* (Tables 4 and 5). Differences in paper type, the type of chemical used for treatment of papers (if not untreated), paper thickness, blood volume applied, and density and viscosity of blood may induce differences in extraction recovery, matrix effects, analyte stability, and chromatography effects in downstream analyses *(19, 32)*. The advantages

Table 3. General preanalytical variables, recommendations, and documentation requirements for biobanking of all biospecimens.

Step	Preanalytical variables	Recommendation	Documentation requirements
Ordering	Ordering forgotten	Laboratory information system	Date and time of ordering
			Other annotation to database: clinical tests, diagnoses, sociodemographic, other measurements
	Consent: none, forgotten, restricted, lost	Secure consent	Consent type
	Typing error	Check spelling	
	Incorrect patient ID Incorrect collector ID	Check IDs Scan IDs, avoid manual typing	Patient ID, name, sex, birthday, age Reference number Tube ID number Collector ID
	Pairing patient ID with primary tube ID	Check pairing	Label errors
	Improper labeling, mislabeling, no labeling	Stable adhesive and unique labeling Check labeling	
Collection	Biological and environmental factors (Table 2)	Follow/use evidence-based literature and guidelines for standardizations	Date and time of collection Biological and environmental variability (see also Table 2) Fasting/nonfasting Time since last meal, smoking, beverage, alcohol, medication, chewing gum
	Forgotten collection Incorrect collection Duplicate collection	Educate staff and patients	Staff collection or patient collection
	Collection device types Collection device age Anatomical location of collection Contamination of specimen: microorganisms, tube material, tube additive	Use same tubes throughout a study and between studies Check expiration date for collection device Sterile collection	Any information on devices, brands, volume, and types Anatomical location Primary tube brand
	Empty tube Insufficient sample volume Diluted sample	Check volume	Volume collected Intended or unintended dilution
	Open container: spill	Secure stopper on tubes	Document spill

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Table 3. General preanalytical variables, recommendations, and documentation requirements for biobanking of all biospecimens. *(Continued from page 918)*

Step	Preanalytical variables	Recommendation	Documentation requirements
Receiving	Label removed, label destroyed	Never relabel: re-collect biospecimen or destroy biospecimen	Label errors
	Biospecimen lost after collection Not received after collection	Secure chain of custody	Lost biospecimens
	Short-term storage temperature and time until processing	Track temperature and time	Short-term storage temperature and time until processing
Processing	Processing duration	Process rapidly	Date and time of processing
	Aliquot volume	Aliquot to secondary tubes Multiple small-volume aliquots instead of few large volume aliquots	Secondary tube brand and type (single tube, plate, matrix, straw) Number of aliquots Volume of aliquots
	Improper labeling, mislabeling, unlabeling Pairing primary tube ID with secondary tube ID	Label on secondary tubes: cryostable, readable unique 2-D (and 1-D) label Coded and anonymized	Coding with linkage to primary tube number and patient ID Link between patient ID, primary and secondary tube IDs (1-D and 2-D labels)
Transport/ shipping	Environmental exposures (Table 2)	Follow short-term or long-term storage temperature recommendations	Temperature during transport (temperature log)
	Sent to wrong laboratory/receiver not on duty	Schedule shipping according to collection time	Date and time from departure, date and time at arrival, duration from destination A to B
	Packaging, labeling	Follow packaging guidelines according to type of shipment Gentle transport Pack for stable temperature Use licensed couriers Ship small amounts, not the whole collection at once Keep duplicates apart	Register which biospecimens have been shipped Name of courier Type of packaging, labeling

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Table 3. General preanalytical variables, recommendations, and documentation requirements for biobanking of all biospecimens. *(Continued from page 919)*

Step	Preanalytical variables	Recommendation	Documentation requirements
Long-term storage	Time from processing to storage Storage duration, temperature, and facility Other environmental impact: Sunlight Humidity Moisture Dehydration, evaporation Oxidation Desiccation	If possible: use evidence-based literature, pilot study, or internal biomarkers to determine long-term storage time and temperature impact on stability and recovery Store at −80 °C or liquid nitrogen (if room temperature stable, store at room temperature)	Date and time of first storage Duration Time from processing to storage Detailed storage information: Box number and placement in box Rack number and placement in rack Freezer number and rack placement in freezer Backup freezer number for each freezer Freezer location Freezer brand Freezer temperature (temperature log) Temperature log
	Freeze–thaw cycles	Avoid multiple freeze–thaw/single-use aliquots only	Freeze–thaw cycles: Number Date and time Purpose Staff name Discard or return
	Especially for emergencies/disasters: Encapsulation in ice after refreezing Microbiological contamination (yeast, mold, fungus, bacteria, and virus causing biological hazards)	Have an emergency or disaster plan for transferring biospecimens in case of power outage, flooding, earthquakes, hurricane, fire Have enough backup freezers Have enough backup freezers Maintain, repair, replace freezers Store in multiple locations	Type of emergency Attempts to rescue biospecimens
	No labeling or destroyed labeling	Make sure labels are cryostable Destroy biospecimens with unreadable labels	Label errors
	Missing aliquots Misplaced aliquots	Secure chain-of-custody	An electronic laboratory information system for documentation

Table 4. Preanalytical variables, recommendations, and documentation requirements for biobanking of blood and dried blood spots.[a]

Biospecimen	Step	Preanalytical variables	Recommendation	Documentation
Blood	Collection	Tube lot-to-lot variation Tube brand Tube additive (anticoagulants, clot activators, separator gels) Tube material (stoppers, stopper lubricants, walls, surfactants)	Use trained personnel Vertical, close-up position For trace elements, special tubes should be used	Tube brand and lot number Tube additive Tube material (stoppers, stopper lubricants, walls, surfactants)
		Inappropriate blood/additive ratio	Fill collection tube as recommended by manufacturer	Appropriate or improper filling
		Order of draw: carryover	Tube for coagulation or hemostasis: should follow discard tube, and kept at room temperature up to 1 h before centrifugation. Recommended order of draw [CLSI H3-A6 *(132)*]: 1. Discard tube 2. Coagulation tube 3. Serum tube 4. Heparin tube 5. EDTA tube 6. Glycolytic inhibitor	Order of draw
		Specimen type: whole blood, plasma, serum	Whole blood should not be chilled precentrifugation.	Specimen type
		Presence of intravenous catheters (IV)	If possible, take sample at other anatomical location. Avoid taking samples in previously flushed IV lines.	Document if blood taken from IV line
		Tourniquet time	1 min	Tourniquet time
		Needle size		Needle size
		Mixing		Mixing
		Hemolysis Icteric Lipemia Clotting	Re-collect, certain downstream analyses may be affected	Hemolysis Icteric Lipemia Clotting time
		Posture of patient		Posture of patient: standing, sitting, supine

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Table 4. Preanalytical variables, recommendations, and documentation requirements for biobanking of blood and dried blood spots.[a] *(Continued from page 921)*

Biospecimen	Step	Preanalytical variables	Recommendation	Documentation
	Processing	Centrifugation: Brand of centrifuge Speed Temperature Duration Gravity (centrifuge speed in *g* force) Number (single or double)	Many analytes stable without centrifugation for 24 h, but some analytes are more labile to temperature and time between collection and centrifugation Contact time of <2 hours is recommended for some analytes Serum should be allowed clotting at room temperature. Separated serum/plasma should not remain at room temperature postcentrifugation for longer than 8 h, otherwise refrigerate. Postcentrifugation many analytes are stable within 48 h at 4 °C with exceptions. If assays are not completed within 48 h from collection (or from separation), serum/plasma should be frozen. For coagulation or hemostasis: double centrifugation may be performed. Leave at room temperature up to 4 h postcentrifugation is acceptable.	Centrifugation: Brand of centrifuge Speed Temperature Duration Gravity Number (single or double)
		Broken tube	Re-collect	Any breakage
Dried blood spots	Collection	Untreated or treated cards	Collect from: ear, heel (newborn, infants), fingertips, or toe (children or adults) Volume: 50–100 μL	Manufacturer of cards Untreated/treated
		Paper thickness		Thickness
		Drying	Dry at room temperature, horizontal position, 3–4 h Do not stack	Drying time

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Table 4. Preanalytical variables, recommendations, and documentation requirements for biobanking of blood and dried blood spots.[a] *(Continued from page 922)*

Biospecimen	Step	Preanalytical variables	Recommendation	Documentation
		Environmental exposure	Avoid air vents, sunlight, heat, contamination, touching, smearing	Environmental exposure
		Package	Pack when completely dry: sealable plastic bag, desiccant and humidity cards	Package
		Clotting, layering, supersaturation, insufficient volume, wet, serum rings, visible traces of hemolysis, or exogenous contamination Hematocrit, concentration in periphery vs center of spot	Reject	Document rejected biospecimens and reasons for rejection
	Transport	Environmental exposure (Tables 2 and 3)	Horizontal position Use glycine paper between DBS cards to prevent cross-contamination Keep at room temperature Transport of DBS is nonregulated	Transport position, temperature, duration
	Long-term storage	Environmental exposure (Tables 2 and 3)	Horizontal position in low gas-permeable, zip-closure plastic bags with desiccant and humidity indicator cards. Low humidity(less than 30%). For DNA punching: use DNA-punch tools	Position and packaging of paper

[a] See text for detailed references. Also refer to CLSI guidelines: http://clsi.org on blood collection [H18-A4 *(5)* and H21-A5 *(30)*] and DBS collection *(34)* [NBS01-A6]. Also see Table 3 for general considerations of preanalytical variables, recommendations, and documentation.

of DBS compared to venipuncture are the low cost, the relatively painless procedure, and the ease of sample collection, transport, and storage (Table 1). But heat, direct sunlight, humidity, and moisture are detrimental to the stability of DBS biospecimens and to analyte recovery *(34)* (Table 2).

Preanalytical collection factors affecting the metabolome and proteome are biospecimen type (whole blood, serum, plasma, DBS) *(19)*, tube additive *(35–40)*, protease inhibitors *(41)*, hemolysis *(19)*, volume *(19)*, polymers contained in different tubes *(39, 42)*, short-term storage temperature until analysis *(38, 40, 41, 43)*, and delay from collection to analysis *(38, 43, 44)*. These factors can cause matrix effects or affect sensitivity, recovery, or resolution. In vitro protein modifications (e.g., proteolysis, oxidation, degradation, aggregation) may be introduced by the effects of handling, processing, and storage on protein integrity, and can be a confounding factor in biomarker studies *(45, 46)*. The disadvantages of DBS in metabolomic and proteomic analyses are the requirements for assay development and validation, and the small volumes of sample which are available from DBS *(19)*.

Biological factors affecting DNA and RNA are sex (higher yields in women than in men), age (decreasing DNA yield with increasing age), body mass index (BMI) (increasing yield with increasing BMI), and tobacco consumption (higher DNA yield in current smokers compared to never-smokers) *(47, 48)*. Powder contamination from powdered gloves may give rise to sporadic false-negative PCR reactions *(49)*.

For circulating cell-free DNA (ccfDNA) plasma is recommended *(50)* and hemolysis should be avoided. ccfDNA concentrations are stable for up to 4–6 h at room temperature or 4 °C *(50)*.

RNA is vulnerable to degradation by naturally occurring enzymes. Preanalytical collection factors affecting RNA quantity, quality, and gene expression analyses are tube type *(51)*, sterility *(7)*, tube additive *(36)*, biospecimen type, volume of blood, and short-term storage temperature until extraction *(48)*, and lag time until extraction *(52, 53)*. RNA yields when extracted from Tempus-stabilized tubes are higher than from PAXgene-stabilized tubes. However, high-quality RNA may be extracted from both tube types *(51)*. Higher RNA yields have been obtained from cord blood (3–4 times higher) than from adult blood *(51)*. Suboptimal blood volumes collected in the tubes may affect gene expression *(51, 53)*.

Plasma, serum, and other biofluids contain very low amounts of RNA. General precautions should be taken to prevent RNase contamination and degradation of the RNA in biospecimens. Circulating microRNAs (miRNAs) are susceptible to many preanalytical variables such as diet, exercise, age, race, altitude, drugs, chemicals, smoking, large interindividual variability, hemolysis, coagulation times, and temperature affecting their detection and quantification *(54, 55)*. EDTA or citrate plasma are preferred anticoagulants *(54, 55)*.

URINE

Urine can be collected in many ways: 24-h, spot, overnight, morning urine, second morning, or other timed collection *(56)*. Urine collection for biobanking may be used for later measurements of many analytes *(57)*, including the proteome *(58)*, metabolome *(40, 57)*, nucleic acids (DNA or RNA), nucleotides, nucleosides *(59)*, and miRNA *(55, 60)* (Table 5). Urine miRNA levels are usually higher in patients (organ specific) or individuals exposed to medication than in healthy individuals *(55)*. If several tests are to be performed, preanalytical requirements for those tests may be conflicting and may require either multiple biospecimens or aliquoting immediately after collection and before processing *(57)*.

Although guidelines have been developed for many immediate urine analyses (dipstick, macroscopic, casts and cells, microscopic, albumin/creatinin) *(56)*, optimal preanalytical handling guidelines for most biomarker studies on biobanked material are analyte dependent.

The use of additives may be helpful for preservation of particular urine analytes during 24-h urine collection *(56)*. There are many different preservative methods, but a universal preservative allowing complete urinalysis does not exist *(57, 61)*. Addition of preservatives and types of preservatives may change urine volume and give rise to potential interference with assay methods *(44, 57)*. Depending on downstream analyses, urine biospecimens may or may not be kept refrigerated or kept on ice during the collection period, depending on the time until processing or storage *(40, 56, 57, 62)* (Table 6). Centrifugation may result in loss of some analytes *(40, 56, 57)*. Urine may be contaminated by dipsticks or bacteria. As is the case for blood collection, leaching of substances into urine may interfere with assays or bind analytes, both important with low concentrations of analyte *(57)*. The completeness of a 24-h urine is the extent to which the entire 24 h is covered. Completeness of 24-h urine collection can be verified using PABA (paraaminobenzoic acid), because it is completely and rapidly excreted in urine *(63)*. To adjust for the dilution of the urine in spot collections, adjustment for creatinine concentration or specific gravity is often used *(64)*. Other preanalytical variables specific for urine *(65)* are listed in Table 5.

SALIVA

Saliva and buccal cell samples have many advantages compared to blood collection (Table 1). They are noninvasive methods, easy to collect at lower cost, can be used in clinically challenging situations (children, handi-

Table 5. Table of collection material for downstream analyses.

	Whole blood	Plasma	Serum	Buffy	ACP	DBS	Urine	Saliva
Chemistry		√	√			√	√	√
Hematology	√					√	√	
Coagulation		√						
Glucose	√	√				√	√	√
Hemoglobin A_{1c}	√					√		
Hormones		√	√			√	√	√
Inflammation		√	√			√	√	√
Cytokines			√			√	√	√
Vitamins			√			√		
Live cells				√				
Proteomics		√	√			√	√	√
Metabolomics		√	√			√	√	√
Genomics/germline DNA	√			√	√	√	√	√
ccfDNA		√					√	√
Transcriptomics/mRNA	√			√		√	√	√
miRNA (circulating)		√	√				√	√

capped individuals, patients afraid of needles), are safer to handle *(66, 67)*, and can be used for self-assessment and thus in cohorts with return of samples by mail. Saliva is used for a variety of analytes also measured in blood *(67)* and biomarker omics studies *(66, 67)*, such as metabolome, transcriptome, genome, proteome, miRNA *(55)*, and microbiome profiling in disease detection (local and systemic) (Table 5). A disadvantage is the low concentration of analytes *(67)*. The advantage of extracting DNA from saliva is that the germline DNA represents only the DNA from the person who donated, compared to DNA derived from blood which could originate from other persons, such as in cases of multiple transfusions or chimerism after bone marrow transplantation *(68, 69)*. Furthermore, salivary DNA is a useful source of germline DNA in studies of hematologic neoplasias *(70)*.

Saliva and buccal cells can be collected in tubes or on cards. Saliva may be collected as whole saliva or gland-specific saliva *(67)* (Table 6). Whole-mouth saliva collection may be obtained by different techniques in a resting mode (draining/passive drooling, spitting, suction, swab) or with stimulation (with sugar, paraffin gum, acid) *(71–73)*. Specific glandular collection is invasive, more complex, and requires skilled personnel. Saliva should be collected at least 2 h after eating and drinking, preceded by a mouth rinse *(74)*, and kept on ice to minimize bacterial action and proteolysis, which may affect saliva composition *(75)*. Furthermore, for proteome analyses, a protease inhibitor cocktail may be added *(76)*. Ambient temperature collection and storage devices (e.g., Oragene) are available *(77)* that reduce storage space and costs and simplify transportation requirements. Stimulated saliva produces a more variable (between- and within-subject) but higher analyte recovery compared to nonstimulation *(71–73)*. Total protein concentrations (proteome) seem to be largely similar among various collection techniques *(72, 73)*, but individual levels of analytes are collection dependent *(72, 73)*. Saliva from passive drooling tends to be more viscous and may be difficult to process in the laboratory *(74)*. The amount and composition of secreted saliva depends on smell, taste, disease status, drugs taken by the donor, age, sex, diet, blood type, physiological status, flow rate, circadian rhythm, type and size of salivary glands, and duration and type of stimulus *(67, 74)*.

Buccal cells may be collected using oral rinse, swabs, or cytobrushes *(10, 78, 79)*. The disadvantage of the oral rinse method is that participants have to swish and spit a solution, which is distasteful *(79)*, and depending on the solution may give a burning sensation in the mouth *(78)*.

Biospecimen Processing

BLOOD

Serum or plasma should be separated from contact with cells as soon as possible, although serum separator tubes should be left to clot for 30–60 min at room temperature before separation. Many analytes are stable without centrifugation for 24–48 h *(5, 80–84)*, but some analytes are more labile to temperature and time between collection and centrifugation. For some analytes, a contact time of less than 2 h is recommended *(5, 30)*.

Table 6. Preanalytical variables, recommendation and documentation requirements for biobanking of urine and saliva.[a]

Biospecimen	Step	Preanalytical variables	Recommendation	Documentation requirements
Urine	Collection	Collection method: a. 24 h, spot, morning, other timed b. Spot: first-void vs midstream	Collection depends on immediate and future downstream analyses. For chemistry analytes and future omics-studies. 24-h collection is recommended. Spot or timed urine specimen may suffice (with creatinine adjustment). Use illustrated instructions for self-collection	Collection method Has the patient intentionally been drinking excessive amounts of water to be able to void
		Improper sampling technique or volume		Volume
		Environmental exposure (Table 2)	Avoid direct sunlight	Document environmental exposures
		Macroscopic inspection: color, turbidity, casts		Macroscopic inspection
		Diluted urine	Avoid overhydration	Excessive hydration
		Dipstick components, contamination of lab analyses	Don't use dipstick for same biospecimen as going to the lab	Dipstick
		pH, specific gravity, urinary tract infection, salt concentration, viscosity, blood		Document chemical measurements
		Preservative (and type) or no preservative	Preservatives may be added depending on downstream analyses, short-term storage temperature, and collection method	Preservative (and type) or no preservative
	Processing	Centrifugation speed	Centrifugation: depends on downstream immediate or future analyses	Centrifugation speed, gravity and time
	Transport	Temperature Tube position	Dependent on collection method and analytes. Vertical, close-up position	Temperature and duration

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Table 6. Preanalytical variables, recommendation and documentation requirements for biobanking of urine and saliva.[a] *(Continued from page 926)*

Biospecimen	Step	Preanalytical variables	Recommendation	Documentation requirements
Saliva	Collection	Amount and composition of secreted saliva depends on: smell, taste, blood type, flow rate, type and size of salivary gland, duration and type of stimulus, collection method	Vertical, close-up position Collect at least 2 h after eating and drinking Collection on ice if not room temperature-stable Depending on downstream analyses: addition of protease inhibitor	Biospecimen collection device (brand, room temperature-stable or not) Biospecimen type: whole saliva, (glandular-specific saliva), or buccal cells Unstimulated or stimulated, type of stimulus Addition of protease inhibitor Short-term collection and storage temperature Use of dry ice
	Processing	Centrifugation speed	Depending on downstream analyses: centrifugation	Centrifugation speed
	Transport	Temperature	Transport temperature depends on collection device: if not room temperature-stable, transport on ice	Temperature and duration

[a] See text for detailed references. Also refer to CLSI guidelines: http://clsi.org on urine collection (GP16-A3) *(56)*. Also see Table 3 for general considerations of preanalytical variables, recommendations, and documentation.

Temperature-controlled centrifuges are recommended. The complete biobanking blood sample preparation work flow can be consolidated in an automated blood fractionating system. The higher the throughput, the larger the need for automated blood fractionating systems, to ensure equal sample aliquoting with respect to volume and equal distribution of sample fraction material *(85)*. The following fractions may be obtained from 9–10 mL whole blood: plasma (6–7 mL); lymphocytes and mononuclear cells (1–2 mL); erythrocytes and other cells (1–2 mL). Mononuclear leukocytes are the only cell type from blood that can be used for developing cell lines, because they are capable of continued viability and growth *(7)*.

Automated systems may be capable of detection of gel separators and buffy layers, as well as fractionation into plasma and serum *(85)*. Automated systems incorporate barcode reading of primary tubes (collection tubes), decapping, fractionation, aliquoting into predefined secondary tubes or plates, and transfer of barcodes onto secondary tubes. Barcodes on secondary tubes should be 2-dimensional (2-D) and preferably should be molded into the tube to ensure the longevity of the coding. The automated systems should have complete sample tracking capability. Benefits of automated fractionation systems include fewer errors in sample handling and prevention of endurance-related injuries due to repetitive work. Such systems are operator independent and ensure proper sample tracking *(85)*. Automated blood fractionation systems may also be connected to automated DNA extraction systems, which are preferable for high-throughput biobanks. This approach ensures tracking of samples, normalization, and high quality and high yield of DNA. In laboratories with low throughput or less financial resources, manual handling may be needed, but this approach increases the risk of errors.

Multiple aliquots should be created at the beginning of processing a biospecimen rather than delayed until the specific assay is conducted, because repeated freeze–thaw cycles may be detrimental in some cases (e.g., RNA) *(7, 86)*. If the collection site is not close to the laboratory, it may be appropriate to perform simple processes such as on-site centrifugation, aliquoting, fractionation of serum, and isolation of buffy coat and plasma, and to store the samples in smaller transportable coolers or freezers. However, more complex processes such as separation into stratified blood cells or cultures require more advanced laboratory equipment and are not suitable for smaller rural on-site processing *(7)*. Multiple aliquoting is advised to reduce future freeze–thaw cycles. A recent study confirmed the validity and reliability of a high-throughput, high-density, low-volume biobank sample processing solution for blood fractionation and archiving biospecimens that used the 384 aliquoting format sample storage tube system *(86)*. A study of high-density scaling

allowed for reproducible aliquoting and processing of 70-μL volumes of blood *(86)*. With this approach the authors introduced the principle of single-use only for samples, circumventing multiple freezing and thawing cycles *(86)*.

Labeling and coding are essential for further tracking of the samples. Label orientation, place, and size should be determined, together with the type of barcoding (1-D, 2-D), and density and resolution of the barcode. Labels should be unique and highly adhesive to tubes. Preferably, the label should be cryostable and embedded into the tube and 2-D barcoded. Specifying types of identifiers, names of institutions, and dates using multiple identifiers and alphanumeric codes should minimize errors *(87)*. The overall biospecimen rejection rate in a clinical chemistry laboratory is approximately 0.2%, and 7.6% of these errors are due to improper labeling (incompletely labeled, mislabeled, not labeled, label removed, label destroyed); repeat sampling is the only solution. Relabeling is strongly discouraged *(88)*.

A study found that storage of blood biospecimens beyond 24 h before centrifugation caused significant changes in most analytes investigated *(80)*. Delayed processing may account for a variability of more than 10% in one-third of chemistry and hematological analytes *(89)*. Thus, it is recommended to immediately separate plasma or serum from cells to provide for optimal analyte stability at room temperature *(80)*. However, if prolonged contact of plasma or serum with cells cannot be avoided, it is recommended to use serum because of the higher instability of plasma analytes *(80)*. Preanalytical processing factors for clotted biospecimens include insufficient centrifugation speed and time, an unbalanced centrifuge, and rough handling and pipetting into the cellular layer when removing plasma *(30)*. Plasma for coagulation testing should preferably be platelet poor (platelet count $<10 \times 10^9$/L), i.e., spun twice at a certain speed *(30)*. If coagulation testing is to be performed at some future time on frozen biospecimens, these should be stored platelet free *(30)*.

Citrate-stabilized blood yields higher-quality DNA and RNA than EDTA blood and lymphocytes collected for culture *(7)*. Fresh and frozen whole blood samples have been shown to yield equal amounts of DNA *(90)*. An all-cell pellet (ACP) yields 80% of DNA compared to frozen whole blood and 99% of the yield of fresh blood. Frozen buffy coat and residual blood cells each yield only half as much DNA as frozen ACP, and the yields are more variable *(90)*. The DNA yields from DBS samples are minute; however, studies have shown that DNA from DBS can be whole-genome amplified and used for genome-wide studies *(91)*.

Processing time is an important source of preanalytical variation in DNA yield. It has been shown that decreasing the lag time between blood collection and refrigeration, and between refrigeration and centrifugation, results in a substantial increase in DNA yield *(47)*. The main factor negatively affecting DNA yield is hemolysis *(47)*.

Double centrifugation of plasma is recommended for ccfDNA as it ensures the absence of any cells (the latter can be done after long-term storage) *(50)*. If extraction is delayed after blood processing, plasma samples must be stored at −80 °C *(50)*. If extraction is not delayed, plasma samples must be stored at +4 °C up to 3 h *(50)*. Plasma samples are sensitive to freeze–thaw cycles and should be aliquoted *(50)* before freezing. ccfDNA extracts may be stored at −20 °C and should not undergo more than 3 freeze–thaw cycles *(50)*.

Delay before fractionation may impact transcriptomic, metabolomic, and proteomic profiles, whereas storage temperature has a lesser impact *(35)*.

URINE

Before aliquoting, the urine sample must be mixed to ensure homogeneity of specific gravity and composition of the urine in the aliquots *(57)*. Depending on downstream analyses, centrifugation may be required *(40, 56, 57)*. For proteomics and metabolomics applications mild centrifugation is recommended *(40, 57)* .

SALIVA

Depending on downstream analyses and the viscosity of the saliva, a centrifugation step may be needed *(75)*, but has the risk of changing or losing some salivary components *(75)*. The most optimal centrifugation speed has not been established *(75)*. Delayed processing may result in increased as well as decreased protein peaks, likely through digestion of some proteins by salivary proteases *(75)*. Stabilizing agents may be added for long-term storage of saliva for later RNA extractions. Overall, whole saliva and oral rinse techniques are superior to cytobrushes or swabs because they provide high-quality, high-yield DNA, and provide a higher percentage of high molecular weight DNA *(77, 78, 92–97)*, but less than blood.

Transport of Biospecimens

Transport of biospecimens includes any method from interdepartmental to international transportation. Incorrect packaging, marking, classification, or labeling or incorrectly completed shipping documentation may cause delays or refusals by customs officials and will most likely affect the biospecimen integrity *(7)*. Variables affecting biospecimen integrity during transport are the season, duration, delays, distance, and method of transportation. International shipments are especially vulnerable to delays in customs clearance. Devices are available to electronically track and monitor temperature during transport. It is advised not to ship the whole collection in one

shipment, and not to ship duplicate samples together, but to ship smaller amounts of the collection, and always to keep duplicate samples separated.

Transport of whole blood, plasma, serum, buffy coat, urine, DNA, and RNA requires refrigerators, freezers, special packaging, and dry ice as appropriate, and the logistics of transport are costly *(19)*. It is important to have sufficient cooling materials for multiple days of transit. All tubes should be transported vertically in the closure-up position. This is especially important for blood tubes because the upright position reduces hemolysis and in nonanticoagulated tubes this position prevents fibrin from attaching to tube closure *(5)*. Gentle handling and transport reduces the risk of shaken samples and subsequent hemolysis. Cushioned transport boxes should be used for long-distance transportation. DBS should be transported to the laboratory at ambient temperature within 24 h of collection *(19, 32)*. Blood, urine, saliva, DNA, or RNA shipped by commercial carrier may encounter extreme seasonal temperatures, and this factor should thus be accounted for in long-term large-scale multinational studies *(51, 98, 99)*. Samples that must be shipped to a processing laboratory cannot be used for the most unstable biomarkers, or processing should begin in the field to ensure stability during transportation *(7)*.

Long-term Storage and Retrieval

Storage encompasses both short-term and long-term storage of biospecimens depending on their planned future use. It should be determined whether to have the biospecimens locally stored, centrally stored, or both. These decisions will depend on many factors, such as sample size, accrual rate, complexity of collection and processing procedures, logistics, cost, quality issues, and biobank governance factors *(100)*. If the samples are expected to be used for multiple purposes, it is recommended to have a duplicate set close to the core laboratory for practical reasons. If sample storage of more than a year is planned, central storage of the samples is recommended. It is also recommended to have a duplicate set of samples stored on different power supplies or in 2 geographically separated locations, to protect against equipment failure or natural disasters. One or more empty backup freezers (10% of the total number of mechanical freezers is recommended) should be operating in case of freezer failure *(101)*. Depending on the downstream analyses, a variety of different storage conditions may apply. Preanalytical variables for long-term storage are listed in Table 3. Of major concern is freeze–thaw cycles that may happen unintentionally during transport of frozen samples or from freezer failure, or intentionally because an aliquot of the biospecimen is repeatedly thawed for analysis and then returned to the biobank for frozen storage.

A LIMS (laboratory information management system) allowing traceability, location chain-of-custody, and management of biospecimens improves retrieval and data reliability. Biobank material is precious and difficult to replace, and if sample integrity is compromised, the biospecimens become useless for the intended purpose of research. Thus, when retrieving biospecimens it is important to retrieve only what is needed and keep that to a minimum. To prevent the complete destruction of all biobank biospecimens, it is recommended to have duplicate collections in geographically distant locations.

BLOOD

Stability studies of analytes after long-term storage compared to the fresh sample value, with estimation of recovery rates, are important to determine the effects of long-term storage. Recovery rates may increase or decrease after long-term storage and thus result in either increased or attenuated risk ratios, respectively, when assessing the associations of the analyte with disease. Chemistry, hormone, and protein analytes are stable when serum samples are stored at −80 °C up to 13 months *(102)*, but various studies of longer-term stability of chemistry, hormone, enzyme, vitamin, and protein analytes have shown different stability patterns depending on the analyte and the time and temperature of storage *(103–109)*. No systematic influence on omics analyses (metabolomics, proteomics, transcriptomics, epigenomics) of time in storage at −80 °C or in liquid nitrogen has been observed in samples collected in heparin, EDTA, or citrate stored over a period of 13–17 years *(35)*, or for metabolomics analytes in DBS stored at −20 °C and −80 °C for 2 years *(110)*. However, long-term storage at room temperature *(110)* and repeated freeze–thaw cycles should be avoided *(38)*. DNA showed sufficient yield, purity, and integrity when extracted from whole-blood samples stored at room temperature (18 °C) using biostabilization technology, at low (−20 °C) and at ultralow (−80 °C) temperatures *(111, 112)*, or buffy coats stored for up to 9 years at −80 °C *(113)*. Live cells are stable at room temperature for up to 48 h, but must be either cultured or cryopreserved in liquid nitrogen to remain viable *(6)*. The transfer of thawed EDTA whole blood or buffy coats into RNA preservative offers a method to recover sufficient RNA of acceptable quality for microarray experiments *(35)*. Plasma or serum for miRNA analysis should be kept at −80 in RNA-free cryotubes or the miRNA should be extracted immediately *(55)*.

URINE

Long-term storage at a temperature lower than −80 °C without additives is preferred unless otherwise specified for specific downstream analyses *(57)*. High long-term stability and measurement validity for numerous clinical chemistry analytes (including creatinine) stored at

−22 °C for 12–15 years without addition of any urine preservative has been demonstrated *(114)*. For proteome and metabolome analyses, urine storage at room temperature causes progressive degradation of proteins *(58)*. Freeze–thaw cycles have minimal impact on protein profiles *(58, 65)* but repeated freeze–thaw cycles should be avoided.

SALIVA

Storage protocols may depend on expected downstream analyses. Protein profiles change with varying storage temperature, storage duration, and freezing rate, whereas freeze–thaw cycles seem to have a minimal impact *(76)*. The recommended storage temperature for protein profiling is −80 °C *(76)*. No differences in mRNA, C-reactive protein, cortisol, and cytokines were noted if saliva samples were split into aliquots and immediately frozen at −80 °C, as compared to storage at 4 °C for 24 h followed by freezing *(115)*. When the Oragene collection self-collection kit was stored for 8 months at room temperature there were no reductions in either the quantity or quality of DNA extracted *(77)*.

EXTRACTED DNA

Freezing at −80 °C is still the most common method of storing DNA. Degradation of DNA increases with dilution, higher storage temperature, multiple suspensions, and repeated freeze–thaw cycles *(99, 116, 117)*. Special technologies for storing DNA at room temperature have been developed, enabling easier shipment of these extracts *(111, 116–118)*. This approach minimizes required storage space, reduces electrical costs and shipping costs, is helpful when mechanical or cryogenic equipment is not available (e.g., during shipping or in rural areas), or may serve as an alternative method for backup storage *(101)*. With this technology, DNA showed no degradation at room temperature or in accelerated aging experiments at high temperature (50 °C and 70 °C) during an 8-month storage period *(116–118)*.

RNA

Preanalytical storage factors affecting analyte quantity, quality, or gene expression are temperature, storage time, concentration of RNA, and repeated thaws *(53, 119, 120)*. As for RNA, new technologies for dry storage at room temperature have been developed *(121–123)*. This technology was comparable to cryopreserved RNA for up to 1 year for downstream analyses, including real-time PCR and RNA sequencing *(121)*.

General Considerations

Where possible, there should be consideration of the types of testing that are expected to take place, but the testing methodologies may not always be known in the planning or collection phase, which may limit or impact analytical results. Any part of the biobanking process should be documented in detail, to ensure valid, reliable, and comparable results within and between studies. Preanalytical best practices and standard operating procedures (SOPs) should be evidence based and a pilot feasibility study should be carried out, because this will clarify the critical steps and reduce the time and costs of repeated analyses in the real study. In case control studies or multicenter studies, preanalytical collection, processing, transport, and storage should be similar and, if possible, centralized, with only minimal local processing to avoid uncontrolled and unmeasured variation *(6, 100)*. Deviations from and differences in SOPs, and poorly documented SOPs, may affect test results, interpretations, and conclusions and potentially also lead to diagnostic errors and inadequate treatment and endanger patient safety. These conditions may be important in international research collaborations and exchange of samples. The more complex the preanalytical steps are for biospecimens in a biobank, the higher the risk that errors will occur, and the greater the need for automating the process. The smaller the study the larger the effects of failure to standardize will become.

The information reported in scientific publications regarding preanalytical conditions for biospecimens varies considerably *(124)*. Such preanalytical data should be documented simultaneously with the biobanking process by the investigators, and reported in the literature *(125, 126)* to serve as quality indicators *(127)* to allow the evaluation, interpretation, comparison, validation, and reproduction of the experimental results. The Biospecimen Reporting for Improved Study Quality (BRISQ) guidelines are a useful tool for this purpose *(124, 126)*.

Studies have attempted to identify internal sensitive molecular biomarkers as well as external noninvasive QC technologies for quality assessment of cryopreserved samples *(128–131)*. A single biomarker is unlikely to provide all the information about sample quality *(131)*; however noninvasive quality control technology seems to be more promising *(128)*.

Costs

It is costly to establish, operate, and maintain biobanks. The preanalytical processes that are established can have large effects on the economics. Centralized processing is cheaper than decentralized *(6)*. Educated staff will reduce collection time and salary costs. Preanalytical errors may result in increased costs and delayed results, because replacement samples have to be collected at additional cost. Poor study quality may lead to overlooking weak associations or establishing spurious associations, resulting in decreased study power *(89)* with requirement for

larger study sample sizes at increased costs *(100)*. Costs of shipment of biospecimens must be included in budgets, and these costs depend on the weight, distance, shipper, and local conditions. Furthermore, costs for operating and maintaining biobanks should be extrapolated for the years the biobank expects to store the samples and compared against the costs for running immediate analyses instead of storing samples, which may result in the loss of stability and predictability of the analytes over time. Furthermore, emerging technologies allow for smaller volumes to be used in analyses, which should be taken into account when collecting biospecimens, because smaller volumes translate into lower costs and potentially an increased participation rate. Ambient temperature storage is an emerging field and minimizes required storage space and reduces electrical costs and shipping costs.

Conclusion

Preanalytical handling of biospecimens is fundamental for their future use in personalized medicine for diagnostic or prognostic purposes. For the purpose of biomarker discovery and development, preanalytical requirements and documentation are as important as analytical requirements for the evaluation of clinical performance of the biomarker, especially when seeking US Food and Drug Administration approval. If the preanalytical step fails, there is no need to analyze the biospecimens because all other downstream measurements will also fail. The preanalytical decision-making process should be planned according to its potential effects on downstream analyses. Preanalytical best-practices and SOPs should be evidence based, and pilot feasibility studies should be conducted before the study begins. Protocol articles from studies should describe in detail the preanalytical process according to BRISQ or other best practice guidelines. Preanalytical variables should be considered and analyzed as covariates in research studies just like age and sex. When comparing or pooling results from different studies, investigators should take into account the differences in preanalytical conditions.

The principles and evidence presented in this review are now generally recognized as important to the success of biospecimen banking and related clinical analyses. However, there is still work to be done to encourage biobank professionals to develop evidence-based methods that will mitigate the effects of preanalytical variables. Of equal importance, studies of preanalytical biospecimen variability need to be reported in the literature and the results incorporated into biobanking best practices. This is especially important in the ever-expanding universe of global collaboration with frequent exchange of biospecimens and data.

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