



Precision Public Health Applications of Liquid Biopsy Genomics for Colorectal Cancer: Evidence, Equity, and Implementation Challenges

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ABSTRACT

Colorectal cancer (CRC) remains a leading cause of cancer morbidity and mortality worldwide, with early detection critical to improving outcomes. Liquid biopsy genomics offers a minimally invasive approach to detect tumor-derived analytes in biofluids, providing insights into tumor burden, genomic alterations, and treatment response. Precision public health applications of liquid biopsy enable population-level risk stratification, integration of genomic, clinical, and sociodemographic data, and targeted interventions for early-stage CRC detection. Evidence indicates that liquid biopsy can enhance screening accessibility, particularly in underserved populations, while supporting real-time monitoring of therapeutic response and disease recurrence. However, challenges persist in implementation, including data integration, health system logistics, workforce capacity, regulatory frameworks, and equity considerations. Addressing these barriers is essential for translating liquid biopsy genomics into actionable population-level CRC interventions.

Keywords: Colorectal Cancer, Liquid Biopsy, Precision Public Health, Genomics and Health Equity.

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent cancer and the second leading cause of cancer-related death globally. Early detection is critical to reducing mortality; population-based screenings improve early detection and reduce mortality, but participation is often low [1]. Although CRC-related technologies have made substantial progress, population-based assays leveraging liquid biopsy remain poorly characterized [2]. Genomic analyses of circulation and urine samples of cell-free molecules prove a promising screening strategy. Genomic alterations in tumor tissue mirror alterations in circulating or urinary samples [2]. A wide variety of circulating-detected genomic alterations and accompanying analytical performance metrics comprise new evidence on the potential role of liquid biopsy in CRC screening [1]. Techniques to interrogate tissue-of-origin-missing genomic alterations from circulation and urine further enhance the possibility of population-based early-stage CRC screening.

Background on Liquid Biopsy Genomics

Liquid biopsy techniques leverage the analysis of analytes shed from tumors into patients' biofluids to deliver clinically relevant information about malignancies [1]. Tumors, including colorectal cancer (CRC), continuously produce and release analytes that can be captured in biofluids such as blood. These analytes may contain tumor-derived exosomes, circulating tumor cells (CTCs), circulating free DNA (cfDNA), and other products that offer insights into tumor genomic alterations [2]. The presence of analytes in biofluids is contingent upon their shedding from the tumor, and CRCs exhibit characteristics that support a liquid biopsy platform. Understanding the basic biological principles underlying liquid biopsy and the particularities of CRC is essential to appreciate the connection between liquid biopsy analytes and population-level health actions pertinent to CRC [2]. For instance, tumor heterogeneity, clonal evolution during therapeutic intervention, and the predominant establishment of secondary tumors must be recognized to ensure that the dynamics of analytes released from tumors typically surveyed for screening do not mislead surveillance [5]. Similarly, knowledge of biological LP characteristics, including analytes present at low levels, and caution regarding the interpretation of allelic fraction at low

detection ranges, are necessary to avoid overestimation of tumor burden at the population level where the fraction of analytes may vary considerably [8]. Thus, an exploration of the fundamentals governing tumor shedding and analytes fluid mechanics under CRC addresses the considerations that play a pivotal role in detecting CRC at the population level [9].

Methods in Precision Public Health for Colorectal Cancer

Precision public health methods tailored to colorectal cancer propose a suite of study designs, data integration strategies, and analysis pipelines to assess lead time, stage shift, and mortality impact at population scale [6]. The study designs evaluated span a range of prospective cohorts, nested case-control studies, and pragmatic trials. To assess and compare screening approaches, study endpoints include lead time, stage shift, and mortality impact [9]. Rigorous consideration of these designs, their trade-offs, and the specific population-health-important questions they can answer is essential for the ultimate development of a precision public health genomics strategy [6]. The integration and fusion of diverse data types enhance precision public health approaches. Liquid biopsy genomics datasets can be linked with other genomic, imaging, electronic health record (EHR), and sociodemographic data to construct predictive models of disease risk and progression [11]. Such approaches have the potential to deepen understanding of disease genesis and spatiotemporal dynamics while also capitalizing on incomplete data for dynamic, anticipated risk assessments [3]. Validation remains a key consideration when deriving and applying models to inform population-level decision support, assuring that predicted outcome distributions match reality; calibration metrics, calibration drift monitoring, and other techniques can be employed [4]. Further reading provides additional depth on these elaborations of study design, integration strategies, and analytic implementation [3].

Evidence Base for Liquid Biopsy in Colorectal Cancer

Liquid biopsy is an emerging technique with the potential to impact patient care across multiple contexts. It is already endorsed for monitoring tumor burden of early-stage cancers and detecting therapeutic resistance options in advanced solid tumors [4]. It provides the opportunity to move from tissue-based to blood-based screening, enabling access to at-risk populations such as those with low socioeconomic status [5]. Sensitive and specific detection of ctDNA or plasma cfDNA-methylation-based changes in a positive sample can signal tumor recurrence or therapeutic response after radical surgery or systemic therapy, and take-home tests can facilitate patient-owned sampling [3]. Detection of plasma cfDNA-methylation-based signals alongside imaging markers informs the need for immediate medical intervention during postcurative surveillance [3]. Population-scale monitoring of genomic, imaging, electronic health record, and sociodemographic information can identify individuals transitioning to high-risk states earlier than traditional screening modalities. Start points at those determined to be at high risk can be determined for early-stage CRC based on population data [4, 8].

Equity Considerations in Deployment

Precision public health applications of liquid biopsy genomics for colorectal cancer: evidence, equity, and implementation challenges [5]. Colorectal cancer (CRC) is the third most common cancer worldwide, with an increasing burden in low- and middle-income countries. Risk factors such as diet, lack of physical activity, diabetes, obesity, smoking, and excessive alcohol intake are associated with CRC [6]. CRC is the third most diagnosed cancer globally, with an estimated 1.9 million new cases in 2020, and it is responsible for almost one million cancer deaths yearly worldwide [2]. Liquid biopsy constitutes an innovative approach for cancer diagnosis that can help improve CRC prevention [4]. Health equity is a growing imperative for public and global health. Equity challenges in liquid biopsy genomics applications for CRC arise due to the potential exclusion of certain population subgroups from implementation, workforce and infrastructure limitations, affordability considerations, and community engagement efforts [7].

Implementation Challenges in Health Systems

Colorectal cancer is a global health burden due to its high incidence and mortality as the second most common cancer [6]. To reduce its burden, precision public health applications of liquid biopsy genomics in CRC have been recommended. However, challenges remain for translating evidence to practice in health systems [9]. Logistics that complicate or delay the transport of the sample to where it can be analysed [8]. In addition, interoperability of data between various entities of the health system is a limiting bottleneck for adopting these precision public health applications [7]. Because much information has to be collected from different sectors of the public health system (i.e., clinical, genetic, socio-economic, etc.), integration of these data into health care systems is a significant hurdle to overcome [3]. Challenges remain regarding policies, regulations, and oversight for routine implementation. Clarity of policies with regard to the viability of using these comprehensive applications is still under discussion on account of various variables [6]. Quality assurance guidelines for liquid biopsy genomics for CRC are increasingly being developed; no globally unified recommendations exist, however, despite regulatory and financial models evolving to accommodate genetic solutions [5]. Furthermore, there is concern of a shortage of workers in both public health and health systems. This shortage is further exacerbated by a lack of educational

and practical program offerings, which in turn affects the ability to generate a workforce for precision public health applications of liquid biopsy genomics in CRC [7].

Policy and Ethical Implications

Liquid biopsy genomics offers improved population-level decision support for colorectal cancer risk mitigation. To maximize health gain and equity, practical precision public health applications are needed [6]. Implementing government-supported precision public health policies and programs creates pathways for deploying the relevant technology [9]. Population-based decision support for colorectal cancer therefore defines the target audience and scope for broader national health implementation of circulating cancer genome technologies. General guidance on approaches and strategies for the implementation of precision public health decision support for colorectal cancer is detailed [8]. The rapid rise of precision public health applications stresses the importance of data privacy and security governance frameworks [9]. The management of public health population databases across diverse sectors in society, coupled with ongoing advancements in data science procedures, poses real risks to privacy and personal genomics data [10]. These transparency and accountability issues must also be addressed alongside existing data governance and models of consent, such as broad, opt-in, or reversible [10].

Future Directions and Research Gaps

Precision public health applications of liquid biopsy genomics for colorectal cancer: evidence, equity, and implementation challenges, methods, challenges, and future directions [11, 12]. Health disparities, ecological fallacies, and limited impact assessment hinder public health. Community-wide approaches as surrogates for population-wide interventions may be inappropriate [13]. Yet more granular sensitivity and specificity metrics by community, township, or other units could prompt local responses while protecting personal confidentiality [10]. Individual community data may help establish settings of confidence within which risk thresholds can be identified [11]. Synthesizing across evidence, equity, and implementation explorations: defining colorectal cancer genomics; consolidating analysis of misinformation; specifying biomarker-targeting and associated populations; measuring chronological versus population-level signals; clarifying intended and unintended health equity consequences. Generating space-saving summaries for legislative use [14]. Expert communities disproportionately represent designated focus areas, generating the risk of temporal disjointness. Retreating from selected emphasis, integrating recurring systemic threats [15]. Close proposals without recapitulation for refresher-aware audiences [16].

CONCLUSION

Liquid biopsy genomics represents a transformative tool for precision public health applications in colorectal cancer, offering the potential to enhance early detection, monitor disease progression, and inform targeted interventions at the population level. While evidence supports its clinical and population health benefits, successful implementation requires addressing logistical, regulatory, equity, and workforce challenges. Future research should focus on integrating multi-dimensional data, validating predictive models, and ensuring equitable access, thereby enabling the full potential of liquid biopsy genomics to reduce CRC burden globally.

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