

Is Phlebotomy a Bottleneck for Genomics Studies? Rethinking and Redesigning Blood Collection Infrastructure for Large Scale Biology

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Abstract

Advances in detection technologies have enabled better molecular insights across a wide array of Omics studies – from genomics to transcriptomics, and from proteomics to metabolomics. A combination of the data from all the omics studies are increasingly applied to large population cohorts, longitudinal clinical studies, and decentralized clinical trials. While the end-detection technologies experienced some significant developments in the last two to three decades, the sample collection and preparation approaches continue to be challenging, complex, time consuming, and lack standardization protocols. The infrastructure used to obtain biospecimens, especially, whole blood has evolved far more slowly than the analytical technologies used to study them. Most blood samples used in research and diagnostics are still obtained through venous phlebotomy performed in clinical environments. While historically adequate for diagnostic testing and small studies, this model presents growing limitations for large scale studies. Workforce shortages, geographic constraints, cold-chain logistics and variability in sample handling collectively limit the scalability of blood-based molecular profiling. Emerging remote blood collection technologies, including stabilized capillary blood sampling systems such as Covaris' truCOLLECT® Whole Blood Collection Solution offer a potential pathway toward decentralized biospecimen infrastructure compatible with modern analytical workflows. Here we examine how evolving blood collection technologies may reshape biological sampling for the laboratories focused on Genomics.

The Needed Revolution for Sample Collection Infrastructure

The past two decades have witnessed rapid advances in molecular measurement technologies.^{1,2} High-throughput sequencing,³ mass spectrometry⁴ and single-cell analysis⁵ have made it possible to profile biological systems across multiple molecular layers including DNA, RNA, proteins, and metabolites.

Large-scale initiatives such as population biobanks and precision medicine programs increasingly rely on genomics analysis of blood samples collected from large cohorts. Whole blood remains one of the most valuable biospecimens⁶ because it enables analysis of multiple biomolecular classes simultaneously and allows longitudinal sampling over time. Modern biomedical research increasingly relies on Genomics approaches that integrate data across multiple molecular layers. Some key examples are listed in **Table 1**.

Table 1. List of typical Omics application areas and their molecular targets.

Omics Application	Molecular Targets
Genomics	DNA Sequence Variation
Transcriptomics	RNA Expression Profiles
Proteomics	Protein Abundance and Modification
Metabolomics	Small-molecule Metabolites
Epigenomics	Chromatin and DNA Methylation

When all the data obtained from each Omics layer detailed in **Table 1** are combined, the resulting datasets provide a systems-level view of biological state,⁷ enabling researchers to study disease mechanisms,⁸ therapeutic response,⁹ and population health.¹⁰

Large scale initiatives such as precision medicine programs, population biobanks and biomarker discovery studies increasingly rely on genomics analysis of blood samples.^{2, 11, 12} Whole blood is particularly valuable because it contains multiple molecular components simultaneously, allowing researchers to generate extensive datasets for DNA, RNA, Proteomes, and metabolomes. from a single specimen.^{7, 12}

Despite several technological advances that the world of end-detection instruments witnessed in the last three decades, the infrastructure used to collect blood samples remains largely unchanged.¹²⁻¹⁴ Most biospecimens are still obtained through venous phlebotomy, a procedure that requires a trained healthcare personnel and specialized clinical environments. As biological research shifts toward population scale datasets, the scalability of this traditional model is increasingly being questioned.^{13, 15}

Whole Blood for Comprehensive Genomics

Whole blood is one of the most information rich biological samples available for human research.¹⁶ It contains:

- Genomic DNA from circulating cells
- Messenger RNA from leukocytes
- Circulating proteins and cytokines
- Metabolites reflecting systemic metabolism
- Immune cell populations
- Extracellular nucleic acids

The wide variety of information offered by whole blood supports multiple analytical approaches such as Whole Genome Sequencing (WGS), proteomics studies, RNA sequencing, etc. Because blood can be collected repeatedly over time, it renders high value for disease monitoring and treatment response in addition to identification of diseases.

Blood Collection: The Hidden Bottleneck in Genomics Research

In discussions about the limitations of large scale biological studies, attention often focuses on sequencing cost or computational analysis. Yet in many research programs the true bottleneck lies much earlier in the workflow, starting at the level of biospecimen acquisition.^{13, 14} In a typical genomics workflow starting with whole blood,¹⁷ the process comprises:

- Participant recruitment
- Biospecimen collection
- Sample stabilization and transport
- Analyte extraction
- Molecular profiling
- Computational analysis

Biospecimens such as whole blood collection remains a manual and labor intensive process, which in turn, exerts a negative impact on the rate at which biological data can be generated.

Workforce Constraints in Phlebotomy

Traditional venous blood collection depends on trained phlebotomists. Many healthcare systems are currently experiencing workforce shortages affecting laboratory and diagnostic services. In the United States alone, approximately 18,400 phlebotomist job openings occur annually,¹⁸ largely due to workforce turnover and retirements. Phlebotomy services in hospitals also experience high turnover rates, in some cases approaching 25% annually, which complicates staffing and training.¹⁹ These shortages are part of a broader crisis affecting clinical laboratories. Surveys indicate that nearly 40% of laboratories report significant understaffing, highlighting the growing pressure on diagnostic infrastructure.²⁰ For research studies, workforce limitations translate into:

- Limited appointment availability
- Delayed sampling schedules
- Higher operational costs
- Restricted sampling frequency

As study sizes increase, reliance on specialized personnel becomes a structural limitation.

Geographic and Accessibility Constraints

Traditional phlebotomy requires participants to visit hospitals, clinics or research centers. This requirement introduces geographic barriers that can affect study participation. These challenges are particularly pronounced for:

- Restricted access for geographically dispersed participants
- Limited appointment availability, especially for individuals with limited mobility
- Difficulty scheduling repeated sampling
- Increased cost/sample

Approximately 43 million rural Americans live in areas with shortages of healthcare professionals, highlighting the limitations of clinic-based sampling models.²¹ These above-mentioned barriers can lead to sampling bias, where participants living near academic medical centers are disproportionately represented in research cohorts. For large population studies and global clinical trials, accessibility remains a major challenge.

Molecular Instability and Cold-Chain Dependence

Beyond logistical constraints, the biochemical properties of blood create additional challenges for genomics analysis. Whole blood contains multiple molecular components that are sensitive to degradation or alteration following collection. After collection, molecular components in blood begin to change rapidly. As an example:

- RNA degradation can occur within hours
- Proteins may undergo rapid proteolysis
- Metabolic pathways continue to alter metabolite levels
- Immune cells respond to environmental changes

Making necessary adjustments to prevent the above-mentioned conditions require rapid processing, refrigeration, or immediate freezing of samples. Cold chain transport and processing infrastructure introduce significant costs and can also create variability between study sites. Variability in processing conditions across sites can also introduce batch effects that affect genomics datasets.²²

The Case of Non-Invasive Collection

The appeal of non-invasive biological sampling is intuitive. Saliva and buccal swabs offer a compelling alternative to venipuncture, particularly in settings where patient compliance, accessibility, or cost are primary concerns. Collection requires no trained phlebotomist, no needles, no specialized clinical infrastructure, and can in principle be collected by every individual at home. These attributes have made non-invasive oral sampling a cornerstone of consumer genetics (e.g., ancestry and direct-to-consumer genomic testing), epidemiological studies requiring large-scale enrollment, pediatric and geriatric populations where venipuncture is challenging, and point-of-care or remote diagnostics in low-resource settings.²³ From a molecular standpoint, saliva and buccal swabs are legitimate sources of human DNA, making them a reasonable source for genomics.²⁴ The human oral cavity harbors over 700 bacterial species, and DNA from these organisms is co-extracted alongside human nucleic acids in any saliva or buccal swab-based workflow.²⁵

In NGS library preparation from oral samples, microbial DNA is indiscriminately amplified and sequenced alongside human DNA. Clinical WGS studies report a median of approximately 13% non-human mapped reads from buccal swab and saliva samples, with over 80% of samples exceeding 5% and a significant proportion exceeding 20%.²⁶ These non-human reads carry no diagnostic value yet represent a direct and unavoidable sequencing cost. In a fixed output sequencing run, every microbial read is a human read lost — wasted flow cell capacity that cannot be recovered computationally. Hence, to achieve whole blood human sequencing depth from an oral sample, laboratories must sequence appreciably more, driving up reagent costs, run times, and bioinformatic overhead. Whole blood (and plasma extracted from it) delivers a substantially higher proportion of on-target human reads for every sequencing dollar spent, making it not just the analytically superior matrix, but the more economical one at scale.²⁷ In some study types such as, germline variant detection,²⁸ pharmacogenetic profiling²⁹ or biobank/population genomics,³⁰ saliva or buccal swab samples have been found to have reduced or inconsistent performance compared with blood-based testing.

Oral Matrices Fall Short

The limitations of oral matrices become significant and clinically important when the diagnostic goal extends beyond simple molecular analyses. Several instances where oral matrices (saliva, buccal swabs, etc.) fail to reach the quality obtained from whole blood samples are shown in **Table 2** and can be described as follows:

- Biological complexity and contamination. Saliva is a mixture of glandular secretions, epithelial cells, food debris, and a high, variable microbial load. Buccal swabs yield inconsistent cell numbers depending on technique and collector. Both introduce variability that is difficult to normalize and incompatible with the reproducibility standards required for clinical diagnostics.
- Rapid analyte degradation. Saliva's high protease and amylase content aggressively degrades proteins and nucleic acids post-collection. Without immediate stabilization, proteomic and transcriptomic signals deteriorate within minutes, thereby making oral matrices particularly poorly suited to protein biomarker detection.
- Low and inconsistent biomarker concentrations. Most clinically relevant markers (e.g. troponin, PSA, CA-125, HbA1c, cytokines, circulating tumor DNA) are either undetectable or unreliably quantifiable in saliva. They are present in blood at concentrations orders of magnitude higher, with validated reference ranges and established clinical thresholds.
- Lack of systemic representation. Most critically, saliva reflects local oral biology, which may not comprehensively mimic a systemic disease. Blood integrates molecular signals from every organ, carrying shed proteins, metabolites, immune mediators, and nucleic acids from diseased tissues throughout the body. A pancreatic tumor, a neuroinflammatory process, or early cardiac injury leaves a detectable footprint in circulation long before it appears in the oral cavity (if at all).

Table 2. Matrix Comparison: Saliva, Buccal Swab, and Blood.

Parameter	Saliva	Buccal Swab	Blood (Plasma/Serum)
Collection	Non-invasive, self-administered	Non-invasive, self-administered	Requires trained phlebotomist
Patient Compliance	High	High	Moderate
Sample Consistency	Poor – high biological variability	Moderate – technique-dependent	High – standardized protocols
Analyte Stability	Poor – rapid protease degradation	Poor to moderate	High – well-characterized
Protein Biomarkers	Very limited / unreliable	Very limited/unreliable	Excellent
Circulating DNA/cfDNA	Not suitable	Not suitable	Gold standard
Genomic DNA	Adequate	Adequate	Suitable
Systemic Disease Representation	Poor – reflects local oral biology	Poor – reflects local oral biology	Excellent – whole-body integration
Clinical Validation	Limited	Limited	Extensive
Omics Suitability	Genomics only	Genomics only	Genomics, proteomics, metabolomics, transcriptomics

Why Blood Remains the Gold Standard

Plasma and serum provide systemic biomarker coverage, well-characterized pre-analytical workflows, and validated assay performance across thousands of clinical applications. Deep plasma proteomics has demonstrated the ability to reveal disease-associated signatures across oncology, neurodegeneration, cardiovascular disease, and metabolic disorders. Liquid biopsy approaches detecting circulating tumor DNA in plasma have reached clinical deployment with sensitivity and specificity that no saliva-based equivalent currently approaches. Compared to blood, while non-invasive oral sampling finds some specific uses, those preferences are usually governed by ease of accessibility where analytical precision is not warranted. However, for most critical applications, from protein biomarkers to circulating nucleic acids, from metabolomic profiling to detection of systemic disease, saliva and buccal swabs are a compromise with measurable diagnostic cost.³¹ As the world of precision medicine aims for confident, earlier detection and multi-omics integration, matrix selection must be driven by what the biology demands, which is whole blood.

Implications for Decentralized Clinical Trials

Clinical research is increasingly moving toward decentralized and hybrid trial models, where participants can enroll and contribute data remotely. Digital health technologies, wearable sensors and telemedicine platforms are enabling new approaches to clinical research. However, biospecimen collection remains one of the most difficult elements to decentralize. Participants need to visit clinical sites solely for phlebotomy, creating friction in otherwise remote study designs. This discrepancy between digital trial infrastructure and physical sample collection highlights the need for new blood collection technologies.

Remote blood sampling approaches have therefore become a key area of innovation. These technologies allow participants to collect small volumes of blood at home and stabilize analytes for downstream analysis. Such approaches can enable geographically distributed sampling while reducing dependence on clinical facilities.

Emerging Technologies for Remote Blood Collection

Several emerging platforms aim to enable self-administered blood collection outside clinical environments. These systems typically involve:

- Finger-stick capillary blood sampling
- Fixed-volume microsampling
- Integrated analyte stabilization
- Ambient temperature shipping

Studies have demonstrated the feasibility of remote blood collection for transcriptomic analysis, with participants successfully collecting and stabilizing capillary blood samples at home.³² Similarly, remote blood sampling devices have been developed for telehealth applications and population monitoring programs.³³

Covaris truCOLLECT Solution

Covaris' truCOLLECT Solution is designed specifically to support remote collection of blood for molecular analysis workflows. The device enables:

- Fixed-volume (50 µL) capillary whole blood collection
- Active immobilization and desiccation to stabilize biomolecules at ambient temperature
- Transport without cold-chain logistics
- Ready-to-deploy laboratory extraction reagents and workflow powered by Covaris' Adaptive Focused Acoustics® (AFA®) Technology

These unique and differentiated features of truCOLLECT can offer stabilized whole blood samples to be processed for multiple molecular analytes, ensuring high quality and integrity for each analyte, ultimately enabling genomics analysis from remotely collected samples. By standardizing sample volume and stabilization conditions, truCOLLECT aims to reduce variability and enable distributed biological sampling at scale across every laboratory focused on working with one form of Omics to genomics studies.

Toward Scalable Biospecimen Infrastructure

As biological research moves toward population scale datasets, the infrastructure used to collect biospecimens must evolve accordingly. An ideal system for blood collection should:

- Enable decentralized sampling
- Maintain stability of multiple molecular analytes
- Minimize dependence on specialized personnel
- Integrate with automated extraction and analysis workflows

In the constantly evolving landscape of genomics studies, whole blood collection can be viewed as a form of biological data infrastructure. Advances in sequencing technologies have already transformed molecular measurement, while the last decade and half witnessed some remarkable growth in Proteomics; similar innovation in sample collection may be necessary to fully realize the potential of genomics research. The truCOLLECT Solution ensures high quality analytes across genomics is delivered from home to the analytical laboratories seamlessly, and with unprecedented ease.

Conclusion

Phlebotomy has served as the foundation of blood collection in medicine and research for more than a century. However, the expanding scale of genomics research and decentralized clinical trials is revealing limitations in this traditional model. Workforce shortages, geographic barriers, and logistical complexity collectively restrict the scalability of venous blood collection. truCOLLECT remote blood collection solution lies in the forefront of the emerging remote blood collection technologies and can offer new solutions by enabling decentralized sampling compatible with modern molecular analyses.

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